KINETIC MODELING IN PHYSIOLOGY

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The author discusses the construction of model biochemical/physiological systems to fit experimental data which is always incomplete. He suggests that the first experiments on any system should be first-order (usually tracer) perturbations of steady-state systems. The proposed model can then be given a preliminary fit to the data; criteria for best fit, consistency, and uniqueness of fit are suggested. More data may then be obtained by perturbations at another steady-state, and finally by studying transient situations.

References are included to some of the author's own publications in which these matters are discussed in detail.

The application of kinetic analysis to physiological systems raises a number of special problems due to the following factors:

(1) The nature of the system studied is not fully known.
(2) The sites available for measurements are restricted.
(3) The times when measurements can be made are restricted.
(4) The data contain fluctuations.
(5) The number of studies that are possible to perform on a single individual is limited.
(6) The system is studied by a number of different experimental techniques. The results obtained with the various techniques are usually interrelated in a complicated way.

To deal with these problems, hypotheses must be introduced and assumptions made. These must be carefully tested against the data. In making assumptions the investigator must be guided by the purpose of his modeling, since assumptions critical with respect to one purpose may not be critical with respect to another.

In dealing with the above problems the following experimental and model building strategies have been evolved over the years:

(1) Start with tracer (or first order perturbation) experiments on steady state system.

Tracer experiments permit the observation of complex non-linear systems as a number of simpler linear subsystems. Although it is not essential to start with tracer experiments on steady-state systems, they make the modeling process more rational and systematic.

References: [11,16].

(2) Propose the "simplest" model (hypothesis) that is consistent with known features of the system, with the nature of the experiment and with the qualitative features in the data.

If the proposed model is too simple it will not fit all the data. If the model is too complex, there will result lack of confidence in the estimates of its parameter values.

Reference: [4].

(3) Fit the model to the data using some criterion of "best fit", such as a least squares fit.

A number of least squares fitting routines are available although other methods have also been used (e.g., linear programming).

References: [1,12].

(4) Test whether the "best fit" is consistent with the data.

There is no simple test for inconsistency although a chi-squared test is frequently adequate. Visual inspection of the graphs drawn for the experimental and theoretical results is very helpful.

Inconsistencies may be due to an inappropriate model or to systematic errors in the data. There is no way to separate the two.

References: [13,14].

(5) For a consistent model, test whether parameter

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values can be estimated with sufficient precision for the intended purpose.

Uniqueness of parameter values may be deduced from the error (covariance) matrix obtained as a by-product of a least squares fitting procedure. The diagonal elements of the matrix are the variances (standard deviations squared). When these become large the corresponding parameter values tend to non-uniqueness.

The covariance matrix contains information not only on the estimates of the precision of the model parameter values but also on any function derived from the parameter values. The latter may be unique even when the parameter values are not unique. Thus, uniqueness must be judged with respect to the functions desired.

References: [4,5,15].

(6) Perturb the system to a new steady state and repeat the tracer studies at the new steady states.

The perturbation of systems is essential for revealing new information through tracer experiments. This permits not only the study of how perturbing factors influence the system, but also the discrimination of some models from others. The simultaneous fitting of the data from perturbed and non-perturbed system studies under a hypothesis (or knowledge) about the nature of the perturbation can eliminate non-uniqueness of a model.

References: [3,4,5].

(7) Perform non-steady state studies.

The study of a system in the non-steady state (transient) usually reflects more variables than in the steady state due to regulation and non-linearities within the system. It is difficult to model the transient responses of a system without some *a priori* knowledge about it. Tracer studies at various steady states can provide such background knowledge first, and make the subsequent modeling of non-steady state system easier.

References: [11,14].

(8) Applications

There are too many applications to list here. Major areas of application include metabolic studies of iodine, calcium, lipids, and glucose in man and in animals. The models developed in these areas indicate the present state of the art and possible trends for further developments.

References: [7,8,10,11,17].

(9) Computer programs

There are many programs for use in modeling. I shall only mention here our own general purpose program SAAM that contains features specially designed for *in vivo* metabolic studies.

References: [1,2,6,9].

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