Challenging Problems in PET Imaging

Estimating the Input Function for a Human Brain FDG-PET Study
A Feasibility Study

Dr. Hongbin Guo, Prof. Rosemary A. Renaut

Department of Mathematics and Statistics,Arizona State Univerisity

Dr. Kewei Chen

Banner Good Samaritan PET center, Phoenix

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OUTLINE

1. Our Goal - FDG Parameter Estimation -What is this?.
2. Methods to find the input function.
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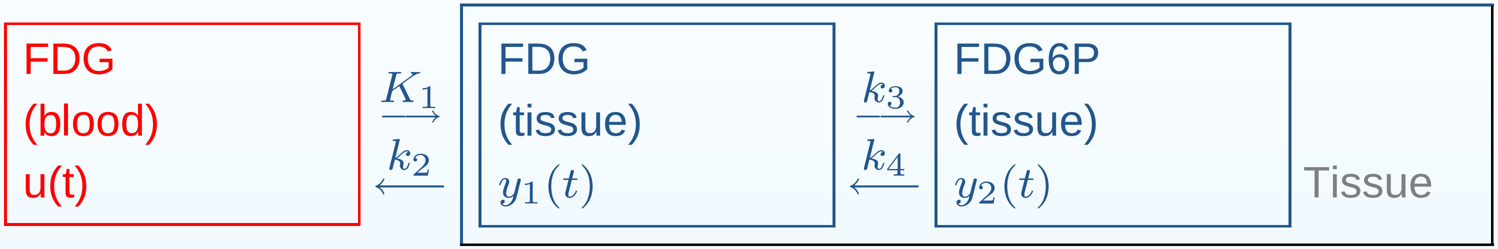
6. Results of Linear Model with ICA defined ROI
7. Conclusion - the Future

1. Ultimate Goal

Automated tool for parametric estimation of brain function for Alzheimer’s Disease studies.

The FDG Tracer Model: What is it?

Input $u(t)$- FDG in blood–measured blood samples;
Output $y(t) = y_1(t) + y_2(t)$, FDG and FDG6P in tissue–from PET images.



$$
\begin{aligned}
\dot{y}_1 &= K_1 u(t) - (k_2 + k_3) y_1(t) + k_4 y_2(t) \\
\dot{y}_2 &= k_3 y_1(t) - k_4 y_2(t).
\end{aligned} \tag{1}
$$

- K_1 and k_2–FDG transport rate
- k_3 and k_4 phosphorylation and dephosphorylation rate.
- LCMRglc: $\frac{K_1 k_3}{k_2+k_3}\frac{C_p}{LC} = K\frac{C_p}{LC}$, a sensitive neuroimaging marker for AD.
- Given $u(t)$ and $y(t)$, estimate K_1, k_2, k_3, k_4 and K.

Solution of the FDG Tracer Model: it is easy!

Denote $\mathcal{K} = (K_1, k_2, k_3, k_4)$,

$$y(t) = u(t) \otimes \left(c_1(\mathcal{K}) e^{-\lambda_1(\mathcal{K})t} + c_2(\mathcal{K}) e^{-\lambda_2(\mathcal{K})t} \right),$$

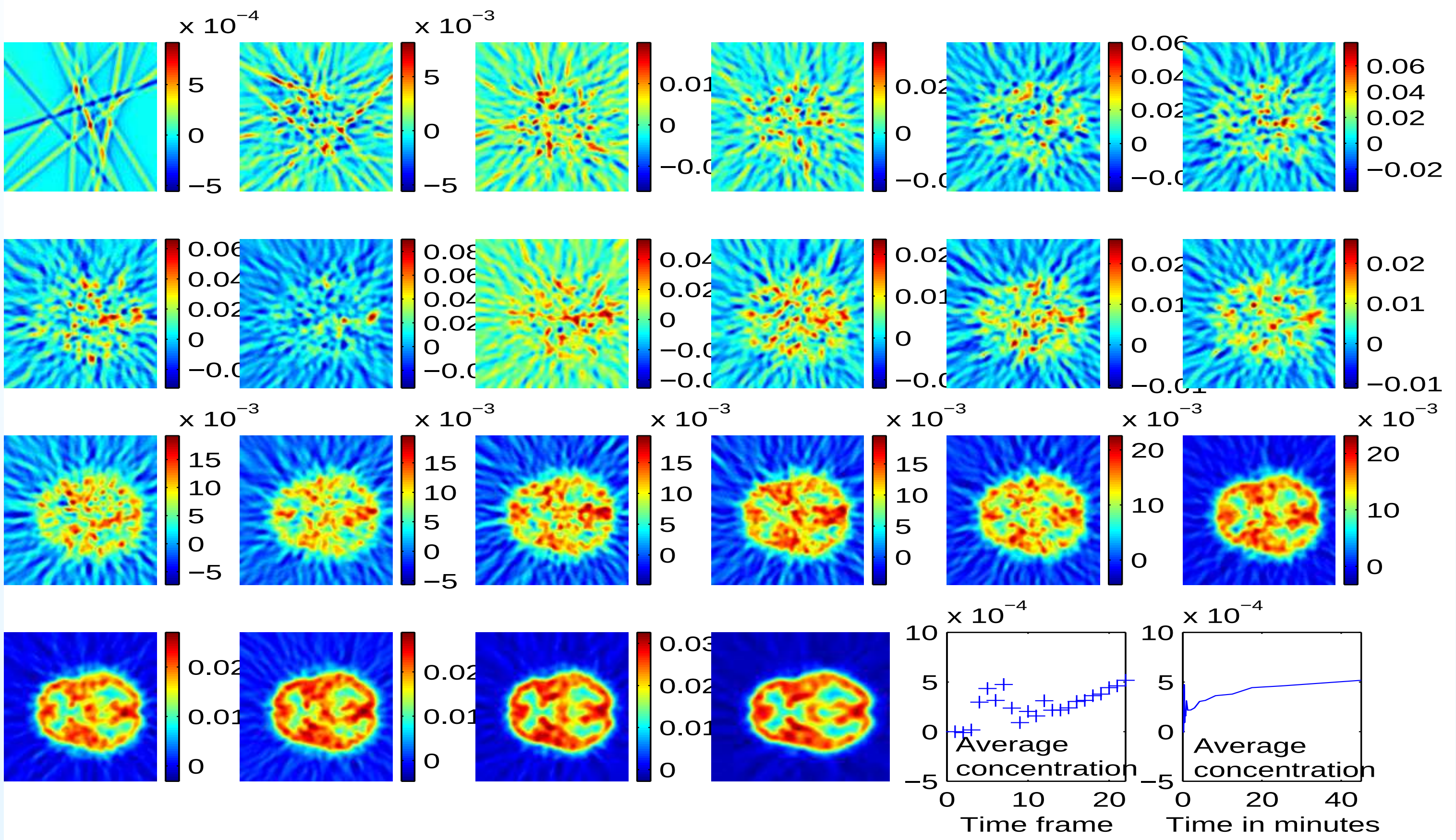
where $\otimes$ stands for convolution.

Parameter k_4 is set to 0, because it is relatively very small and the scanning time, 60 minutes, is not long enough to provide a reliable estimate of k_4, [Huet]. Then

$$y(t) = u(t) \otimes \left(\frac{K_1 k_3}{k_2 + k_3} + \frac{K_1 k_2}{k_2 + k_3} e^{-(k_2+k_3)t} \right). \qquad (2)$$

It is easy to solve the problem to find the parameters given the input function $u(t)$ and the output function $y(t)$, when the data are clean and equally spaced!

Consider data: Images of One Slice over Time



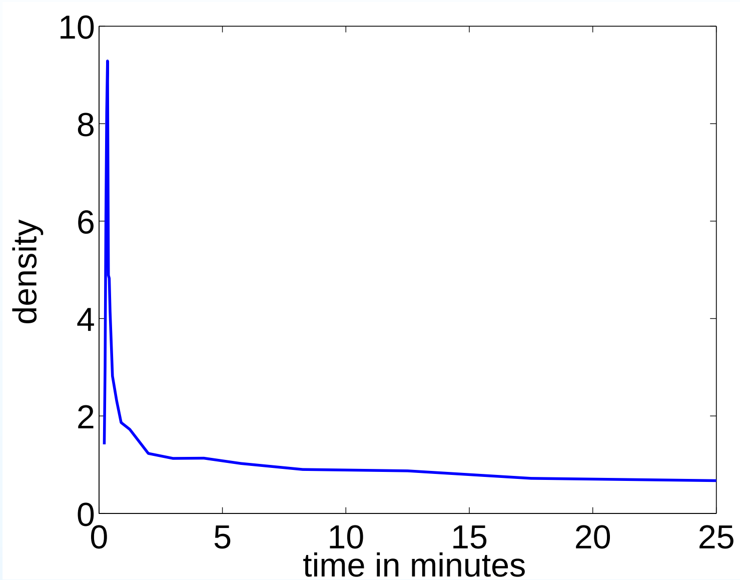
The Reconstructed PET data over one hour. Time Space Dynamics for slice 16 over 22 time intervals.

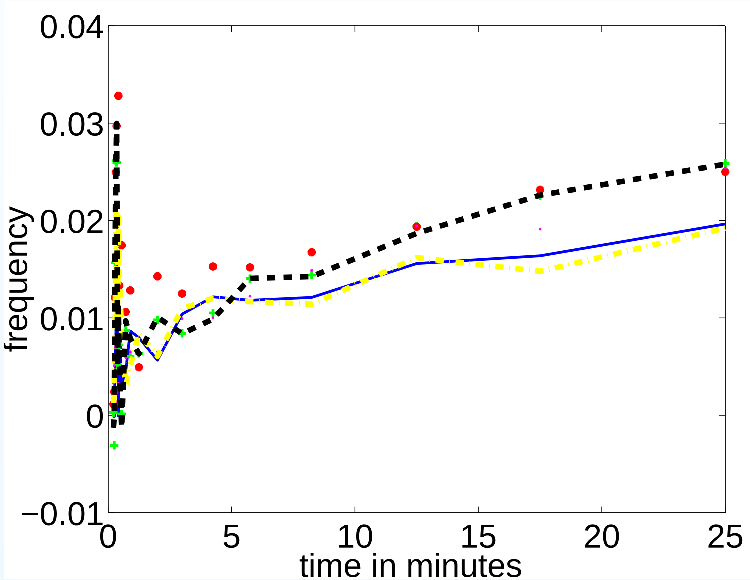
Issues with this parameter estimation problem

1. Expression for the input function - what is this exactly?
2. Noise in the output: estimation is made difficult because noise is corrrelated
3. Clustering of data Optimization is assisted by using constraints on the parameters
4. Model Simplification Actual model used is more complicated.
5. Cost Volumetric data analysis is expensive,

Emphasis here on the input function step

Representative input/output



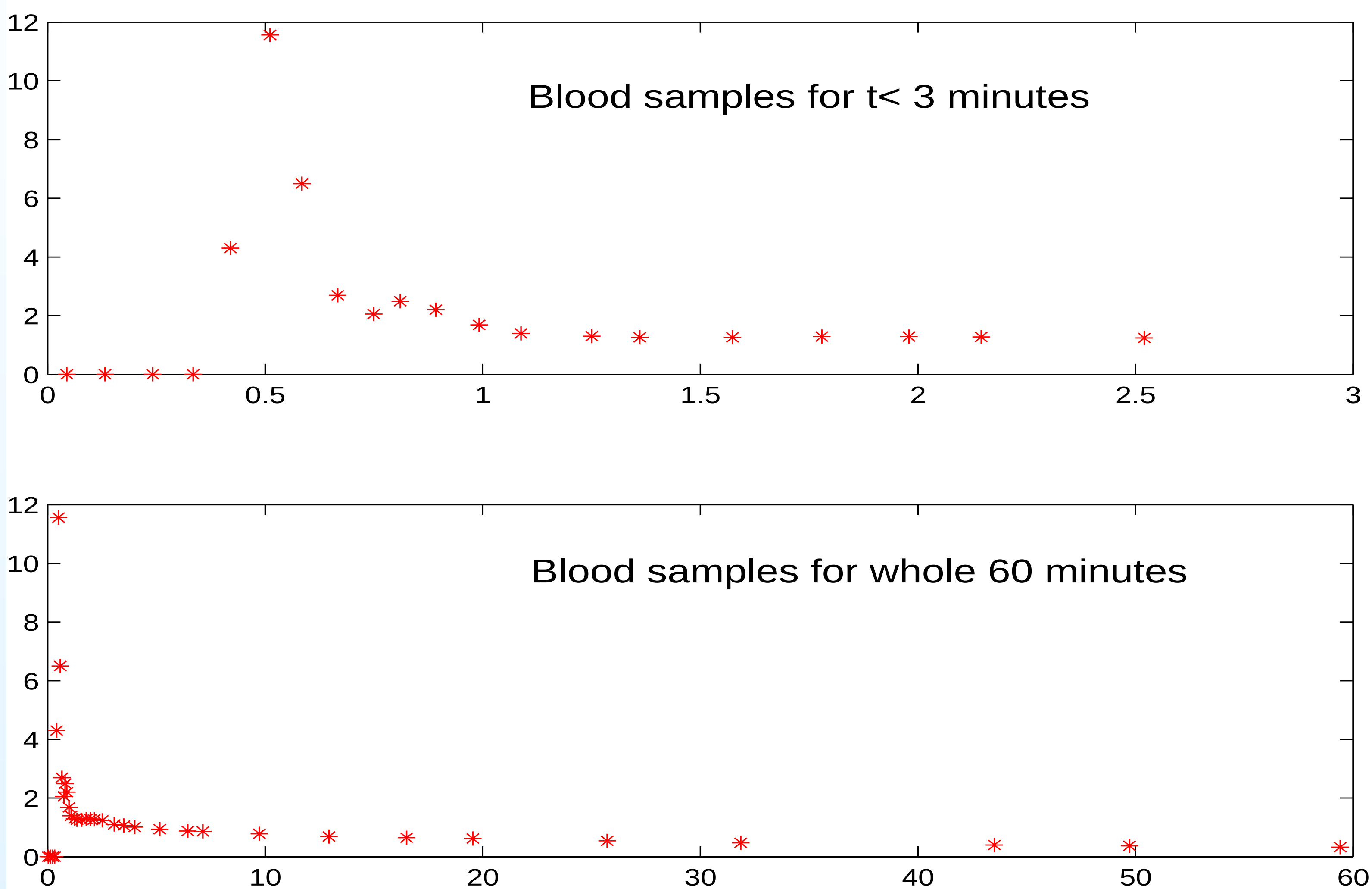


Left:input Function $u(t)$;

Right: output functions $y(t)$ for 6 pixels.

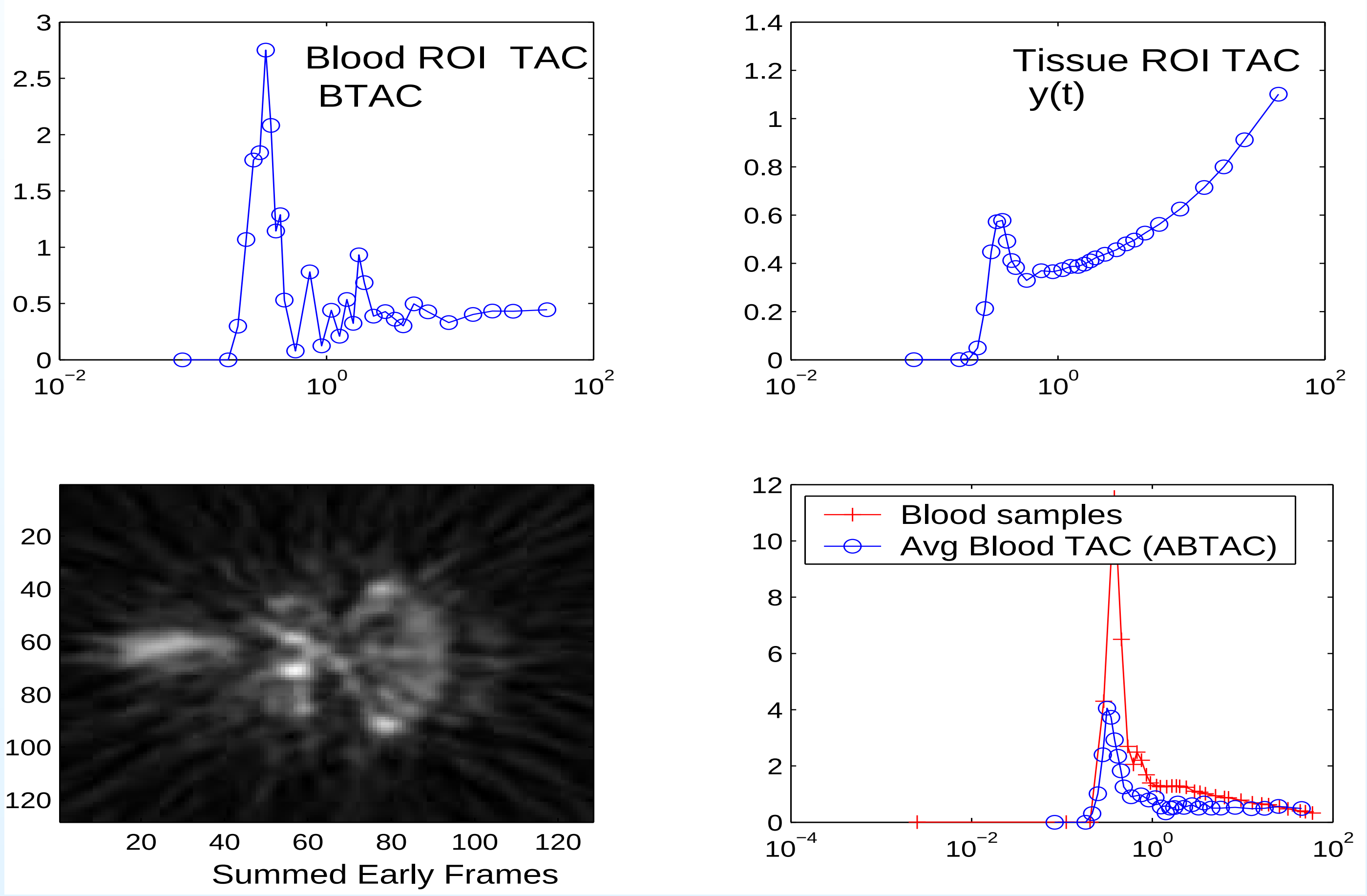
The data are only illustrated through time $t_{21} = 25m$.
The functions change little over the last scanning duration,
$\Delta t_{22} = 30m$.

Measured Input Function–Arterial Blood Samples

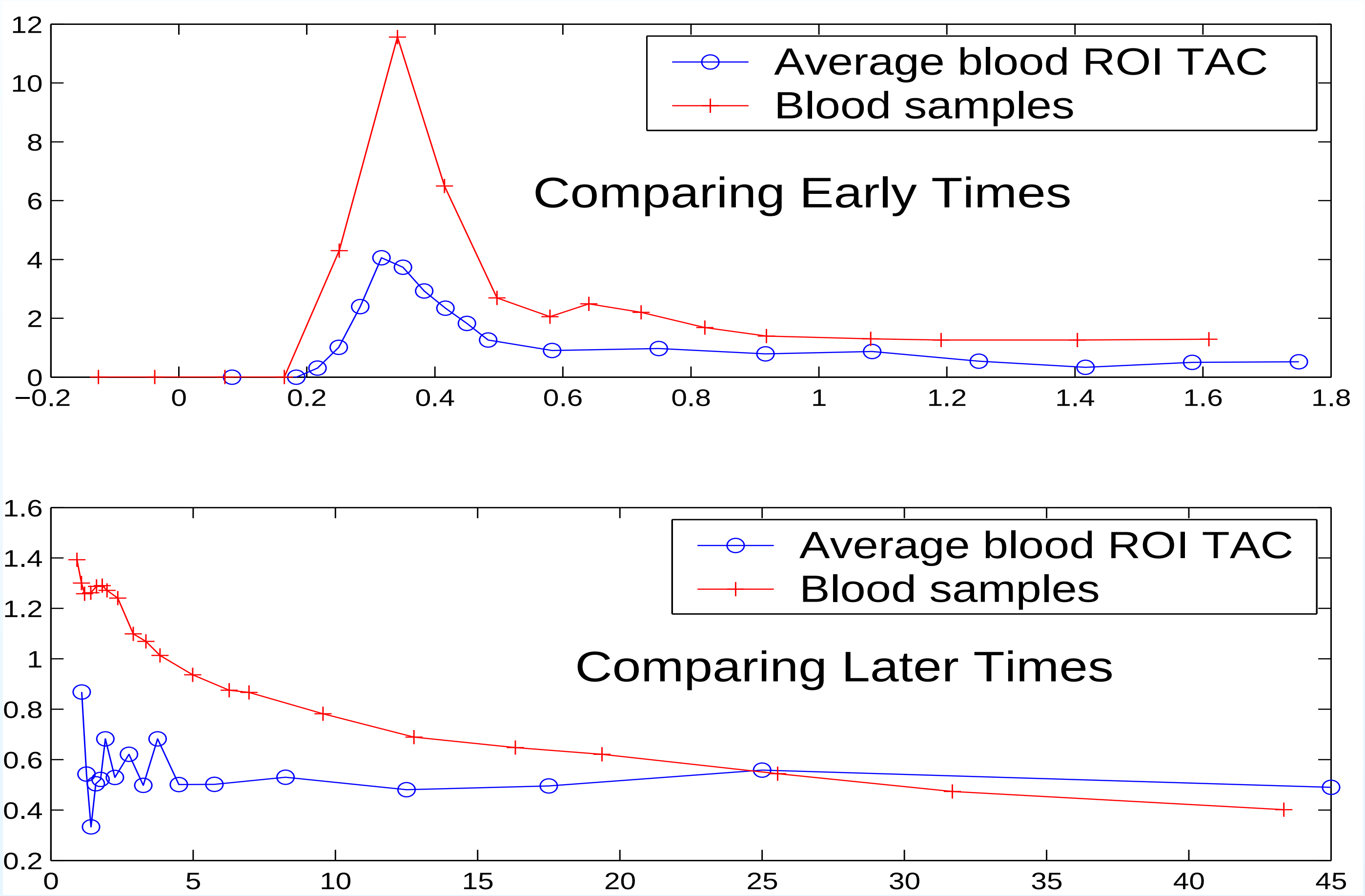


Arterial blood samples, $u_{bs}(t_j), j = 1, 2, \cdots, 34.$

Illustrating the Difficulty: Time Activity Curves of Blood and Tissue Regions



Time Activity Curve From Blood ROI



2. Some Methods for Identifying the Input

1. **Golden Standard:**, arterial sampling.
   Causes discomfort, potential problems of arterial thrombosis, arterial sclerosis, and ischemia to the extremity.
2. Arterialized venous sampling method:
   limb is heated to avoid the discomfort,([Phel],1979), still needs frequent blood sampling
3. Population based input function, ([Taki],1993 and [Eberl],1997).
   Fit arterial or arterialized venous samples from subject population samples to an analyt expression.
   Estimated input function does not show differences between individuals.
4. An Imaged-derived input function, Only corrects partial volume effects of the Average Blood TAC (ABTAC). ([Litt],1997; [Lipt],2004)

5. Imaged-derived input function correcting partial volume and spillover effects. ([Chen],1998). Linear Model:

$$ABTAC(t) = \alpha \cdot u(t) + \beta \cdot y(t).$$

6. Simultaneous Estimation, SIME. Two models of the input:
   - $$u(t) = (A_1 t - A_2 - A_3)e^{\lambda_1 t} + A_2 e^{\lambda_2 t} + A_3 e^{\lambda_3 t}.$$

     Simultaneously estimate A_i, λ_i and k_j by deconvolution, [Feng],1997.
   - $$u(t) = \alpha \cdot ABTAC(t) + A \cdot te^{-\lambda t},$$

     α is determined by three blood samples at 20, 40 and 60 minutes by least squares.
     Simultaneously estimate A, λ and k_j by deconvolution,[SanBo],2003.
     Ignore the spillover effects in later window of $ABTAC(t)$.

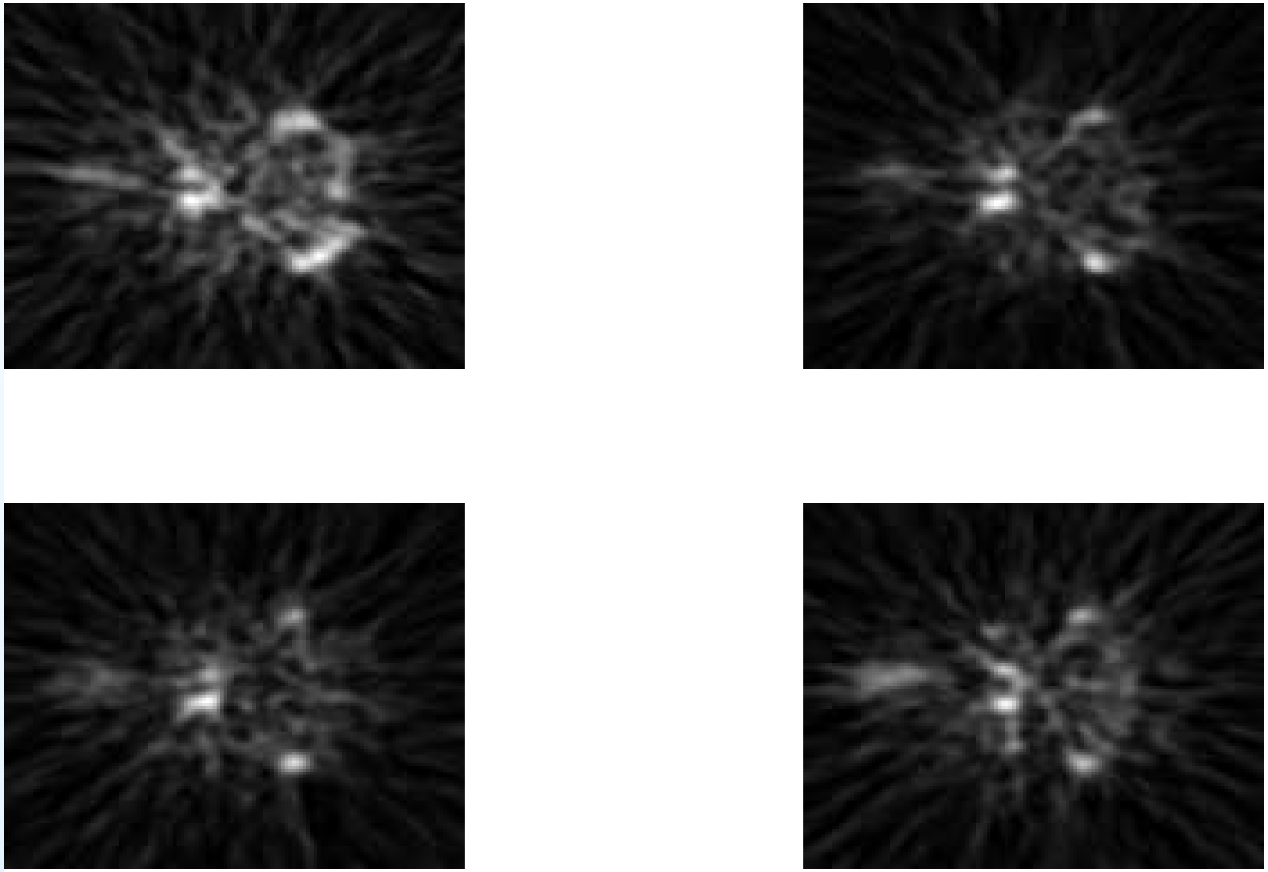
3. Development of a Novel Simultaneous Estimate Algorithm

A new image-derived SIME method. To express the input function $u(t)$ we partition the time interval into two regions. An early window and a late window. *In the early window* we use *information from BTAC* and correct the partial volume effects, and *in the late window* we *fit three blood samples*. This fitting avoids using the later window of the BTAC. Only the reliable information from the early window on the BTAC is used for the estmation.

Data Acquisition

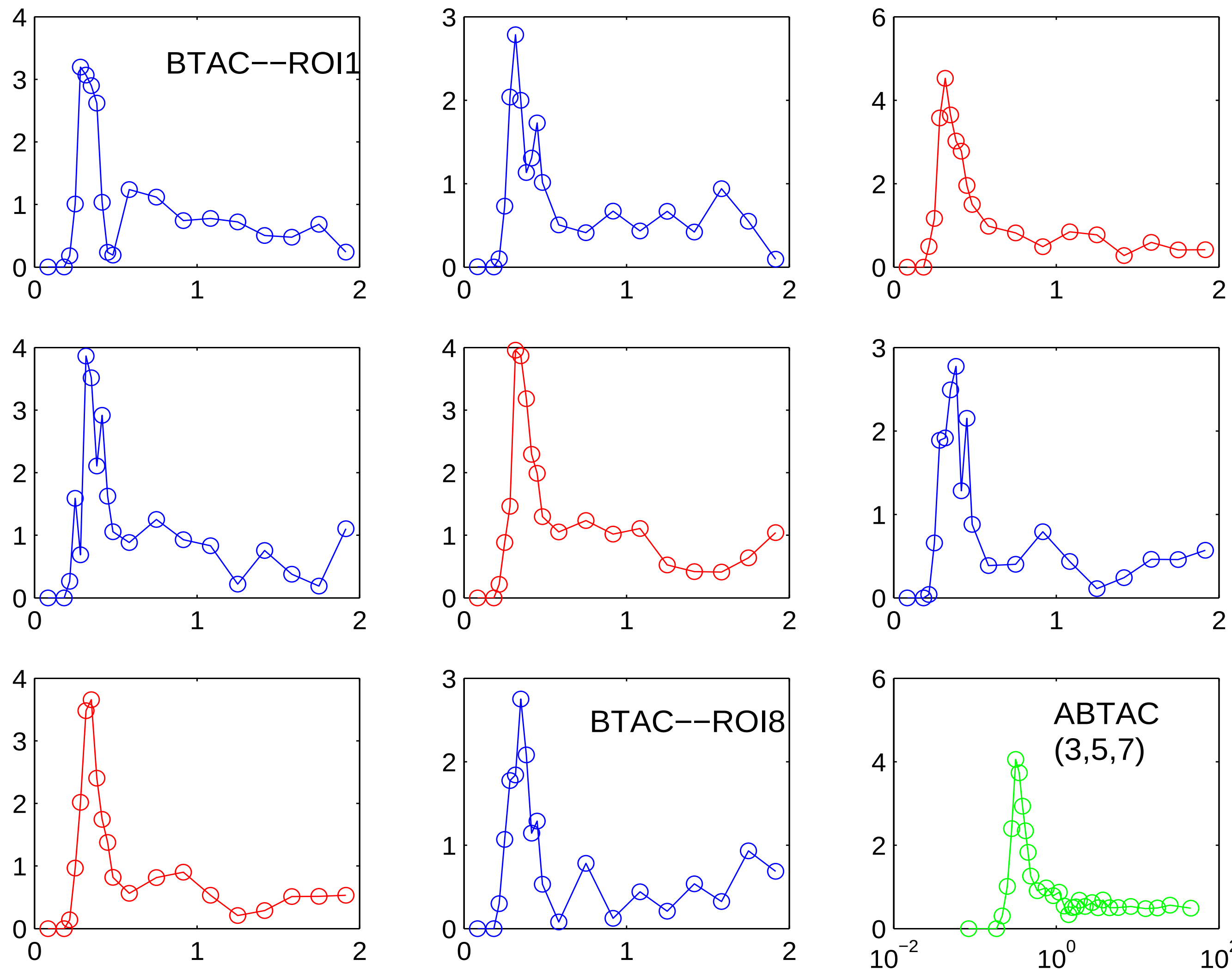
- Data from 20 healthy subjects are used for this study.
- Filtered back projection is used for image reconstruction (*out of our control*) Each reconstructed data set includes 31 slices with 3.375 mm separation and each slice has 128×128 voxels with resolution of approximately 9.5 mm full width at half maximum(FWHM).
- The scanning time durations in minutes for frames are $0.2, 8 \times 0.0333, 2 \times 0.1667, 0.2, 0.5, 2 \times 1, 2 \times 1.5, 3.5, 2 \times 5, 10$ and 30.
- Sequential arterial blood samples are drawn every 5 seconds for the first minute, every 10 seconds for the second minute, every 30 seconds for the next 2 minutes, then at 5, 6, 8, 10, 12, 15, 20 , 25, 30, 40, 50 and 60 minutes, $u_{bs}(t_j)$, $j = 1, 2, \cdots, 34$.

Summation of early Frames to emphasize Blood ROI



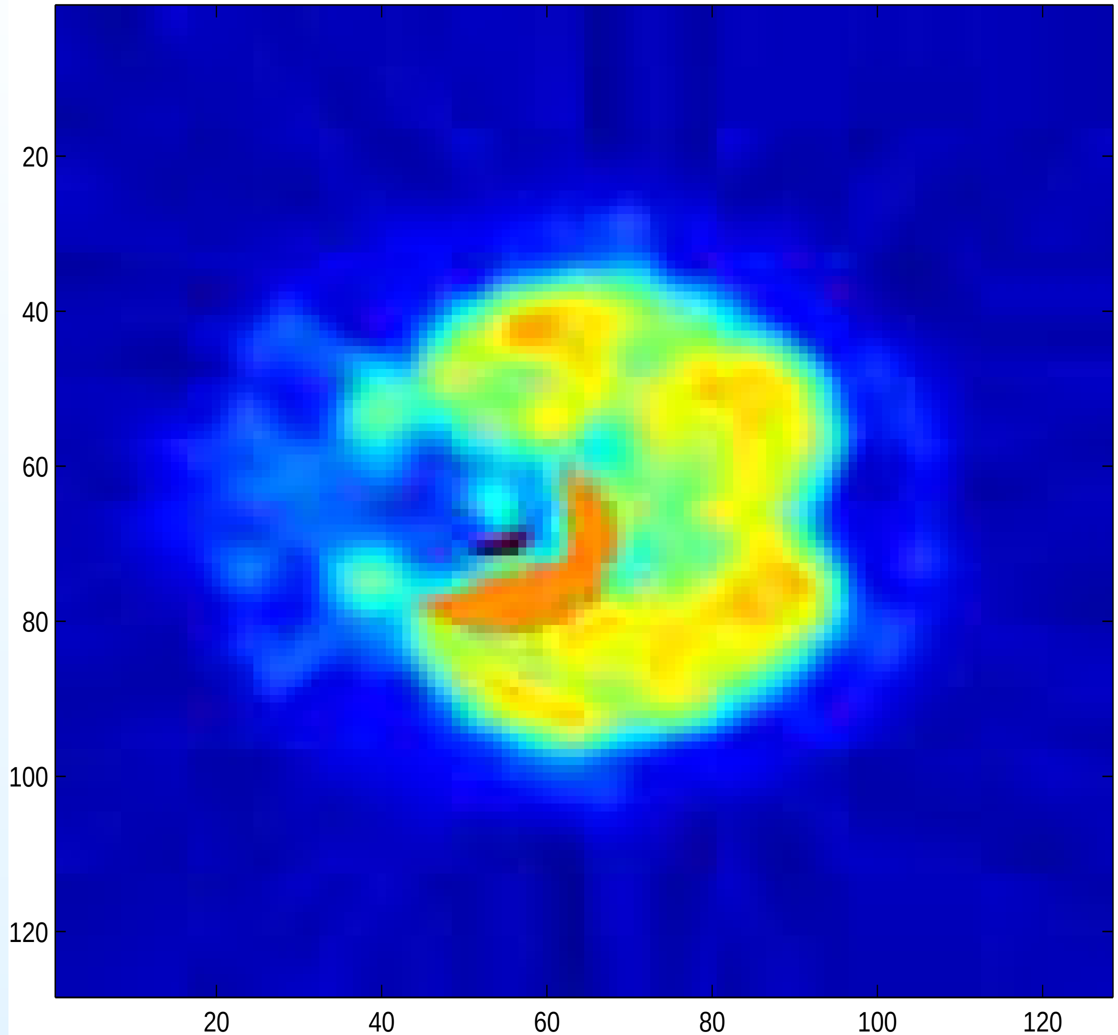
Summed frames for t<48 seconds, slice 25 to 28

The Blood ROI TACs Different Slices



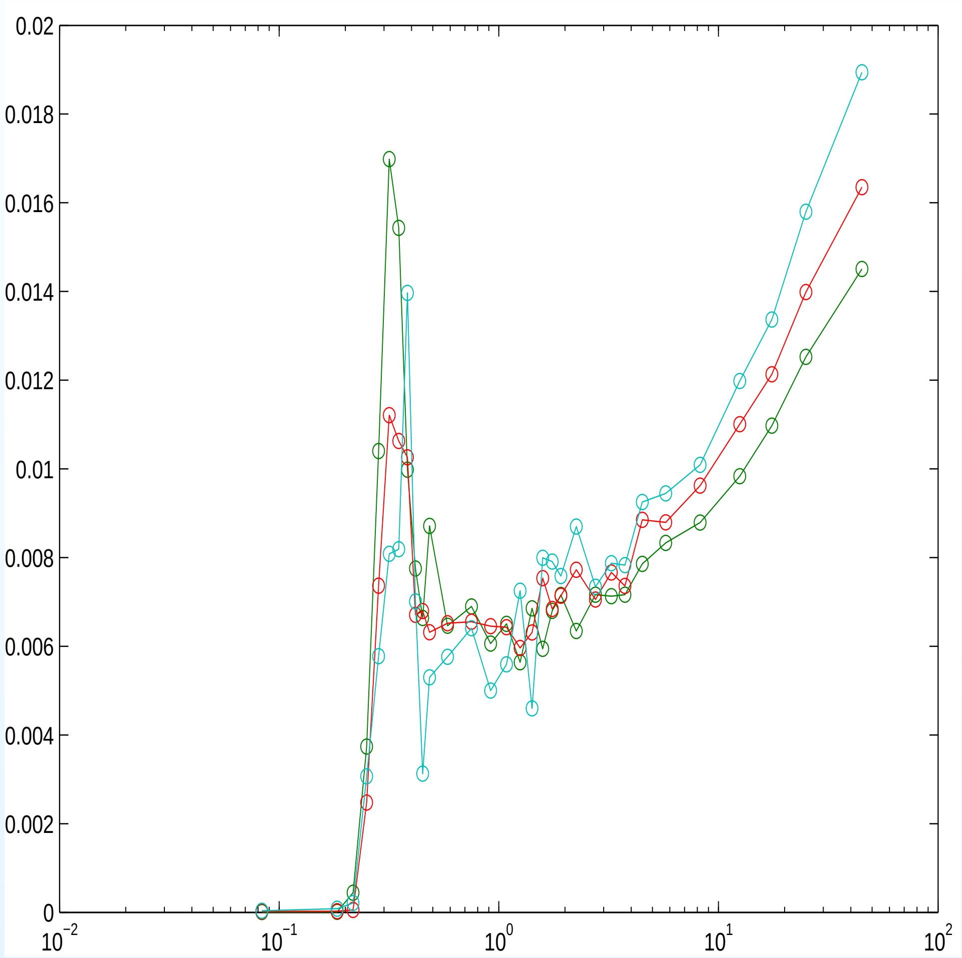
Early window of 8 Blood ROI TACs. ABTAC=Average 3rd, 5th and 7th TACs.

Neighboring Tissue ROI- to estimate Spillover



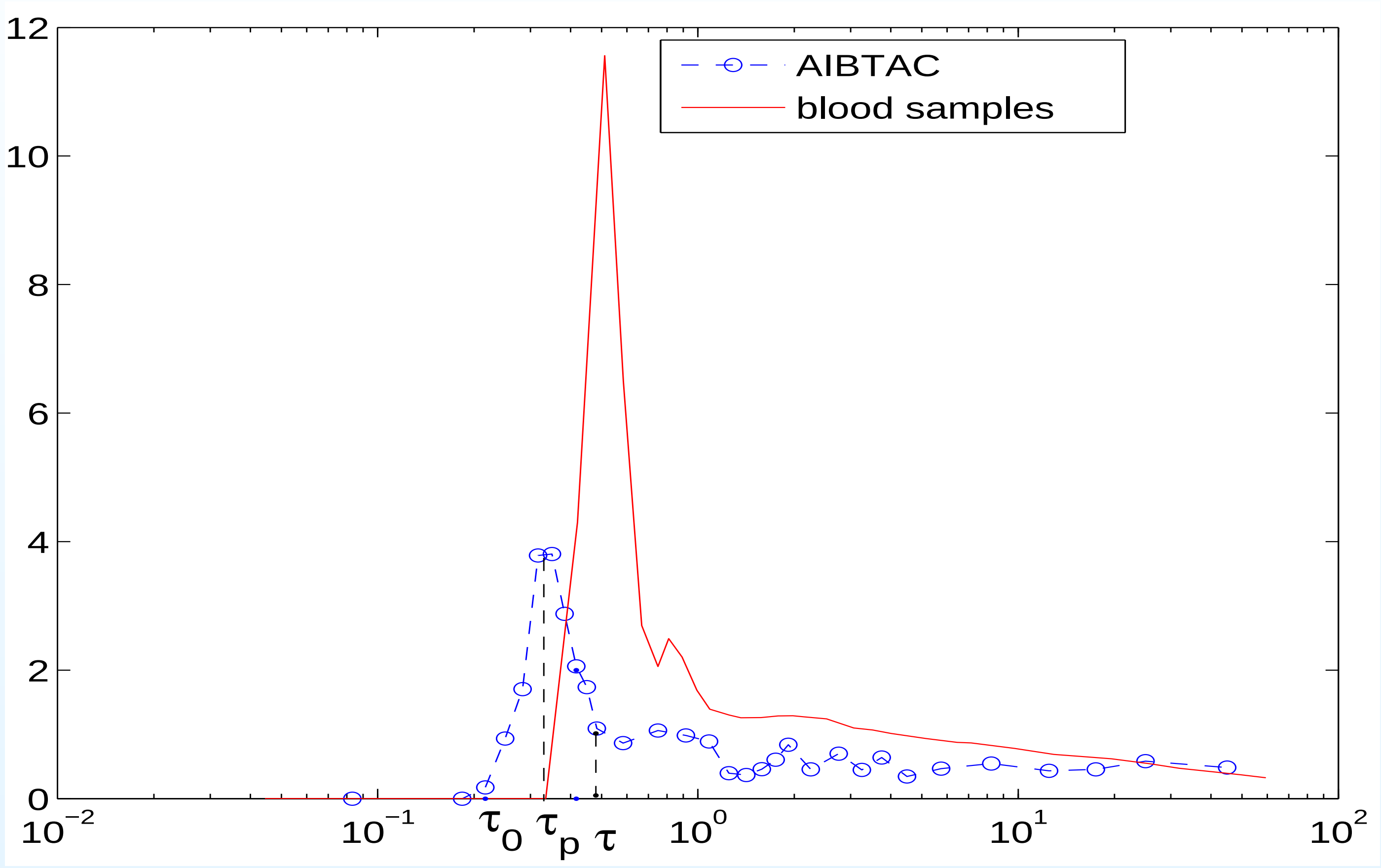
Internal carotid artery (Red) and neighbor tissue (Green)

Neighboring Tissue TACs : Apply Clustering



Several neighbor tissue TACs dependent on number of clusters used in optimization.

Comparison of Obtained AIBTAC vs. Blood Samples



Consider the two windows on the AIBTAC partitioned at point τ and only use the early window.
τ_0–activity start point. τ_p–time at which activity peaks.

A Novel Expression of $u(t)$

$$u_{\mathrm{e}}(t,c_1) = c_1\tilde{u}(\tau_p)\begin{cases} 0 & t \le \tau_0, \\ \frac{(t-\tau_0)}{(\tau_p-\tau_0)} & \tau_0 < t \le \tau_p \\ \frac{(\tilde{u}(\tau)/\tilde{u}(\tau_p)(t-\tau_p)+(\tau-t))}{(\tau-\tau_p)} & \tau_p < t \le \tau \\ \frac{\tilde{u}(\tau)}{\tilde{u}(\tau_p)} e^{-\gamma(t-\tau)^\delta} & t > \tau \end{cases} . \qquad (3)$$

For a given scaling coefficient c_1, unknowns γ, δ are determined by fitting the four blood samples at 10, 30 and 60 minutes, and the point $(\tau, c_1\tilde{u}_1(\tau))$ to the decay portion ($t > \tau$) using nonlinear least squares (NLS).

Equivalently, c_1 is the only unknown in the determination of $u_e(t)$, $u_e(t,c_1)$.

Estimation of the input function

Simultaneously estimate c_1 and $K_1^{(i)}, k_2^{(i)}, k_3^{(i)}$, (Set $k_4^{(i)} = 0$):

$$\min_{c_1, K_1^{(i)}, k_2^{(i)}, k_3^{(i)}} \sum_{i=1}^{m} \sum_{j=1}^{n} w_j \left[y_i(t_j) - \alpha^{(i)} \cdot g_i(t_j) - (1 - \alpha^{(i)}) \cdot u_e(t_j, c_1) \right]^2,$$

$$\text{subject to}$$

$$0.015 \le K_1^{(i)} \le 0.3, \quad 0.024 \le k_2^{(i)} \le 0.54,$$

$$0.01 \le k_3^{(i)} \le 0.2, \quad 0.9 \le \alpha^{(i)} \le 1,$$

$$1.2 \le c_1 \le 4$$

where

$$g_i(t) = u_e(t, c_1) \otimes \left(\frac{K_1^{(i)} k_3^{(i)}}{k_2^{(i)} + k_3^{(i)}} + \frac{K_1^{(i)} k_2^{(i)}}{k_2^{(i)} + k_3^{(i)}} e^{-(k_2^{(i)} + k_3^{(i)})t} \right),$$

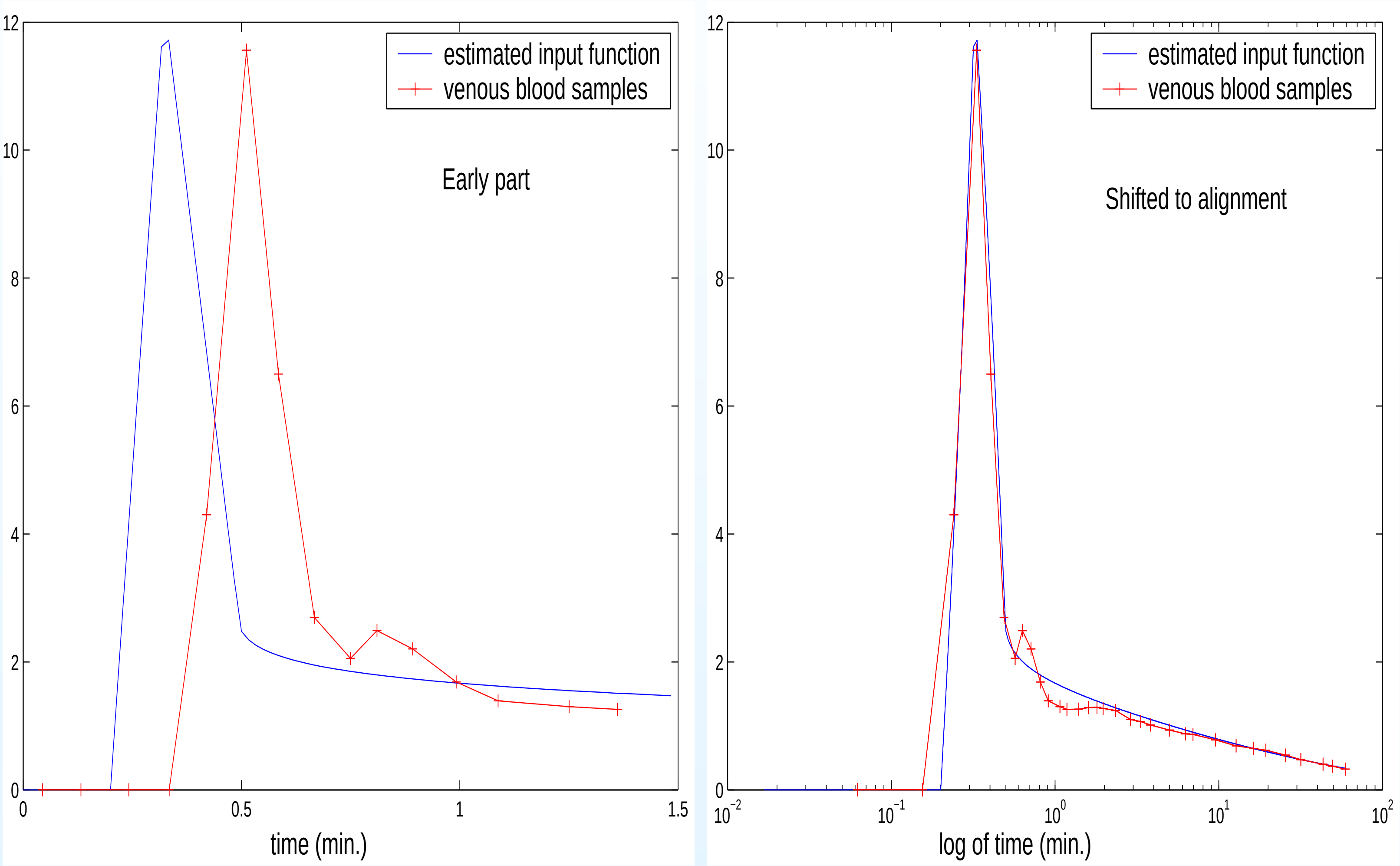
weight w_j is set to the time duration of each frame, and parameter $\alpha^{(i)}$ is used to correct the spillover from blood vessel to tissue, for each tissue ROI i.

4. Results of SIME

Table 1: Parameters of u_e

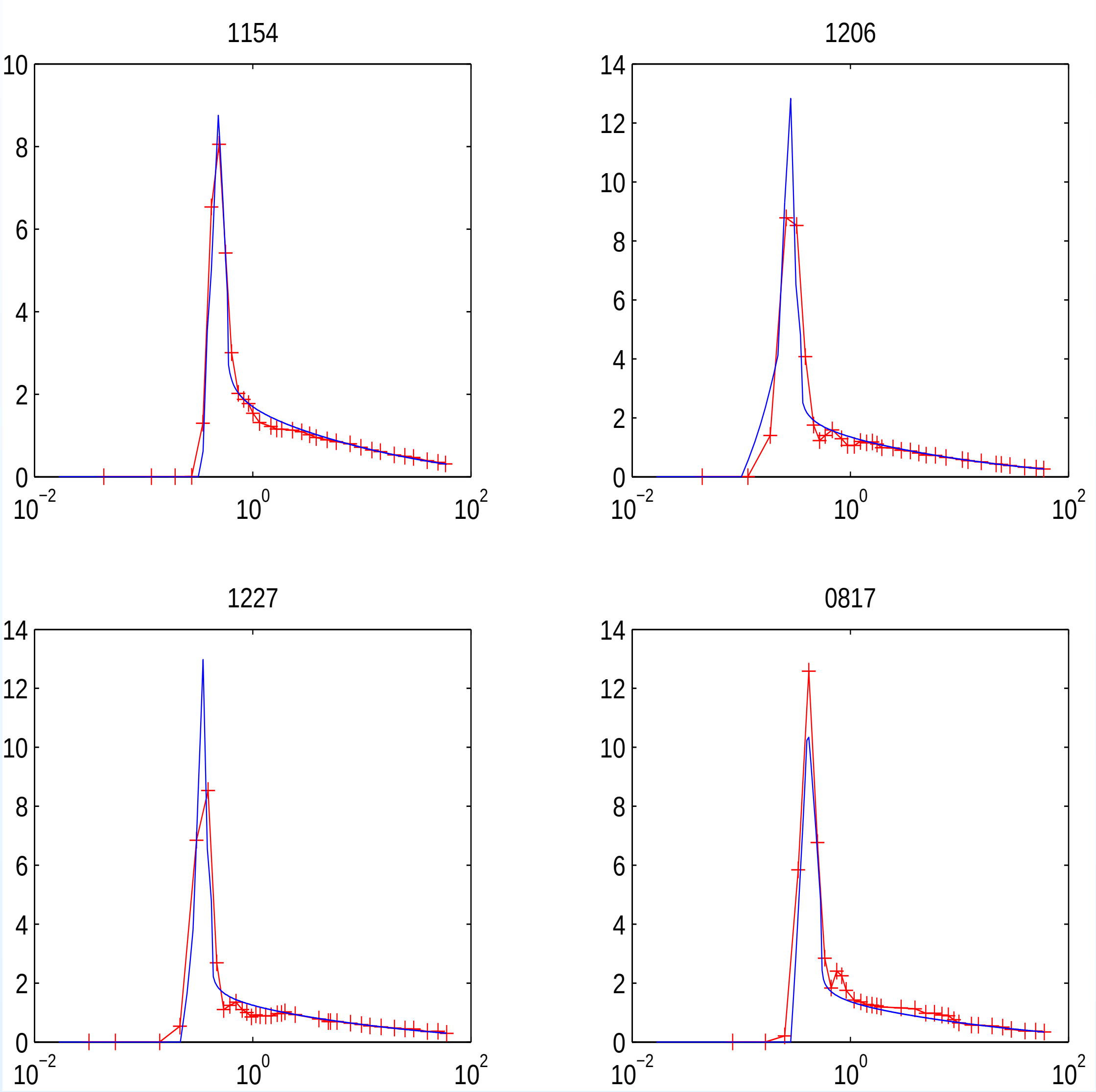
Subject	c_1	γ	δ	Subject	c_1	γ	δ
1206	1.87	-0.64	0.28	1241	2.60	-1.66	0.14
1227	3.50	-1.12	0.19	0817	2.45	-1.48	0.15
1154	3.01	-1.01	0.22	1208	1.98	-1.08	0.21
1231	2.77	-1.91	0.12	1245	2.10	-0.71	0.25
0827	2.13	-0.80	0.26	1182	2.61	-1.00	0.22
1226	2.55	-0.95	0.20	1233	2.60	-0.74	0.24
1264	2.24	-0.82	0.23	1078	2.50	-0.93	0.25
1234	2.45	-1.25	0.21	1086	2.35	-1.02	0.20
1191	2.14	-0.52	0.32	1235	1.95	-1.26	0.16
1121	2.28	-1.16	0.19	1229	2.47	-0.65	0.29

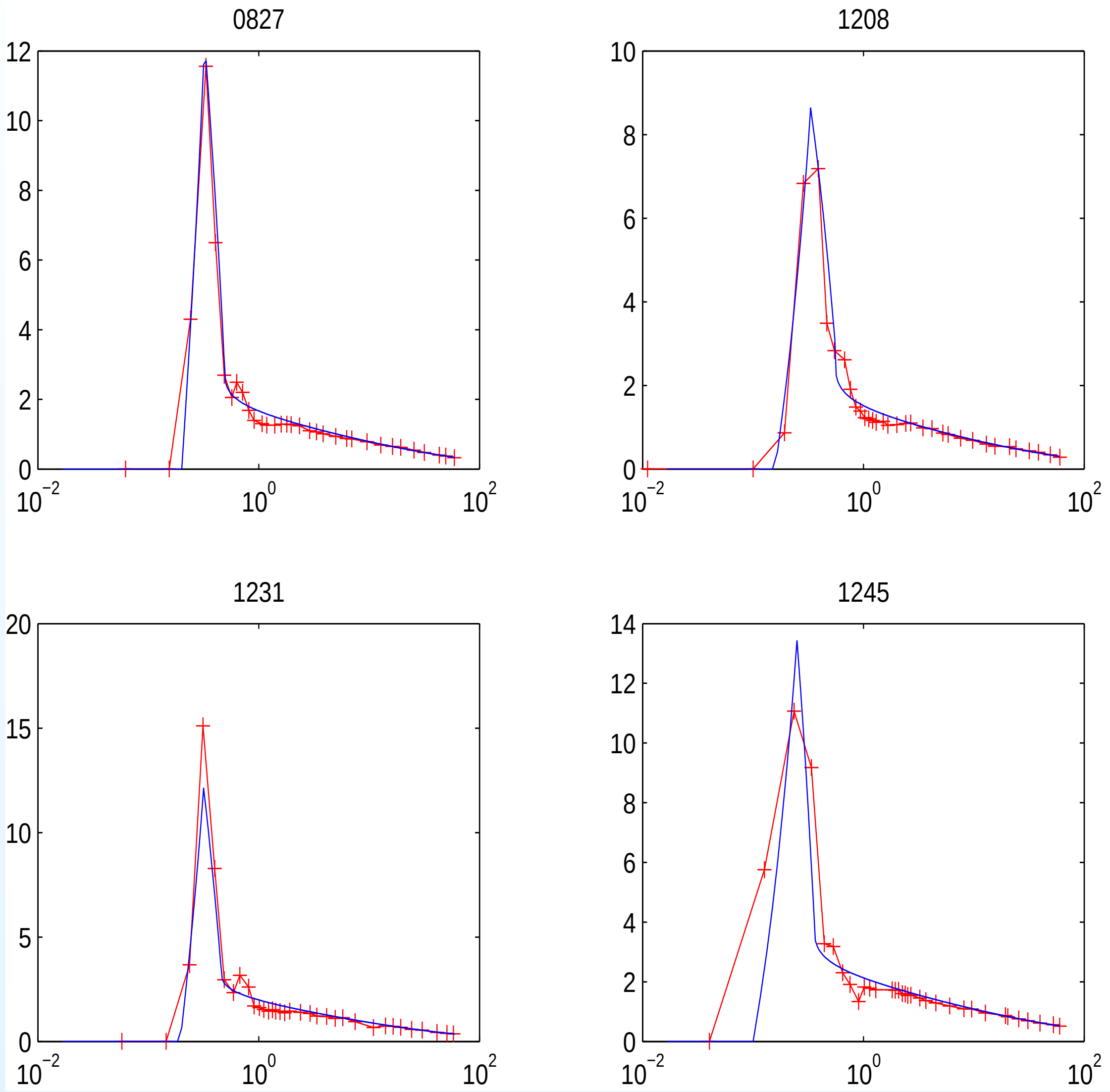
Estimated Input Function for Subject 0827

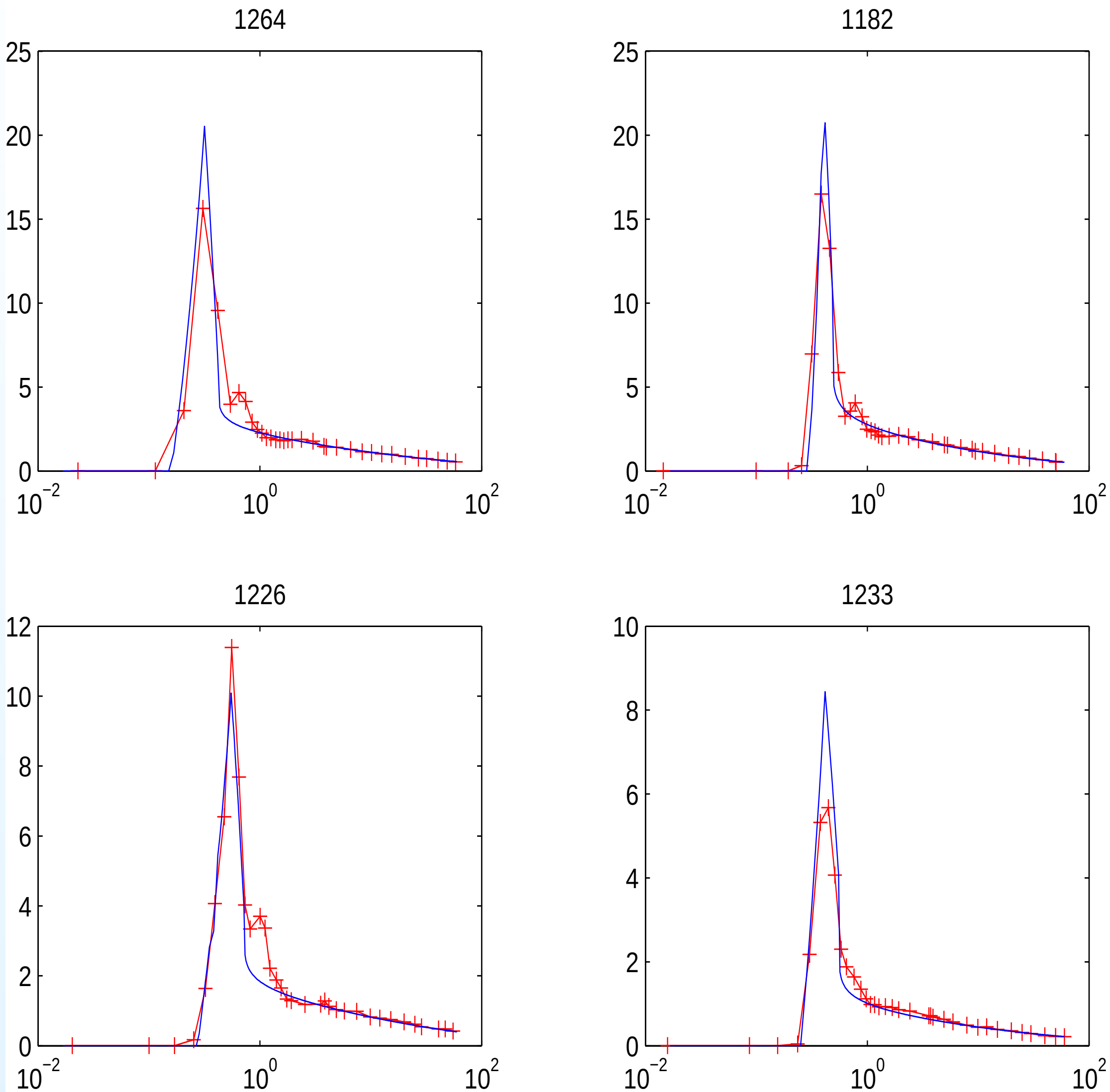


Subject 0827, estimated input function, u_e and blood samples, u_{bs}. Left: early window, right: shifted curves for whole time duration in logarithm scale.

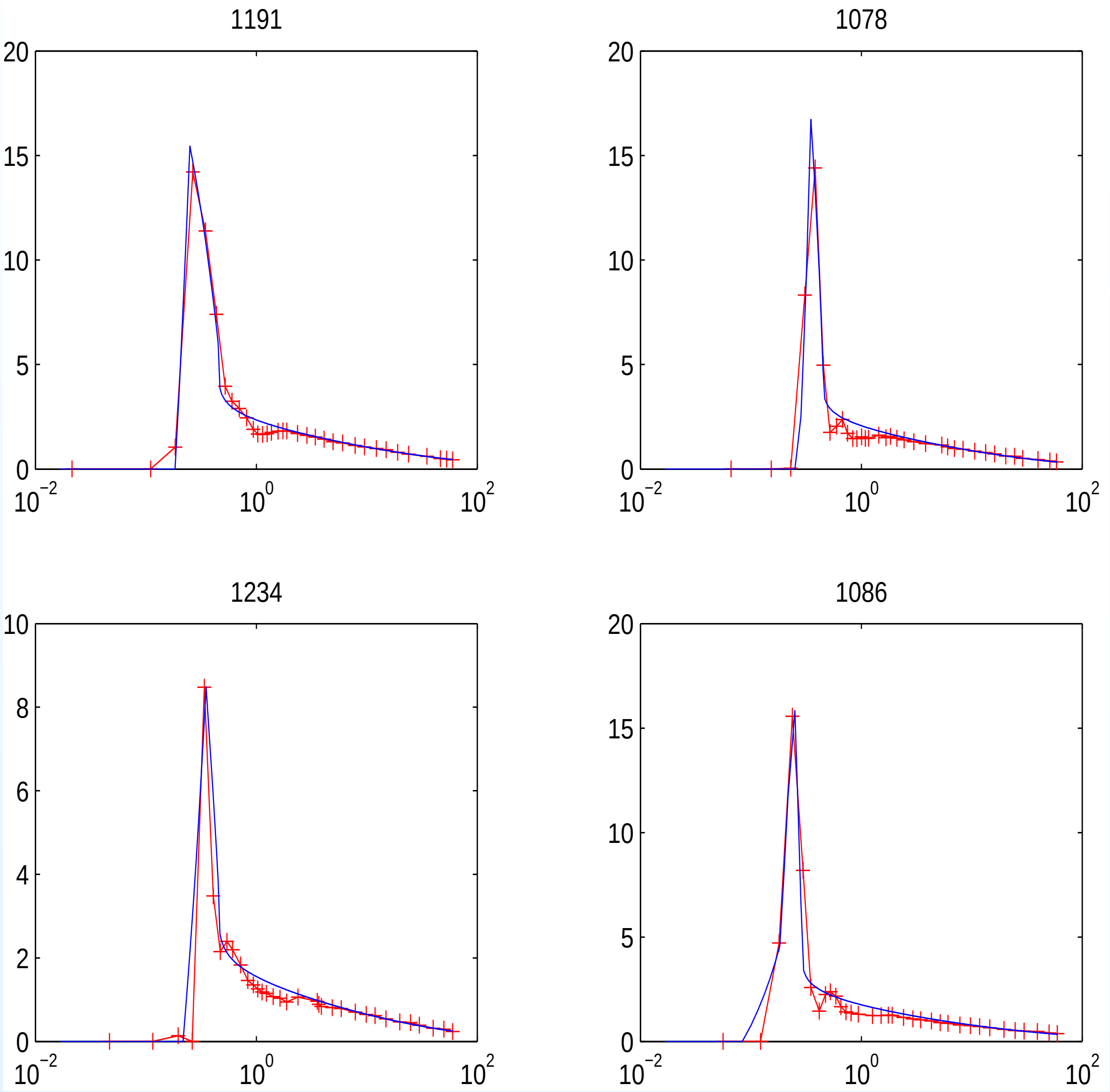
Estimated Input Function for All Subjects



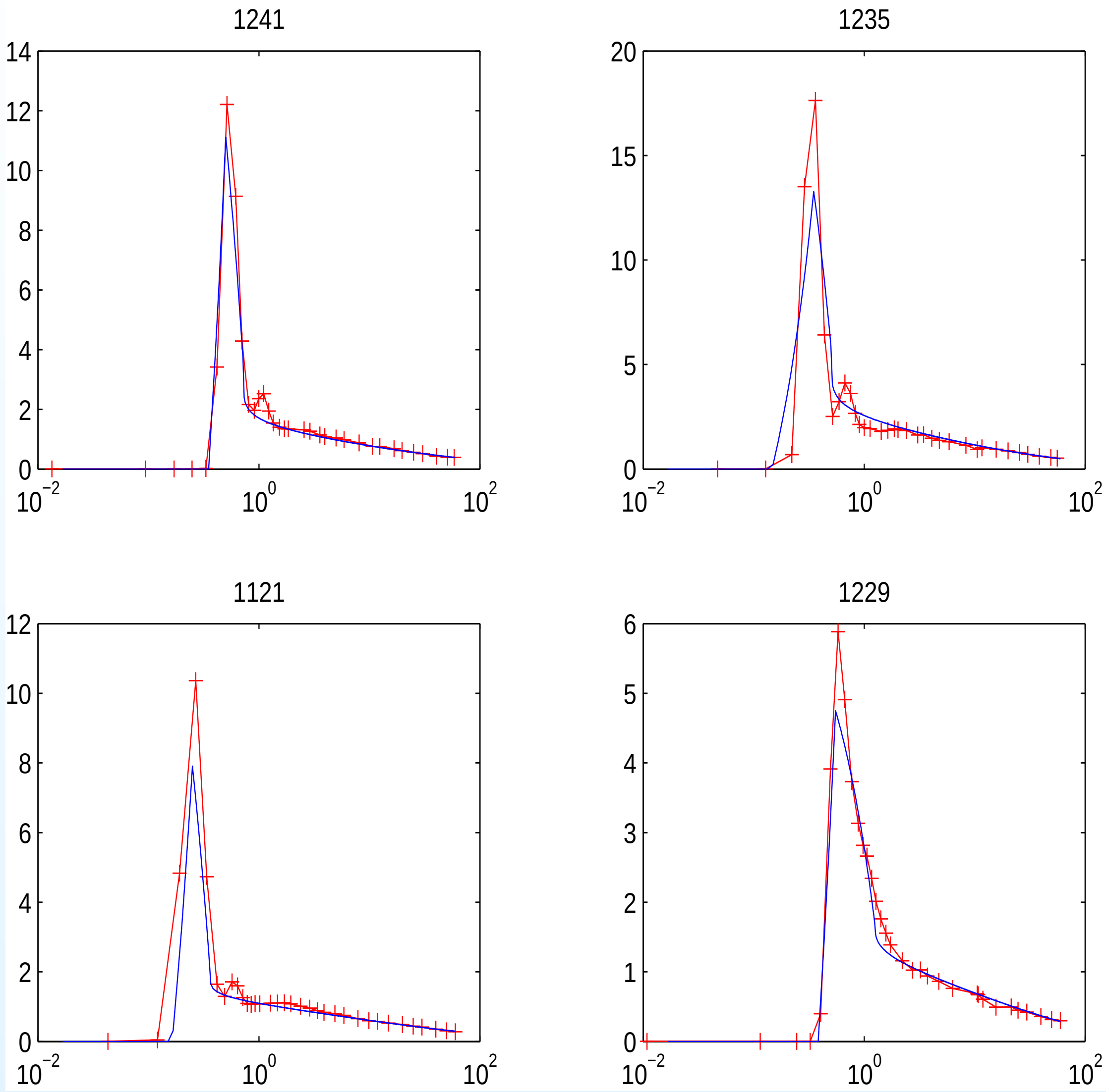

0827
1208
1231
1245
12
10
8
6
4
2
0
14
20
15
5
10^{-2}
10^{0}
10^{2}


1264
1182
1226
1233
25
20
15
10
5
0
12
10
8
6
4
2
10^{-2}
10^{0}
10^{2}

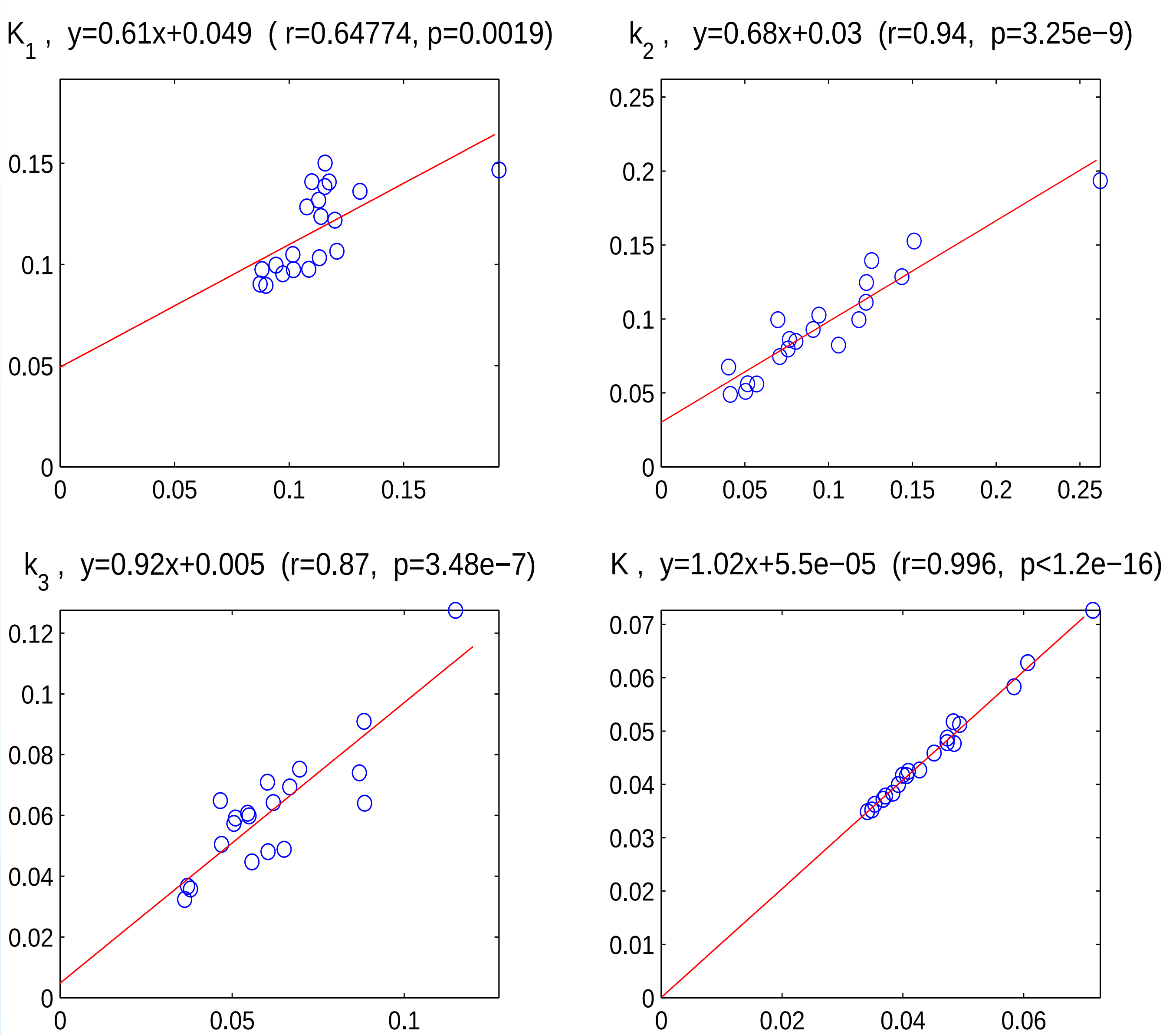
—


1191
20
15
10
5
0
10^{-2}
10^{0}
10^{2}
1078
20
15
10
5
0
10^{-2}
10^{0}
10^{2}
1234
10
8
6
4
2
0
10^{-2}
10^{0}
10^{2}
1086
20
15
10
5
0
10^{-2}
10^{0}
10^{2}

PET Analysis



Validation by Quantification



Examine Worst case: subject 1234

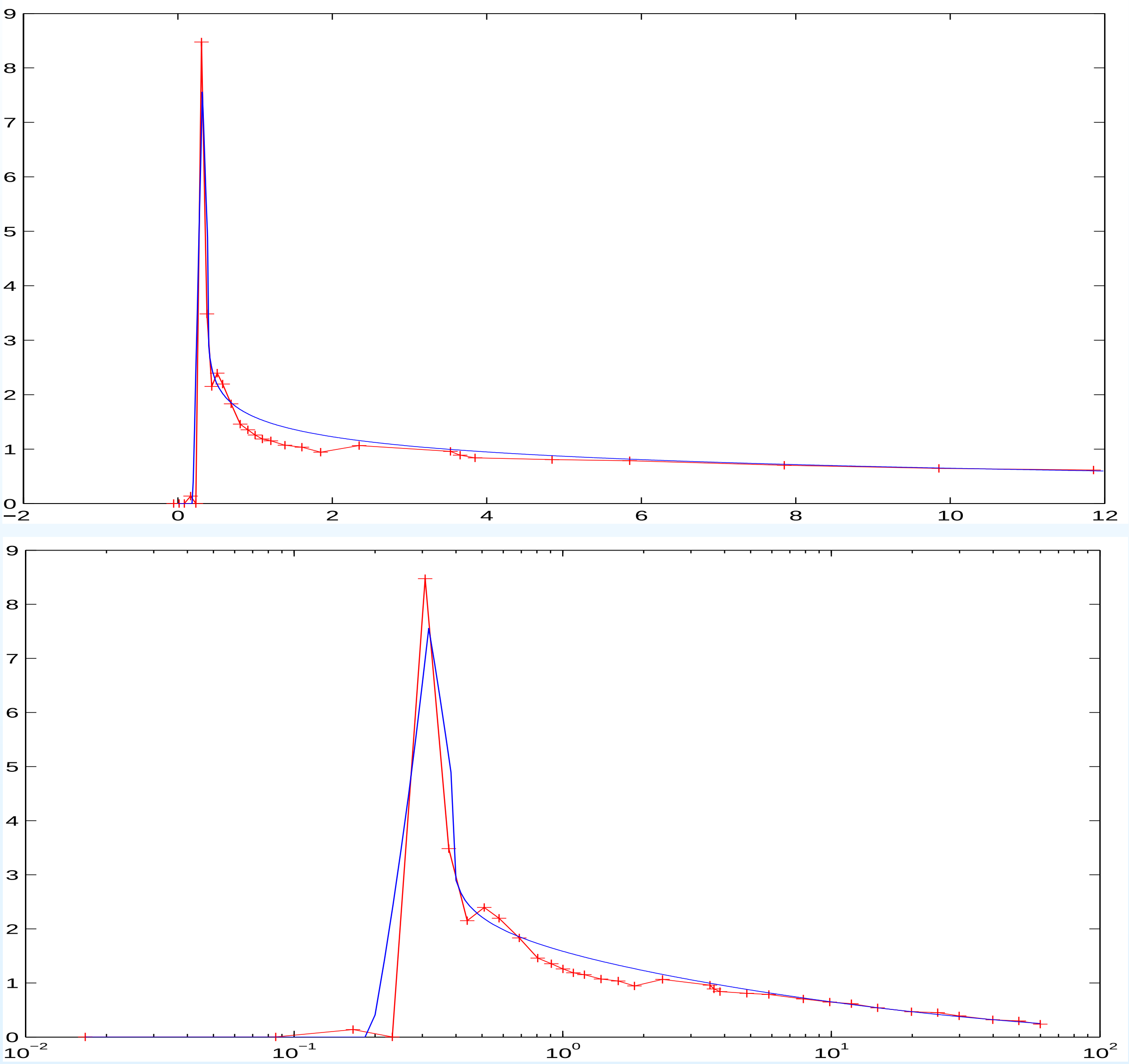


Table 2: Parameters calculated by u_e / u_{bs}

Subject	K_1	k_2	k_3
1227	0.121 / 0.107	0.122 / 0.111	0.051 / 0.057
817	0.110 / 0.141	0.151 / 0.153	0.089 / 0.064
1154	0.090 / 0.090	0.071 / 0.075	0.055 / 0.060
1208	0.102 / 0.097	0.076 / 0.080	0.060 / 0.071
1231	0.116 / 0.150	0.091 / 0.093	0.065 / 0.049
1245	0.120 / 0.122	0.126 / 0.139	0.070 / 0.075
827	0.113 / 0.103	0.118 / 0.099	0.067 / 0.069
1182	0.094 / 0.100	0.050 / 0.051	0.037 / 0.037
1226	0.116 / 0.138	0.077 / 0.086	0.036 / 0.032
1233	0.113 / 0.132	0.080 / 0.085	0.060 / 0.048
1264	0.108 / 0.128	0.070 / 0.100	0.055 / 0.061
1078	0.109 / 0.098	0.106 / 0.082	0.088 / 0.091
1234	0.192 / 0.147	0.262 / 0.193	0.115 / 0.128
1086	0.097 / 0.095	0.094 / 0.103	0.051 / 0.059
1191	0.114 / 0.124	0.041 / 0.049	0.047 / 0.050
1235	0.117 / 0.141	0.123 / 0.125	0.056 / 0.045
1121	0.087 / 0.090	0.057 / 0.056	0.038 / 0.036
1229	0.088 / 0.098	0.040 / 0.067	0.047 / 0.065
1241	0.102 / 0.105	0.144 / 0.129	0.087 / 0.074

Observations

- macro parameter K is well estimated as compared to blood sampled approach.
- micro parameters are reasonable in comparison, and note that the blood samples may also not be correct so precise comparison is impossible.
- parameters of the estimate have negative decay but the power is not unity as used in other studies, specifically it is nearer 0.25 on average.
- Does the last result indicate a different model for FDG decay in blood -nonlinear because of mixing?
- Scaling factor c_1 is an indication of the measured loss seen in images compared to actual values.

Future Work

- Automate the determination of blood ROI- extend ICA analysis
- Question the FDG model for tracer decay with mixing in tissue.

5. Independent Component Analysis for the ROI

- Assume linear combination of input and output

$$ABTAC(t) = \alpha \cdot u(t) + \beta \cdot y(t)$$

  for average blood region TAC, ABTAC(t), and neighbor tissue's TAC, $y(t)$, [Chen], K. Chen, et al., 1998.
- Parameters α and β account for partial volume and spillover effects respectively.
- Use three blood samples of $u(t)$ to solve for α and β by least squares, [Chen], K. Chen, et al., 1998.
- In [Chen] ABTAC(t) was obtained from manually defined carotid artery.
- New progress, Independent Component Analysis (ICA)-defined Carotid Artery.

ICA Theory

- Statistical technique that *uncovers* hidden independent factors in mixed set of signals.
- Here hidden factors are those from blood vessel and different brain tissues.
- Hidden factors are estimated as linear combinations of signals from all brain regions.
- Positive linear coefficients higher than threshold (z-threshold) indicate blood vessel region.

ICA Procedure

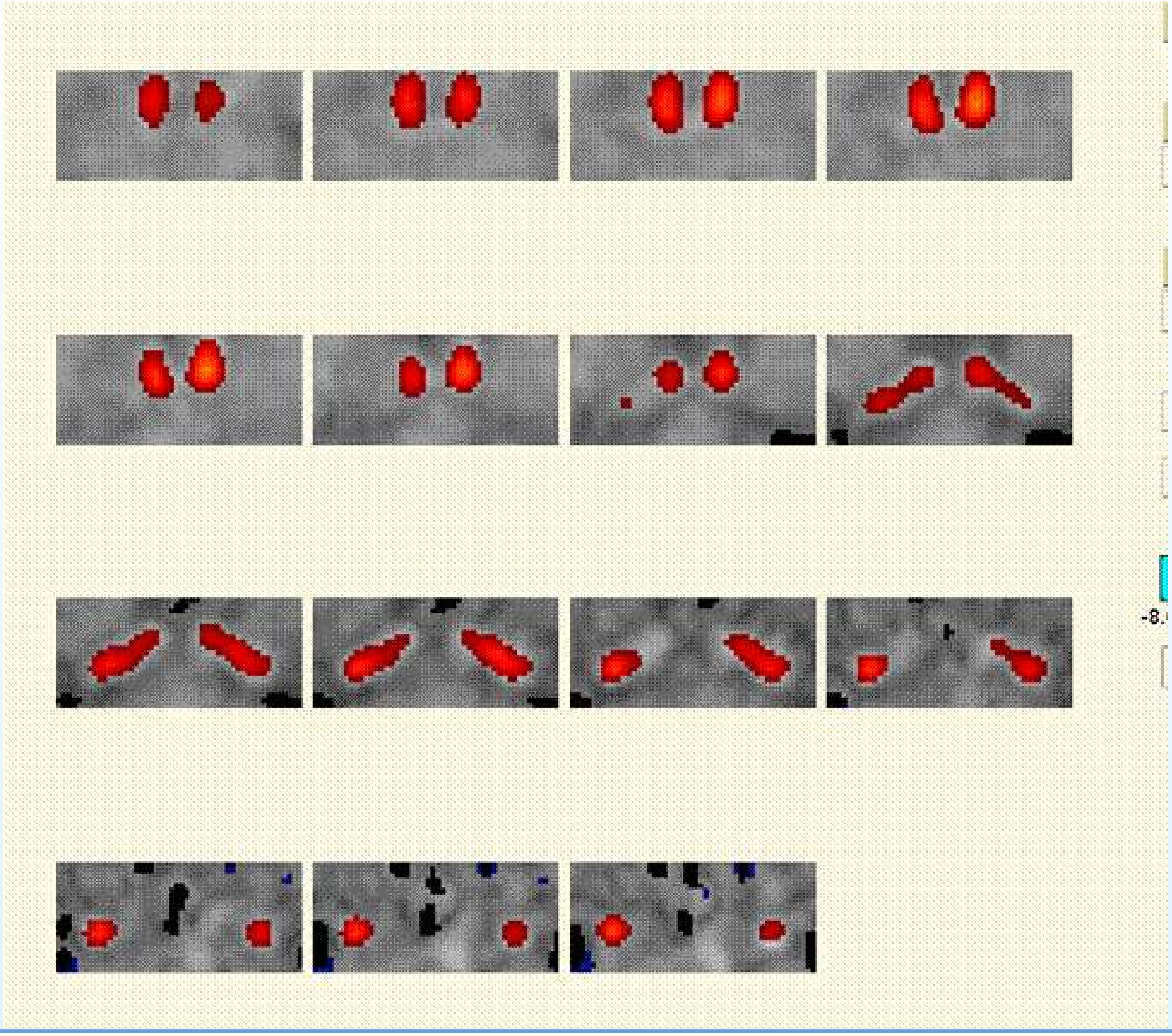
Software adopted: FMRLAB www.sccn.ucsd.edu/fmrlab (Duann, et al., 2002)

- Define a cubical sub-brain volume that contains the carotid artery.
- Use the first 5 PCAs for ICA analysis.
- Superimpose each ICA over PET for the first 20seconds - to identify that for blood vessel.
- Correct the partial volume and spillover effects.

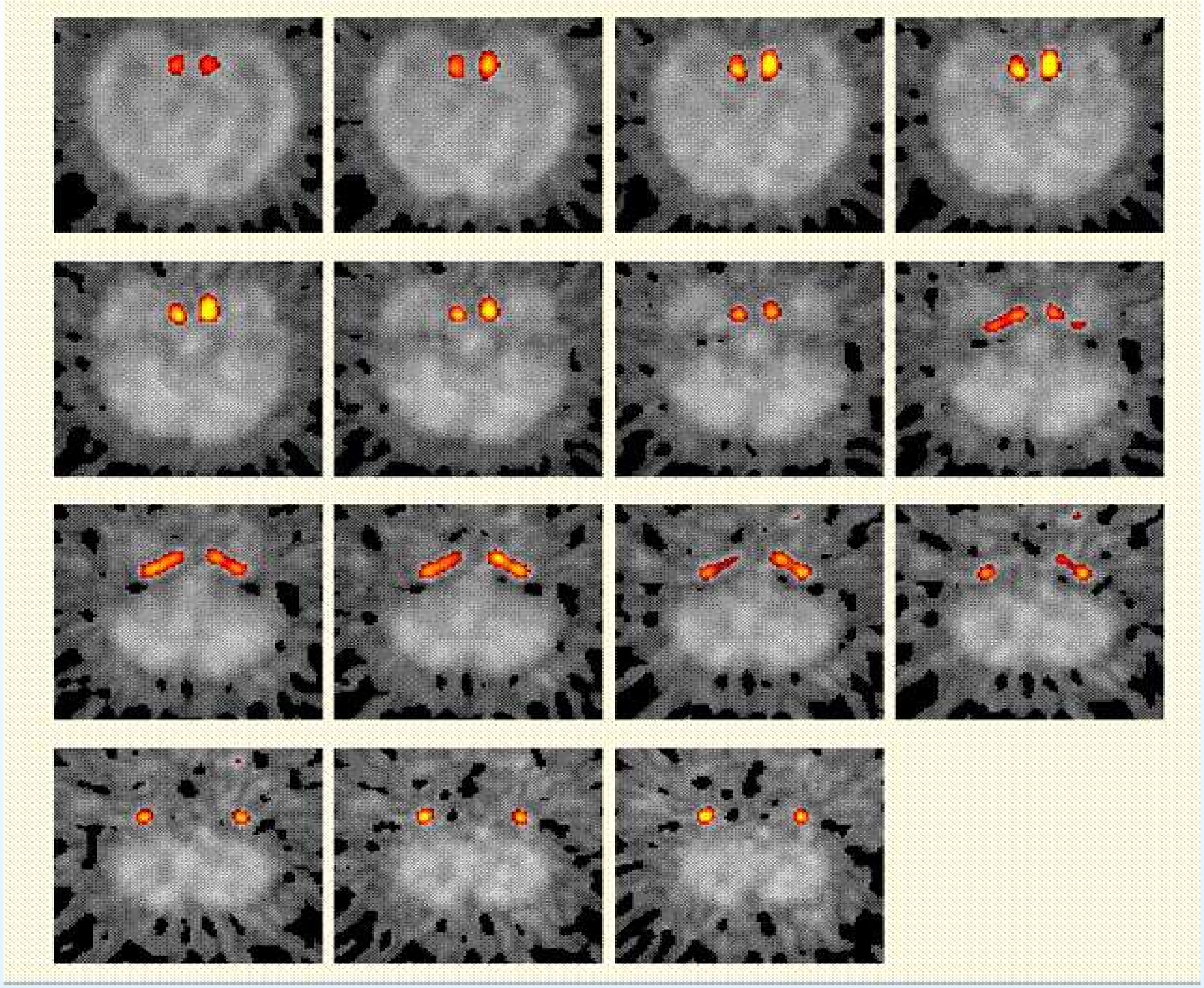
ICA Setting Determination and Validation

- Evaluate robustness of the sub-brain volume size, shape and location.
- Determine the z-threshold (Zinput) for carotid artery region definition.
- Determine the z-threshold (Zoutput) for the adjacent tissue region definition.
- Compare the image-derived Input function via ICA to that by blood sampling.
- Compare the Patlak estimated CMRgl (K) with ICA input function to that with blood sampled input function.

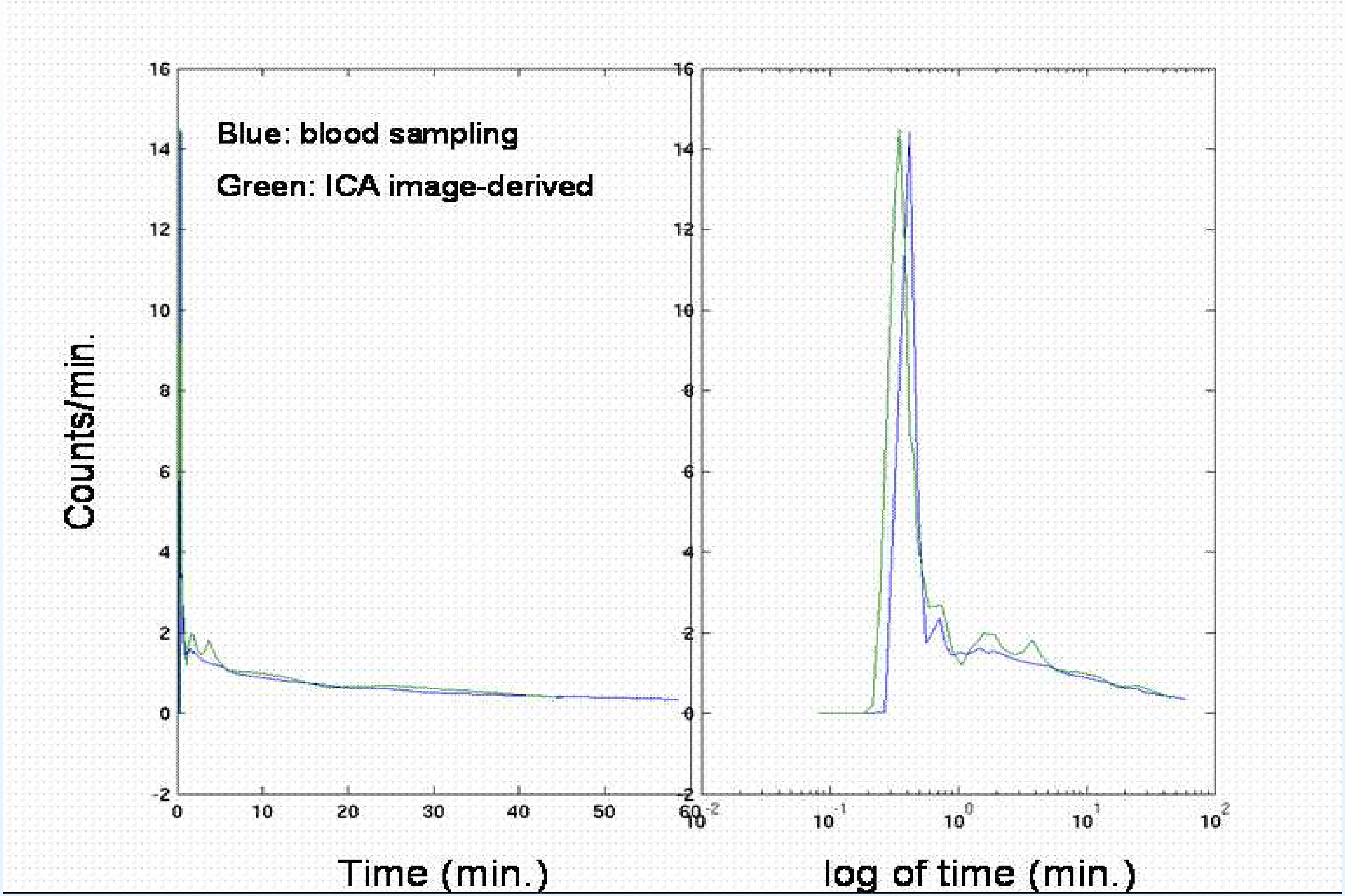
6. Results of ICA defined ROI : Subvolume



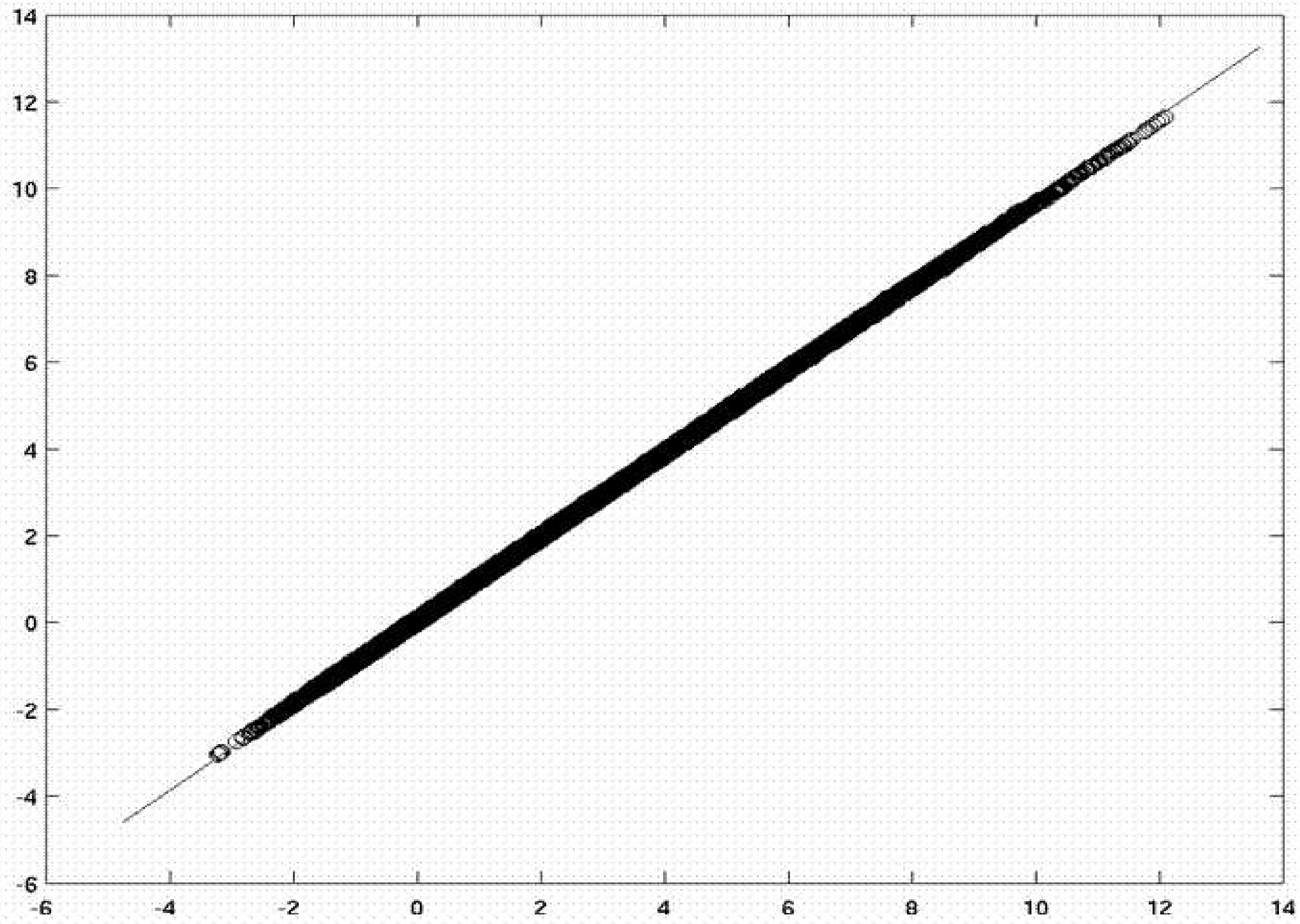
ICA Determined Carotid Artery Region: Whole Brain



blood-sampled and ICA image-derived input functions

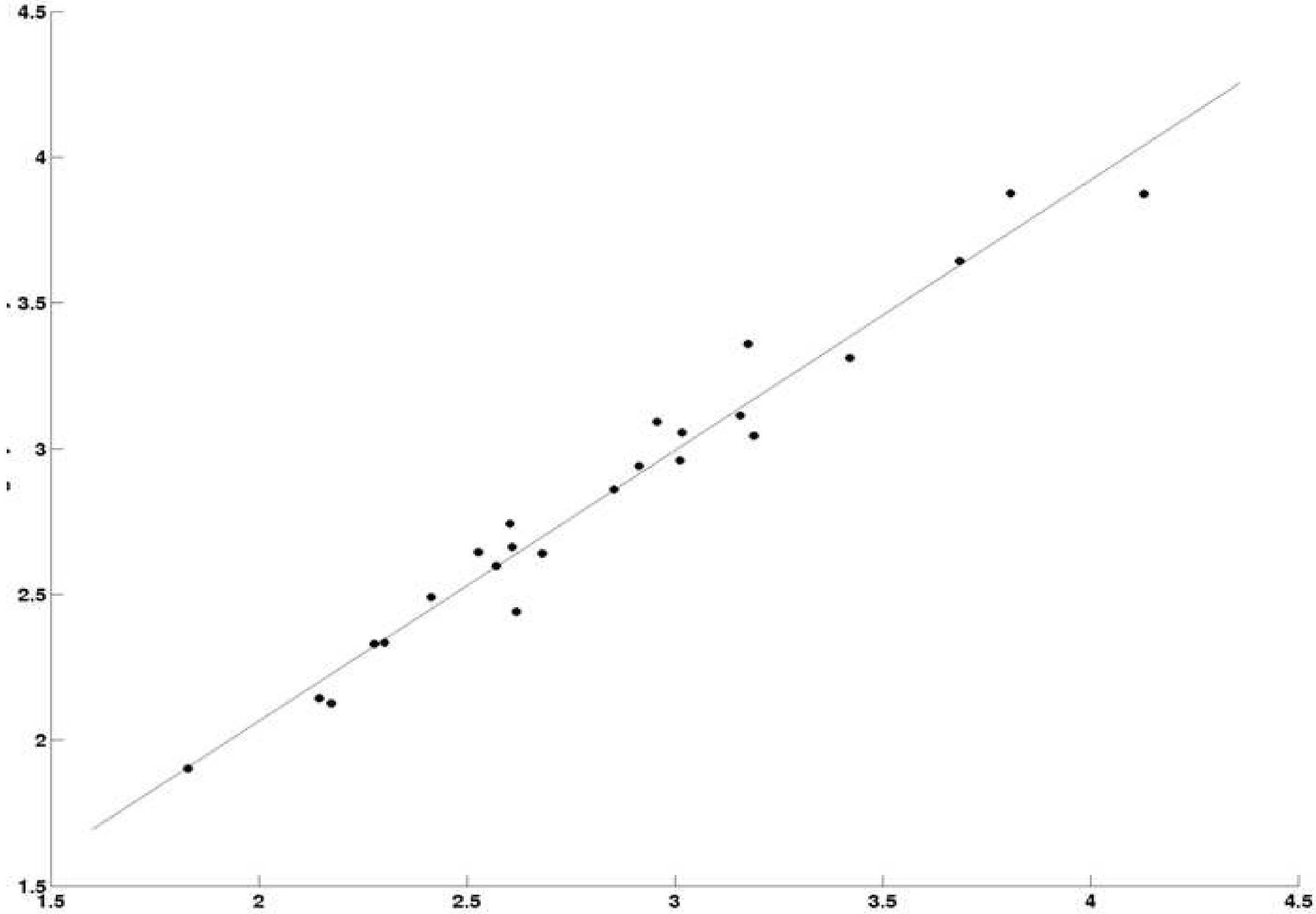


Voxel-by-voxel CMRgl (K) comparison for one subject



x-axis: CMRgl with blood samples; y-axis: CMRgl with ICA image-derived $u(t)$.

Global CMRgl comparison (24 subjects)



x-axis: CMRgl with blood samples; y-axis: CMRgl with ICA image-derived $u(t)$.

Voxel-by-voxel CMRgl comparison (24 subjects)

Subj #	Slope	Intercept	R square	Slope(V)	Intercept(V)	R square(V)
P01086dy	1.0135	0.0010	1.0000	1.0223	0.0071	0.9992
P01078dy	0.9691	0.0164	0.9997	1.0224	0.0088	0.9999
P00817dy	1.0584	0.0133	0.9995	1.0324	0.0027	1.0000
P00827dy	1.0174	0.0069	0.9999	1.0316	0.0043	1.0000
P01121dy	0.9242	0.0140	0.9996	1.0087	0.0095	0.9996
P01229dy	0.9690	0.0049	0.9999	0.9798	0.0527	0.9974
P01206dy	0.9365	0.0075	1.0000	0.9867	0.0531	0.9986
P00781dy	0.9800	0.0077	0.9996	0.8269	0.0026	0.9999
P00770dy	1.0067	0.0032	1.0000	0.9904	0.0034	1.0000
P00796dy	0.9869	0.0032	1.0000	0.9904	0.0034	1.0000
P00734dy	1.0434	0.0065	0.9998	1.0442	0.0227	0.9985
P01227dy	1.0313	0.0041	1.0000	0.9822	0.0094	0.9999
P00737dy	0.9996	0.0018	1.0000	0.9567	0.0132	0.9997
P00774dy	0.9554	0.0007	1.0000	0.8657	0.0046	0.9994
P00794dy	1.0059	0.0085	0.9999	0.9078	0.0065	0.9999
P01208dy	1.0613	0.0087	0.9998	1.0625	0.0134	0.9991
P01154dy	1.0505	0.0115	0.9996	0.8804	0.0052	0.9999
P01241dy	0.9801	0.0036	1.0000	0.7671	0.0820	0.9927
P01245dy	1.0064	0.0058	0.9999	1.0562	0.0034	1.0000
P01235dy	1.0245	0.0054	0.9999	0.9941	0.0062	0.9999
P01233dy	1.0450	0.0014	1.0000	0.8947	0.0093	0.9998
P01234dy	1.0185	0.0027	1.0000	0.9773	0.1049	0.9894
P01231dy	0.9837	0.0029	1.0000	1.0624	0.0076	0.9978
P01264dy	1.0139	0.0015	1.0000	0.9364	0.0252	0.9993

Conclusion

- Image-derived input functions via both methods, novel simultaneous estimate algorithm and linear model with ICA defined ROI, are excellent alternatives to the blood sampled input functions.
- The novel simultaneous estimate algorithm can also generate robust rate constants, K_1, k_2 and k_3.
- These methods will be helpful in our longitudinal study of AD and AD risk associated with apolipoprotein E-4 genotypes.
- Essential to extend the ICA approach for microparameter estimation.
- Comparison between these two methods is necessary.

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