Principles and philosophy of modeling in biomedical research

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ABSTRACT **Despite widespread applications in biomedical research, the role of models and modeling is often controversial and ill understood. It is usual to find that fundamental definitions, axioms, and postulates used in the modeling process have become tacit assumptions. What is essential, however, is a clear vision of the fundamental principles of modeling. This is even more compelling for new and emerging interdisciplinary fields that use techniques from previously separate scientific disciplines. This article outlines and reviews the central nature and philosophy of modeling, the rules that govern it, and its underlying key integral relationship to the 'scientific method'. A comprehensive understanding of these issues is indispensable to successful research and meaningful progress in all facets of biomedicine.—Massoud, T. F., Hademenos, G. J., Young, W. L., Gao, E., Pile-Spellman, J., Viñuela, F. Principles and philosophy of modeling in biomedical research. *FASEB J.* 12, 275–285 (1998)**

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To muddle or to model, that is the question.
A. A. Verveen (1)

Humankind's discoveries about itself and the surrounding world have created that vast structure of knowledge we now call 'science' (2). The search for explanations began with humans' first observation of the 'movement' of the sun. No sooner were the questions phrased than controversy about the explanations began. For it is of the very nature of the scientific mind to question established patterns of knowledge, to suggest new explanations, and to defy those who claim to know better (2). Today, scientific research is looked upon as synonymous with progress; and without progress, the elaborate structure of modern life would collapse.

Models are an indispensable ingredient of the scientific method; as deductively manipulatable constructs, they are essential to the evolution of theory from observation (3). The intention and the result of a scientific inquiry is to obtain an understanding and a control of some part of the universe. No significant part of the universe is sufficiently simple that it can be grasped and controlled without abstraction. Abstraction consists in replacing the part of the universe under consideration by a model of similar but simpler structure. Models are thus a crucial necessity of scientific procedure (3) and the modeling process itself represents the essence of the hypothetico-deductive approach in science (4).

Unfortunately, scientific research is one of those highly complex and subtle activities that usually remain quite unformulated in the minds of those who practice them (5). This lack of focus not uncommonly extends to the creation and use of experimental models in biomedical research. The act of modeling (its principles, guidelines, and techniques) is generalizable, even though the models themselves are not (6). A number of illuminating treatises on models are available that offer insight from diverse points of view (7). However, a single comprehensive review article on the general principles and key ideologies of experimental modeling is unavailable to the biomedical community. This work is based on a number of these previously reported discourses–it is intended to bring together and highlight the salient fundamental aspects (the philosophy, nature, purpose, and rationale, relation to the 'scientific method', advantages, limitations, etc.) of the process of experimental modeling, a comprehensive understanding of which is indispensable to successful research in all biomedical disciplines.

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TERMS AND DEFINITIONS

When otherwise stated in this article, the term model is used synonymously with analog to mean that which is similar in function but differs in structure and origin from that which is modeled (7). This is a deliberate oversimplification, introduced only for the sake of convenience. However, in this section, a more profound exposition of the diverse terms and definitions relevant to this discussion is provided.

At the outset it is necessary to clarify that by *overt* modeling we mean studies explicitly designed to complement scientific research, not the *tacit* modeling that always accompanies experimental design, measurement, description, and interpretation of results (7). Furthermore, care should be exercised at all times to maintain the distinction between a *normative* model (which describes how the system ought to operate) and an *empirical* model (which is based purely on measured data). Only the latter type must be used in the scientific method (7).

Dainty (8) states that an *analog* (a model based on analogy) involves 'a simplification of the actual subject for analysis into sufficiently few elements that a mathematical or experimental treatment of its behavior under any desired conditions may be possible'; and it 'crystallizes in one diagram (or piece of apparatus) the characteristics of a system that otherwise requires much apparently complex mathematical or verbal explanation'. Thus, an analog both simplifies and puts into familiar terms a complicated phenomenon and hence enables one to think much more clearly about the subject; things are more 'intuitively' obvious (8). The use of analogy can be defined as follows (8): 'if two different phenomena A and B are described by the same mathematical formulas, quantitative conclusions can be drawn about the phenomenon A by studying the phenomenon B'. The apparatus or 'model' of B designed to investigate A by analogy is the analog.

Further insight into the distinction between an analog and a model is offered. According to Kacser (9), several terms currently in use: 'hypothesis', 'theory', 'law', 'analog', and 'model' appear to be synonyms of only 'analog' and 'model'. Analog and model differ fundamentally from each other. An analog is 'a device (in which entities are related to one another) that can be used for the purposes of making a model'. A model is 'a statement or a series of statements in language'. Models are, therefore, propositions that may be either verbal or mathematical, in which entities are related according to the rules of a particular language. Whenever a device is used as an analog, it is to derive or confirm some form of deductive verbal system. Why are analogs used and how do they help in formulating models? We use analogs when we cannot formulate intuitively the propositions that will yield the conclusions corresponding to the empirical situation. The analog, particularly if it is a human-made device, is much more amenable to the process of extracting the logical model than most situations we encounter. The analog having been constructed in a known way, should it be found to behave in the expected manner, is capable of being 'translated', so to speak, into language either verbal or mathematical. The words 'hypothesis', 'theory', and 'law' have subtle distinctions among them, but all have the same logical status as a model insofar as all of them are propositional in nature and in fact meant for use in the same way (9).

When we use the term model in biomedical research, we do not necessarily mean an actual apparatus whose appearance or properties are similar to the system we are studying (10). More often we mean that we think the properties of the entire system derive from the properties of certain defined constituent parts, and that from a knowledge of the functioning of these components and of their interactions with each other, we could give an explanation of the functioning of the whole that would be more readily understood than if we tried to describe the whole at once (10). This definition of a model by Pringle (10) makes it conceptual rather than actual. In contrast to *actual* models whose performance can be subjected to experimental examinations to determine their degree of similarity to the original system, *conceptual* models have to rely on logic for their justification. In this case, the ultimate test of validity is a mathematical one. A conceptual model is satisfactory if the mathematical formulation of its performance is identical with that of the original system. It is not necessary in this instance for the component elements to be physically/chemically realizable. The biomedical researcher, however, is often wary of purely imaginary analytical concepts, and has a natural tendency to try and visualize component parts (10). Furthermore, it is rare in biomedical research to be able to apply the full rigors of a mathematical test to a conceptual model. More often one has to be satisfied with a more intuitive test in which: *1*) the quantitative features of the overall performance appear to be explained by the combined properties of the conceptual units, *2*) the qualitative features of the overall performance appear to be explained by the combined properties of the conceptual units, and *3*) the quantitative comparison is at least not grossly in error (10).

PHILOSOPHY AND RATIONALE FOR MODELING

It is imperative that any scientific research, especially if it requires an interdisciplinary approach, be grounded in the philosophy of science and furnished with the logical tools that permit the translation of empirical data into useful knowledge and worthwhile means of advancement (11).

The purpose of scientific investigation is the accumulation of knowledge about the nature and behavior of the real world (which may be defined as any and all measurable entities and processes within the physical universe) (11). In this respect, the making of models is universal in the search for a consistent and instructive picture of nature (7). The active use of models and analogs is necessary because the subject of investigation is usually too complex to work with. The complexities may arise from (12): *1*) the very large number of interactions of elements whose individual existence and properties we know or think we know, or *2*) because there is a 'black box' in the system that is inaccessible to us; in fact, it may be impossible to make direct contact with the subject in any manner, especially at the time desired. The use of pure trial and error as a design procedure has long been far too costly both in time and money (11). Good science practice dictates that each successive trial design be based on past experience, which indicates the most efficient direction in which to reach the next step. Such directed development and progress results from following the dictates of good experimental modeling. Certainly the more adequate the model, the more rapid, will be the approach to success, and at minimum expenditure (11). Thus, worthwhile models are predictive: new relevant properties are deducible from them (7). Furthermore, a model often suggests constraints that may exist in the system being modeled. If these constraints are valid, they can guide subsequent experimental interpretation. To thus reveal, test, compute, extrapolate, and predict is to accelerate the process of learning about the real world (7).

As collected data accrue during scientific research, it becomes possible to consider different models in search of some rationale for the evidence (11). These models may be used to foretell the next observation, and as subsequent data are gathered it soon becomes apparent that some models are more beneficial than others in this way. In fact, it may be possible to choose a particular model that achieves minimum error toward estimating any previously unobserved datum point. Having such a model available is the first step in understanding the observed data. It offers some knowledge of the conduct of the real world and, within its degree of precision, may be used to predict other observations for the purpose of analysis or synthesis. The use of such conceptual models is fundamental to scientific thought (11).

Obviously, proper selection of an appropriate model is critically important. The value and power of any model as a deductive or inductive tool will depend on the speed and freedom with which the investigator can visualize relationships in it and concepts based on it (11). Perhaps the mathematical model approaches the ideal most closely in the rigorousness of its specifications and the flexibility of its manipulation in expert hands (11). However, there may be a number of different, yet equally successful, models for the same subject of investigation. Having achieved one model does not earn one the right to state, 'this is how it works'. To establish a particular model above all others is to erect a barrier to open thought and to the amendment that could someday further clarify the subject. A model is an invention, not a discovery. It may prove to be a valid description, but this is far cry from being the essential truth (11).

All good experiments are good abstractions (3). An experiment is a question; a precise answer is seldom obtained if the question is imprecise. Not all biomedical questions are directly accessible to experimentation. There is a hierarchy of questions whose levels are determined by the generality of the answers sought. The low level in the hierarchy deals with a narrowly restricted and specific phenomenon. As a rule, high-order, very abstract and general questions are not directly amenable to an experimental test (3). They have to be broken down into more specific terms that can be translated directly into experimental procedure. There are thus two qualitatively different operations involved in formulating research of a general statement (3): *1*) moving up and down the scale of abstraction, and *2*) translation of the abstraction into an experiment. The good experimenter has particular ability in the second procedure. The theorist deals mainly with the first. All scientific experiments begin with closed-box problems: only a few of the significant variables are identified. Scientific advancement consists in progressive opening of those boxes. The successive addition of variables leads to gradually more elaborate models, and hence to a hierarchy from the relatively simple and highly abstract models to the more complex and concrete theoretical pictures. Therefore, at an intermediate stage in the course of scientific inquiry, the model may be a heterogeneous assembly of elements, some treated in detail—specifically or structurally—and some treated merely with respect to their overall performance: generically or functionally (3).

Each biomedical investigation should begin with a clearly defined hypothesis. A model is devised to implement this hypothesis and allow investigation (11). All scientific modeling proceeds from the 'principle of contradiction': 'A and non-A' is an invalid statement (4). Beyond this point, the logical force of a model is exactly the same as that of a scientific hypothesis generally (4): to be logically forceful it must be capable of undergoing tests that may falsify it (the well-known criterion of Karl Popper; ref 13). Furthermore, the model should be: *1*) heuristic in nature (a good 'fit' both to the hypothesis and the available data), i.e., be appropriate to the primary features of the real world, *2*) permit application of the

TABLE 1. *The purpose of experimental modeling according to Yates (4, 6) and White et al. (15)*

Experimental modeling provides:

(1) A systematic and effective way of assembling and codifying current facts and beliefs (knowledge) about a system of interest (that part of the real world being modeled). This in turn allows:
  - (a) The exposure of contradictions in data sets or beliefs of this system,
  - (b) The identification of important parameters of this system,
  - (c) The identification of the essentials of system structure,
  - (d) The determination of the overall system sensitivity to variation in each parameter,
  - (e) The explorations of the major implications of the beliefs about the system (and which implications may be strongly counterintuitive).

(2) Identification of specific elements or information gaps about the system that must be further quantified, thus leading to the development of important experiments or quantitative measures.

(3) Prediction of system performance under new conditions.

(4) Prediction of quantitative values of experimentally inaccessible variables or parameters.

(5) A method to test hypotheses rapidly, efficiently, and inexpensively. More specifically, it is a method to demonstrate hypothesis rejection (when the model fails).

(6) A method to represent the overall current 'understanding' and to predict the behavior of the system of interest.

available/desired techniques for its manipulation (*vide infra*), and *3*) accessible to evaluation by a specified set of criteria measures (*vide infra*) (11). Proving a hypothesis to be untrue is not a complete defeat so long as the investigation was carried out in a scientific manner. These negative findings serve to prevent future fruitless searches in that same specific direction. Review of the work may also offer new hypotheses and even indicate new models that could prove to be successful in the future (11).

Each model should be an unambiguous expression of a hypothesis, but not all models are acceptable for hypothesis testing. The scientific method requires that the model also be both self-consistent and 'public information' (11). The former constraint requires that the same set of fundamental assumptions cover all aspects of the same set of data under investigation: the 'ground rules' cannot change once the 'game' has started. It is this constraint that 'eliminates scientific expectation of ever finding a centaur or mermaid in the real world' (11). The second constraint implies that the model can be used by any observer at any time and, if properly used, with the same consequences. This constraint eliminates models that may be called 'visions' or 'inspirations'. If a model is not repeatable in hypothesis testing, its value is nil (11). In this regard, mathematical models represent a large class of acceptable models that always yield the same scientific consequences from a given set of definitions, axioms, postulates, and data. Further insight into the meaning and uses of models in mathematics and the empirical sciences can be found in the work of Suppes (14).

A significant aspect of a model's utility lies in its ability to focus disparate evidence and interpretations into one coherent view: ''parsimony of explanation often leads to revealing unity'' (7). Models are also valuable to the extent that they raise new questions and suggest new relationships, perhaps leading to new experiments that otherwise might not have been considered. These are some of the advantages of using models. Accounts of the overall purpose and specific advantages of experimental modeling have been provided previously by Yates (4, 6) and White et al. (15). **Table 1** lists the benefits of using experimental models. Several of these advantages will become more apparent upon discussion of the techniques involved in the creation and use of models (*vide infra*). What is evident is that the act of modeling leads to greater knowledge of the real world. Although all models are in greater or lesser degrees false (8) (*vide infra*), this does not necessarily detract from their value because they often bring out important points about the real world that would otherwise have been missed. Even the blatantly false ones have served a useful purpose: one cannot construct a model without contemplating the problems involved and so asking new questions and uncovering obscurities that had previously been accepted passively (8). It bears reiterating that even if a model should fail as a predictor of the real world, all is not lost. If the model–hypothesis has been well stated, it serves to identify a path unworthy of future attention (11). Furthermore, we sometimes forget the importance of apparently simple, unrealistic, obscure, or more difficult (than what is being modeled) models in their own time. The historical value of some of these models cannot be doubted (7). Humankind's knowledge of nature is evolving. Admittedly, a model or a theory that leads to a dead end is of limited interest, but one that forms a link in a continuing chain is extremely valuable, whether or not subsequent events far outreach it (7).

NATURE OF MODELS

The biomedical investigator should consider the nature of all potentially applicable models to the area of research at hand. Several classifications of the fundamental nature of models are available. For a detailed examination of the nature of *analytic* and *synthetic* models (within mathematics), refer to the work of Rosen (16).

Fogel (11) has stated that models may be *analogic* (an analogy of some aspect of the real world) or *symbolic* (a symbol intended to represent some aspect of the real world), and *descriptive* (generated directly by a measuring transducer) or *constructive* (constructed by the investigator). The more analogic the model the less symbolic, and vice versa. An example of an analogic descriptive model is an X-ray; it is a model of internal body structures. On the other hand, an analogic constructive model may be exemplified by a computer: it is a human-made model of aspects of human functioning. Another example is the game of chess, which was originally intended as a model to optimize war strategy. Movements of chess pieces possess a high degree of analogy, and the layout of the board is a constructed analogic model for the battleground. Language is a symbolic descriptive model for real-world subjects. Also, the number system is a set of symbols used to quantify aspects of the real world. Conversely, vocabulary and its subtle use serve to select and group the elements of language into more complex constructed symbolic models. Algebra (the relating of known and unknown quantities) is an expression of symbolic constructive models, because complex algebraic operations may be symbolized in short form to render an otherwise unwieldy operation manageable (11).

The degree of complexity of a descriptive model is usually dependent on the nature of the transduction process through which it is formed (11). This is not the case with constructed models. Here the complexity is up to the investigator, who must use good judgment. A simple model offers certain advantages: It can be mentally manipulated to offer rapid insight into its value and it allows ease of description and communication, which also makes it a worthwhile teaching device. However, too simple a model results only in weak, gross results that may not be adequate for the investigator interested in new findings of substance (11). At the other extreme, one may consider models of such great specificity and resulting complexity, where it becomes necessary to collect and manipulate vast amounts of data in order to reach even a most modest conclusion. Here, practical limitations of cost in both time and money come into play. Nowadays, the availability of computer facilities permit consideration of models of increased sophistication. All in all, there is a subtle and powerful value in simplicity since a proven simple model leaves open a wider choice of directions to 'explain' an increased domain of the real world. An overly specific model may satisfy a present need, but by its very nature prevent further expansion into new alternatives (11).

Kacser (9) distinguishes between two types of models: *heuristic* and *conceptual*. A heuristic model is one that makes statements, more or less precise, that lead to further experiments. It contains statements about the outcome of future experiments or observations whereby it may be tested for its applicability. Conceptual models are alleged to have none of these characteristics, but are merely frameworks into which existing information is placed and arranged in a certain manner. There are no clear demarcation lines between these two types of models, because it will depend on the state of experimental techniques whether certain consequences of the model are or are not verifiable experimentally.

Rosenbleuth and Wiener (3) state that a *material* model is the representation of a complex system by a system that is assumed to be simpler and to have some properties similar to those selected for study in the original complex real-world system. A *formal* model is a symbolic assertion in logical terms of an idealized relatively simple situation sharing the structural properties of the original factual system. Material models are useful because they: *1*) may assist scientists in replacing a phenomenon in an unfamiliar field by one in a field with which they are more at home, and *2*) may enable the execution of experiments under more favorable conditions than would be available in the original system. Sometimes the relation between the material model and the original system may be no more than a change of scale (e.g., the use of small experimental animal model vs. large animal subject) or of space or time (e.g., the use of *Drosophila* in genetic studies) (3).

Finally, a useful classification of models of biomedical relevance was provided by Yates (4): *1*) *heuristic models*, which include loose talk (words and stories); metaphors and definitions; classifications and correlations; pictures and diagrams; and statistical representations of data. Statistical models refer to properties of data but do not directly assert anything about the structure of the system that produces the data. *2*) *Equivalent network models*: these include *a*) analogs (having functional similarity) such as physical devices (machines) or formal (empirical) equations that represent a function classified as similar to that of the system of the real world of interest. 'Similarity' depends on the purpose of the modeler (also, *vide infra*). If quantitative similarity is chosen as the criterion, the issue becomes a statistical one, after a specific criterion is chosen for 'goodness of fit' of the two functions. *b*) Homologues (structural as well as functional similarity) attempt to provide one-to-one structural similarities that lead to one-to-one functional similarities between model and the real world. Here the question of validity rests both on bookkeeping (does the model output match the system output to criterion closeness, as with analogs?) and on prediction (does the model produce appropriate outputs, according to the criterion of fit, when tested against a new data set not used in its construction?) (2).

Equivalent network models are of research interest, but each model describes only a special case. It is a working hypothesis, not a theory (2). In fact, it is usually composed of equations of convenience, even if it is a homologue. Because analogs or homologues are not complete representations of physical theory, they may inadvertently escape the restraints of physical theory. In that sense, they are 'unscientific' (2). Equations of convenience are not fundamental in any sense, no matter how well they perform.

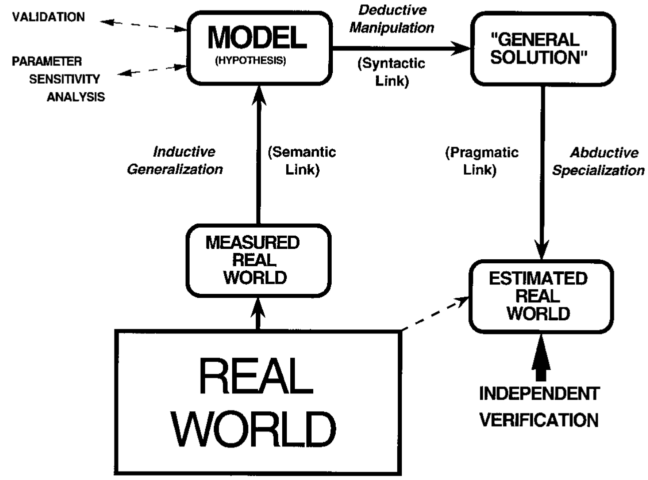

Figure 1. The scientific method. Adapted from Fogel (11).

FUNDAMENTAL TECHNIQUES OF MODELING

A general understanding and familiarity with the scientific method offers a foundation for fruitful specific endeavors in biomedical modeling and research. **Figure 1** illustrates the scientific method (11). The real world is represented by observed data. To make some estimate of the as yet unmeasured region of the real world, a model is selected or constructed that is consistent with the real-world data obtained at measurement. Generation of this model may be called the *semantic link* (the study of the relations of signs to the objects represented). The chosen model is then manipulated experimentally to result in a set of observable consequences. This process may be called the *syntactic link* (the study of the relations between signs and other signs). The solution is then related to some inferred real-world behavior. This may be termed the *pragmatic link* (the study of the relations between signs and the uses of signs). The process is incomplete without investigation of the validity of such inference. Serious error may be introduced at each of the above links (11). Because this chain of events is crucial to the act of modeling, a detailed discussion of individual links follows.

THE SEMANTIC LINK

Induction is that logical process that takes specific cases and derives from them what appear to be generally applicable governing rules (11). The generation of a hypothesis—the formulation of any model—is just such a process. The semantic link is concerned with the description of some specific aspect of the real world in such a way as to generate a model that is then presumed to remain valid over a wider domain than that identified by the available empirical evidence. The data provided to construct the model may originate from natural observations or performed experiments.

The proper description of the real world in terms of a model often offers pitfalls and unforseen difficulties; three issues of relevance require further elaboration. First, an intrinsic problem remains for data from both natural observations or performed experiments: the transducer used to sense the real world introduces a certain amount of error into the data obtained (11). Therefore, it is advisable to remove as much of this error or noise before model selection/construction. This introduced *noise* is of two general types: *deterministic* and *stochastic* (11). The measured real world—that is, the real world as we know it—is always noisy. Not only are we incapable of measuring precisely, but we cannot be sure that the very act of measuring does not change that which is being measured. This fact is borne out well in the microscopic world, where Heisenberg's 'principle of uncertainty' gives a lower limit to possible error (see ref 17). It is not within human capability to ever know whether all of the error in the observed real world is from the process of measurement or not. This uncertainty is inherent; the finer the observation, the greater the relative noise content of the measured data, and the greater the difficulty in attaining an improved amendment of the model. In fact, this logic leads to the conclusion that the 'truth' concerning the behavior of the real world can never be formulated in exact statements (11). It stands to reason, even without embarking on a theosophical discussion, that the search for knowledge of the real world is necessarily unbounded.

A second compounding factor is that all real-world transduction is nonlinear (17). Some degree of nonlinearity can be incorporated into a model in order to maintain some level of precision even under expected saturation characteristics. Yet there always remains some additional nonlinearity that cannot be formulated into any finite descriptive model. This is one more reason why a model cannot fully describe the real world nor can the extracted data be without error. The model selection and construction must be predicated on the best available known description of the real world (17).

Third, because all empirically observed behavior is stochastic in nature (i.e., there is some essential variability in all processes that are available for measurement), the investigator can introduce statistical techniques to assess aspects of this variability and take these into account in the construction of his model. However, the statistical behavior itself is constantly changing, so that there remains some essential error even in the most precise statistical description (17).

The semantic link is characterized by the formation of a model (albeit 'noisy' or 'false' to some extent) to describe the real world. In its ideal role of providing a coherent, parsimonious description of nature, a model is necessarily a simplified representation of the original (7). Were this intrinsically lesser representation of no use, complete replication of the object modeled would be necessary and the idea of 'model' would lose all meaning. Thus, systems are modeled in a useful manner by constructs that have some functional equivalence but are not identical in detail; the essential properties of the original are represented whereas the obscuring irrelevancies are ignored (7). However, this imposes a requirement for selection that lies at the heart of the modeler's dilemma. There are two distinct philosophies in the selection of parameters for model construction, both affecting the simplicity/complexity (*vide supra*) of the resultant model (7) and each with important application: *1*) A very large number of properties and features are reproduced with high accuracy. Initially the model is overspecified, and the tacit intention is to simplify if and when it seems reasonable to do so. *2*) A more limited set of properties is used, but the restrictions have been made on the basis of an a priori set of assumptions as to the most significant ones. It is assumed in such 'minimum-parameter' models that the essential features have been retained; the tacit intention is to introduce more complexities if it becomes necessary to do so. There are advantages and disadvantages to each approach. Models of the first type are more complete, but are more difficult to realize and more costly. Models of the second type are more amenable to analysis, but are in greater danger of important omissions. Although a more nearly complete model can contain the features of several minimum-parameter models, the addition of accessories to the latter is equivalent to the changing of parameters in the former (to model different situations) (7).

There are situations in which the data available to describe the real world are inadequate for full quantitative description of a model. Berman (18) proposed a technique to aid in model building under these circumstances, which involves the use of minimal system perturbation experiments for parameter manipulation in order to develop unique models.

A model must also be suitable to the specific intent of the investigator: there must be recognition of a set of criteria measures that allow evaluation of the model (11). This system intent must be included as part of the model in some directly definable/computable form. Adjectives such as 'best', 'most efficient', and 'simplest' blind the unwary researcher from attaining knowledge of the exact intent and purpose of the model. Too often, adequate models are offered for real-world problems, but no specific purpose has been designated that the subject system is intended to fulfill (11). Identification and use of an appropriate set of weighted criteria can yield a worthwhile evaluative measure.

In constructing a model, therefore, it is necessary to define an 'adequate' model (19). In this regard, the engineer is usually much better than the biologist. The action of one quantity on another is often known, but if it is not, the engineer can usually take the model apart and measure the response of each element to suitably chosen provocations. For biomedical researchers, it is usually technically difficult or impermissible to measure experimentally the separate dependencies that constitute the model and its similarity to the real world. Most systems of interest to biologists involve nonlinear relationships. In such cases, no general analytical methods are available to check the adequacy of a model, but solutions may be sought by the use of physical models or analogs with parameters that can be adjusted until the behavior of the model corresponds with the observed behavior of the system. It is essential to test and modify unceasingly in order to obtain convergent qualitative and quantitative agreement between the model and what is being modeled (parameter sensitivity analysis (15)). Adequacy of the model is inferred as long as there is continual testing for appropriateness and there is no serious violation of physiological evidence (7). Analytical mathematical methods are available for linear systems, some aspects of which may also suggest approaches to analogous problems in biomedical research (19).

THE SYNTACTIC LINK

The syntactic link of the scientific method is concerned with the manipulation of the model into some form that may be interpreted as a general solution (11). That is, the syntactic link must be accomplished in such a way as to facilitate the pragmatic link that is to follow. The manipulation of the model may be simple or extremely difficult, depending on the particular problem being investigated. What is certain is that it is always deterministic as well as being 'public information': any investigator should find the same solution to a given problem (11).

Once a model is realized, three kinds of action must be taken (7): *1*) preliminary validation by testing the model's accuracy. This is mandatory, and is achieved by matching the model's behavior with scientific observations. Successive refinements of the model may then lead to convergence to an accurate and revealing abstraction. *2*) With validity tentatively established, one may attempt to discover novel properties of the model (operations not considered explicitly in the original design). Although such 'discovered' properties are implicit, due to the choice of model parameters, it is most unlikely that all of them will have been foreseen. If these new properties also match those known to exist for the modeled system, or if on subsequent testing they are shown to have successfully predicted functions not previously known, then the model's validity is given additional support. *3*) More speculatively, but often of great value, the model can test hypotheses and explore their consequences more rapidly and economically than direct scientific measurement permits. In this way, many theoretical ideas can be tested and evaluated. Furthermore, such preliminary observations can reveal the necessary consequences of a particular hypothesis, which in turn can be used as a basis for planning more effective scientific experiments (7).

Often the complexity of a fully descriptive elaborate model may be temporarily disregarded during its manipulation in order to examine only the limiting conditions (11). Evaluation of extremes may provide insight into the chances of success with more complete and costly manipulation of the model that yields a full solution. In practical problems of evaluation, it is sometimes beneficial to sidestep the analytic solution, favoring the insertion of estimated numerics. The resulting approximation is not presumed to be a solution, yet it serves to form a frame of reference for the results of a more detailed and complete analysis (11).

It is often possible for the investigator to follow intuitively the model as it passes through various stages of manipulation. This is especially true for models that maintain a high degree of analogy with their real-world counterpart. But great care must be taken sometimes to avoid pitfalls that can mislead or, even worse, lead to anomalies that fall outside the logic of common experience (11). Naturally, every effort should be exerted to avoid errors or mistakes in carrying out the required manipulation of the model.

THE PRAGMATIC LINK

The pragmatic link is the inverse of the semantic link, being accomplished through use of the abductive logical process (11). The constructed model, which is presumed to be properly chosen and manipulated, is examined to reveal specific values relevant to the problem at hand. In this regard, the process may be considered as descriptive; however, here what is being described is some form of the model rather than the real world. Specific data are extracted from the transformed model (now in the form called a general solution) under the tacit assumption that, if the model is truly representative of the predicted real world, then excitation of the real world in this certain manner would yield that particular resultant (11).

A complete model must include a clear definition of its domain of validity (11). Since only a finite set of data points was available for its construction, it necessarily follows that the model may be valid only over some finite domain. It is not always clear to investigators that the particular point in which they are interested may not remain under the 'awareness' of the model, so that the abduction, even though straightforward, may prove of limited value. Even if the model corresponds exactly with the given data points of the real world, it does not necessarily follow that interpolated values remain valid unless an attribute of continuity or some similar constraint has been embedded within the model itself (11).

Independence of parameters or characteristics is not exactly realizable in the real world. This assumption greatly simplifies models and is an extremely useful analytic device (11). Under certain circumstances, however, it allows the neglect of important conditional relations among parameters that can change the very nature of the achieved solution.

The realization that statistical behavior governs the real world dictates that traversing the pragmatic link be accomplished by techniques of statistical inference (11). The abduced values must be accompanied by some statement as to the level of confidence with which these extracted values may be stated. The theory of probability provides the tools that bound inference. Investigators should expect more than some degree of error in their inferential conclusions, even when taken from a well-constructed and manipulated model (11). Indeed, it might be asked whether we can draw any conclusions from a model (17). In general, clearly we may not. Even with a mathematical law, every logical deduction is open to experimental verification; if it is verified, the law is discarded as being inapplicable. A model may point the way, but it must not lead us (17). The exception is the statistical model, where we may make inferences in terms of probability statements about the real world.

Probably the most important consequence of the pragmatic link is evaluation of the interpreted data through access to new empirical evidence about the real world (11). Throughout scientific investigation, there must remain a ''conservative spirit that attempts to revalidate the gains accomplished at every possible opportunity'' (11). Until actual measured data back up theoretical predictions, these predictions remain in the world of uncertainty. Their use for the estimation of further data or the construction of new models may initiate a cascade of increasingly significant errors. No matter how carefully created or complete a theoretical analysis may be, there always remains the danger that such scientific extrapolation may be logical but not at all descriptive of the real world. The scientific method frowns upon ambiguous statements and models. There is only one cure for this problem, and that is a return to investigation and measurement of the real world (11). Rosen (20, 21) has addressed in detail the nature, limitations, and dangers of extrapolation of the results of modeling to the real world. A proper understanding of the principles of this extrapolatory action in modeling is necessary.

Yates (4) has provided a simple but useful overview of the fundamental logical relation between an imaginary real-world system (A), its model (B), the response (C) to model manipulation, and a response (X) if an analogous manipulation were later to be applied to the real system (A). There are three possible outcomes: *1*) It is found that (X) is the same as (C). This case is the one popular with modelers: the data 'fit' the predictions of the model. *2*) It is found that (X) is different from (C). This is the most useful outcome, because it suggests that our knowledge of (A) is incomplete and a search is necessary for a different form of the real world (one that we were not aware of and that would produce the (X) obtained). *3*) (X) is not determined, and instead it is assumed that it would be the same as (C). This is the classical syllogism, which is trivial/irrelevant here because it requires that we have already proved (A) $\equiv$ (B); this is the whole point of the test (i.e., should a model thoroughly realize its purpose, the original real world could be grasped in its entirety and a model would be unnecessary). Note the paradox: when the real world does what the model predicts, we have proved nothing logically (an insight into the real world is not obtained this way). Thus, we see that models satisfy logic when they fail (''but satisfy the lust of the modeler when they succeed!'') (4). It is hard to lose when you model: if an experiment produces results that your model predicted, you feel good; if it does not, you learn something new (4).

LIMITATIONS, PITFALLS, AND CRITICISMS OF MODELING

Many potential pitfalls in the act of modeling have been alluded to already. The limitations of the modeling process as applied to biomedical systems may be summarized (6). *1*) The process is subjective. *2*) Models represent isolated systems, whereas the real systems being modeled are rarely isolated or even isolatable in principle. *3*) Minimal-parameter models may not be explanatory to one's satisfaction because they may neglect properties that are emphasized in more traditional physiological work. Thus, it may be necessary to 'overmodel' in the mathematical sense, to provide a model that has appeal to a community of scholars who have arrived at their understandings of the real world through a different route. *4*) Models are logically strongest when they fail, but psychologically most appealing when they succeed. *5*) Physiological models almost always deal with special cases and have only limited generalizability. Results of modeling should never be extrapolated directly to a clinical setting, but used only as a framework within which clinical phenomena can be better understood (22). *6*) Science is a community activity, and to be part of science, a model must be communicable. Many models are implemented in forms that are difficult to comprehend by any but the modeler himself. *7*) Physiological models are not usually strongly based on natural law as defined in physics. Thus, their scientific status is weak.

Not all models are useful for a variety of reasons, which can be appreciated from the discussion above. Three significant reasons deserve repeating (3). *1*) If they are weak and trivial they might be useless, i.e., a gross analogy to the real world may not be scientifically fruitful. *2*) If they do not suggest any experiments, then they are superfluous. *3*) If they are more elaborate and less readily amenable to experiment than the real world, then their availability and use do not represent progress.

Despite widespread applications, the role of models and modeling is often controversial and ill understood. One interesting criticism denies the value of any model that is not 'primary' (i.e., a direct representation of the real world) (7). It is said that no ''model of a model'' can really add anything valid to scientific knowledge (7). However, it is difficult to conceive of a genuinely primary model. It seems clear that all models as we know them are secondary (i.e., that they are models of models); our conceptions of our environment are themselves models and, indeed, are structured from more basic models (7).

Finally, and of relevance to the biomedical researcher, it is in the realm of biological regulation/control/feedback that models have been disappointing (4). Apart from the usual inherent complexities of the systems involved (i.e., many internal/component elements) (23), biological regulators often depend more on saturating mechanisms or other nonlinearities than on simple feedback.

COMMUNICATING THE RESULTS OF EXPERIMENTAL MODELING

The characteristics that are welcome in a paper on modeling have been summarized by Yates (6), and apply specifically to the publication of articles making use of mathematical models in biomedical/physiological research. However, the spirit of these guidelines can be extended to encompass the many other forms of modeling (animal, in vitro, computer, mechanical, etc.) at the disposal of the biomedical researcher. A sound paper on modeling has the following features. *1*) The model is presented with all equations demonstrated in full; if a computer program is used, this is also submitted and is made available to the reader. *2*) All parameters of the model are defined and their units made clear. *3*) All equations are consistent in their dimensions and can be verified by the reader. *4*) Data from the real system being modeled are offered to validate the model, and criteria used to justify claims of goodness of fit of model to data are given. *5*) The domain of real time wherein the simulation is intended to be valid is given. *6*) Any assumptions about structure, parameter values, initial conditions, etc., are justified by carefully checked citations. *7*) The model is clearly presented, its interesting points are highlighted, and its validation is properly documented. *8*) The content does not show manifestations of the 'reminiscence syndrome' (7). Early in a paper, the author may describe some outputs from models as being 'reminiscent' of this or that phenomenon. Toward the middle of the paper, the word 'reminiscent' is omitted in the apparent hope that the reader will infer equality between the model's performance and the phenomenon. By the end of the paper, equality is overtly implied. Skillful use of the excluded middle is often seen. *9*) Models are hypotheses. Therefore, for effective inference, the ideal paper on modeling would offer two different models, each of which can be rationalized according to current knowledge but can predict significantly different outcomes of a (critical) experiment not used in their creation. The different predictions would be reported, along with the results of the same experiment performed on the real system. The possibilities then would be that one model fails and one succeeds, or they both fail. In either case, the utility of models for hypothesis rejection is demonstrated and the reader learns something new (6).

CONCLUSIONS

With growing emphasis being placed on the information processing aspects of biomedical investigation, theoretical and experimental studies assume increasing importance. In many instances, however, there are questions that appear to be unanswerable by present experimental techniques; in such cases, models can usefully augment direct scientific experimentation. The essential ingredient of the scientific method is the use of models. Good modeling is more likely to be achieved by following the rules of good thinking (6). However, the ideal model cannot be achieved. Partial models, imperfect as they may be, are the only means developed by and available to scientists for understanding the universe (3). This statement does not imply an attitude of defeatism but the recognition that the main tool of science is the human mind, and the human mind is finite (3). This notwithstanding, the advances obtained so far suggest that experimental modeling may be expected to exert an increasing influence on the course of biomedical research and progress. FJ

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REFERENCES

1. Verveen, A. A. (1971) In search of processes: The early history of cybernetics. *Math. Biosci.* **11**, 5–29
2. Rook, A. (1964) *The Origins and Growth of Biology*, Penguin Books, Harmondsworth
3. Rosenblueth, A., and Wiener, N. (1945) The role of models in science. *Philos. Sci.* **12**, 316–321
4. Yates, F. E., (1977) Modeling endocrine systems: An overview. In *Endocrinology* (James, V. H. T., ed) Vol. 1, pp. 240–244, Excerpta Medica, Amsterdam
5. Beveridge, W. I. B. (1961) *The Art of Scientific Investigation*, Vintage Books, New York
6. Yates, F. E. (1978) Good manners in good modeling: Mathematical models and computer simulations of physiological systems. *Am. J. Physiol.* **234**, R159–R160
7. Harmon, L. D., and Lewis, E. R. (1968) Neural modeling. In *Advances in Biomedical Engineering and Medical Physics* (Levine, S. N., ed) Vol. 1, pp. 119–241, John Wiley & Sons, New York
8. Dainty, J. (1960) Electrical analogues in biology. In *Models and Analogues in Biology* (Symposium of the Society for Experimental Biology No. 14) (Beament, J. W. L., ed) pp. 140–151, Academic Press, New York
9. Kacser, H. (1960) Kinetic models of development and heredity. In *Models and Analogues in Biology* (Symposium of the Society for Experimental Biology No. 14) (Beament, J. W. L., ed) pp. 13–27, Academic Press, New York
10. Pringle, J. W. S (1960) Models of muscle. In *Models and Analogues in Biology* (Symposium of the Society for Experimental Biology No. 14) (Beament, J. W. L., ed) pp. 41–68, Academic Press, New York
11. Fogel, L. J. (1963) *Biotechnology: Concepts and Applications*, Prentice-Hall, Englewood Cliffs, N.J.
12. Harris, J. E. (1960) A review of the symposium: Models and analogues in biology. In *Models and Analogues in Biology* (Symposium of the Society for Experimental Biology No. 14) (Beament, J. W. L., ed) pp. 250–255, Academic Press, New York
13. Popper, K. R. (1973) *Objective Knowledge*, Oxford University Press, Oxford
14. Suppes, P. (1969) A comparison of the meaning and uses of models in mathematics and the empirical sciences. In *Studies in the Methodology and Foundations of Science*, pp. 10–23, D. Reidel Publishing Company, Dordrecht, Holland
15. White, R. J., Fitzjerrell, D. G., and Croston, R. C. (1983) Fundamentals of lumped compartmental modeling of the cardiovascular system. *Adv. Cardiovasc. Phys. 5 (Part I)*, 162–184
16. Rosen, R. (1991) Analytic and synthetic models. In *Life Itself: A Comprehensive Inquiry Into the Nature, Origin, and Fabrication of Life*, pp. 152–181, Columbia University Press, New York

17. Edwards, A. W. F. (1960) Models in genetics. In *Models and Analogues in Biology* (Symposium of the Society for Experimental Biology No. 14) (Beament, J. W. L., ed) pp. 6–12, Academic Press, New York
18. Berman, M. (1963) A postulate to aid in model building. *J. Theor. Biol.* **4**, 229–236
19. Westcott, J. H. (1960) Estimation of values of parameters of a model to conform with observations. In *Models and Analogues in Biology* (Symposium of the Society for Experimental Biology No. 14) (Beament, J. W. L., ed) pp. 102–121, Academic Press, New York
20. Rosen, R. (1983) Role of similarity principles in data extrapolation. *Am. J. Physiol.* **224**, R591–R599
21. Rosen, R. (1991) Some necessary epistomological considerations. In *Life Itself: A Comprehensive Inquiry Into the Nature, Origin, and Fabrication of Life*, pp. 49–66, Columbia University Press, New York
22. Cape, E. G. (1996) Mathematical modeling in the evaluation and design of surgical procedures. *J. Thorac. Cardiovasc. Surg.* **111**, 499–501
23. Hoffman, O. (1987) Biomathematics of intracranial CSF and hemodynamics. Simulations and analysis with the aid of a mathematical model. *Acta Neurochir. (Suppl.)* **40**, 117–130