Physiologic Smoothing of Blood Time-Activity Curves for PET Data Analysis

Michael M. Graham
Department of Radiology, Division of Nuclear Medicine, University of Washington, Seattle, Washington

Blood or plasma time-activity curves (TACs) are used as the input function for mathematical models of tracer kinetics in several applications including PET. Uncertainty associated with both the blood data and the PET tissue data can result in uncertainty in the estimates of metabolic rates, blood flow, etc. **Methods:** This article presents an approach to reduce the uncertainty in the blood TAC by fitting a model to the curve. The model includes a choice of bolus or infusion input and has three compartments (plasma, interstitial fluid and tissue fluid) with exchange between them. There is a parameter for loss from the plasma compartment. To test the utility of smoothing blood TACs with this approach, a program was set up, using the fluorodeoxyglucose (FDG) model, with simulated noisy blood and tissue TACs. The smoothed blood TAC was compared to a linearly interpolated TAC as the input function with a compartmental model parameter estimation program and with graphical analysis. **Results:** With a well sampled blood TAC (19 points), the model approach is somewhat more accurate than linear interpolation if the s.d. of noise added to the data exceeded 10%. With sparsely sampled blood TACs (five points) or with a large gap in the blood TAC, the modeled approach was markedly better. For graphical analysis, the model smoothed TAC was also more accurate, although, in general, the results were not as sensitive to the input function. **Conclusion:** This approach, using a physiologically reasonable model to smooth the blood TAC, is a useful aid in PET data analysis, particularly when the data are quite noisy or when there are large gaps in the data.

Key Words: kinetic analysis; blood sampling; PET

J Nucl Med 1997; 38:1161–1168

A commonly used approach in the analysis of tissue time series data obtained with positron tomography is parameter estimation. This technique requires an input function (typically arterial plasma activity determined at several times), a mathematical model (a set of differential equations describing the simplified kinetics of the radiotracer), reasonable starting guesses for the model parameters, a tissue time-activity curve (TAC) derived from the PET images and a program to manipulate the parameter values such that the output of the model achieves a "best" fit to the tissue data.

Considerable work has been done in the physics of PET imaging to ensure that the tissue data is as accurate as possible. Since both tissue and blood activity determine the final accuracy of the estimated parameters, it is important that the blood TAC also be as accurate as possible. The focus of this article is improving the accuracy of the blood TAC before using it as the input function in subsequent kinetic modeling.

A typical FDG plasma TAC is shown in Figure 1. The activity was injected as a bolus. It is apparent from examination of the curve that some errors have occurred in time of collection, dilution of the samples, pipetting or in counting that result in some irregularity of the curve. A common approach to dealing with this kind of data (which is typical of such blood time-activity curves) is to use linear interpolation between the points and assume the model will produce accurate parameter estimates.

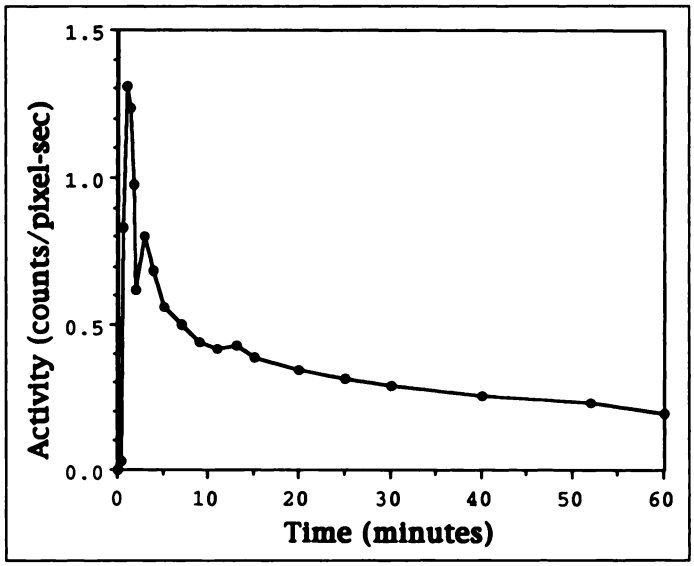

FIGURE 1. A typical plasma TAC from a patient after bolus injection of ^{18}F-FDG.

Another approach is to smooth the blood data so as to avoid the physiologically unlikely abrupt changes in slopes that occur with linearly interpolated data. Several different spline fitting approaches have been used for this task (*1,2*). An alternate approach is to use a reasonable kinetic model for the disappearance of tracers from the vascular space to smooth and interpolate the raw blood TAC data. Feng et al. (*3*) have proposed one such model. A somewhat different model is presented in this article. The input to the model can be either a bolus injection or an infusion for a specified time. The model includes several parameters that can be adjusted by hand or with a Marquardt-Levenberg optimizer to achieve a "best" fit to the blood TAC. A major advantage of this program is a convenient graphical interface that allows the user to easily adjust any parameter and see the effect of the change on the output. Overall, this is a simple, practical and effective approach for smoothing blood TACs.

MATERIALS AND METHODS

Model

The model used is shown in Figure 2. It depicts slowly varying plasma activity over several minutes for tracers such as fluorodeoxyglucose. It is not intended to model the first-pass kinetics of tracers such as ^{15}O-water. The bolus injection is simulated by a decaying exponential with an adjustable time constant. The constant infusion also incorporates exponentials on both the leading and trailing edges. The equations for the model with bolus input are:

$$V_p \frac{dC_p}{dt} = H * e^{-kt} - PS1 * (C_p - C_i) - GFR * C_p, \quad \text{Eq. 1}$$

Received Apr. 1, 1996; accepted Jul. 31, 1996.
For correspondence or reprints contact: Michael M. Graham, PhD, MD, Division of Nuclear Medicine, Box 356113, University of Washington, Seattle, WA 98195-6113.

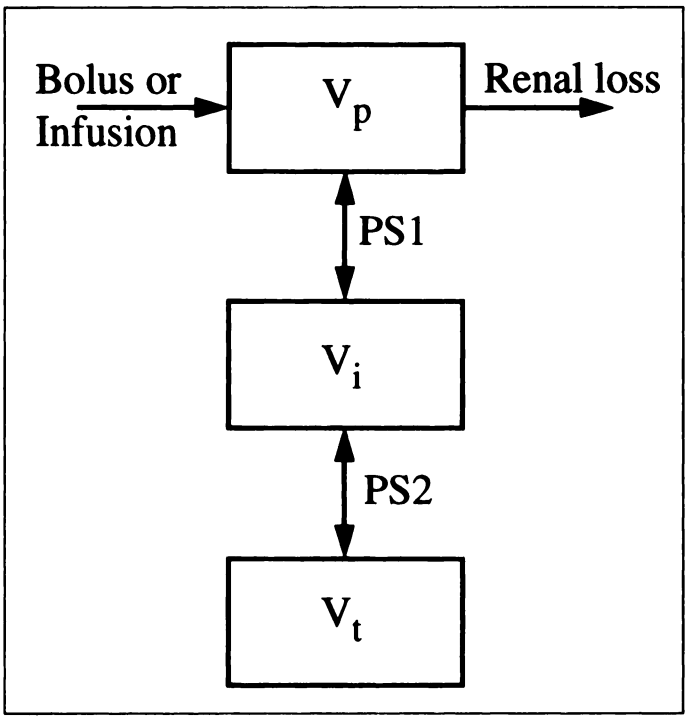

FIGURE 2. Model used to fit blood TAC.

$$V_i \frac{dC_i}{dt} = -PS1 * (C_i - C_p) - PS2 * (C_i - C_t), \quad \text{Eq. 2}$$

and

$$V_t \frac{dC_t}{dt} = -PS2 * (C_t - C_i). \quad \text{Eq. 3}$$

If the input is an infusion then the $H * e^{-kt}$ term is replaced by $H * (1 - e^{-kt})$ for the duration of the infusion and by $H' * e^{-kt}$ for the remaining time, where H' is the value of $H * (1 - e^{-kt})$ at the end of the infusion period. The other variables are defined as follows:

C_p is the concentration of tracer in plasma (μCi ml^{-1}); this is the output variable that must be adjusted to approximate the measured plasma activity.

C_i is the concentration of tracer in interstitial fluid (μCi ml^{-1}).

C_t is the concentration of tracer in tissue (μCi ml^{-1}).

V_p is the volume of plasma (ml g^{-1}).

V_i is the volume of interstitial fluid (ml g^{-1}).

V_t is the volume of tissue fluid (ml g^{-1}).

PS1 is the permeability-surface area product for exchange from V_p to V_i (ml min^{-1} g^{-1}).

PS2 is the permeability-surface area product for exchange from V_i to V_t (ml min^{-1} g^{-1}).

GFR is the glomerular filtration rate (i.e., the loss rate from the plasma) (ml min^{-1} g^{-1}).

H is the amount of activity infused per min (μCi min^{-1}).

Implementation

The model was implemented in Pascal on a Macintosh computer with the main interface screen as shown in Figure 3. The screen explicitly shows the model being used. The program is called B-Opt, since it is used to optimize the fit to blood TACs. In the input section (upper left) either bolus or infusion input is selected. The height, time constant, length of infusion and delay of output relative to blood activity are displayed. The values can be entered directly or changed with the slidebars. Note that the length of infusion has to be set. The other parameters shown in Figure 3 are all available for adjustment, and all can be "floated" during optimization. The checkboxes indicate a parameter will be adjusted during optimization. Each time a parameter is changed a new solution is displayed on the screen. The "%COV" displayed below the plot is the mean absolute percent difference between the model output and the data points. The "Accept" button is used to accept new values of parameters which have been typed into their associated boxes. The "Clear" button clears the screen of all old output and plots the current output. The steps per min for the model solution can be adjusted with the slidebar in the lower right. The

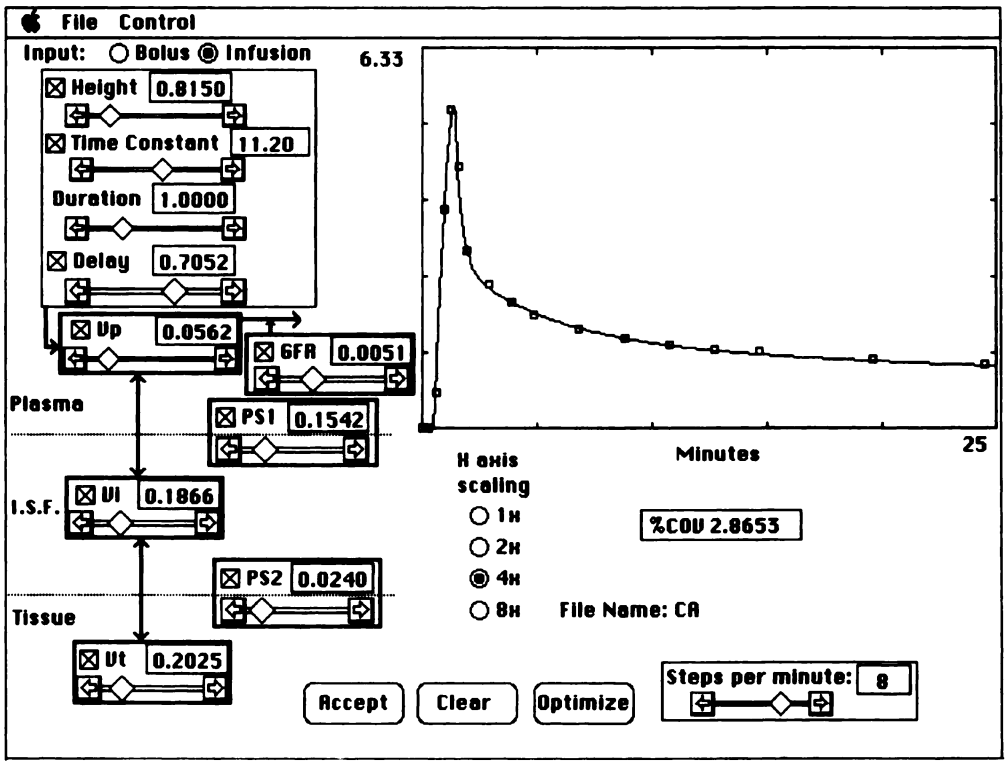

FIGURE 3. Control screen of the B-Opt program. The model used is explicitly shown. The input parameters are defined in the box in the upper left. All parameters are adjustable via the slidebars or by entering new values in the appropriate boxes. The checkboxes indicate that a parameter will be adjusted during optimization. The goodness of fit is shown by the average percent covariance (%COV), i.e., the average percent difference between the data points and the model output.

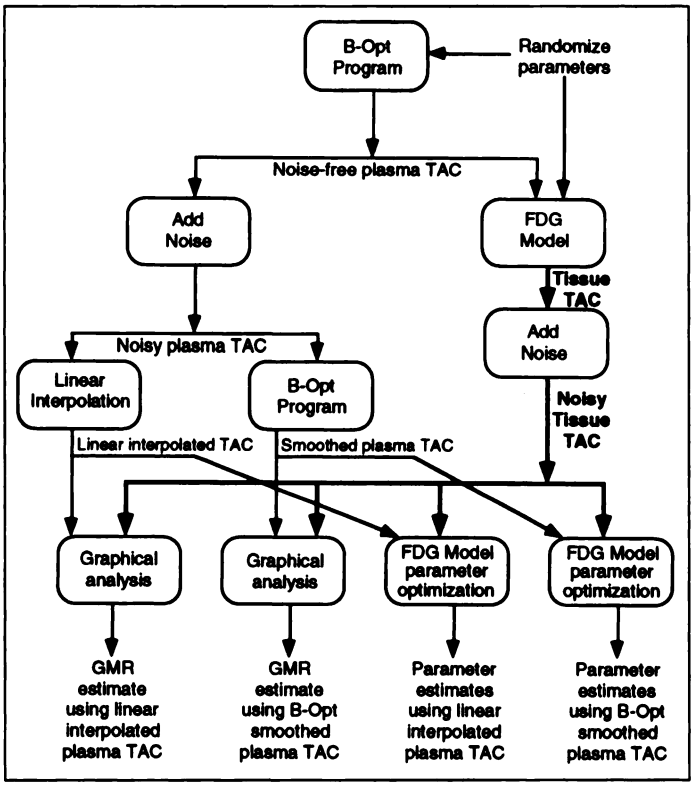

FIGURE 4. Flow diagram for the repeated simulations with noise. This sequence was repeated 100 times at each level of added noise.

horizontal scale can be expanded by selecting the appropriate "Radio" button to allow more detailed view of the early part of the data. The "Optimize" button invokes a Levenberg-Marquardt optimizer (*4*) to obtain a best fit of the model output to the data. Data is read in from tab-spaced text files that can be created with virtually any word processing or spreadsheet program. The fitted output can be saved as a similar text file for further use in subsequent modeling programs.

Simulation Tests

To test the utility of this approach for smoothing plasma TACs, a program was set up to compare the fitted, smoothed curves with simple linear interpolation. The scheme is illustrated in Figure 4.

1. By randomizing the model parameters, a smooth, noise-free, plasma TAC as in Figure 3, was generated through numerical integration of the differential Equations 1−3 above. The parameters were randomized ± 20% s.d. with a normal distribution around a set of parameters found for a typical patient FDG plasma TAC. This produced a wide range of different TACs, similar to those encountered in patient imaging. Either 19, 9 or 5 points were selected to form the blood TAC as follows:

   19 points: 20, 40 sec, 1, 2, 3, 4, 6, 8, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80 and 90 min.
   9 points: 30 sec, 1, 2, 3, 4, 5, 60, 70, 80 and 90 min. Note the large gap in the middle.
   5 points: 1, 2, 4, 40 and 90 min.

2. Using randomized parameters (20% s.d. variation around gray matter values) and the five-parameter model for FDG (*5*), a noise-free FDG tissue TAC was generated. The tissue TAC sample times were: 1, 2, 3, 4, 5, 7, 9, 11, 13, 16, 19, 22, 24, 33, 42, 51, 60, 70 and 80 min.
3. Different amounts (0%, 5%, 10%, 20%, 30% s.d.) of normally distributed noise was added to the plasma TAC.

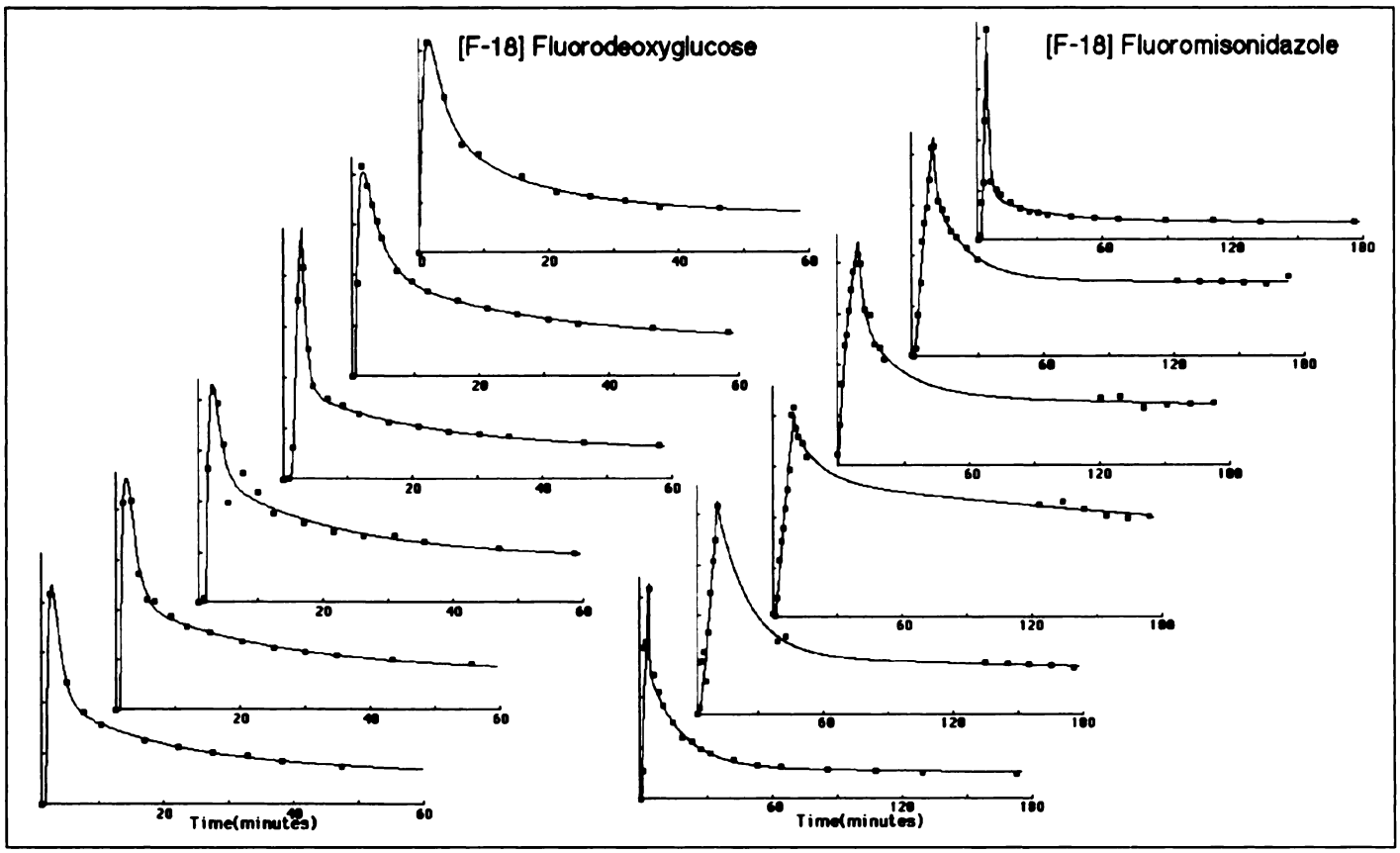

FIGURE 5. Typical [^{18}F]FDG and [^{18}F] fluoromisonidazole TACs from patients, along with the B-Opt best fits. Note that there are large gaps in some of the fluoromisonidazole datasets.

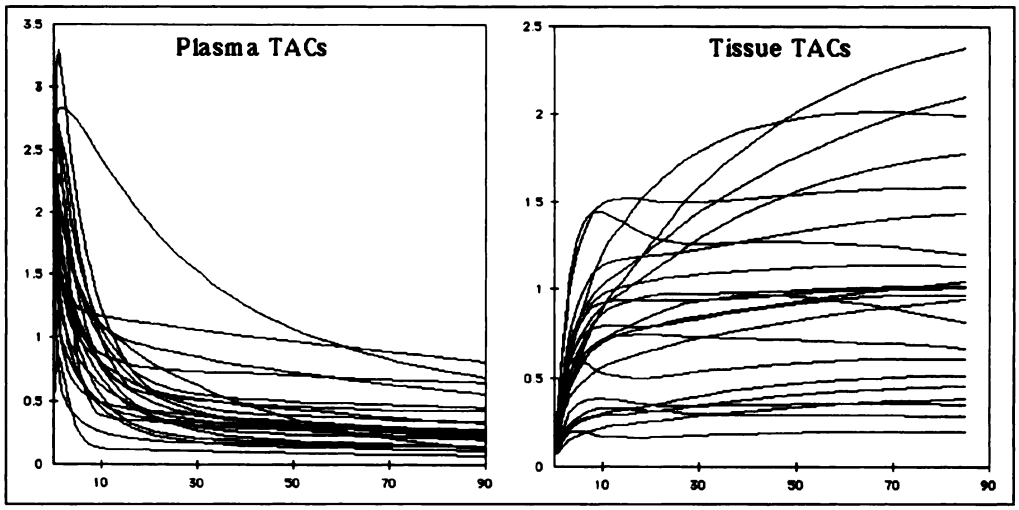

FIGURE 6. Typical simulated FDG blood and tissue curves used in the repeated simulations with noise. Noise was added to both the blood and tissue curves before analysis. The curves indicate the wide variety of curves that were included in the analyses.

4. Normally distributed noise was added to the FDG tissue points. The noise added was 10% for the early (1 min) time points and appropriately less noise (inversely proportional to the square root of the counts) was added to the longer, later time points.
5. The noisy plasma TAC was fit with the B-Opt program to create a smooth plasma TAC.
6. Both the fitted and linearly interpolated plasma TACs were used as input functions for subsequent parameter optimization using the FDG model to fit the noisy simulated FDG tissue data.
7. The results (parameter estimates and glucose metabolic rates) were saved.
8. Steps 1 through 7 were repeated 100 times at each level of added noise.

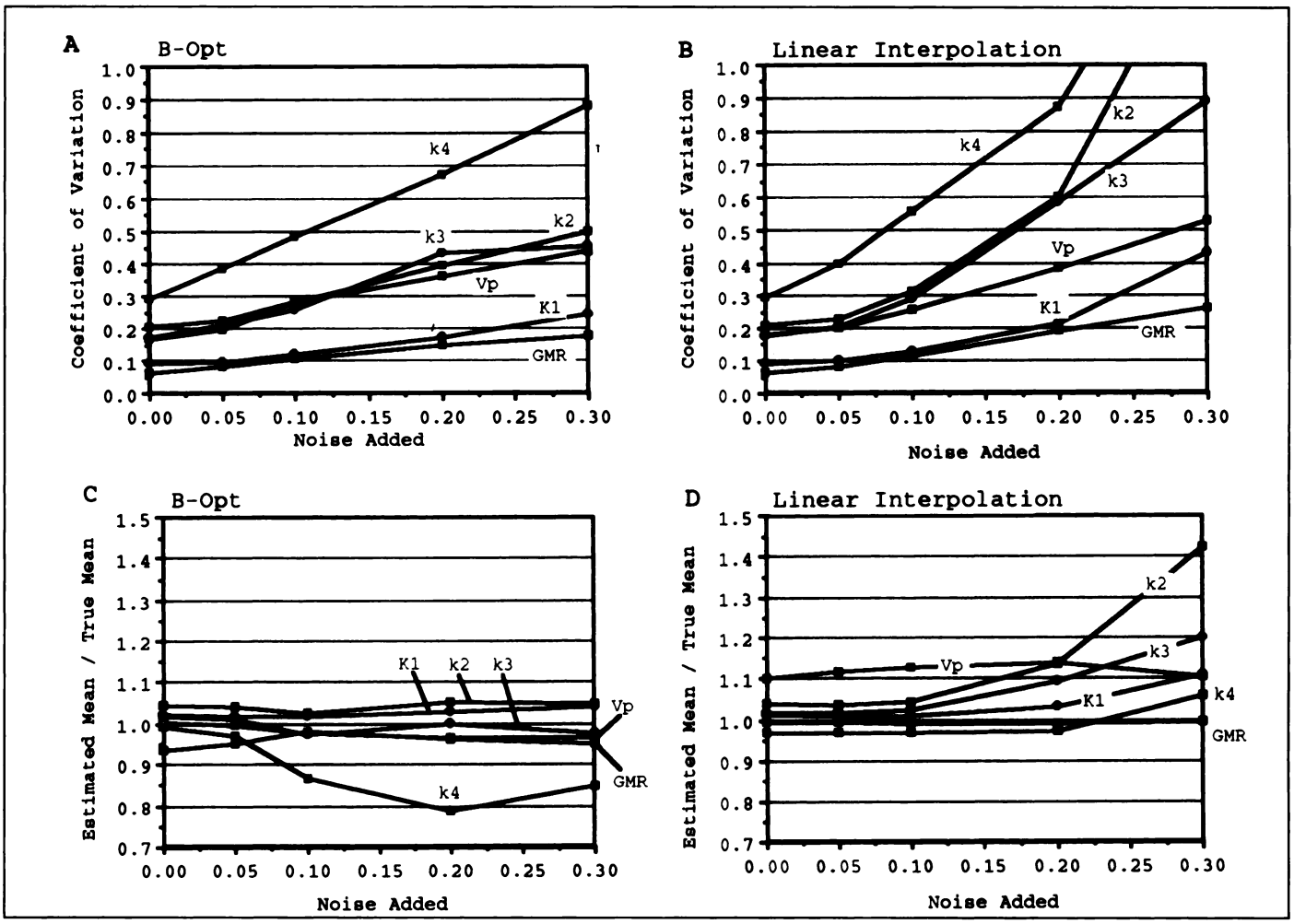

FIGURE 7. Results from the repeated simulations with noise of FDG plasma data after bolus injection of FDG with a frequently sampled curve (19 points). (A, B) The coefficients of variation (s.d./mean) of parameter estimates at different noise levels using the B-Opt program and linear interpolation, respectively, are shown. (C, D) The relative values of the mean parameter estimates as noise levels increase are shown.

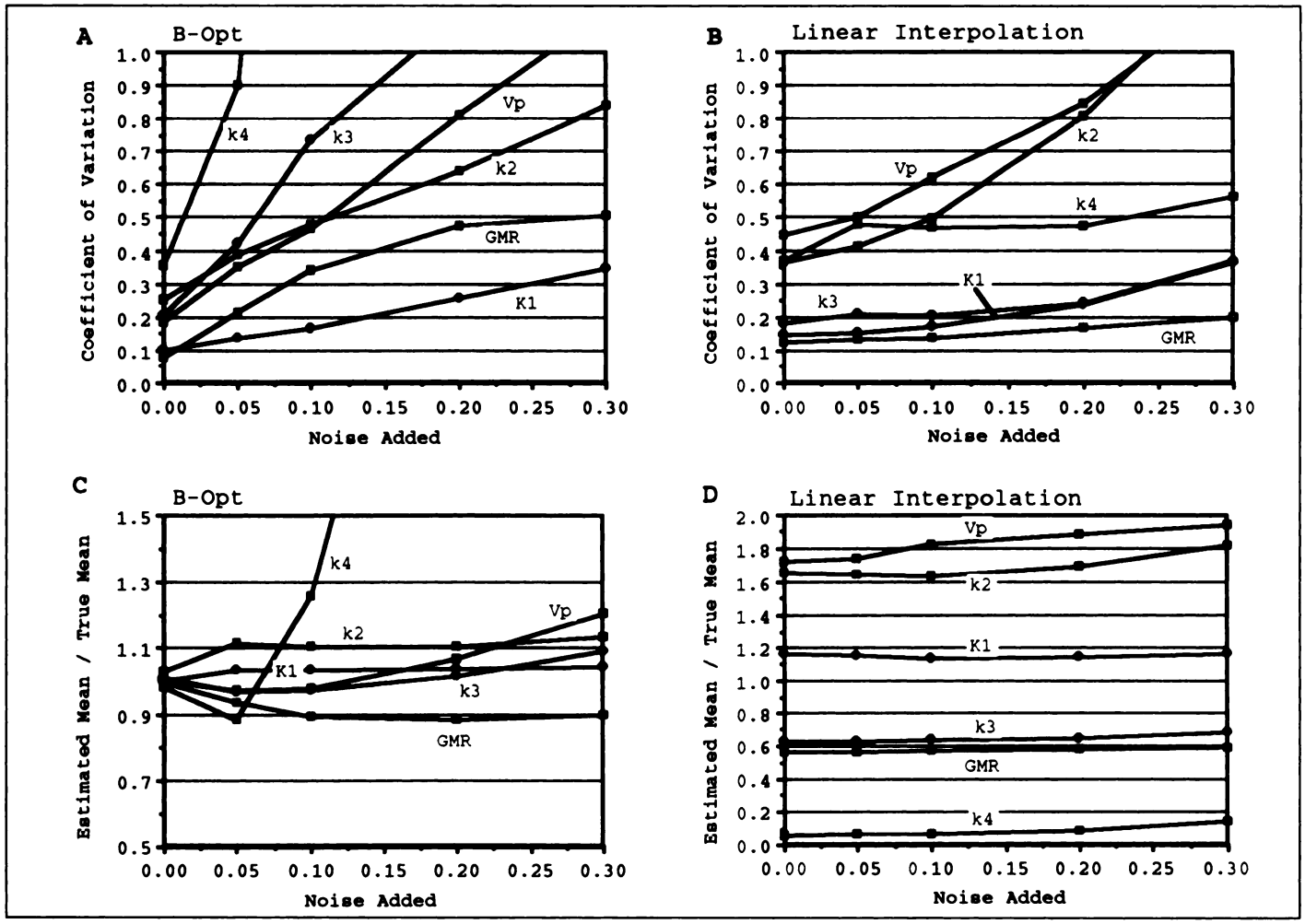

FIGURE 8. Results from the repeated simulations with noise of FDG plasma data after bolus injection of FDG with a curve containing a large gap in the middle (9 points: 30 sec, 1, 2, 3, 4, 5, 60, 70, 80, 90 min). (A, B) The coefficients of variation (s.d./mean) of parameter estimates at different noise levels using the B-Opt program and linear interpolation, respectively, are shown. (C, D) The relative values of the mean parameter estimates as noise levels increase are shown.

9. Similar datasets with k4 = 0 (B-Opt fitted and linearly interpolated blood TACs with noisy tissue TACs) were also analyzed by graphical analysis (*6,7*).

Statistical Analysis

Following the above simulations with noise, the means, s.d. and coefficients of variation (s.d./mean) for all parameters and glucose metabolic rate (GMR) were calculated as a function of added noise level.

RESULTS

Performance with Typical Datasets

B-Opt fits are shown for several sets of patient plasma TACs for [^{18}F]fluorodeoxyglucose and for several sets of blood TACs for [^{18}F]fluoromisonidazole (Fig. 5). The program has been able to produce good fits for all the FDG and fluoromisonidazole curves that have been examined. Approximately 250 FDG and 50 Fmiso curves have been examined.

Simulation Tests

Plasma TACs typical for FDG studies were produced as described in the methods section. A sample of the input functions is shown in Figure 6. Noise added to the plasma TAC points varied from 0%–30% s.d. The simulated tissue TACs were generated using the complete noise-free input plasma TACs with a range of parameter values centered on appropriate values for brain gray matter with s.d. of 20% for all parameters. Ten percent noise was added to the 1-min points of the simulated tissue TACs and appropriately less noise to longer points. One hundred iterations were done at each plasma TAC noise level.

Figure 7 shows that with 19 points in the blood TAC, B-Opt smoothing and linear interpolation give reasonably similar results. The coefficients of variation, i.e., the average error in parameter estimation, for the various tissue parameters of FDG is slightly worse with linear interpolation. Interestingly the B-Opt smoothing seems to introduce a small bias in the estimate of glucose metabolic rate, underestimating it for the noisy datasets, by about 5%. B-Opt smoothing resulted in a decrease in the coefficient of variation, especially when the plasma TAC noise was greater than 10%.

Figures 8 and 9 show that linear interpolation does not perform well if there are large gaps in the data (Fig. 8) or if there are very few data points (Fig. 9). In both simulations there were large errors in the parameter estimates using the linearly interpolated blood TACs. Except for k4, which was poorly estimated with both methods, the parameter estimates obtained with B-Opt smoothed blood TACs were much more accurate than with the linearly interpolated plasma curves.

Figure 10 shows that graphical analysis is not as sensitive to smoothing of the blood TAC but both the five-point and nine-point simulations result in more accurate estimates of glucose metabolic rate with the B-Opt smoothed TACs.

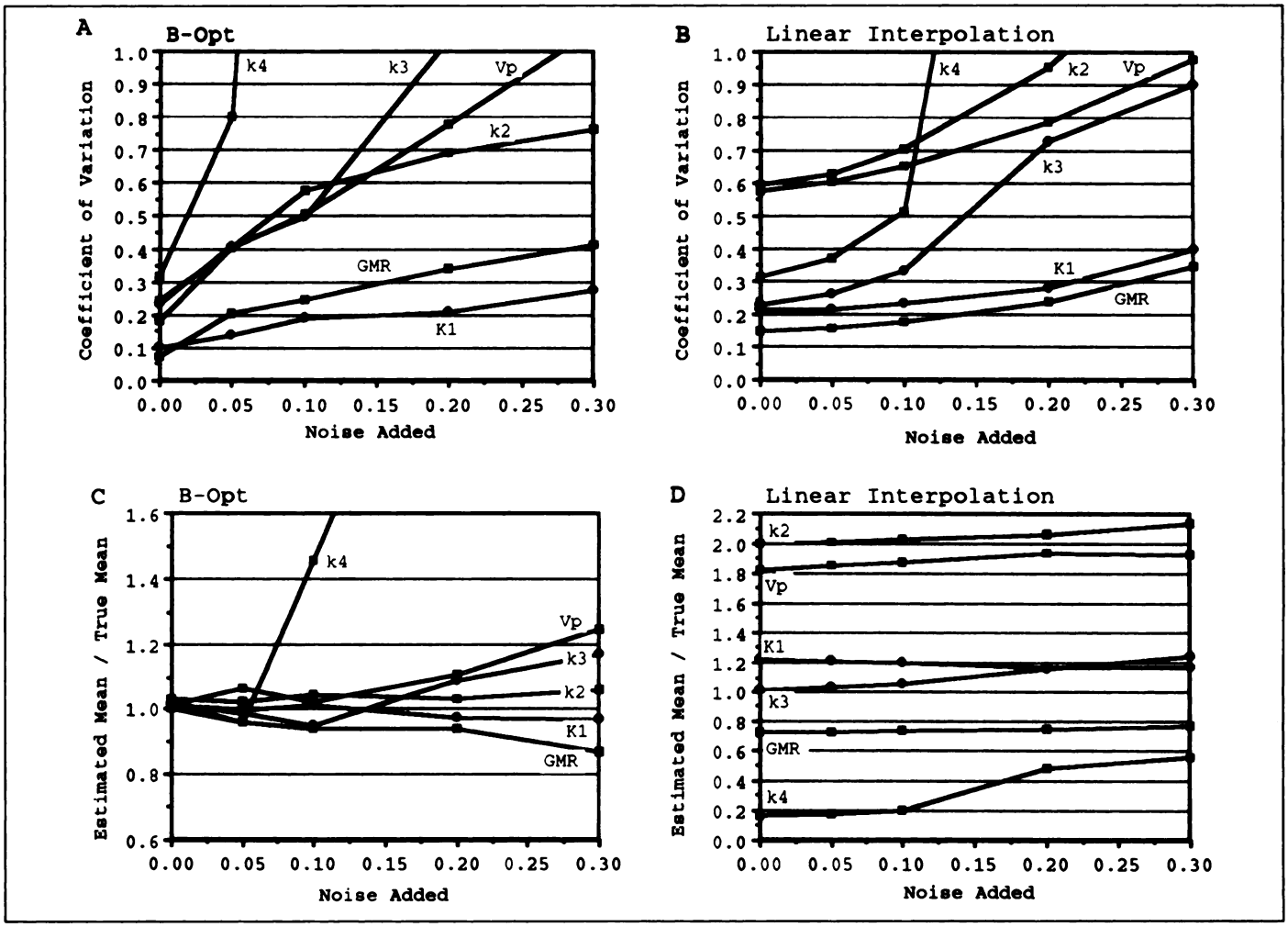

FIGURE 9. Results from the repeated simulations with noise of FDG plasma data after bolus injection of FDG with a sparsely sampled curve (5 points: 1, 2, 4, 40, 90 min). (A, B) The coefficients of variation (s.d./mean) of parameter estimates at different noise levels using the B-Opt program and linear interpolation, respectively, are shown. (C, D) The relative values of the mean parameter estimates as noise levels increase are shown.

DISCUSSION

Blood or plasma TACs are used as the input function in kinetic analysis of tracer residue functions (PET, probe studies, planar gamma camera imaging) and of outflow activity in studies of isolated perfused organs. The accuracy of the input function is as important as the residue or outflow activity in analyzing the data and in attempting to estimate model parameters describing the relationship between input and output (*8–10*). Because of a variety of potential problems, there is often significant noise added to the blood TAC. Sources of noise include: pipetting errors, dilution of samples, errors in timing, errors in decay correction and stochastic uncertainty in counting radioactive material. Some of these errors tend to be in only one direction (dilution, decay correction), while the others tend to be more or less random and should introduce no significant bias. The optimization scheme described in this article assumes the errors are essentially random.

In the past, there have been several approaches explored to smooth blood TACs. The simplest approach is to fit a reasonable mathematical function, such as a gamma variate (*11*), to the data. This works reasonably well in limited circumstances, such as cardiac first-pass studies with a well-formed bolus. A more general approach (*1,2*) is to use a series of functions to fit different portions of the curve with the constraint that the functions and the first and second derivatives must not change abruptly. Another important constraint is that the curve must always be convex upward during the late phase.

Chen et al. (*8*) have shown that an accurate physiologic model of the blood TAC results in more accurate subsequent parameter estimation than other smoothing methods. However, they do not present an explicit formulation of a model. Feng et al. (*3*) present a reasonable model incorporating venous and arterial mixing volumes which exchange material with an extravascular space. The extravascular space can exchange material with a tissue space from which loss can occur.

An alternative model is presented in this article. Inherent in this approach is continuity of the curve and its derivatives as well as upward concavity late in the study. This model is intended to describe the activity in blood over several minutes or hours after bolus injection or a short infusion of tracer. It does not include any provision for recirculation effects and thus is not appropriate for first-pass studies when recirculation may have a prominent role in defining the blood TAC.

The model begins with an input module that represents mixing in the central blood pool of the heart and lungs. The activity from the input module enters a vascular volume that exchanges with an extravascular pool which connects to a tissue pool. Loss from the vascular pool can occur, representing loss via the kidneys or any other loss mechanism such as biliary or pulmonary. This scheme for simulating a bolus input is equivalent to the gamma-variate function which has been shown to be

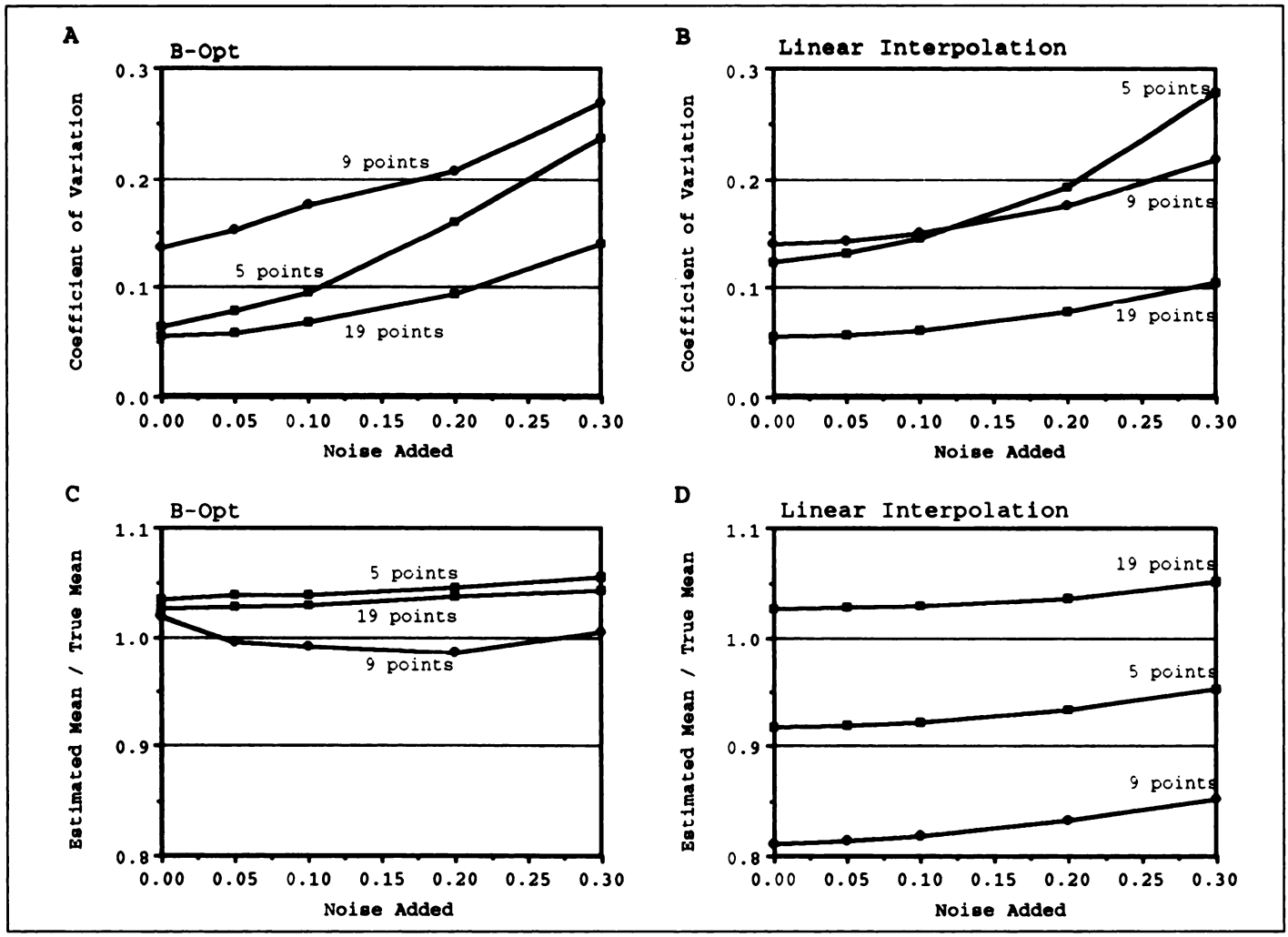

FIGURE 10. Results from the repeated simulations with noise of FDG plasma data after bolus injection of FDG. The same sampling sequences as defined in Figures 8, 9 and 10 were used. The tissue data was analyzed with graphical analysis to estimate glucose metabolic rate. (A, B) The coefficients of variation (s.d./mean) of parameter estimates at different noise levels using the B-Opt program and linear interpolation, respectively, are shown. (C, D) The relative values of the mean parameter estimates as noise levels increase are shown.

an excellent depiction of bolus TACs (*11*). When tested with gamma-variate data, the program achieved an exact fit with PS1 and PS2 equal to zero.

The differences between this model and that of Feng et al. (*3*) are relatively minor. The main advantages of this model are that it can easily handle both constant infusion or bolus inputs, and it has a more realistic incorporation of a loss term directly from the blood.

The situation where this approach for smoothing a blood TAC will not work well is when the injection is not a simple bolus or constant infusion. If the input is irregular, such as multiple small boluses of different sizes, then the assumption of a single bolus or infusion will clearly be wrong. In this instance, it may be sufficient to use a short constant infusion to simulate the multiple small boluses, but this will inevitably result in some error in the early part of the curve. The preferred approach is to use a consistent method of injection, such as an infusion pump.

The results show that for fluorodeoxyglucose, the B-Opt approach to smoothing the plasma TAC generally results in an improvement in the accuracy of parameter estimation. In actual practice, the results are likely to be somewhat different: possibly worse because the underlying curve may be shaped differently than the model curve, or better because the operator will exercise judgement about the adequacy of the fit. In the repeated simulations at different noise levels, the optimizer occasionally got stuck in a local minimum, thus missing the actual best fit of the global minimum. If a human operator was supervising the fit, they would recognize the fit was not adequate, adjust a few parameters and try again. This was not feasible during these simulations with 100 iterations each time. For the types of curves fitted by the model (smooth, single bolus injection or constant infusion with abrupt start and stop), the B-Opt program should do very well in smoothing the blood TAC and improving the final parameter estimates. As the input functions begin to differ from these two possibilities, the ability of the program to perform useful smoothing will be degraded.

The results, since they were based on simulated data generated with the B-Opt model, presumably favor smoothing with the B-Opt model during data analysis. This is certainly to be expected, but it is difficult to devise an alternative way to generate the test data. Because of the problem of getting stuck in local minima, the B-Opt approach might actually do worse. There were certainly examples where this was the case, but in spite of this, overall, it achieved good fits and improved parameter estimates. The range of parameter values explored resulted in a broad range of curves (Fig. 6) and should be

sufficient to represent most of the possibilities for blood TACs and FDG metabolic rates in brain.

Graphical analysis (Fig. 10) is apparently not as sensitive to the accuracy of the input function as parametric estimation. This likely stems from its dependency primarily on the integral of the blood TAC. The main problem that arises in graphical analysis is that with linear interpolation there is a consistent bias in the estimated glucose metabolic rate, particularly when there are relatively few data points. This is a result of the fact that linear interpolation results in an overestimate of the area under the typically convex blood TAC which, in turn, results in an underestimate in the glucose metabolic rate.

The reader should be aware that although the modeling scheme presented here is a reasonable physiologic description of tracer blood TACs, it is not guaranteed to be correct for all tracers. For instance, many tracers when examined closely, particularly at relatively long times after injection, will continue to have a slight upward convexity when plotted on semilogarithmic paper (*12*). Compartmental models, such as the B-Opt model, will always have simple exponential behavior at late times. This late upward convexity is presumably because of tissue heterogeneity and of the distributed nature of exchange that is not accounted for in a compartmental model. Other tracers may bind to proteins, either intravascularly or within tissue. Intravascular binding can result in biphasic curves (*13*) that cannot be accounted for with the B-Opt model. In some circumstances, these errors may be significant. In many practical situations involving blood TACs obtained as part of a PET study, the advantage of this scheme for smoothing outweighs the small error that might be introduced by an incorrect model. However, as with most modeling tools, the reader should be familiar with the behavior of the tracer being modeled before using this program.

There is nothing unique about the B-Opt model that makes it significantly better than any of the other approaches for smoothing blood TACs. It is a physiologically reasonable way to smooth most blood TACs. It will be most useful when there is noisy data or when there are significant gaps that need bridging. The main advantage of this approach is that it has a particularly convenient interface and is quite convenient to use. It is also widely available in that it can be downloaded over the Internet from "ftp.u.washington.edu" (Password is "anonymous"; directory is "pub/user-supported/positron"). A 68000 version is in the file named "P-Opt B-Opt.sea.hqx". A PowerPC version will also be posted.

The following approaches to improve the program performance are currently being explored: (a) determine the mean parameter values for a particular tracer and start at these values; (b) explore reparameterization of the model to define combinations of parameters that will lead to more efficient optimization; (c) explore different sequences of selection of which parameters to float. It is likely the process will work better if only 3–4 parameters are floated at one time; and (d) as other optimizers become available, they will be tested in the program. Some optimization approaches, such as simulated annealing (*14*) apparently do much better in finding the global minimum than simpler optimizers such as the Levenberg-Marquardt.

Another enhancement we are working on is to extend this approach to metabolized tracers and their metabolites. Huang et al. (*15*) have proposed this approach in studies of dopamine and its metabolites. We are beginning to develop such a model for thymidine and its metabolites (*16*), including carbon dioxide. This should be a particularly appropriate use of blood curve modeling, since it is impossible to obtain large numbers of samples of metabolites labeled with short-lived radiotracers, such as ^{11}C which has a $T_{1/2}$ of 20 min.

CONCLUSION

The B-Opt model is a reasonable physiologic approach for smoothing blood time-activity curves. The resultant fits are useful for subsequent modeling using the B-Opt output as the input function for fitting tissue residue or outflow data with another program. The PET investigators at the University of Washington have been using this approach for the past 4 yr and have found it to be convenient to operate and that it yields excellent fits to fluorodeoxyglucose and fluoromisonidazole blood TACs.

ACKNOWLEDGMENT

This study was supported by National Institutes of Health grant CA42045.

REFERENCES

1. Bassingthwaighte JB, Chan IS, Goldstein AA. An efficient method for smoothing indicator-dilution and other unimodal curves. *Comput Biomed Res* 1988;21:192–202.
2. Beyer RP. Fitting smooth curves to noisy indicator-dilution and other unimodal data. *Comput Biomed Res* 1992;25:144–152.
3. Feng D, Huang SC, Wang X. Models for computer simulation studies of input functions for tracer kinetic modeling with PET. *Int J Biomed Comput* 1993;32:95–110.
4. Press WH, Flannery BP, Teukolsky SA, Vetterling WT. *Numerical recipes in Pascal.* New York: Cambridge University Press; 1989:574–590.
5. Hawkins RA, Phelps ME, Huang SC. Effects of temporal sampling, glucose metabolic rates and disruptions of the blood-brain barrier on the FDG model with and without a vascular compartment: studies in human brain tumors with PET. *J Cereb Blood Flow Metab* 1986;6:170–183.
6. Patlak CS, Blasberg RG, Fenstermacher JD. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. *J Cereb Blood Flow Metab* 1983;3:1–7.
7. Gjedde A. Calculation of cerebral glucose phosphorylation from brain uptake of glucose analogs in vivo: a re-examination. *Brain Res Rev* 1982;4:237–274.
8. Chen KW, Huang SC, Yu DC. The effects of measurement errors in the plasma radioactivity curve on parameter estimation in positron emission tomography. *Phys Med Biol* 1991;36:1183–1200.
9. Feng D, Wang X. A computer simulation study on the effects of input function measurement noise in tracer kinetic modeling with PET. *Comput Biol Med* 1993;23: 57–68.
10. Feng D, Wang X, Fulton R, Hutton B, Morris J. Effects of tracer blood measurement noise on glucose metabolic rate estimation. *Biomed Sci Instrum* 1991;27:43–48.
11. Davenport R. The derivation of the gamma-variate relationship for tracer dilution curves. *J Nucl Med* 1983;24:945–948.
12. Bassingthwaighte JB, Beard DA. Fractal ^{15}O-labeled water washout from the heart. *Circ Res* 1995;77:1212–1221.
13. Graham MM, Nelp WB. Cardiac blood pool activity after in vivo and in vitro red blood cell labeling [Abstract]. *J Nucl Med* 1980;21:P7.
14. Kirkpatrick S, Gelatt CD Jr, Vecchi MF. Optimization by simulated annealing. *Science* 1983;220:671–680.
15. Huang SC, Barrio JR, Yu DC, et al. Modeling approach for separating blood time-activity curves in positron emission tomographic studies. *Phys Med Biol* 1991;36:749–761.
16. Shields AF, Mankoff D, Graham MM, et al. Analysis of 2-carbon-11-thymidine blood metabolites in PET imaging. *J Nucl Med* 1996;37:290–296.