Monographs on Endocrinology

Volume 16

J.E.A. McIntosh
R.P. McIntosh

Mathematical Modelling and Computers in Endocrinology

With 73 Figures and 57 Tables

Springer-Verlag
Berlin Heidelberg New York 1980

James E.A. McIntosh M.A., Ph.D. (Cantab.)
Department of Obstetrics and Gynaecology,
University of Adelaide, Adelaide, S.A., Australia

Rosalind P. McIntosh Ph.D. (Cantab.)
Lucy Cavendish College, Cambridge, U.K.

ISBN-13:978-3-642-81403-7 e-ISBN-13:978-3-642-81401-3
DOI: 10.1007/978-3-642-81401-3

Library of Congress Cataloging in Publication Data.

McIntosh, James Edward Alister, 1942-. Mathematical modelling and computers in endocrinology. (Monographs on endocrinology; v. 16) Bibliography: p. Includes index. 1. Endocrinology – Mathematical models. 2. Endocrinology – Data processing. 3. Biological models. I. McIntosh, Rosalind Phyllis, 1943- joint author. II. Title
QP187.3.M36M34 591.1′42′028 79-28283

Softcover reprint of the hardcover 1st edition 1980

2125/3020 – 543210

Preface

The building of conceptual models is an inherent part of our interaction with the world, and the foundation of scientific investigation. Scientists often perform the processes of modelling subconsciously, unaware of the scope and significance of this activity, and the techniques available to assist in the description and testing of their ideas.

Mathematics has three important contributions to make in biological modelling: (1) it provides unambiguous languages for expressing relationships at both qualitative and quantitative levels of observation; (2) it allows effective analysis and prediction of model behaviour, and can thereby organize experimental effort productively; (3) it offers rigorous methods of testing hypotheses by comparing models with experimental data; by providing a means of objectively excluding unsuitable concepts, the development of ideas is given a sound experimental basis.

Many modern mathematical techniques can be exploited only with the aid of computers. These machines not only provide increased speed and accuracy in determining the consequences of model assumptions, but also greatly extend the range of problems which can be explored. The impact of computers in the biological sciences has been widespread and revolutionary, and will continue to be so.

The aim of this book is twofold: we wish to portray to endocrinologists the productive interplay of concepts in biology and mathematics, and at the same time provide illustrative examples and practical information about computing to enable the reader to apply many of the techniques presented to his or her own subject of interest. The approach is descriptive, with the minimum of mathematical nomenclature and equations. Although the formulation of ideas in words rather than in mathematical symbols necessarily entails some loss of precision, the text should thereby be made approachable for the biologically trained reader. It would be pleasing also if mathematicians could perceive here some of the richness, challenge and reward of working with biological systems, difficult and "imperfect" mathematically but "perfect" in their ingenuity of adaptation to biological purpose.

Mathematical modelling is not the answer to all endocrinological problems, but where applied appropriately it offers substantial reward for effort. Some kinds of mathematical modelling can contribute to endocrinological investigations at the descriptive level. Knowledge of endocrine systems is, however, becoming increasingly quantitative and the relevance of mathematical methods suited to more precise measurements is growing rapidly. Mathematics appears to be essential for formulating and testing hypotheses on biological control and organization.

The techniques described in this monograph are completely general – the examples, however, reflect the experience and interests of the authors, many being related to reproductive endocrinology. Computer techniques are given prominence throughout.

The scope of the book is as follows. Chapter 1 discusses in general terms the nature, purposes, advantages and limitations of mathematical modelling, and some of the mathematical and biological concepts involved. Chapter 2 concerns the characteristics and utility of a selection of mathematical techniques appropriate to the formulation of a varied range of biological models; these also are presented generally. Chapter 3 shows how models can be compared with data, and how to determine when a model is adequate, or requires modifying. Computer methods are introduced using two computer programs for comparing models with experiments, and illustrative examples are given of how they are applied. Chapter 4 describes statistical techniques for designing effective experiments, and includes a computer program to control sequential experimentation. Chapters 5 and 6 deal with several subjects of endocrinological interest to which the quantitative computer methods of earlier chapters are applied. Chapter 7 is concerned with rhythmic processes. The first part describes how theories of cyclic processes have begun to be applied in modelling biological rhythms, while the second outlines methods for analysing rhythmic behaviour empirically. Chapter 8 illustrates the mathematical modelling of large endocrinological systems by discussing the use of several approaches described in Chap. 2 in modelling the ovulatory cycle. Chapter 9 contains examples of two kinds of statistical models of great practical usefulness in endocrinology.

Appendix A briefly introduces statistical concepts and tests required in mathematical modelling, while Appendix B provides details of the computer programs referred to above.

While this monograph is the result of an enjoyably co-operative effort, particular responsibility is taken for Chaps. 1, 2, 7 and 8 by R.P.M., and for Chaps. 3–6, 9 and the appendices by J.E.A.M.

The latter is grateful to the Department of Obstetrics and Gynaecology, University of Adelaide, and the Agricultural Research Council's Unit of Reproductive Physiology and Biochemistry, University of Cambridge, for encouraging and supporting his research, and we are appreciative of the generous policies of both Universities in providing free access to excellent computing facilities. R.P.M. thanks the Department of Obstetrics and Gynaecology, University of Adelaide for an honourary Research Associateship.

We welcome this opportunity to express gratitude to our friends and colleagues in Adelaide, Cambridge, Bethesda and elsewhere (and particularly Dr C. Lutwak-Mann, Dr R.F. Seamark, and Mrs B. Godfrey) for helpful discussions, and for kindly reading and commenting upon many sections of the typescript. Mrs Godfrey also assisted in the coding of the computer programs SIMUL and DESIGN. The reviewers made several helpful suggestions and we are grateful to them for their careful reading of the text.

Most of all we happily acknowledge the unfailing inspiration, enthusiasm and encouragement of Cecelia and Thaddeus Mann.

December 1979

J.E.A. McIntosh
R.P. McIntosh

Contents

1 Modelling in Biology

A *model* describes, recites the characteristics of, or defines, the workings of a system.

Modelling is a fundamental human activity. We each carry in our mind a conceptual model of our "world", a conscious or subconscious structure of many levels, rational or irrational, formed from expectations, experiences and learning. All perceptions are compared with this malleable model and found to be irrelevant, confirmatory or contradictory. From the comparison can develop action, emotion, new models.

The activity of scientific investigation is an attempt to use controlled observations or experiments to rationally build or modify conceptual models derived from our imagination, experience and learning. Our perceptions may thereby become richer and more meaningful, and our expectations more reliable.

Much of this book is concerned with ways of comparing scientific observations with models. This is not a new pursuit; it is at the basis of all scientific investigation. The teaching of the necessary skills is essential to scientists in training, but too often the details have been expected to be acquired unguided while learning the all-important conclusions from the modelling efforts of others.

Every experimental design, performance and analysis involves modelling. One may unconsciously use models which follow the well-tried, acceptable paths of history. Or one can purposefully seek to reassess assumptions and to select anew from all conceivable possibilities, interactions, elements and conditions for study, those ever more appropriate to our increasing experience of the system of interest.

Even so-called facts are based on models. To quote von Bertalanffy (1973):

> According to widespread opinion, there is a fundamental distinction between 'observed facts' on the one hand – which are the unquestionable rock bottom of science and should be collected in the greatest possible number and printed in scientific journals – and 'mere theory' on the other hand, which is the product of speculation and more or less suspect... such antithesis does not exist... when you take supposedly simple data in our field – say, determination of Q_{O_2}, basal metabolic rates or temperature coefficients – it would take hours to unravel the enormous amount of theoretical presuppositions which are necessary to form these concepts, to arrange suitable experimental designs, to create machines to do the job – and this all is implied in your supposedly raw data of observation. If you have obtained a series of such values, the most 'empirical' thing you can do is to present them in a table of mean values and standard deviations. This presupposes the model of a binomial distribution – and with this, the whole theory of probability, a profound and to a large extent unsolved problem of mathematics, philosophy and even metaphysics. ... Thus even supposedly unadulterated facts of observation already are interfused with all sorts of conceptual pictures, model concepts, theories ... The choice is not whether to remain in the field of data or to theorize; the choice is only between models that are more or less abstract, generalized, near or more remote from direct observation, more or less suitable to represent observed phenomena.[1]

---

[1] Words taken from Ludwig von Bertalanffy; General System Theory (Allen Lane The Penguin Press, 1971; Penguin University Books, 1973) pp 163–164. Copyright by Ludwig von Bertalanffy, 1968. Reprinted by kind permission of Penguin Books Ltd., London, and George Braziller Inc., New York.

The simplest measurement is the outcome of an interaction between a measuring instrument and a model of a system, rather than a direct property of the real system itself. The way in which measurements are made depends on how the information is to be applied; a measuring tape is used differently in assessing the distance between two points depending on whether it determines the length of the path taken by an insect crawling over rough ground, or the same route travelled by a flying crow. Determinations of the "level" of a hormone depend on the model of its mode of action. The property of the hormone that we think is effective in producing a response dictates whether we measure its total molecular concentration in blood, the amount not bound to plasma protein or the rate of fluctuation in level.

Biological models reach the printed page in many forms. A model can be a simple mathematical equation such as $y=x^2$. It can be pages of closely packed, personalized symbols in fine print linked by multiple, angular arrows. Neither the use of complexity, nor the constraint of a model to an easily soluble mathematical equation guarantees its effectiveness.

There are other kinds of modelling which do not use mathematical equations. Sometimes models containing precise verbal statements may embody a biological concept in a more useful form than do mathematical equations (Williams, 1977). The response of one organism may be used to model that of another, as when drugs are administered to animals to test likely effects in humans. Mechanical or physical models may be studied where experiments on the system of interest would present insurmountable practical difficulties. The problems specific to these types of models will not be discussed here; our concern is with models involving mathematical descriptions. All models have in common an attempt to capture the significant aspects of a system in a form which is useful for investigating the properties of the system.

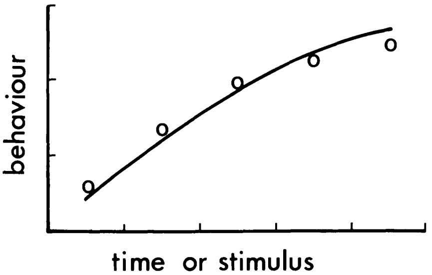


Fig. 1.1. Comparing experimental data with behaviour calculated from a model of the system. The *points* (○) represent the experimental measurements, and the *smooth curve* the model

1.1 The Nature of Scientific Models

A real system is a source of behaviour. We convert our observations of a system's behaviour into experimental data (either the variation of something with time, or in response to a stimulus). A model is a set of instructions designed by us to generate data resembling those of the real system. These instructions may merely describe the data, or they may embody our concept of what causes the behaviour. Comparison of the two sources of data, measured and generated (see Fig. 1.1), shows how compatible are the concepts of the model with experimental observations, and

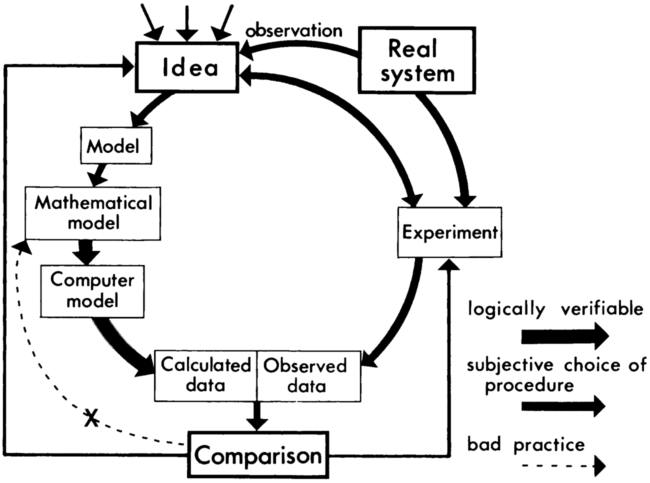


Fig. 1.2. The processes of mathematical modelling

whether our ideas are worth further development. Figure 1.2 shows a generalized scheme of the procedure of modelling mathematically. Other aspects of the modelling process illustrated in this diagram will be considered later.

1.1.1 Different Kinds of Models

Levins (1970) describes a model as an attempt to replace

> the universal or trivial statement "things are different, interconnected and changing", with a structure that specifies which things differ in what ways, interact how, change in what directions.

There are several different levels at which this model structure can be specified; the one selected depends both on the aims of the modeller and on the amount of information available about the system.

An *empirical model* is the most superficial. It describes accurately the values of a particular set of experimental data; under the same conditions, response to any suitable stimulus can be predicted from the model. However, the model *is not unique* and the particular mathematical form chosen may not reflect mechanims within the system. An empirical model bears little direct relation to the biological structure or to general physical laws. There may not even be a direct causal relationship between the stimulus and the response – merely a correlation.

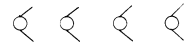
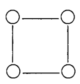
A *theoretical model* (sometimes called analytical or mechanistic) *embodies our concept* of what causes the behaviour observed. The model description is based on biological and physical laws believed to be acting between components of the system. The consequences of the proposed mechanism can be calculated and agreement with experimental data strengthens the hypothesis. Prediction should be possible under a broader range of conditions than in empirical modelling. Two tendencies in theoretical modelling may be further distinguished: those that attempt to capture the essential, minimal aspects of the mechanisms required for reproducing the results, and those that try to be as complete as possible by simulating behaviour in terms of all known effectors and interactions. In building a model it is important to distinguish between empirical and theoretical aspects so that the ability of the model to explain, as opposed to describe, is not overestimated.

A third approach, known as *metaphoric* modelling, uses a *generalized description* of the system behaviour, without concern for details of the particular components. The belief underlying this kind of model is that any particular system behaviour can be classified according to the types of interactions involved. The consequences of these classes of interaction can be investigated mathematically, or are already known. The qualitative insights arising from these models may be surprising. By simply describing the dynamic type of the system the possibilities for its behaviour can be deduced, even without understanding the specific nature of the components involved. A description is made of the functional properties of a system rather than its structure. A metaphoric model becomes a theoretical one when the mathematical components are all identified with some observable entities in the system. However, the generality of such mathematical descriptions may make comparison of the model with any particular real set of data and real structural elements difficult. This is because those aspects of the system behaviour from which are derived the equations describing the dynamics, need not correspond in a direct and simple way to structural elements (although they will undoubtedly be a more complex function of them) (Rosen, 1977). Just as the reality of gravitational forces "applies to both the cosmos and to apples", physical disparity need not preclude powerful unifying concepts stemming from common organizational or control principles.

Some models combine aspects from several of these approaches. Examples of them all will be found throughout this book.

1.1.2 Reductionism in Biology

Another way of considering a system, biological or otherwise, is as a set of components that interact. A model attempts to describe relevant components and their interactions in such a way that it mimics the features of interest in the system. The finding and describing of components and their individual interactions is referred to in philosophy as reductionism.

Interactions between components often produce an organized total that is more than the sum of its parts. For example four isolated elements ○ ○ ○ ○ and their interactions  when organized as a whole  clearly take on new or emergent properties and possibilities (von Bertalanffy, 1973). The emergent behaviour relates to the consequences of interactions which were not understood in making the model description, but which ultimately affect the result. Such emergent properties can frequently be derived from mathematical models and are one of the main rewards of modelling. Many believe, however, that there are limits to such revelations and that in complex biological systems general principles of organization are unlikely to be revealed from the study of the minutiae of particular systems. An idea of general function, of course, necessarily precedes the construction of a detailed model. This does not deny that general principles, manifested in particular circumstances, cannot be described in terms of chemistry and physics. Crick (1966, p. 55) discussing replicating nucleic acids writes:

> There is nothing, therefore, in the basic copying process, as far as we can see, which is different from our experience of physics and chemistry except, of course, that it is exceptionally well designed and rather more complicated.

Pattee (1970) and others contend that it is precisely "this exceptional design", those principles of adaptive self-organization or programming bringing about functions that distinguish living from non-living matter, which are the focus of the biologist's attention, and which cannot be revealed solely by reductionist study of biological systems in terms of physics and chemistry.

Are the laws of physics, chemistry and mathematics derived for inanimate matter sufficient to describe the properties peculiar to biological systems, such as self-organized responses to the environment, self-maintenance and development through the building of highly ordered structures, reproduction and evolution? Certainly, recent advances in these fields have produced generalized metaphoric models exhibiting strikingly "biological" behaviour (Sect. 2.6).

In conclusion, it seems that while reductionist analysis is necessary to confirm a hypothesis concerning the overall functioning of a system, an exclusively analytical emphasis will probably result in the loss of essential characteristics of the whole. This conflict between the need to test hypotheses using models in which specified biological components and interactions are compared with data obtained from real systems (theoretical modelling), and the difficulty of identifying the components of metaphoric models describing generalized organizational principles with real physiological structures, recurs in our discussions.

1.1.3 The Scope of Modelling

A model is a structure to play with – and in so doing to discover new behavioural possibilities of the system. A model is not definitive. It simply works out the consequences of proposed solutions to the perceived problem, in order to determine how these results compare with experimental observations. A model should be no more than a guide to constructive and efficient experimentation. It should lead to better models. It should grow, transform or become obsolete when tested, and yet have served its purpose well. It should never be finished or ready for publication in the "quod erat demonstrandum" form. Models are necessarily simplifications, concerned with one or a few very limited aspects of the system studied.

Whether models explain phenomena or merely describe them is a subjective matter. More relevant is whether they predict new, testable phenomena, show up deficiencies in current knowledge, suggest new experiments or create new perspectives that unify hitherto disparate facts.

An explanation renders phenomena more meaningful or intelligible. Obviously, whether something is made more meaningful depends on one's experience, learning and the paradigms of one's discipline of expertise. Bradley (1968) emphasizes the importance of tolerance between fields of learning. A model can still be very useful even if it is constructed without complete awareness of all the contextual material from another field. However, collaboration across disciplines may be more effective or even essential where models at one level (e. g. behavioural) are explained using the components of another discipline at a different level (e. g. biochemical).

An illuminating study of the historical usefulness of mathematical modelling in the development of ideas is presented by Provine (1977), applied to the subject of evolution. He concludes that although models that have been described may not correspond precisely to reality, nor all the claims made for them be justified, they have given observations a new significance by placing them in a framework of quantitative analysis. That is, mathematical modelling, even when applied to a field which is not readily quantifiable, has been shown to make experimental observations more meaningful or explicable. Modelling has offered effective guidelines based on experiment for the development of ideas. Provine gives the following illustration of the kind of contribution that mathematical modelling has made. Natural selection acting on the small variations known or reasonably supposed to exist in natural populations, was shown by this technique to be sufficient to account for evolution at the population level; Darwin's qualitative hypotheses were adequate and an additional factor proposed by disbelievers was not required.

Mathematical modelling in some form appears capable of making useful or essential contributions in most endocrinological investigations. For example, in a long list of problems related to contraception in the female reproductive tract, which according to Greep et al. (1976, pp. 138–147) require investigation, few topics are apparent in which mathematics would not be helpful.

1.2 Clarity from Complexity

A system needs first to be identified and distinguished from its surroundings in order to permit description, measurements and observations. In endocrinology such things as function, a chemical which can be analysed or physiological structures, may delineate a system for investigation. The system is described in more detail than its environment, the effects of which are held constant where possible, or lumped (defined in Sect. 1.2.4). Interactions within the system need to be stronger than those with the environment; weak interactions can be used to define the limits of a system. Exclusion of a component interacting strongly with the system precludes a viable model.

The selected system is made up of a set of components which interact. Components can be identified for systems as diverse as the chemical reaction between a substrate and its enzyme, or the interaction between the moon and ovulation in certain monkeys.

Any real biological system may contain a very large number of internal elements and interactions. In addition, many environmental factors influence biological systems: time, light, temperature, the availability of nutrients and the rate at which they are supplied, previous history and so on. And any individual biological entity may behave differently from another, which is apparently very similar.

The complexity necessary to describe such a system may seem unmanageable. Even computer technology may not be able to deal with all these factors within finite space, time and financial resources! Those most relevant to the behaviour of interest must be selected for experimentation and for devising a mathematical model. Selection of components ought to be an individual, creative activity; a model is a personal statement.

1.2.1 Experimental Frames

Complexity can be described as a function of the number of possible ways of interacting with a system. Modelling is an abstraction of experience, and limits these interactions by defining an *experimental frame* within which the model is expected to be effective. An experimental frame describes a chosen, limited set of conditions in which experiments or observations are carried out. Those factors known to influence the system but which are assumed to be constant, or are held constant, must be clearly stated. (Of course there may be other affectors which are unknown.)

A model of a system may be valid in one experimental frame (or set of conditions) but not in another. Real systems may have many possible experimental frames. As models satisfactorily reproduce experimental results from a progressively wider range of experimental frames, they become stronger or more "robust". The model becomes more general and therefore has richer, more meaningful things to say about the nature of the system.

One of the major aims of modelling is to make valid *general* statements about systems which apply to individuals or samples of individuals other than those actually measured. Bridgeman's operational philosophical principle, however, goes so far as to state that physical entities are to be described only within the operational contexts in which they are measured. No generalizations allowed! Should then predictions from successful modelling be applied only within the experimental frame in which they were tested? Certainly it is necessary to recognize that extrapolation is involved in using models outside their tested frames, and to proceed with suitable caution.

A more difficult problem is to ensure that all the effective agents are known and can be controlled under the chosen experimental conditions. A model will surely not describe the behaviour of a real system effectively where an unknown agent is influencing its function. Establishing physiological systems in the laboratory to elucidate "normal" behaviour contains traps of this kind. For example, concluding that biological clocks in crabs are internal because they persist when obviously linked external factors such as tides and light are removed, does not allow for the possibility of other external effects such as geomagnetism. One can never be sure that every possible condition relevant to physiological function has been accounted for. This is where imagination, experience and sensitive observation of the system outside controlled conditions are essential, and why biologists can never be replaced by mathematicians!

1.2.2. Variables and Parameters

Once the system has been identified, the experimental frame defined by selecting the range of behaviour of interest, and the components thought relevant to this behaviour are named, the relationships governing the interactions of these components must be described by mathematical equations. Concepts useful for clarifying mathematical relationships are discussed here. Choice of the mathematics appropriate to the perceived nature of the system is the topic of Chap. 2.

Variables are simply those measurable attributes of a system which vary. Those which are active in initiating or maintaining changes in behaviour of the system are called *independent variables*, while those which show that the behaviour is changed are called *dependent variables*. These variables have been distinguished in different disciplines by a variety of names:

Cause and effect,
Stimulus and response,
Input and output,
Independent and dependent variables,
x and y.

They can be discriminated by the property that whereas changes in independent variables alter dependent variables, changes in dependent variables will not usually influence the independent ones. For example, time is an independent variable. Its passing may result in a continuous reduction in the concentration of a hormone in the blood. But increasing the dependent variable – the hormone concentration – by other means will not reverse time. The dependence of y on x may be written in a generalized mathematical form, $y=f(x)$, meaning that y can be described by some particular, but here unspecified, function of x.

However, sometimes variables are interdependent, for example, in a reversible chemical reaction such as

$$\text{enzyme} + \text{substrate} \rightleftharpoons \text{enzyme–substrate complex}$$

or where the variables are part of a closed causal chain (feedback loop), such as in the model

$$\begin{tikzcd} \text{LHRH} \arrow[r] & \underset{\text{(pituitary)}}{\text{LH}} \arrow[r, bend left] & \underset{\text{(follicle)}}{\text{oestradiol}} \arrow[l, bend left] \end{tikzcd}$$

The concentrations of estradiol and LH are postulated to mutually influence one another but, unlike the reversible reaction, at quite different places and by different mechanisms.

Parameters are factors which influence the behaviour of a system but which are held *constant* either naturally or by experimental design. Because they are constant, parameters characterize the behaviour of a model by constraining the form of its response. In the equation of a straight line $y=A_1+A_2x$, x the independent variable can take a range of possible values which produce a corresponding range of values of y, but the parameters A_1 and A_2 are held constant to give the line its particular form. Parameters may also be thought of as inputs which are invariant. It is wise to ensure that entities selected for description by this term actually are effectively constant within the chosen experimental conditions. The values of parameters are estimated when the behaviour of a model is compared with experimental data (Chap. 3). In theoretical models, parameters have real physical interpretations and therefore their estimates must be physically feasible if the model is to be acceptable. In empirical models parameters have no such physical meaning because the form of the equations is not related to the causal mechanism.

Other terms necessary for mathematical descriptions of the behaviour of systems are absolute constants such as π and e, and also statistical measures (Appendix A and Chap. 9).

A technique providing a useful internal check that particular equations contain sufficient variables and parameters is dimensional analysis, outlined by Riggs (1963).

1.2.3 Diagrams

A diagram showing interactions of components in a visual form is a powerful aid to comprehension and simplification. A particularly useful notation for showing causal relationships is the symbol and arrow diagram described by Riggs (1970). Block diagrams, (discussed in Sect. 2.3.4), analogue notation (Roberts, 1977, Chap. 10) and flow diagrams (Davies, 1971, pp. 32–36), are other helpful means of presenting and comprehending connective links between variables in models.

1.2.4 Lumping

Although a great deal of detail may be known about relationships governing the behaviour of a system, inclusion of every detail of a complex mathematical equation may be unnecessary or unhelpful, or even preclude the possibility of any investigation because of limited resources of time or computation.

Lumping is a process of simplifying models by combining elements into a single variable, or by simplifying interactions. For instance, instead of dealing with a large number of single molecules and their interactions, we can lump them into some sort of average, such as a probability function like concentration or pressure. Similarly, concentrations of several kinds of substances and their interactions can be lumped and treated as a "pool". An illustration from the study of the metabolism of cells might be that all molecules relating to the breakdown of nutrient carbohydrate be lumped together into a single pool, with inputs and outputs suitable for the pool as a whole. If the focus of the model is some other property of the system, this simplification may be appropriate, and much time and effort is saved by not describing mathematically each individual enzyme in the chain and its interaction with substrate and affectors. If this initial simplification does not reproduce experimental data, a more complex treatment should be tried.

The relationship between input and output in a "pooled" system may often be an empirical equation that summarizes many unknown intermediate steps in a simplified, fixed mathematical form. Of course, the lumping method necessarily assumes that intermediate steps are uninfluenced by any other changes in the system. The validity of this assumption may be hard to check when the natures of the intermediate steps themselves are unidentified. In such cases lumping may weaken the model.

One or more variables or parameters that are thought to be less important within the experimental frame of interest can be omitted altogether. By testing the effects that changing the values of parameters have in model behaviour, some parameters or variables may be revealed as irrelevant within the chosen experimental frame. These may then be lumped or discarded. Methods of choosing the model which best fits the data from several models with different structures and parameters are discussed in Chap. 4. Another simplification, sometimes appropriate, is to restrict the range of the independent variables or experimental frame so that interaction terms, or even the effects of some components, are made negligible.

Selection of the time frame of interest usually results in helpful lumping. Variables influenced only by time intervals much longer than that selected can be lumped as constant; variables responding relatively very quickly can be assumed to be already at equilibrium, or regarded as being instantaneous switches between one type of behaviour and another. If one is examining enzyme reactions in the millisecond