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OPTIMIZATION USING SENSITIVITY FUNCTIONS FOR FITTING MODELS TO DATA

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Abstract

The analysis of multiple indicator dilution curves to estimate the rates of transport of ions and substrates across the sarcolemma of myocardial cells requires the formulation of models for the blood-ISF-cell exchanges. The fitting of models to the sets of experimental data is dependent of acquiring a large enough data set, in one physiological state, that there is at least as much information in the data as there are unknown model parameters to be determined. Since data are necessarily noisy, redundancy of data and overdetermination of the unknowns is highly desirable. Sensitivity functions are useful in demonstrating which portions of the data relate to which unknown parameters. They are also useful in adjusting model parameters to fit the model to the data, and therefore in parameter evaluation.

INTRODUCTION

The estimation of unidirectional rates of transport into the cells of intact organs is complex. The transport process cannot be isolated, so that its kinetics can only be assessed as a part of a larger system including the flow (and its heterogeneity), transport across capillary membranes, diffusion and distribution throughout the interstitial and cellular spaces, and perhaps intracellular consumption. The analysis therefore depends upon defining a mathematical analog of the system, acquiring as much data on the system as is possible within a short time while the system is stable, and then analyzing the data by fitting the mathematical model to all of the data at once. The formulation of the model which best fits the data is considered then to provide estimates of the kinetic parameters governing each of the processes involved. In the presence of some variability in the data, and some imperfections or inadequacies in the model compared to reality, one has to question the reliability and accuracy of the parameter estimates. The answer depends upon a number of features of experimentation, data collection, and model design as well as model fitting. Sensitivity analysis plays a role in experiment design as well as in analysis, but its contribution is dependent upon accurate data collection and good model design, to neither of which can sensitivity analysis contribute.

The separability of influences of various components of a system on its responses can be examined via modeling analysis using sensitivity functions. The sensitivity function $S_p(t)$ for a model function with respect to a parameter p is defined as:

$$S_p(t) = \frac{\partial \hat{h}(t)}{\partial p} \quad (1)$$

where t is time or other independent variable, and $\hat{h}(t)$ is a solution to a model function. [Later we will approach the problem of fitting the model function $\hat{h}(t)$ to an experimentally observed function $h(t)$.] Separability of the influences of components of a system is demonstrable by analogy, i.e. if the sensitivity functions calculated from the model differ,

then, so long as the model is a reasonable facsimile to the real system, the components of the system can be individually examined by appropriate experiments.

A second use of sensitivity functions is more novel. Adjustment of the parameters of a model solution to cause it to fit observed data functions can be facilitated by using the sensitivity functions to select subsets of the data that are particularly strongly influenced by each of the parameters. This selective, local approach directs the adjustment of a set of parameters with good efficiency.

METHODOLOGIC APPROACH

A number of considerations go into any modeling analysis of data. Included are: the information content of the observations, the accuracy of the data set as a whole and the relative accuracy of its subsets, the stability of the observed system during the period of data acquisition, the appropriateness of the model (the goodness of its approximation to reality), the complexity of the model itself and the number of free parameters to be determined from the data.

Let us consider a typical set of dilution curves obtained from the venous outflow from an organ following the injection of a bolus containing several tracers into the arterial inflow. Such a set might contain a reference intravascular indicator (albumin), an extracellular indicator (L-glucose or cobaltic EDTA), and one that enters cells (for example, D-glucose). Each dilution curve might be fitted with descriptive equations having a minimal number of parameters; perhaps 5 or 6 per curve would suffice. Given that the curves have some likenesses, they can probably be described by fewer parameters, perhaps as few as 10 for the three curves. The critical question is whether there is enough information to provide good estimates of cellular transport rates. Descriptive expression, while adequate for efficient data storage and for some comparisons, provide little insight and are not predictive. Insight and prediction evolve from a precise and integrated definition of the physical system: a model, which, if appropriate, is both descriptive and predictive. Model descriptions tend to be compact, so a model may also be the most efficient descriptor with the fewest degrees of freedom. The corollary to this is that the model parameters would be overdetermined by the data set, giving good accuracy in parameter values.

Modeling Analysis

The model that we have chosen for myocardial blood-tissue exchange processes is one in which there is dispersive transport through arteries and veins without exchange, and transport through sets of capillary-tissue regions having a range of flows, as indicated in Fig. 1. (The specific model is that developed from Bassingthwaight (1); the rationale for such models is provided in detail by Bassingthwaight and Goresky (2).) The capillary-tissue exchange region is longitudinally distributed, not lumped, and so requires partial differential equations. The parameters are the capillary transit time, the capillary volume divided by the flow, the capillary permeability-surface area product PS_C , the volume of distribution of the solute in the ISF, V'_p , the permeability-surface area product of the sarcolemma of the myocardial cell, PS_{Cell} the intracellular volume of distribution or equilibrative volume of the entering solute V'_{cell} , and a rate constant for intracellular consumption, K_{seq} . For the reference intravascular solute only two of these are relevant, capillary flow and volume. For extracellular solute two more are needed, capillary PS_C and interstitial volume V'_p . For the cellular solute, two more yet are needed, PS_{Cell} and V'_{cell} , and sometimes a third the rate constant K_{seq} for sequestration or consumption. Each capillary-tissue unit therefore requires a minimum of 7 parameter values for a consumed tracer. At least 1 is needed to account for

heterogeneity of regional flows (2). The presence of an additional solute in the experiment can give more data without requiring more parameters; for example, the L-glucose uses parameters for flow, V'_c , PS_C and V'_{cl} identical to those for D-glucose, and uses no others since PS_{Cell} is zero.

Some information may be obtained from other experiments. For example, if the permeating solutes do not enter red blood cells, the relevant flow of “solute-containing mother fluid” is not the capillary blood flow but is the plasma flow; the “other experiment” is therefore simply to measure the large vessel hematocrit. Capillary volumes are estimated from morphometric estimations from vascular casting, but are limited in applicability because of variation in the number of functional capillaries from one physiological state to another. The volumes of distribution V'_c , V'_p and V'_{cell} can be obtained for the heart from steady-state tracer measurements. Heterogeneities in volumes of distribution are difficult to incorporate into the modeling because their interrelationships are not well defined. Steady-state measurements give no information on transport rates PS_C and PS_{Cell} .

When only the mean flow is known and the heterogeneity of regional flows must be defined via the modeling, then the variance and perhaps the shaping factors (equivalent to skewness and kurtosis) must be defined via the modeling. This adds up to a need to evaluate by one means or another, 9 parameters. In analyzing the multiple indicator dilution curves for D- and L-glucose only 5 parameters, PS_C , V'_p , PS_{Cell} , K_{seq} , and V'_{cell} required evaluation. Flow and its heterogeneity were measured, and the reference albumin dilution curve determines the intravascular transit times.

When only 4 to 5 items need to be determined from the modeling of the indicator distribution curves, and the set of curves themselves contain a larger number of items of information, then on the fact of it, one should be able to estimate the model parameter values with some assurance. Such comparisons of “information items needed” with “information items available” suggest that there is some extra information available. This is surely the desired situation, for noise in the data and fluctuations in the physiological state create inconsistencies which the redundancy helps to offset. Confidence that parameters can be evaluated is reasonable, given the proviso that the data are adequate to allow their distinction, that is, given that the experiment design was such that the data are influenced by each of the parameters requiring evaluation. Sensitivity analysis can help to see if this is so.

Sensitivity Functions

Sensitivity analysis can be used in the assessment of the experiment design. A set of sensitivity functions are shown in Fig. 2 for the model system described above. The sensitivity function of a parameter p is defined:

$$S_p(t) = \frac{\partial \hat{h}_D(t)}{\partial p} \div \frac{\Delta \hat{h}_D(t)}{\Delta p} \quad (2)$$

For calculation of the curves, the parameter values were perturbed by 1%. The $S_p(t)$'s are the magnitude of the change of $\hat{h}_D(t)$, the model solution for the permeating tracer, per unit change in parameter value around the current value; the units are therefore sec^{-1} divided by the units of the parameter. Sensitivity functions may be used in a dimensionless fashion, e.g. the fractional change in $\hat{h}_D(t)$ per fractional change in the parameter value. How they should be calculated depends on both one's point of view and the objective. For example, the

fractional change in a parameter value around zero makes no sense while the absolute change gives clear information on the influence of turning a process on or off.

The simplest question that sensitivity analysis can answer is whether or not the parameters are mathematically independent. (This can also be done formally via singular value decomposition.) If two parameters appear inseparably as a product in the equation, as do the permeability P and surface area S of the barriers, then their sensitivity functions are identical. If two parameters occur inseparably as a quotient, then their sensitivity functions will be reciprocal. Fig. 1 shows that neither of these simple dependencies occur in this model. This result was easily anticipated since the partial differential equations are simple, but in more complex systems dependencies or similarities in sensitivities can be demonstrated that are not so obvious from the form of the equations.

The differences in positions and shapes of the sensitivity functions in Fig. 2 illustrate the separability of the influences of these parameters. The sequence of peak influences is just what one would expect. The ordering is the same as for the processes involved: permeation of the capillary wall, dilution in the interstitial fluid volume, permeation of the sarcolemma, dilution in the intracellular space and finally, removal or sequestration by an intracellular reaction, e.g. the irreversible hexokinase reaction for D-glucose. Not only do the times of maximal influences differ but also the directions may be opposite. The plots show that estimation of parameters from the observed curves is possible. [Sensitivity functions are shown here only for the permeant solute. The reference curve, $h_R(t)$, is critically important as input data; not even the most accessible parameter, PS_L , can be calculated without it since it defines the form of the concentration-time curve passing by the capillary exchange region.]

The sensitivity functions are dependent upon values of other parameters. For example, if PS_{Cell} is close to zero, so little tracer enters the cell and leaves again that V'_{Cell} and K_{seq} remain unknown. A subtler situation is the influence of PS_C on the sensitivity to PS_{Cell} : the higher the value of PS_C the less sensitive $h_D(t)$ is to changes in PS_C and the more it is sensitive to PS_{Cell} and the other processes beyond the capillary barrier. The extreme case is obvious: if capillary PS_C is infinitely high then it has no influence at all; all remaining sensitivities are due to processes in the interstitial fluid and the cell. In this sense, the parameters have interacting influences on the importance of the others, but they nevertheless remain separable, and each remains identifiable so long as there is significant sensitivity to it.

Sensitivity Functions in Experiment Design

The form of the sensitivity functions, and their magnitudes, give some hint as to the design of the experiment. Referring to Fig. 2, if the goals of the experiment were to estimate only PS_C and V'_r , and if PS_{Cell} were zero, then data need to be collected over only the first 20 seconds. This would be economically sensible.

However, if estimates of cell volume or consumption were required, then data are required at longer times. This is particularly so for these 2 parameters since their influences overlap so much. The data should be collected for 1½ to 3 minutes--it is only at such late times that the influence of V'_{Cell} becomes positive and therefore opposite in sign to that of K_{seq} . K_{seq} always has a negative influence on $h_D(t)$ since it represents a unidirectional process of removal, and therefore inhibits return flux to the outflow.

Sensitivity Functions in Parameter Optimization

This is a new application of sensitivity functions which is in the process of development (5). The goal is to use local values of the sensitivity functions and estimates of the local distances between the model function and the data curve to adjust all the model's free parameter values at once. Other approaches have used global rather than local distance functions, which is more complex and less efficient (7,3). An example is shown in Fig. 3 for a case in which there are only 2 unknowns, the capillary permeability-surface area product PS_C and the interstitial volume of distribution V_i' . The two "data" curves (actually model solutions) are $h_R(t)$ and $h_D(t)$. A model solution $\hat{h}_D(t)$ is shown for only the permeating tracer; $h_R(t)$ is fitted exactly by the model. Proper adjustments of the 2 parameters of $h_D(t)$ would give a perfect fit to $h_D(t)$. The approach is the same as is used for determining the elements of a composite spectrum. The differences in each time window $\bar{D}_1$ and $\bar{D}_2$ are explainable in terms of the sensitivities to each of the parameters in each window. The system is not linear but, keeping only the first term of a Taylor series expansion, the linear approximation can be written as:

$$\begin{aligned}\bar{D}_1 &= \bar{S}_{11}\Delta p_1 + \bar{S}_{12}\Delta p_2 \\ \bar{D}_2 &= \bar{S}_{21}\Delta p_1 + \bar{S}_{22}\Delta p_2\end{aligned}\quad (3)$$

where Δp_1 and Δp_2 are the steps in PS_C and V_i' required to reduce D_1 and D_2 toward zero. Then by Cramer's rule we solve for the Δp 's:

$$\begin{aligned}\Delta p_1 &= \left(\bar{S}_{22}\bar{D}_1 - \bar{S}_{12}\bar{D}_2 \right) / \det S \\ \Delta p_2 &= \left(\bar{S}_{11}\bar{D}_2 - \bar{S}_{21}\bar{D}_1 \right) / \det S\end{aligned}\quad (4)$$

The vector $\vec{p}$ in parameter space is adjusted so that $\vec{p}_{\text{new}}$ is $\vec{p}_{\text{old}} + \Delta \vec{p}$, and new solutions are obtained. The process can be repeated until the fit is satisfactory: the criterion for stopping the iterations may be some measure of goodness of fit, locally or globally. A least squares assessment of the goodness of fit may be made even though it is not used in the algorithm for parameter adjustment.

For each iteration, new sensitivity functions are computed, and new window positions chosen in accordance with the shifts in peak sensitivities, the maximal separability of the influences, and with the regions of major difference between $h_D(t)$ and $\hat{h}_D(t)$. The method of Levin et al. (5) used only the distant function at the points of peak sensitivity. This simplification allowed oscillations to occur sometimes in the parameter vector $\vec{p}$ as a good fit was approached. Smoothing of the data and using finite window widths help prevent such instabilities. There are therefore a number of improvements to be made in the interests of gaining further efficiency.

Sensitivity Functions and the Accuracy of Parameter Estimates

In the neighborhood of the best fit, the slopes in the N-dimensional error domain give an estimate of the confidence limits for the parameter estimates. The slopes are the sensitivity functions, so they can be used in a standard approach following that of Gauss (see for example reference 8).

CONCLUSION

Sensitivity functions are useful in giving an investigator a semi-quantitative feeling for the influences of changes of parameter values on the behavior of a system of equations. When the system is complex but still describable to some extent by sets of equations then the sensitivity functions may be useful in the optional design of experiments which will elucidate the parts of the system least well known. As a corollary to this, the sensitivity functions can be used directly to adjust parameters of models of the system to fit experimental data, and to assess their accuracy.

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REFERENCES

1. Bassingthwaight JB. A concurrent flow model for extraction during transcapillary passage. *Circ. Res.* 1974; 35:483–503. [PubMed: 4608628]
2. Bassingthwaight, JB.; Goresky, CA. *Handbook of Physiology. Sec. II The Cardiovascular System. Vol. 4, The Microcirculation.* 1983. Modeling in the analysis of solute and water exchange in the microvasculature..
3. Bekey GA, Grove T. Analysis of errors in the identification of biological systems. 1980 IEEE Internat. Symp. on Circuits and Systems Proc. 1980; 2:444–447.
4. King RB, Bassingthwaight JB, Hales JRS, Rowell LB. Stability of heterogeneity of myocardial blood flow in normal awake baboons. *Circ. Res.* 1982 submitted.
5. Levin M, Kuikka J, Bassingthwaight JB. Sensitivity analysis in optimization of time-distributed parameters for a coronary circulation model. *Med. Progr. Techn.* 1980; 7:119–124.
6. Rose CP, Goresky CA, Bach GG. The capillary and sarcolemmal barriers in the heart. An exploration of labeled water permeability. *Circ. Res.* 1977; 41:515–532. [PubMed: 902358]
7. Vemuri V, Raefsky A. On a new approach to parameter estimation by the method of sensitivity functions. *Int. J. Systems Sci.* 1979; 10:395–407.
8. Whittaker ET, Robinson G. *Calculus of Observations.* Blackie and Son. 1924

Fig. 1.
Model of system.

Fig. 2.

Solutions and sensitivity functions for a model of blood-tissue exchange in the heart. **Upper panel:** Impulse responses for a system consisting of arteries and veins and a set of capillary-tissue units in parallel. The large vessel transport functions are described by a lagged normal density curve with mean transit time 7.9 sec, relative dispersion 0.34 and skewness 0.75. The curve for the intravascular reference $h_R(t)$ is the lagged normal density curve convoluted with the weighted sum of 2, 5th order Poisson operators representing the intracapillary transport and dispersion. The mean capillary transit time was 3.0 sec. The curve $h_D(t)$ for the permeating tracer has parameters suitable for D-glucose in the heart. The flow F_S was $1 \text{ ml g}^{-1} \text{ min}^{-1}$; the parameters governing the exchange and the intracellular sequestration, K_{seq} , are listed in the figure. **Lower panel:** Sensitivity functions for each of the governing transport parameters. Note that all are different from the others, and that they are ordered in time in accordance with the sequence of solute transport from blood onto the cells. The functions $S(t)$ are for 1% changes in parameter values and multiplied by scalars for display purposes: the scalars are: 1 for PS_C ; 160 for V'_I ; 5 for PS_{Cell} ; 500 for V'_{Cell} , and 1500 for K_{seq} .

Fig. 3.

Calculation of adjustment in parameter vector for fitting a model to data. There are 2 unknowns, PS_C and V_1' . The intravascular reference data curve is $h_R(t)$. The model curve $\hat{h}_D(t)$ differs from the data curve $h_D(t)$: the differences in each of the two "time-windows" are given by the average differences D_1 and D_2 , the area divided by the window-width. The average values of the sensitivity functions in the two time windows are given by the $\bar{S}_{ij}$. These give the coefficients defining the influences of the 2 parameters in each of the two regions along $h_D(t)$.