Effect of Vasodilation and Flow Rate on Capillary Permeability Surface Product and Interstitial Space Size in the Coronary Circulation

A Frequency Domain Technique for Modeling Multiple Dilution Data with Laguerre Functions

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SUMMARY We investigated the effect of vasodilation and flow rate on derived estimates of capillary permeability surface (PS) product and interstitial space size in the in situ canine heart. We used the multiple indicator dilution technique, with labeled red cells and albumin as reference tracers, Na ion as an interstitial space marker, and tritium-enriched water as a substance entering both interstitial and sarcromeric spaces. The simultaneous outflow curves for these substances were analyzed with a model of the coronary microcirculation which contained unique parameters representative of capillary and sarcolemmal PS products, the ratio of myocyte to interstitial space sizes and the heterogeneity of capillary transit times. Parameter optimization was accomplished by an efficient algorithm based on frequency-domain representations of the model and the data. Vasodilation at constant flow rate with decreased perfusion pressure in the heart working at a constant basal level had no significant effect on the permeability and space size parameters, but the capillary transit time heterogeneity was reduced. Restoration of control perfusion pressure by increased flow (in the face of continuing vasodilation) caused an increase in both capillary PS product and relative interstitial space size, but no change occurred in the sarcolemmal PS product. We conclude that there is no significant recruitment of myocardial cells with increased flow rate and that, when capillary recruitment occurs, it is only an effect of increased flow rate and unrelated to vasodilation per se. At high flow rates, with normal perfusion pressures, a mild but significant degree of interstitial edema accumulation is found.

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IT previously has been difficult to explore the linkage between coronary tone and effects at the level of the microcirculation in the heart precisely because the methods used for the exploration must be not only nondestructive but also accurate enough to provide both permeability surface products and space sizes. In the present work we use the multiple indicator dilution technique (Chinard et al., 1955), together with the analyses we have recently developed (Rose and Goresky, 1976; Rose et al., 1977), which utilize both the upslope and downslope data of the dilution curves, to obtain a set of data reflecting this linkage.

It is useful to review previous ideas and explorations in this area. When arterioles dilate and flow

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increases in the coronary circulation in response to increased oxygen demand or decreased oxygen supply, there are a number of potential effects at the level of the capillaries. Classically, the major response has been considered to be recruitment of previously unperfused capillaries. Krogh (1919) first demonstrated this phenomenon in skeletal muscle with India ink injections and Honig's group has shown it more recently in the heart, with stop-motion in vivo microscopy (Bourdeau-Martini et al., 1974). L'Abbate et al. (1976) used a double-indicator ramp input-dilution method to measure the extravascular water space in the heart and found this apparent tissue space to increase with vasodilation and increase in coronary flow. These investigators attributed the observed increase to a recruitment of perfused areas of myocardium. If this is true, then in a low flow state there will be areas of myocardium which, at least temporarily, are isolated from the perfused portions and, with capillary recruitment, these areas will somehow become "visible" to the diffusing tracer. The phenomenon envisaged would be analogous to that observed in the lungs, where with the increase in cardiac output during exercise, the apical segments...
sign by vasodilating the coronary circulation with papaverine while maintaining a constant basal level of cardiac work.

A more likely explanation of these observations is that a set of Starling effects occurs, that the observed increase in total extravascular water space in the heart with increase in flow is confined to the interstitial space, and that this expansion of the interstitial space is the result of increased capillary filtration. Reduction in arteriolar resistance would be expected to increase capillary pressure at a given arteriolar pressure, and this, together with capillary recruitment, would be expected to promote fluid transfer into the interstitium. Haddy et al. (1976) recently reviewed the topic of exercise edema in muscle which occurs spontaneously in skeletal muscle during large and protracted increases in activity. They concluded that, in this tissue, exercise edema is due not only to the increase in capillary hydrostatic pressure during exercise, amplified by concomitant recruitment of capillary surface area (Renkin and Rosell, 1962), but also to the local release of osmotically active substances in the muscle. If fluid accumulation occurs in cardiac muscle, during manipulation of the coronary tone in the face of a constant work load, the differential contribution of osmotically active substances would be expected to be negligible and no forces leading to changes in sarcomeric volume would be expected. Only change in the interstitial volume would be expected. From this point of view, the problem presented by the data of L’Abbate et al. (1976) is to measure the size of the interstitial space in the heart (as well as the total tissue space) non destructively in vivo.

The multiple indicator dilution technique is ideal for the examination of this problem. With this technique, we have carried out a set of studies in the heart and have introduced, as part of the injection bolus, not only suitable vascular reference substances but, also, a characteristic extracellular reference and labeled water. We previously have shown (Rose et al., 1977) that coronary sinus outflow curves for labeled water can be understood only if the limiting effect of the sarcolemmal membrane is taken into account (and, with this, the extravascular water space is separated into interstitial and intracellular water spaces). We reasoned that if interstitial edema occurred at high flow rates, then the calculated ratio of interstitial to cellular space would increase, but that the cellular space itself would not change significantly. To assure the latter point, the possible effect of osmotically active metabolites was eliminated in our experimental design by vasodilating the coronary circulation with papaverine while maintaining a constant basal level of cardiac work.

We thus were able to define the normal range, in which a “control” run could be carried out.

We initially used an injection mixture containing $^{51}$Cr-labeled red cells and $^{125}$I-labeled albumin as vascular references, $^{14}$C-labeled sucrose as an interstitial reference, and $^3$H-enriched water. It was found that, at the high-flow levels reached in some of these experiments, the extraction of labeled sucrose became relatively small and there was consequently some uncertainty in the estimate of interstitial space size. The protocol was therefore revised and $^{22}$Na (New England Nuclear) was substituted. With its larger extraction, we found that the interstitial space size could be estimated reliably, even at higher flow rates. The activity of each isotope was determined as described previously (Rose and Goresky, 1976).

**Experimental Protocol**

After the chest wound had been closed and chest drainage begun, the preparation was allowed to stabilize with respect to blood pressure and coronary resistance. The autoregulatory plateau was mapped and a “control” run carried out (see Fig. 1). Papaverine then was infused into the cannulated coronary artery so that maximal coronary vasodilation was achieved (maximal vasodilation, in this sense, was defined as a lack of change in the coronary resistance after 15–20 seconds of zero flow). The second run was performed at the same flow rate as the control run, but with reduced perfusion pressure (since the coronary tree was dilated). While the papaverine infusion was continued, the flow rate was increased until the control perfusion pressure was attained. Concomitantly, the papav-
Flow pressure relationships before and after vasodilation with papaverine (the data are from experiment 2). The unfilled circles indicate the conditions during which the experimental runs were carried out.

Autologous blood was infused throughout the experiment so as to maintain the systemic blood pressure (the cardiac load) constant. In none of the experiments did the hematocrit decrease by more than 0.06. Plasma oncotic pressure was not measured but no significant change would be anticipated.

Analysis of the Data

Figure 2 shows typical multiple indicator dilution curves from a low- and high-flow-vasodilated preparation. There is an obvious shift in the relation between the sodium ion and labeled water curves. At the higher flow, the peak of the sodium curve is closer to the labeled albumin reference, and the later part of the curve is lower and flatter in relation to the labeled water curve. It is appropriate to note that the labeled sodium ion should be considered to have entered the interstitial space only. The small amount that eventually does enter the myocyte would be undetected, over the period of time encompassed by a dilution experiment.

To gain insight into the events occurring at the level of the microcirculation we analyzed the data, utilizing the two-barrier mathematical model of labeled water exchange reported previously (Rose et al., 1977). However, instead of using the time-domain analytical solution to optimize the parameters (a procedure that we found previously uses a large amount of computer time), we have used the simpler Laplace transformed version of the model. This technique allows a trade-off between computer processing time and computer memory utilization. By using the total allowable capacity of the PDP-11/70 computer, we achieved a reduction of approximately 90% in computing time (and costs), with no detectable loss in parameter resolution. The procedure is detailed in the Appendix.

The labeled sodium ion curve was fitted first. In the fitting procedure, the labeled plasma albumin reference curve was taken to be the appropriate reference, to define the form the labeled sodium outflow curve would have had in the absence of transcapillary passage. Four unambiguous parameters were obtained:

\[ k_{Na} = \text{the capillary permeability surface product for sodium ion per unit accessible extravascular (extracellular) space, with the dimensions, ml/sec per ml,} \]

\[ \Phi_{Na} = \text{plasma flow per unit accessible extravascular space. This is most conveniently calculated as the re-} \]
circular of the difference between
the mean transit times of the la-
beled sodium and albumin curves,
again with dimensions, ml/sec per
ml, and

\[ a_{\text{Na}}' \text{ and } b_{\text{Na}}' = \]
the intercept and slope, respect-
ively, of the initial linear portion
of the log ratio-time plot, the
graph of \( \ln[\text{C}(t)_{\text{Na}}/\text{C}(t)_{\text{ab}}] \) vs.
time, where \( \text{C}(t)_{\text{ab}} \) and \( \text{C}(t)_{\text{Na}} \)
are the outflow fraction per ml vs.
time curves for the two indicators.
The parameter \( a_{\text{Na}}' \) is dimension-
less, and \( b_{\text{Na}}' \) has the dimensions
sec\(^{-1}\).

The parameters, \( a_{\text{Na}}' \) and \( b_{\text{Na}}' \), which reflect the
distribution of capillary transit times (Rose and
Goresky, 1976), were then used in the fit to the
water curve, which yielded four other unambiguous
parameters:

\[ k_{\text{c}} = \] the capillary permeability surface product
for labeled water per unit interstitial space,
with the dimensions ml/sec per ml,
\[ k_{\text{m}} = \] the sarcolemmal permeability surface
product for labeled water per unit intersti-
tial space, with the dimensions ml/sec per
ml,
\[ \gamma_{w}/\theta_{w} = \] the ratio of interstitial to intracellular
spaces for water. Note that \( \gamma_{w} \) is defined
as the ratio of interstitial to capillary vol-
umes accessible to water; and \( \theta_{w} \), as the
ratio of cellular to capillary volumes for
water; and
\[ \Phi_{w} = \] the flow per unit interstitial space for wa-
ter (ml/sec per ml). This value is larger
than that for \( \Phi_{\text{Na}} \) because, unlike labeled
sodium, the labeled water is carried not
only in the plasma space of blood but also
in red cells. In the fitting procedure the
vascular reference for labeled water is rep-
resented as a combination of the labeled
red cell and albumin curves, weighted ac-
cording to the blood-water fraction in the
red cell and plasma phases, at the hema-
tocrit of the experiment (Goresky et al.,
1978).

Each parameter was assigned a confidence limit
on the basis of the procedure outlined in the Ap-
pendix. This was defined as the variation expected
in each parameter if the data varied by
1% around
the measured value. Since all of the measured val-
ues were varied in the same direction simultane-
ously, and not randomly, these confidence limits
represent a worst-case analysis.

Results

Twenty-one technically satisfactory runs were
obtained from six preparations (Table 1). The re-
sults of the parameter optimization are listed in
Table 2. The parameter \( \Phi_{w} \) is proportional to the
plasma flow per gram heart (see Fig. 3), as expected.
The heterogeneity parameter, \( b_{\text{Na}}' \), decreases
with vasodilation, with the logarithm of the specific
coronary resistance, in a fashion independent of
blood flow (see Fig. 4). The decrease in the param-
eter corresponds to a diminution in the heteroge-

table 1 Hemodynamic Parameters

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<th>Plasma flow (ml/min per g)</th>
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neity of perfusion, to an approach to a more uniform perfusion. This phenomenon was observed previously, in qualitative form, at low flow rates, with labeled sucrose as the interstitial space marker (Rose and Goresky, 1976).

The parameters $k_{na}$ and $k_{ca}$, the capillary barrier rate constants for the sodium ion and for labeled water, both increase with the $\Phi_{na}$ (see Figs. 5 and 6). In each instance the values from "control" experiments and from vasodilated runs with similar flows were intermixed, despite the great drop in coronary arterial pressure in the vasodilated state. Then, in the vasodilated state, increase in flow is accompanied by increase in the capillary barrier rate constants (the capillary permeability surface products per unit interstitial space). In contrast, $k_{mc}$, the sarcolemmal rate constant for water transfer (the sarcolemmal permeability surface product per unit interstitial space), did not change significantly with $\Phi_{na}$ (see Fig. 7). No evidence was found for significant recruitment of myocardial cells.

In terms of the problem being approached, the most important finding is illustrated in Figure 8. There is a significant increase in the size of the interstitial space relative to the cell space with flow. Once again, the values from the "control" experiments are interspersed with the values arising in the vasodilated preparations at similar levels of flow.

**Discussion**

In our previous analysis of outflow curves for labeled water in the heart, we established the con-
Figure 3  Plot of $\Phi_{Na}$, the plasma flow per unit interstitial space obtained from the best fit to the sodium data, vs. the plasma flow rate per gram of perfused heart, $F$ (obtained from the dilution estimate of flow and the heart weight). The equation for the linear regression through the origin is $\Phi_{Na} = 0.113F$. The correlation coefficient was 0.851. Note that $\Phi_{Na}$ is also a function of the size of the interstitial space. A progressive increase in this space size with flow would reduce the slope of the line.

cept of two barriers to water diffusion, one at the capillary membrane and one at the sarcolemmal membrane (Rose et al., 1977) and devised a way to measure the permeability surface products of both capillary and sarcolemmal membranes, and the ratio of interstitial to cellular spaces. With this, in the present work, we analyzed a set of experiments designed to test the recently proposed theory that there is recruitment of myocardial cells with increased coronary flow (L'Abbate et al., 1976), particularly focusing on the effect of vasodilation on the size of the interstitial space. Our original procedure was costly, in terms of computing time, and,
before analyzing another large set of experiments, we felt that we had to find a way to reduce the large computing time and expense so that the technique could be applied more easily in a routine fashion. The development of the frequency domain optimization using Laguerre functions achieved this goal. Our analysis, with this, indicates that there is no recruitment of myocardial cells with increased coronary blood flow, but that the size of the interstitial space increases with coronary flow. In this preparation, with a substantial work load (the heart is maintaining a normal cardiac output), no increase in capillary surface is found to occur with vasodilation and constant flow; but with vasodilation and increase in flow, capillary recruitment is found.

Assumptions of the Frequency Domain Model

Of necessity, the use of frequency domain analysis requires that the frequency spectrum of the observed phenomenon be obtained. Since we are dealing with truncated data and can never observe the complete output of tracer, some form of extrapolation is necessary. Thus we must make explicit our assumptions about what happens after the completion of the sampling period. Time domain analysis does not require these assumptions as explicitly, because the analysis can be curtailed at the point in time at which data collection has ceased. Nevertheless, the same assumptions are present implicitly. All single capillary models predict monotonically declining functions late in time. In order for the frequency domain analysis to be applied, the data must be completed in some such fashion. Fortunately for the heart, we know from nonrecirculating tracer experiments that all of the outflow curves eventually decay exponentially, after crossing the reference curve (Ziegler and Goresky, 1971). With this information, it is appropriate to complete the curves with exponentially declining tails.

In the case of sodium ion and water, we have the additional information that all of the material eventually must be recovered at the outflow since these tracers are not consumed. The addition of monoeponential tails which give complete recoveries of labeled sodium ion and water therefore represent the appropriate choices. In the general case of tracers extracted in net fashion, the expected area cannot be projected and the extrapolation must be made by a best fit through that last few points. The recovery will, of course, be less than complete, in this instance.

An exact reproduction of the data points would require an infinite number of Laguerre functions. By using a finite number, however, the data can be approximated. In the time domain optimization used previously, we have obtained continuous functions from discrete data by the use of a spline fit through the data points. Whereas this approach exactly reproduced the discrete data, continuity between the points was represented by the cubic equations of the spline. In the present frequency domain optimization, the whole curve is fitted by what amounts to a 15th-order polynomial, which has an easily manipulated Laplace transform, the sum of the transforms of the component Laguerre functions. The choice of the highest order of the Laguerre functions used for the fit is the result of a trade-off between goodness of approximation and, in this instance, computer capacity. Figure 2 demonstrates that the use of the sum of Laguerre functions up to the 15th order reproduces the curves to within the experimental error and the required matrices were able to be accommodated in the PDP-11/70 computer. Experience has shown us that data below about 1% of the peak of a curve will not be
well represented. Whereas this degree of resolution is not required in the present analysis, it could be achieved by simply increasing the order of the Laguerre functions.

The final decision required in the frequency-domain modeling is the choice of the upper bound and integration interval of the integral used in calculating the Laguerre coefficients of the model (Equation 46 of the Appendix). Again, the choice is a trade-off between resolution and computer capacity. We have used an upper bound of 3 cycles/sec and an integration interval of 0.01 cycle/sec, since it was found that increasing the upper bound or decreasing the interval did not change the value of the integral significantly.

Variation in Capillary Transit Time Heterogeneity with Coronary Resistance

In our initial investigations of the effects of vasodilation, we studied a preparation in which we attempted to maintain constant flow during vasodilation without too precipitous a fall in coronary perfusion pressure (Rose and Goresky, 1976). To carry through this experimental design, we gathered data from preparations in which, in the baseline state, the heart was somewhat overperfused, in terms of its metabolic needs (the coronary resistance values were high in relation to the mid-plateau baseline values used in the present study); and similar perfusion values were attained, although at low pressure, after vasodilation. We found a marked decrease in heterogeneity after vasodilation. In the present set of experiments, we have investigated the whole range of normal pressure-flow relationships (from the midpoint of the autoregulatory plateau to low and high pressure studies after vasodilation) and have found a consistent relation across the broad sweep: high coronary resistance is associated with a large degree of capillary transit time heterogeneity; and low coronary resistance, with a diminution in the heterogeneity.

Definition of the heterogeneity parameter b' depends, at the experimental level, on the relation between the early throughput component of the interstitial tracer and the vascular tracer. The capillaries are more permeable to the sodium ion than to sucrose, and the initial throughput component of the sodium curve is contaminated earlier by material returning from the interstitial space. The difference is small, however, and our analysis indicates that the values obtained for b' are quite secure.

From the data, we can now say that the relationship between coronary resistance and the parameter b' as an index of capillary transit time heterogeneity, holds independently of either the coronary perfusion pressure or flow rate, considered separately. The presence of some macroscopic heterogeneity due to overperfusion of the epicardium at high perfusion pressure or to underperfusion of the endocardium at low flow rates in these preparations cannot be excluded absolutely, but the data suggest that these will exert secondary effects, compared to the control of the degree of heterogeneity at the level of the microcirculation.

Failure to account for this heterogeneity may result in misinterpretation of tracer outflow data, especially when the throughput component of the data is not obvious. Thus, in the heart, we have found that only the two-barrier model fits outflow-labeled water curves precisely, when the heterogeneity is taken into effect. The one-barrier model, on the other hand, is found to overestimate the upslope of the water curve and, in the presence of even a small amount of heterogeneity, is quite inadequate. One-barrier modeling has been used by other authors. Thus Harris et al. (1978) have analyzed labeled water outflow curves from the heart, neglecting both transit time heterogeneity and barriers beyond the capillary surface. We have already shown that the limitations of this approach in the heart are major and that the approach is inappropriate.

Variation in Capillary Permeability Surface Product with Flow Rate

Our finding of increased capillary permeability surface product per unit interstitial space with increased flow confirms some previous observations in both heart and skeletal muscle (Ziegler and Goresky, 1971; Renkin, 1959; Alvarez and Yudilevich, 1969). However, our results show also that this change is not due to the vasodilation per se, since vasodilation at constant flow rate is not accompanied by increased capillary rate constants. When it does occur, the capillary recruitment seems to be caused only by an increase in hydrostatic pressure at the level of the microcirculation. The alternative explanation, that increased flow causes an increased capillary permeability with constant capillary surface area, is impossible to rule out. Such a mechanism has been proposed to be responsible for certain forms of pulmonary edema (Ohkuda et al., 1978).

The results of our studies, carried out in a working heart maintaining a normal systemic blood pressure and, presumably, cardiac output, differ from those of Durán et al. (1973), carried out in an isolated nonworking, spontaneously beating, perfused preparation. Durán found that these preparations, perfused at constant flow, exhibited an increased capillary permeability surface product for glucose and sodium, after vasodilation. The reason for the discrepancy is not clear but there are two possible explanations. The baseline metabolic stress was less in the nonworking preparation and the proportion of the microcirculatory bed perfused in the control situation may have been smaller. In this situation, the effect of vasodilation may differ from that in the normally working heart (that is, there may be recruitment with vasodilation, in the face of constant flow). Alternately, the Durán interpre-
tation may have arisen because of a difference in the approach to analysis of the data. Durán applied the Crone (1963) approximation to the first 5-6 seconds of the outflow curves, and necessarily assumed that perfusion homogeneity was present. Choice of early values would lead to low permeability surface products if, in the baseline state, Durán's preparation had a moderate degree of heterogeneity. In the data illustrated in the Durán paper this does not appear to be the case (the extractions do not increase markedly along the upslope). It therefore seems that the former explanation of the discrepancy between the two sets of data is more likely.

On the basis of our present findings we can conclude that vasodilation, unaccompanied by increased flow in the working heart, causes a reduction in capillary transit heterogeneity but no recruitment. However, if flow is then allowed to increase, the transport capacity of the capillaries is increased, either by increased surface area, or permeability, or both.

**Interstitial Space Size**

The data presented in this paper indicate that, so long as a sufficient period is allowed for the establishment of a steady state at each level, increase in blood flow to the heart is accompanied by expansion of the interstitial space, and that, when flow is varied from the normal range to higher values, there is no evidence of change in the proportion of heart muscle perfused. The data indicate that the observations of L'Abbate et al (1976) that the apparent extravascular water space in the heart is recruited with increasing flow can be accounted for by the fluid accumulation in the extracellular space, rather than the recruitment of formerly non-perfused muscle, with increasing flow. If, in the kind of experimental protocol being pursued here, the period between runs is made short so that, following an increase in flow, the extracellular space has not yet been expanded by net filtration, the capillary recruitment which occurs with increase in flow may be perceived in a fashion separable from the expansion of the extracellular space. This kind of phenomenon appears to account, in part, for the failure of Ziegler and Goresky (1971) to perceive expansion of the interstitial space, with labeled sucrose, in high-flow vasodilated preparations. At the same time, we have found that labeled sucrose does not provide secure estimates of the interstitial space, in high-flow situations. When blood flow is high, the upslope and peak extraction of labeled sucrose becomes small and the later low-in-magnitude return component becomes difficult to measure and consequently subject to some uncertainty. Labeled sodium was found to provide much more certain estimates of the parameters, especially in the high-flow situation, and it was the use of this label which enabled us to secure unequivocal evidence of the expansion of the interstitial space in high-flow vasodilated preparations, in the present series of experiments.

**Implications of the Results**

It should be emphasized that all of the observed changes are unrelated to coronary perfusion pressure within the range of flows that would be encountered with normal heart function. Thus, the ability of the arteriolar sphincters to regulate coronary flow is important, not only in increasing the delivery of metabolites during increased heart work, but also in protecting the interstitial space when high flows are not required. We also believe that, as a result of these experiments, we can now supply at least one rationale for the presence of a continuous capillary membrane in the heart. At first inspection, it seems to make no sense that a membrane should be interposed between blood and tissue, restricting the diffusion of important metabolites to the myocyte. About 50% of the free fatty acid present in arterial blood do not cross this membrane in a single passage so that predicted intracellular concentrations of labeled free fatty acids can be as low as one-twentieth of the arterial concentration, due to the high rate of intracellular sequestration (Rose and Goresky, 1977). If the cardiac capillaries were fenestrated, as are the liver sinusoids, the delivery of metabolites would be more efficient but the filtration coefficient would also be high and, in the presence of high capillary pressure during arteriolar dilation, gross interstitial edema would occur. The structure of the capillary barrier in the heart thus appears to be a trade-off between the needs for unrestricted metabolite diffusion and for prevention of interstitial edema.

**Appendix**

**Part 1: Transfer Function of the Whole Organ-Outflow, in the Well-Perfused Case**

Consider a two-barrier system, in which there are constraints to the passage of materials both at the level of the capillary and at the surface of the surrounding parenchymal cells, beyond the interstitial space. Assume plug flow in the capillary, dimensions and flows such that radial gradients in the interstitial and cell spaces are negligible, and negligible longitudinal diffusion (Rose et al., 1977). The partial differential equations describing the distribution of tracer within this system include an equation of conservation

\[
\frac{\partial u}{\partial t} + W \frac{\partial u}{\partial x} + \gamma v \frac{\partial v}{\partial t} + \theta \frac{\partial z}{\partial t} + k_3 z = 0
\]

and two rate equations, describing the accumulation of material in the interstitial space

\[
\frac{\partial v}{\partial t} = k_{1u} u - k_{2v} v - k_{3v} v + k_z z
\]

and cellular space

\[
\frac{\partial z}{\partial t} = \gamma \frac{v}{\theta} k_{3v} v - \gamma \frac{v}{\theta} k_z z
\]
where the symbols are defined as follows: u(x, t), v(x, t), and z(x, t) are the concentrations of tracer in the capillary, extracellular, and intracellular spaces; W is the velocity of flow in the capillary; γ is the ratio of interstitial space to intracapillary space size; θ is the ratio of intracellular space to intracapillary space size; υ and ψ are rate constants (dimension time⁻¹) for efflux from and influx into the capillary (at the phenomenological level, these are unidirectional permeability-surface products per unit interstitial space); ψ and η are rate constants for influx into and efflux from the tissue cells (these are once again unidirectional permeability-surface products per unit interstitial space); and η is the rate constant describing sequestration (expressed as volume flux per unit space).

Suppose that the amount of tracer, q₀, is injected at the origin of a capillary of length L with flow F. Define the Laplace transform of the outflow concentration of label as

$$U(L, s) = \int_0^L u(L, t) e^{-st} dt$$

Then, from the partial differential equations,

$$U(L, s) = \frac{q_0}{F} e^{-s\tau_c} e^{-k_1\tau_c} e^{i\omega t}$$

where

$$f(s) = \frac{k_1k_2(s + [\gamma/\theta]k_4 + k_5)}{s^2 + (k_2 + k_3 + [\gamma/\theta]k_4 + k_5) s + ([\gamma/\theta]k_k2 + k_3k_5 + k_3k_5)}$$

and τ_c = L/W, the transit time for flow of materials confined to the capillary. The time domain inversion of this transform is quite complicated, viz,

$$u(L, t) = \frac{q_0}{F} e^{-k_1\tau_c} \delta(t - \tau_c) + \frac{q_0}{F} e^{-k_1\tau_c} \times \left[ \exp\left(\frac{\gamma k_1k_2c \alpha}{t - \tau_c}\right) \cdot I_1(2\sqrt{\gamma k_1k_2c \alpha}(t - \tau_c)) + \exp\left(\frac{\gamma k_1k_2c \beta}{t - \tau_c}\right) \cdot I_1(2\sqrt{\gamma k_1k_2c \beta}(t - \tau_c)) \right] \cdot S(t - \tau_c)$$

where d and f are the roots of the quadratic equation,

$$s^2 + (k_2 + k_3 + [\gamma/\theta]k_4 + k_5)s + ([\gamma/\theta]k_1k_2 + k_3k_5 + k_3k_5) = 0$$

and

$$A = \frac{d + ([\gamma/\theta]k_4 + k_5)}{d - f}$$

$$B = \frac{f + ([\gamma/\theta]k_4 + k_5)}{f - d}$$

When these expressions are combined with a whole organ model, the computation of the resulting simulated indicator dilution curve requires about 30 seconds of control processing unit (CPU) time on an IBM-360 model 158 computer. The repeated calculation of the model in order to optimize the parameters has required up to an hour of CPU time. This has proved to be a major economic limitation.

The simplicity of the Laplace transform of the single capillary model has stimulated attempts to use this, particularly since modern computer science has resulted in the development of surprisingly fast algorithms for the numerical inversion of some transforms (Kolata, 1978). In tissue exchange modeling, Harris et al. (1976) have found computing time to optimization to be shortened if numerical inversion of the Fourier transform of an exchange model is used in place of an analytical time domain solution. They optimized parameters by comparing the resultant time domain case with the data. The approach requires repeated numerical inversions. It would appear that the procedure as a whole could be shortened further by optimizing the parameters in the frequency domain and then inverting to the time domain only once, when the parameters have been optimized. Computation in the frequency domain also permits a sensitivity analysis of the derived parameters.

We therefore developed a frequency domain method for deriving, from a set of multiple indicator dilution curves, optimized estimates of the exchange parameters of the two-barrier blood-tissue exchange model outlined above. It has proved to be accurate, and rapid and economical, in terms of computing time.

The Laguerre functions can be made to fit indicator dilution curves closely, and they possess simple transforms. It seemed reasonable to attempt to represent both the data and the model in the frequency domain in terms of Laguerre functions. This procedure is described in part 2 of the Appendix. To use this approach it is necessary first to obtain a transformed version of the whole organ outflow which incorporates the relation between large vessel and capillary transit times. Observations are made at the outflow and the space variable, L, is then observed in terms of the corresponding transport lag, L/W = τ_c. The time domain expression (4)
for the whole organ outflow is, from this point of view
\[ c'(t) = \int_{\tau_{cm} + \tau_{cm}}^{t} \frac{F_c}{\tau_{cm}} u[\tau_{c}(t'), t - \tau_{c}(t')] w[t'] \, dt' \]  
(6)

where \( c'(t) \) is the concentration of an exchanging tracer at the outflow of the organ, \( w(t') \) is the concentration of the reference or nonexchanging tracer, \( \tau_{c}(t') \) and \( \tau_{l}(t') \) are the capillary and large vessel transit time, and \( t' \) is the elapsed time, including transit time through exchanging and nonexchanging vessels. The relations between these are defined as follows:

\[ \tau_{c}(t') = \tau_{cm} + b(t' - \tau_{cm} - \tau_{cm}) \]
\[ \tau_{l}(t') = \tau_{cm} + (1 - b)(t' - \tau_{cm} - \tau_{cm}) \]  
(7)

where \( 0 < b < 1 \), and \( \tau_{cm} \) and \( \tau_{cm} \) are minimum capillary and large vessel transit times; \( b \) is a factor which partitions each pathway into exchanging and nonexchanging vessel transit times. It incorporates the assumption that the transit times are linked in such a fashion that a more rapid capillary transit time is associated with a more rapid large vessel transit time, a slower capillary transit time with a slower large vessel transit time, and that each increases proportionately with increase in time at the outflow. The experimental studies leading to this formulation were described previously (Rose and Goresky, 1976).

The Laguerre functions are defined in the half plane \( 0 < t < \infty \). The first step in developing the appropriate corresponding transform expression will be to translate the origin to a time corresponding to the outflow appearance time. Recognizing the delay of \( \tau_{c} \) represented by the term \( \exp(-\tau_{c} s) \) in the transform of Equation 4, we may write

\[ u(\tau_{c}, t) = \frac{q_0}{F_c} e^{-k_{l\tau_{cm}}^2} g(\tau_{c}, t - \tau_{c}) \]  
(8)

where

\[ g(\tau_{c}, t) = \mathcal{L}^{-1}\{e^{(t_0-t_1)}, \} \]  
(9)

where \( \mathcal{L}^{-1} \) stands for the inverse Laplace transform. We may use this in Equation 6 to obtain

\[ c(t) = \int_{\tau_{cm} + \tau_{cm}}^{t} e^{-k_{l\tau_{cm}}^2} [g(\tau_{c}(t'), t - \tau_{c}(t')) w[t'] \, dt' \]
\[ = \int_{\tau_{cm} + \tau_{cm}}^{t} e^{-k_{l\tau_{cm}}^2} [g(\tau_{c}(t'), t - t') w[t'] \, dt'. \]  
(10)

Whereas this equation has the general appearance of an ordinary convolution integral, it is not directly transformable into a product of two functions in the frequency domain, because \( g \) is a function of both \( \tau_{c}(t') \) and \( t - t' \), and \( \tau_{l}(t') \) and \( t' \) are linked according to Equations 7. The expression will become an ordinary convolution integral only when the capillary transit time is a constant.

Now let \( t'' = t' - \tau_{cm} - \tau_{cm} \)  
and define \( w_0(t) = w(t + \tau_{cm} + \tau_{cm}) \).

This definition displaces the time origin of the reference curve to its appearance time. The integral becomes

\[ c(t) = \int_{0}^{t'' - \tau_{cm} - \tau_{cm}} e^{-k_{l\tau_{cm}}^2} g(\tau_{c}, t - t'' - \tau_{cm} - \tau_{cm}) w_0(t'') \, dt''. \]

We now displace the origin of \( c(t) \) in the same way, i.e.,

\[ c_0(t) = c(t + \tau_{cm} + \tau_{cm}). \]  
(12)

Then

\[ c_0(t) = \int_{0}^{t''} e^{-k_{l\tau_{cm}}^2} g(\tau_{c}, t - t'') w_0(t'') \, dt''. \]  
(13)

From Equations 7 we note that \( \tau_{c} = \tau_{cm} + bt'' \). Thus

\[ c_0(t) = \int_{0}^{t''} e^{-k_{l\tau_{cm}}^2} g(\tau_{cm} + bt'', t - t'') \cdot e^{-k_{l\tau_{cm}}^2} w_0(t'') \, dt''. \]  
(14)

With the time-displaced function, we now proceed to define the Laplace transform for the whole organ outflow. Note that since \( g(\tau_{cm} + bt'', t - t'') = 0 \) for \( t'' < 0 \), i.e., for \( t'' > t \), the upper limit of \( t \) may be replaced by infinity. Hence,

\[ C(s) = \int_{0}^{\infty} e^{-st} \int_{0}^{\infty} e^{-k_{l\tau_{cm}}^2} e^{-k_{l\tau_{cm}}^2} \cdot w_0(t'') g(\tau_{cm} + bt'', t - t'') \, dt'' \, dt. \]  
(15)

Interchanging the order of integration

\[ C(s) = e^{-k_{l\tau_{cm}}^2} \int_{0}^{\infty} e^{-k_{l\tau_{cm}}^2} w_0(t'') e^{-st} \, dt''. \]  
(16)
C(s) = e^{-k_1\gamma t_m} \int_0^{\infty} e^{-k_1 \beta t} w_0(t) e^{s(t-t_m+b\gamma +1)} e^{-st} \, dt'' \tag{17}

where Equation 9 has been used for the transform of \(g\). Now write Equation 17 as

\[
C(s) = e^{k_1 \gamma (s+b)} \int_0^{\infty} e^{-k_1 \gamma t - b(s) t'} w_0(t') \, dt''.
\]

The integral is, in fact, a transform which may be written as \(L[w_0(t')]\), to be evaluated using as the transform variable \(s + k_1 \gamma b - bf(s)\). Thus

\[
C(s) = e^{k_1 \gamma (s+b)} W_0(s + k_1 \gamma b - bf(s)). \tag{19}
\]

Equation 19 now describes the transfer function of the whole organ.

For \(s = j\omega\), the transform \(W_0(s)\) is evaluated at \(s = j\omega + k_1 \gamma b - bf(j\omega)\). The operation will be valid only if the complex number lies in the region of convergence of the transform. Since \(w_0(t)\) is absolutely integrable, the region of convergence of \(W(s)\) surely includes the right half of the complex plane. Fortunately, it is easy to show that \(\text{Re}[k_1 \gamma - f(j\omega)] > 0\) for all \(\omega\) if the model parameters are positive. Thus Equation 19 is valid for \(s = j\omega\).

Part 2: Frequency Domain Representation of the Model and the Data in Terms of Laguerre Functions and the Error Optimization of Model Parameters

The Laguerre Functions

The Laguerre functions are the members of an orthonormal set formed from the set of linearly independent functions \((pt)^n e^{-pt}\). The range of definition is \(0 < t < \infty\). The first few Laguerre functions are

\[
\ell_n(t) = \sqrt{2p} e^{-pt}
\]

\[
\ell_1(t) = \sqrt{2p} (2pt - 1) e^{-pt}
\]

\[
\ell_2(t) = \sqrt{2p} (2pt^2 - 4pt + 1) e^{-pt}
\]

and the general term is

\[
\ell_n(t) = \sqrt{2p} \left[ \frac{(2pt)^n}{n!} - \frac{n(n-1)}{(n-1)!} (2pt)^{n-1} + \frac{n(n-1)(n-2)}{2!(n-2)!} (2pt)^{n-2} - \frac{n(n-1)(n-2)(n-3)}{3!(n-3)!} (2pt)^{n-3} + \cdots + (-1)^n \right] e^{-pt} \tag{20}
\]

or, more compactly,

\[
\ell_n(t) = \sqrt{2p} e^{-pt} \sum_{i=0}^{n} C_m(2pt)^{n-i} \tag{21}
\]

where

\[
C_m = (-1)^m \frac{n!}{m!(n-m)!} \frac{1}{n(n-1)!} \frac{1}{(n-m)!} . \tag{22}
\]

Note that the quantity \(p\), where \(p > 0\), is a timescaling parameter. Figure 9 shows the first four Laguerre functions. Of course, by construction,

\[
\int_0^{\infty} \ell_n(t) \ell_m(t) \, dt = \begin{cases} 0 & \text{if } n \neq m \\ 1 & \text{if } n = m. \end{cases} \tag{23}
\]

The Laplace transforms of the Laguerre functions are

\[
L_n(s) = \sqrt{2p} \frac{(p - s)^n}{(p + s)^{n+1}} \tag{24}
\]

It is not difficult to calculate the spectra of the Laguerre functions. One finds

\[
|L_n(j\omega)| = \frac{\sqrt{2p}}{\sqrt{\omega^2 + p^2}} \tag{25}
\]

and

\[
\text{Arg}[L_n(j\omega)] = -(2n + 1) \tan^{-1} \left( \frac{\omega}{p} \right) . \tag{26}
\]

Note that, as the order of the Laguerre function increases, the number of oscillations of \(\ell_n(t)\) increases; note also that, in the frequency interval \(0 \leq \omega \leq p\), the angle of \(L_n(j\omega)\) goes through \(\frac{2n + 1}{8}\) cycles.

To expand a given function \(y(t)\), \(0 \leq t < \infty\), into Laguerre functions, one may write

\[
y(t) = \sum_{n=0}^{\infty} a_n \ell_n(t) \tag{27}
\]

For this sum to converge, it is necessary that \(y(t)\) be square-integrable, i.e., \(\int_0^{\infty} y^2(t) \, dt < \infty\). This in turn implies that \(y(t)\) tends to zero as \(t\) tends to infinity.

Using the orthonormality property,

\[
a_n = \int_0^{\infty} y(t) \ell_n(t) \, dt . \tag{28}
\]

If the transform \(Y(s)\) is known, then Parseval's theorem may be used to write

\[
a_n = \frac{1}{2\pi} \int_{-\infty}^{\infty} Y(j\omega) L_n(-j\omega) \, d\omega . \tag{29}
\]

If \(y(t)\) is the impulse response of a linear system, then \(Y(s)\) is its transfer function. Using Equation 24, the system may be synthesized as in Figure 10.

If a finite number of Laguerre functions is to be used, say \(N\), it turns out that the \(a_n\) as given by Equations 28 or 29 minimize the integral-square criterion

\[
J = \int_0^{\infty} \left[ y(t) - \sum_{n=0}^{N} a_n \ell_n(t) \right]^2 \, dt . \tag{30}
\]
It is easy to show that the minimum value of $J$ is given by

$$J_{\text{opt}} = \int_0^\infty y^2(t) \, dt - \sum_{n=0}^N a_n^2$$  \hspace{1cm} (31)

or

$$J_{\text{opt}} = \frac{1}{2\pi} \int_{-\infty}^\infty |Y(j\omega)|^2 \, d\omega - \sum_{n=0}^N a_n^2.$$  \hspace{1cm} (32)

Note that $J_{\text{opt}}$ decreases monotonically with $N$.

Thus far, we have said nothing about the choice of the time-scale parameter $p$. While the Laguerre set is complete for any positive $p$, it is clear that many terms will be required to fit a time function for an ill-chosen value of $p$. Roughly speaking, $1/p$ should approximate the time constant of the function to be fit. Parks (1971) has suggested the following formula:

$$p = \left( \frac{M_2}{M_1} \right)^{1/2}$$  \hspace{1cm} (33)

where

$$M_1 = \frac{\int_0^\infty t y^2(t) \, dt}{\int_0^\infty y^2(t) \, dt}$$  \hspace{1cm} (34)

$$M_2 = \frac{\int_0^\infty t (\dot{y}(t))^2 \, dt}{\int_0^\infty y^2(t) \, dt}.$$  \hspace{1cm} (35)

Here, $M_1$ is a measure of how rapidly $y(t)$ decays, whereas $M_2$ reflects the smoothness of the decay.

**Application to Parameter Identification**

We assume that the transfer function of a process can be calculated as $Y(s, \rho)$, where $\rho$ is a vector of unknown parameters to be identified. We assume also that the process impulse response, $y(t, \rho)$, has been characterized in terms of its Laguerre expan-
sion, with coefficients $a_n$. In practice, this can be done using Equation 27 if the input is an impulse, e.g., a sudden injection of tracer material.

The Laguerre coefficients of the model are given by the integrals

$$a_n(p) = \frac{1}{2\pi \int_{-\infty}^{\infty} Y(j\omega, p) L_n(-j\omega) \, d\omega. \quad (36)$$

The difference $e(t)$ between the measured impulse response and the model impulse response is given by

$$e(t) = \sum_{n=0}^{\infty} [a_n - a_n(p)] \alpha_n(t). \quad (37)$$

Therefore, the integral-square error is

$$ISE = \sum_{n=0}^{\infty} [a_n - a_n(p)]^2. \quad (38)$$

The problems presented by finite duration sampled records

In practice, all experimental records will be of finite duration and sampled for digital processing. Both aspects deviate from the theory and must be addressed with some care.

If the observation interval is from 0 to $T$, the Laguerre functions are no longer orthogonal, and Equation 27 may not be used.

It is possible to choose the Laguerre coefficients for least-squared fit over an observation interval, say 0 to $T$. Our experience dictates, however, that to ignore the time interval $t > T$ is to invite disaster; the likely outcome is an excellent fit from 0 to $T$, but large oscillations for an appreciable interval thereafter. We have found it preferable to make use of known attributes of the behaviour for $t > T$. For example, if the curve is known to be positive and monotonically decreasing, it is reasonable to complete the available data by an exponential tail. If an exponential is used for $t > T$, then Equation 9 becomes

$$a_n = \int_0^T y(t) \alpha_n(t) \, dt + \int_T^\infty ke^{-\lambda t} \alpha_n(t) \, dt. \quad (39)$$

The details of the computation of the second term are given in part 3 of the Appendix.

The second modification is brought about by the sampled nature of the data. This means that Equation 28 must be approximated. If we assume that the sampling is fast enough to represent the phenomenon, we may approximate $y(t)$ by a piece-wise linear curve, i.e.,

$$y(t) = y(k\Delta) + (t - k\Delta) \quad (40)$$

There results an expression of the form

$$\int_{k\Delta}^{(k+1)\Delta} y(t) \alpha_n(t) \, dt = a_n y(k\Delta) - \beta_n y((k+1)\Delta) \quad (41)$$

where the forms of $a_n$ and $\beta_n$ are given in part 3 of the Appendix. The first term of Equation 39 is then given by

$$b_n = a_{n,0}y(0) + [a_{n,1} - \beta_{n,1}]y(\Delta)$$

$$+ [a_{n,2} - \beta_{n,2}]y(2\Delta) + \cdots + [-\beta_{n,N}]y(K\Delta) \quad (42)$$

where $K\Delta$ is the duration of the record of data.

Using Equation 41, as well as Equation 28, one may write the vector expression

$$\mathbf{b} = \mathbf{C} \mathbf{Y} + \mathbf{f} \quad (43)$$

where

$$\mathbf{Y} = [y(0) y(\Delta) y(2\Delta) \cdots y(K\Delta)]$$

$$\mathbf{C} = \begin{bmatrix}
  a_{0,0} & a_{0,1} & \cdots & a_{0,K-1} & -\beta_{0K} \\
  a_{1,0} & a_{1,1} & \cdots & a_{1,K-1} & -\beta_{1K} \\
  \vdots & \vdots & \ddots & \vdots & \vdots \\
  a_{N,0} & a_{N,1} & \cdots & a_{N,K-1} & -\beta_{NK}
\end{bmatrix}$$

$$\mathbf{f}^T = [f_1 f_2 \cdots f_N]$$

$$f_n = \int_0^\infty y(t) \alpha_n(t) \, dt. \quad (44)$$

Note that, given $K$, $p$, and $N$ ahead of time, one may compute $\mathbf{C}$.

The sampling phenomenon also requires that Equations 34 and 35, leading to the determination of $p$, be modified. A simple discretization yields

$$M_1 = \frac{\Delta \sum_{k=0}^{K} ky^2(k\Delta)}{\sum_{k=0}^{K} y^2(k\Delta)} \quad (44)$$

$$M_2 = \frac{\sum_{k=0}^{K-1} k[y(k\Delta + \Delta) - y(k\Delta)]^2}{\Delta \sum_{k=0}^{K} y^2(k\Delta)} \quad (45)$$

Finally, it is also necessary to address the problem of frequency-domain quadrature represented by
Equation 36. Using the fact that both $Y(j\omega)$ and $L(j\omega)$ are the spectra of real time functions, we obtain

$$
\alpha_n = \frac{1}{\pi} \int_0^\infty \left[ \text{Re}Y(j\omega, \rho)L_n(-j\omega) \right] d\omega
$$

$$
= \frac{\sqrt{2\pi}}{\pi} \int_0^\infty \text{Re}[Y(j\rho\Omega, \rho)]
\cdot \cos\left[(2n + 1)\tan^{-1}\Omega \right] \sqrt{\Omega^2 + 1} d\Omega
$$

$$
- \frac{\sqrt{2\pi}}{\pi} \int_0^\infty \text{Im}[Y(j\rho\Omega, \rho)]
\cdot \sin\left[(2n + 1)\tan^{-1}\Omega \right] \sqrt{\Omega^2 + 1} d\Omega
$$

(46)

where we have used the normalized frequency $\Omega = \omega/\rho$.

The quantity in the integrals which changes most rapidly will usually be the angle $(2n + 1) \tan^{-1}\Omega$; as $\Omega$ goes from 0 to 1, this angle changes from 0 to $(2n + 1)\pi/4$. Since $Y(j\rho\Omega, \rho)$ appears in each of the $n + 1$ integrals, a fixed-interval quadrature method is indicated since the $Y(j\rho\Omega, \rho)$ can then be evaluated once for all the integrals. If a straightforward method, e.g., Simpson's rule, is used, the integration interval $\delta$ would be dictated by the angle $(2n + 1) \tan^{-1}\Omega$, and would be quite small for even fairly low $n$. We note, however, that the functions $\text{Re}Y$, $\text{Im}Y$, $\tan^{-1}\Omega$ and $1/\sqrt{\Omega^2 + 1}$ are relatively smooth. This may be used to construct piecewise-linear approximations over the intervals $k\delta$ to $(k + 1)\delta$. Note that it is $\tan^{-1}\Omega$, and not the sine and cosine of $(2n + 1) \tan^{-1}\Omega$, that is linearly approximated. As shown in part 3 of the Appendix, there results an expression

$$
\alpha = DR \frac{\text{Re}Y}{\text{Im}Y} + DI \frac{\text{Re}Y}{\text{Im}Y}
$$

(47)

where

$$
\alpha^T = [a_0, a_1, \ldots, a_N]
$$

$$
Y^R = [\text{Re}Y(0, \rho) \text{Re}Y(j\rho, \rho) \ldots \text{Re}Y(j\rhoK, \rho)]
$$

$$
Y^I = [\text{Im}Y(0, \rho) \text{Im}Y(j\rho, \rho) \ldots \text{Im}Y(j\rhoK, \rho)]
$$

The matrices DR and DI may be computed once and for all, given $\rho$ and the frequency step $\delta$.

**Error Analysis**

In this section, we consider the error analysis problem, with the purpose of obtaining tolerances on the parameter estimates.

We define the vector $\alpha(\rho)$, whose ith component is $a_i(\rho)$. Equation 38 can then be written as

$$
\text{ISE} = (\alpha - \alpha(\rho))^T(\alpha - \alpha(\rho))
$$

(48)

Let $\alpha$ and $\rho$ be perturbed, to $\alpha + \Delta\alpha$ and $\rho + \Delta\rho$, respectively. Then we may write

$$
\text{ISE} = \|\alpha - \alpha(\rho)\|^2 + 2\Delta\alpha^T(\alpha - \alpha(\rho)) - 2\Delta\rho^T \frac{\partial\alpha}{\partial\rho} (\alpha - \alpha(\rho)) + \|\Delta\alpha\|^2
$$

$$
+ \Delta\rho^T \frac{\partial\alpha}{\partial\rho} \frac{\partial\alpha}{\partial\rho} \Delta\rho - 2\Delta\rho^T \frac{\partial\alpha}{\partial\rho} \Delta\rho
$$

(49)

where $\frac{\partial\alpha}{\partial\rho}$ is the Jacobian matrix, with the $(i, j)$-th element $\frac{\partial a_i}{\partial \rho_j}$.

With $\Delta\alpha = 0$, the ISE is a minimum with respect to $\rho$; this means that the first-order term in $\Delta\rho$ must vanish, i.e.,

$$
\frac{\partial\alpha}{\partial\rho} (\alpha - \alpha(\rho)) = 0
$$

(50)

Given $\Delta\alpha$, we find the $\Delta\rho$ that minimize the ISE by setting the gradient of the right hand side of Equation 48 to zero. There results

$$
\frac{\partial\alpha}{\partial\rho} \frac{\partial\alpha}{\partial\rho} (\alpha - \alpha(\rho)) = \frac{\partial\alpha}{\partial\rho} \Delta\alpha.
$$

(51)

Now, Equation 43 can be used to express $\Delta\alpha$ in terms of changes $\Delta Y$ in the data. We obtain

$$
\Delta\rho = \left(\frac{\partial\alpha}{\partial\rho} \frac{\partial\alpha}{\partial\rho}\right)^{-1} \frac{\partial\alpha}{\partial\rho} \Delta Y
$$

(52)

or, for brevity,

$$
\Delta\rho = R\Delta Y
$$

(53)

This can be used to yield tolerances on $|\Delta\rho|$; for example, if the measurement error is bounded, then

$$
|\Delta\rho| \leq \sum_{k=0}^K |R_{ik}| E_k
$$

(54)

where

$$
|\Delta Y_k| \leq E_k
$$

**Algorithm for Parameter Optimization in the Frequency Domain**

The overall procedure for parameter optimization is carried out as follows:

1. The appropriate vascular reference indicator curve is extrapolated, using an exponential least squares fit through the last three data points. The set of Laguerre coefficients which approximate the curve, $a_0, a_1, \ldots, a_N$ is calculated. $N = 15$ usually provides a very close fit to the data.

2. The permeating tracer curve is also extrapolated. In the case of an interstitial tracer like sucrose or the sodium ion, or a nonmetabolized tracer like
water, the curve is extrapolated from the last data point so that the area under the curve is identical to that of the reference curve. In the case of an extracted metabolized tracer, the procedure is less clear. In general, an extrapolation can be made in the same way as that for the reference curve. The recovery will be less than that of the reference. The set of Laguerre coefficients approximating the permeating tracer curve \( az_0, az_1, \ldots, az_N \) can then be found.

3. Parameter values are then assumed and Equation 19 of part 1 of the Appendix is used to calculate \( C(j\omega) \) at equal intervals over the frequency range. The spectrum \( W_0(s) \) required by Equation 19 is calculated from the Laguerre expression derived for the vascular reference, i.e.,

\[
W_0(s) = \sum_{n=0}^{N} a_n \frac{(p - s)^n}{(p + s)^{n+1}}
\]

with \( s = j\omega \). The real and imaginary part of the model response \( \Re Y \) and \( \Im Y \) are calculated with the library complex functions of the computer. The Laguerre coefficients of the whole organ model \( az_0, az_1, \ldots, az_N \) are found with Equation 47 and the performance index \( \sum(az_n - \bar{az}_n)^2 \) evaluated. Rosenbrock's method (1966) is used to improve parameter estimates until a minimum value of the performance index is reached.

4. A confidence interval is estimated for each of the unknown parameters. The largest error in the data is that due to the statistics of radioactive decay. We have assumed an average of 1% error in this measurement, based upon the number of disintegrations counted in each sample.

Part 3: Numerical Computations Necessary to Carry Out the Evaluations

The coefficients \( C_{n,i} \) of Equation 22 of part 2 of the Appendix may be computed recursively as follows:

\[
C_{0,i} = \frac{1}{n!}
\]

\[
C_{n+1,i} = \frac{(n - i)^2}{i + 1} C_{n,i}
\]

The elements of the vector \( f \) of Equation 43, which correspond to the exponentially extrapolated part of the response outlined in Equation 39, are given by the integral

\[
f_n = \int_{T}^{\infty} k e^{-\omega} \epsilon(t) \, dt
\]

\[
= k \sqrt{2p} \sum_{i=0}^{n} C_{n,i} \int_{T}^{\infty} e^{-\omega + p\tau}(2pt)^{n-1} \, d\tau.
\]

A change of variable leads to

\[
f_n = k \sqrt{2p} \sum_{i=0}^{n} C_{n,i} \frac{(2p)^{n-1}}{(a + p)^{n+1}} \int_{(a + p)T}^{\infty} e^{-\tau} \tau^{n-1} \, d\tau.
\]

Define

\[
I_k = \int_{(a + p)T}^{\infty} e^{-\tau} \tau^k \, d\tau.
\]

Integrating by parts leads to the recursion

\[
I_{k+1} = (a + p)^{k+1} e^{-(a + p)T} + (k + 1) I_k
\]

with \( I_0 = e^{-(a + p)T} \). To evaluate the integral of Equation 28 we write Equation 27 as

\[
y(t) = K_1 + K_2 t, k\Delta \leq t < k\Delta + \Delta
\]

where

\[
K_1 = y(k\Delta) - k[y(k\Delta + \Delta) - y(k\Delta)]
\]

\[
K_2 = \frac{y(k\Delta + \Delta) - y(k\Delta)}{\Delta}
\]

Integrating Equation 28 over the range of the data then requires the computation of

\[
\sqrt{2p} \sum_{i=0}^{n} C_{n,i} \int_{k\Delta}^{k\Delta + \Delta} [K_1 + K_2 t](2pt)^{n-1} e^{-\tau} \, d\tau
\]

\[
= \sqrt{2p} k \sum_{i=0}^{n} C_{n,i} 2^{i-1} \int_{k\Delta}^{k\Delta + \Delta} \tau^{n-1} e^{-\tau} \, d\tau
\]

\[
+ \sqrt{2p} k \sum_{i=0}^{n} C_{n,i} 2^{i-1} \int_{k\Delta}^{k\Delta + \Delta} \tau^{n-1} e^{-\tau} \, d\tau.
\]

Define

\[
II(k, m) = \int_{k\Delta}^{k\Delta + \Delta} \tau^{m} e^{-\tau} \, d\tau
\]

then,

\[
II(k, m + 1) = -(k\Delta + p\Delta)^{m+1} e^{-(k\Delta + p\Delta)}
\]

\[+ (k\Delta)^{m+1} e^{-k\Delta} + (m + 1)II(k, m)
\]

with

\[
II(k, 0) = e^{-(k\Delta + p\Delta)} - e^{-(k\Delta + p\Delta)}.
\]

This leads to

\[
\int_{k\Delta}^{k\Delta + \Delta} f_n(t)y(t) \, dt
\]

\[
= \sqrt{2p} \left[ (1 + k) \sum_{i=0}^{n} C_{n,i} 2^{n-i} II(k, n - i) \right. \overline{y(k\Delta)}
\]

\[+ \frac{1}{p\Delta} \sum_{i=0}^{n} C_{n,i} 2^{n-i} II(k, n - i + 1) \right] y(k\Delta)
\]

\[
- \frac{1}{p\Delta} \left[ k \sum_{i=0}^{n} C_{n,i} 2^{n-i} II(k, n - i) \right. \overline{y(k\Delta + \Delta)}
\]

\[+ \frac{1}{p\Delta} \sum_{i=0}^{n} C_{n,i} 2^{n-i} II(k, n - i + 1) y(k\Delta + \Delta) \]
where the coefficients of the terms \(y(k\Delta)\) and \(y(k\Delta + \Delta)\) correspond to the terms \(\alpha_{n,k}\) and \(\beta_{n,k+1}\) of Equation 41.

Finally, we suggest a method to handle the quadrature of Equation 46 in part 2 of the Appendix. We use the following approximation in the interval \(k\delta \leq \Omega \leq k\delta + \delta\):

\[
\frac{1}{\sqrt{\Omega^2 + 1}} = a + \beta(\Omega - k\delta), \quad a = \frac{1}{\sqrt{k^2\delta^2 + 1}},
\]

\[
\beta = \frac{1}{\delta} \left[ \frac{1}{\sqrt{(k + 1)^2\delta^2 + 1}} - \alpha \right],
\]

\[
\tan^{-1}\Omega \approx a + b'(\Omega - k\delta), \quad a = \frac{1}{\delta} \left[ \tan^{-1}(k + 1)\delta - a \right], \quad b' = -\left[ \tan^{-1}(k + 1)\delta - a \right]
\]

\[
\Re Y(j\Omega, p) \approx A + B(\Omega - k\delta), \quad A = \Re Y(jpk\delta, p), \quad B = \frac{1}{\delta} [\Re Y(jp(k + 1)\delta, p) - A]
\]

\[
\Im Y(j\Omega, p) \approx C + D(\Omega - k\delta), \quad C = \Im Y(jpk\delta, p), \quad D = \frac{1}{\delta} [\Im Y(jp(k + 1)\delta, p) - C].
\]

Letting \(P = (2n + 1)a, Qn = (2n + 1)b\delta\) and \(\Omega* = (2n + 1)b\delta\) there results:

\[
\int_{k\delta}^{k\delta + \delta} \Re Y(jpk\delta, p) \cos[(2n + 1)\tan^{-1}\Omega] \frac{d\Omega}{\sqrt{\Omega^2 + 1}} \approx \Re Y(jpk\delta, p) \cdot \cos P \left( \frac{\beta - a/\delta}{\Omega^*} \right) \cdot \left( \cos Qn - 1 \right) - \frac{\beta}{\Omega^* \delta} \sin Qn + \frac{2\beta}{\Omega^* \delta} \sin Qn - \frac{2\beta}{\Omega^* \delta} \sin Qn - \frac{2\beta}{\Omega^* \delta} \sin Qn - \frac{2\beta}{\Omega^* \delta} \sin Qn - \frac{2\beta}{\Omega^* \delta} \sin Qn - \frac{2\beta}{\Omega^* \delta} \sin Qn - \frac{2\beta}{\Omega^* \delta} \sin Qn - \frac{2\beta}{\Omega^* \delta} \sin Qn.
\]

\[
\Im Y(jpk\delta, p) \approx \Im Y(jpk\delta, p)
\]

From these results, the matrices DR and DI can be constructed.

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