

Challenges in Improved Sensitivity of Quantification of PET Data for Alzheimer's Disease Studies

Clustering the data and Estimating the Input Function

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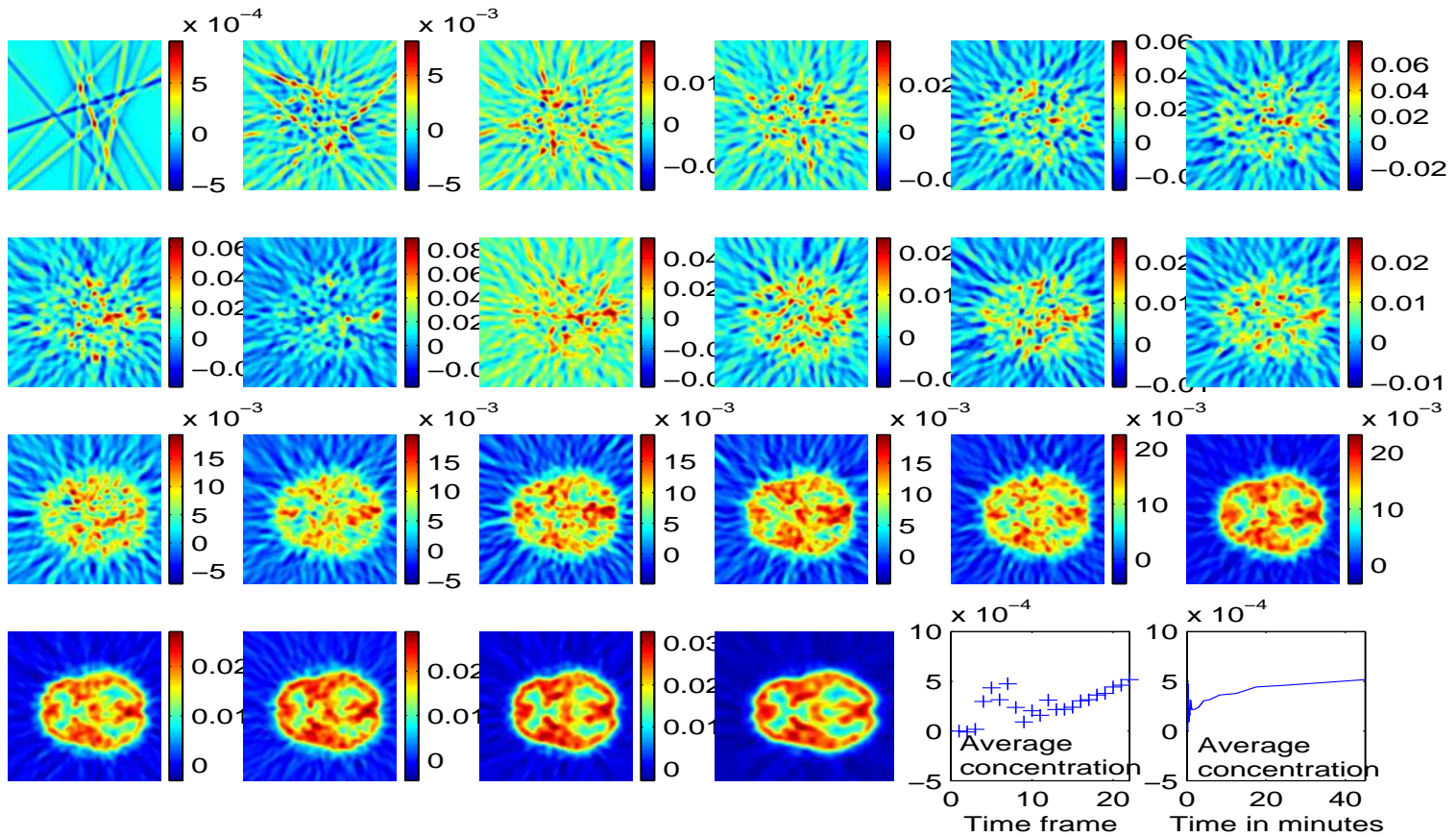
OUTLINE

- Our Goal - FDG Parameter Estimation.
- Methods to find the input function.
- A Simultaneous-Estimate Algorithm
- Clustering : a novel clustering algorithm
- Results
- Other Approaches: Image Registration
- Independent Component Analysis
- Conclusions - Extensions

1. Ultimate Goal

Automated tool for parametric estimation of brain function in AD

Output Data of One Slice

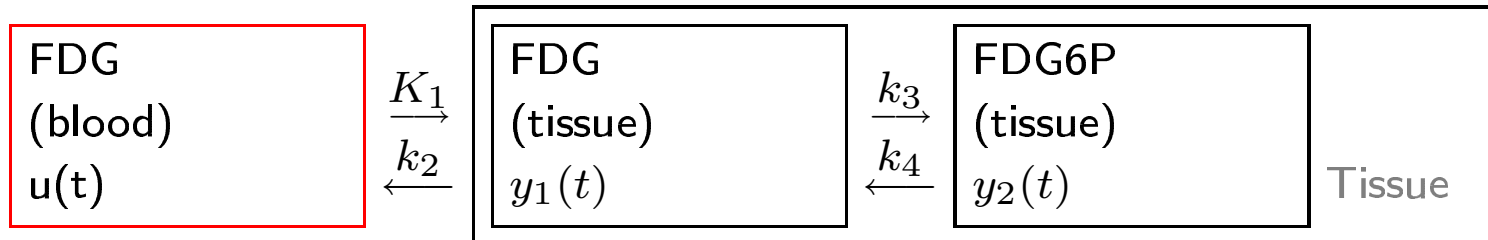


The Reconstructed PET data over one hour. Time Space Dynamics for slice 16 over 22 time intervals.

What is the FDG Tracer Model?

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.



$$\dot{y}_1 = K_1 u(t) - (k_2 + k_3)y_1(t) + k_4 y_2(t)$$

$$\dot{y}_2 = k_3 y_1(t) - k_4 y_2(t).$$

(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 .

The Solution of the FDG Tracer Model

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.

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

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

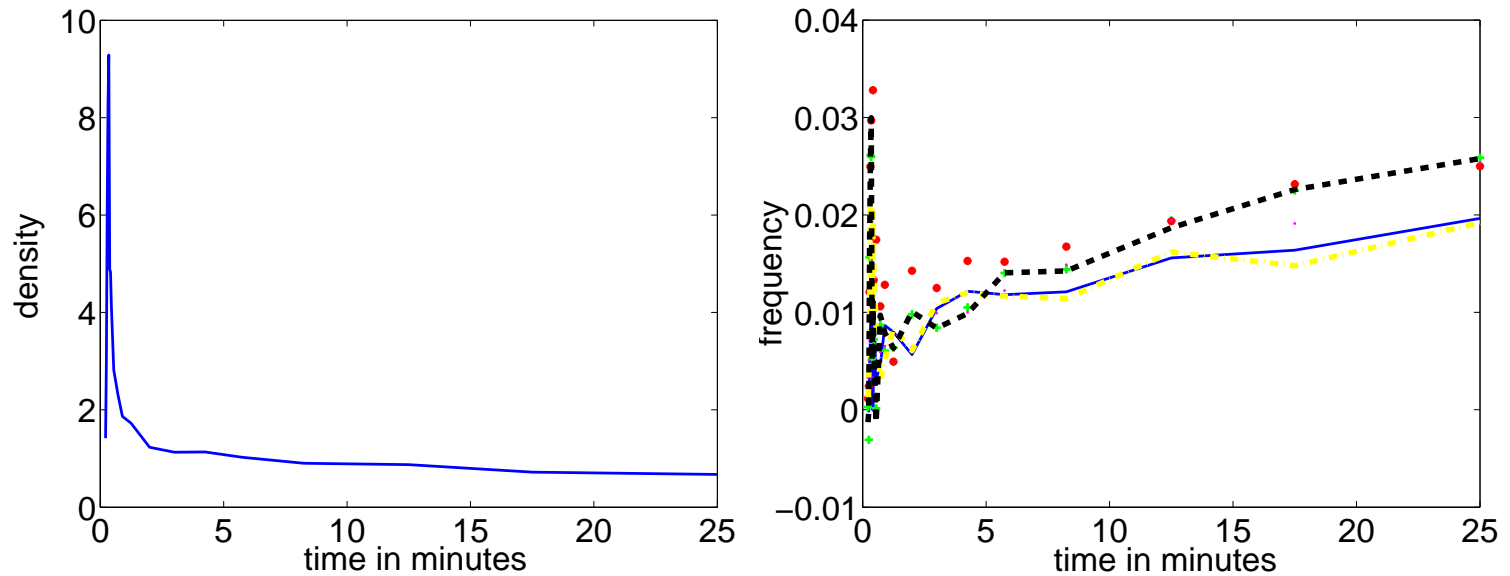
It is easy to solve the problem to find the parameters given the input function $u(t)$ and the output function $y(t)$, when the data are clean and equally spaced!

What are issues with this parameter estimation problem?

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

Emphasis here on the input function step

Representative input/output



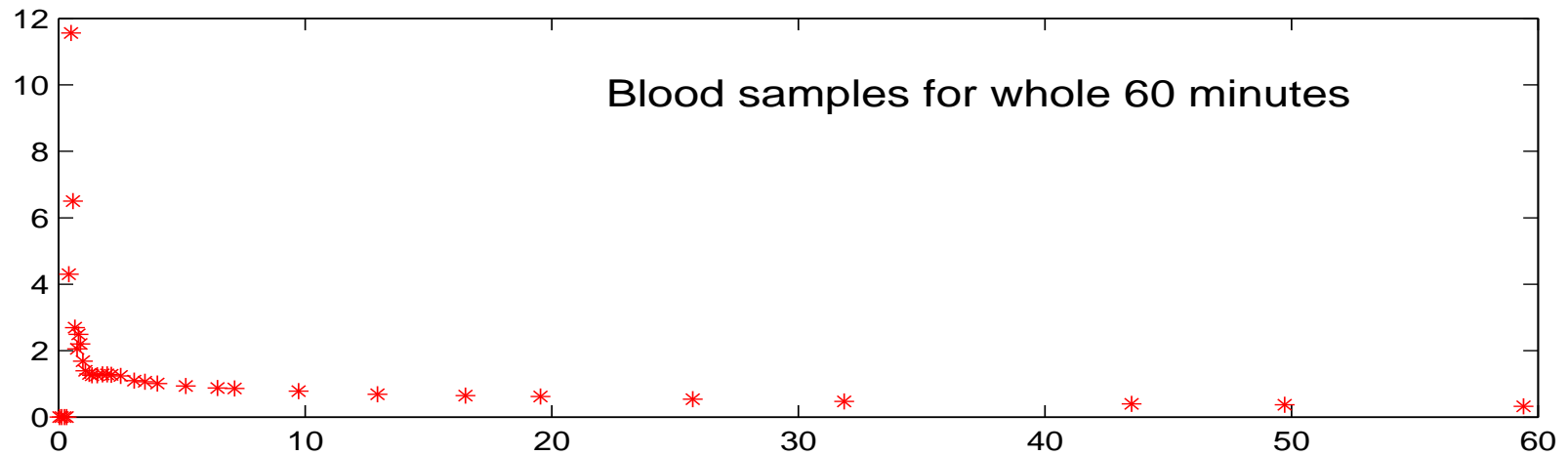
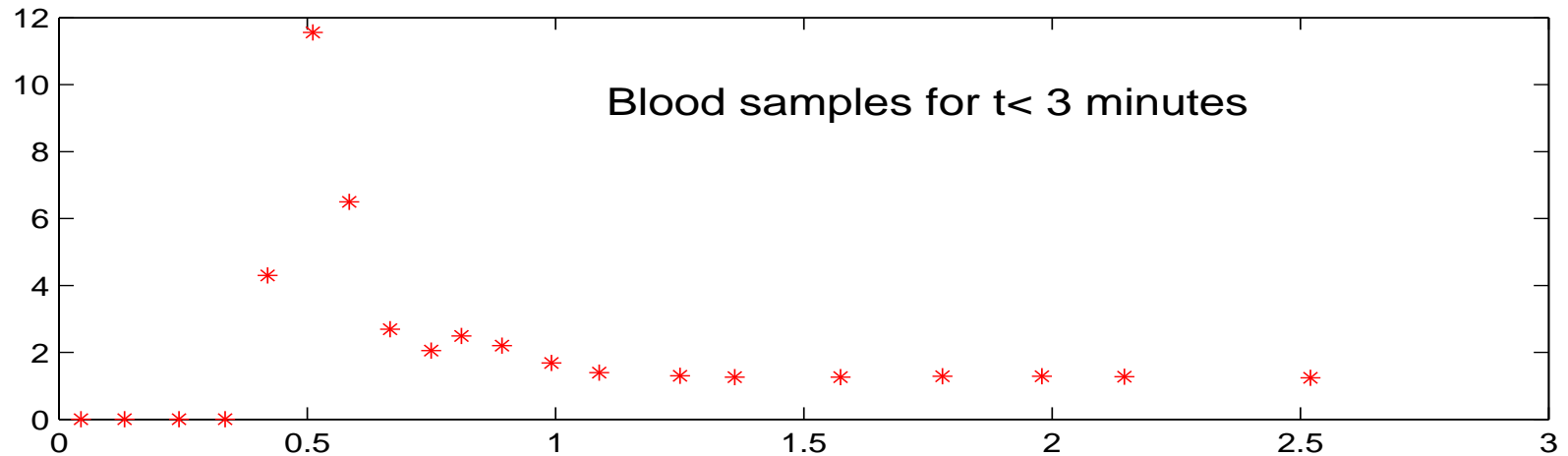
Left: input Function $u(t)$;

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, $\Delta t_{22} = 30m$.

Approximate Input Function–Arterial Blood Samples



2. Some Methods for Identifying the Input

- *Golden Standard*, arterial sampling method **invasive**.
- **Population based input function**, ([Taki],1993 and [Eberl],1997). Fitting arterial or arterialized venous samples from subject population samples:

$$u_{\text{Phelps}} = A_1 e^{\lambda_1(t-\tau)} + A_2 e^{\lambda_2(t-\tau)} + A_3 e^{\lambda_3(t-\tau)},$$

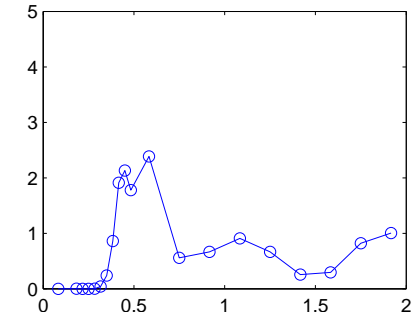
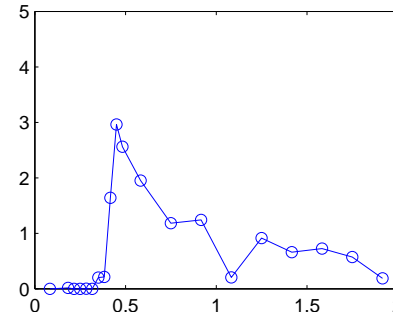
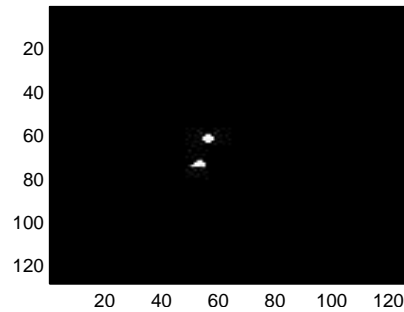
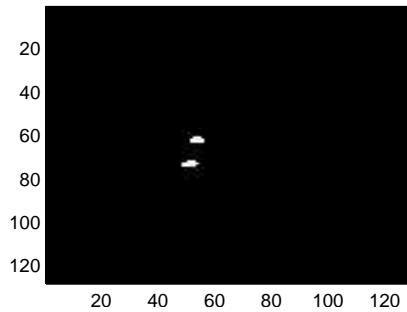
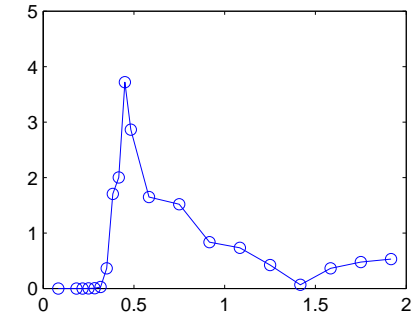
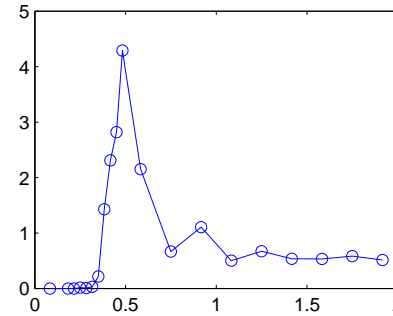
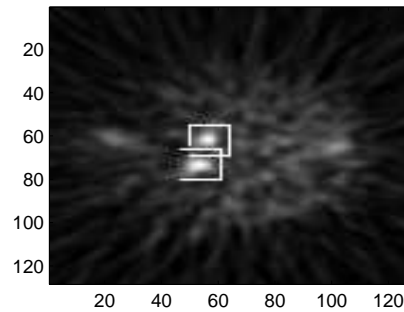
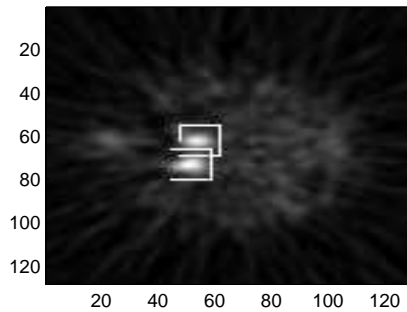
or

$$u_{\text{Feng}} = (A_1(t - \tau_0) - A_2 - A_3)e^{\lambda_1(t-\tau_0)} + A_2 e^{\lambda_2(t-\tau_0)} + A_3 e^{\lambda_3(t-\tau_0)}.$$

Requires the populations- not subject specific

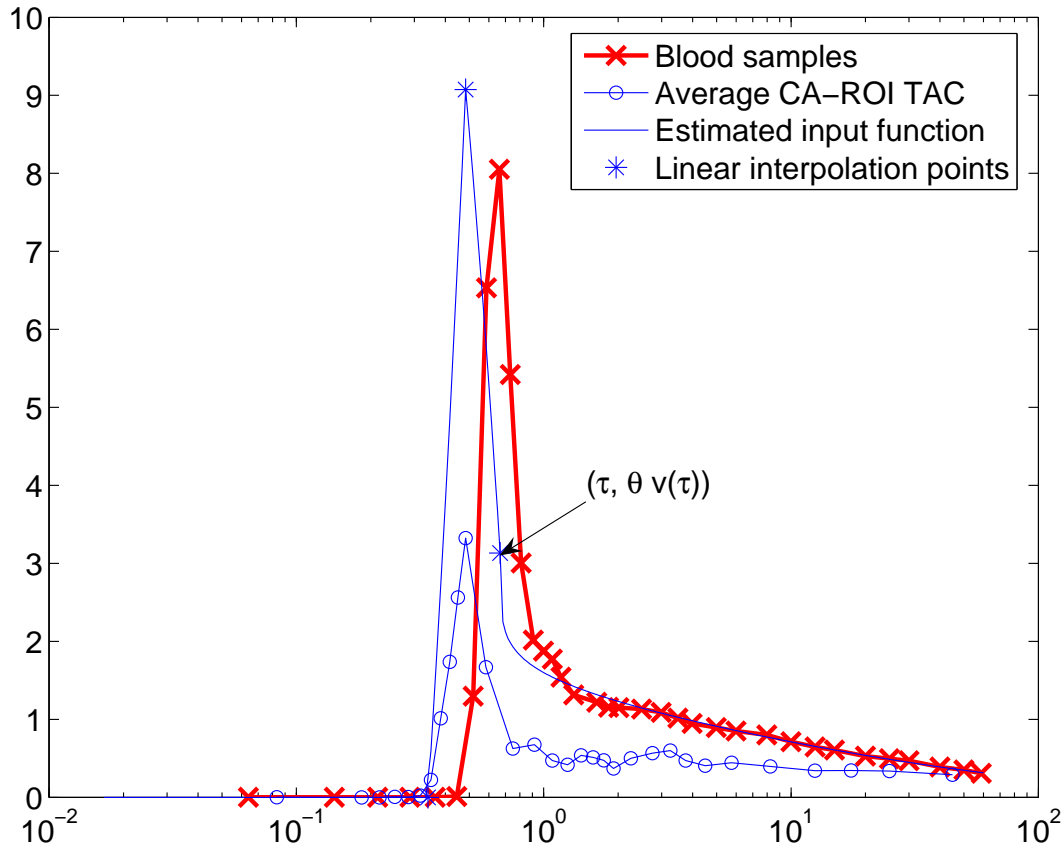
- **An Imaged-derived input function** requires finding the carotid artery in image ([Litt],1997; [Lipt],2004)

Finding the Input from the Image



Slices 26 and 27 of subject 1154: summed frames over two minutes. Semi-automatically defined squares identify blood regions of interest. Lower row: identified CA-ROIs just a few voxels. On the right corresponding image derived blood time activity curves.

Time Activity Curve of Blood Region



Comparison of the arterial blood samples (solid line with cross), uncorrected average blood time activity curve (circles) and estimated input function. Also illustrated is the time at which the average blood tracer activity is initiated in the ROI, the time point for the peak value, the time point which separates the fast and slow phases and three blood samples used for the fit. Time on logarithm scale.

A Composite Input Function

Observations

- Early activity very fast, sharp increase and decrease
- Later activity is a gradual decay

$$u_e(t, \theta, \lambda, \delta) = \begin{cases} 0 & t \leq \tau_0, \\ \theta v(\tau_p) \left(\frac{(t - \tau_0)}{(\tau_p - \tau_0)} \right) & \tau_0 < t \leq \tau_p \\ \theta \left(\frac{v(\tau)(t - \tau_p) + v(\tau_p)(\tau - t)}{(\tau - \tau_p)} \right) & \tau_p < t \leq \tau \\ \theta v(\tau) e^{-\lambda(t - \tau)^\delta} & t > \tau \end{cases} .$$

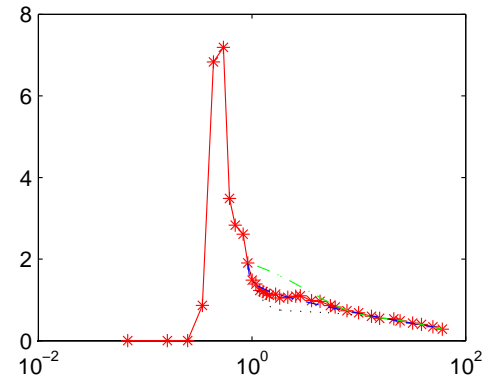
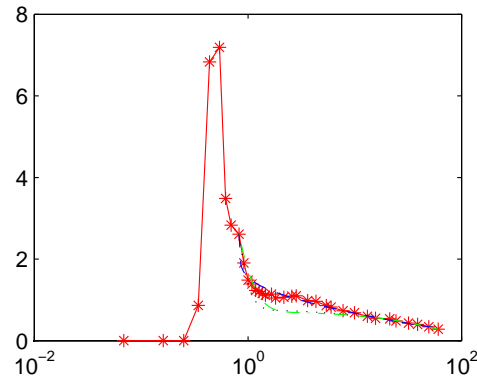
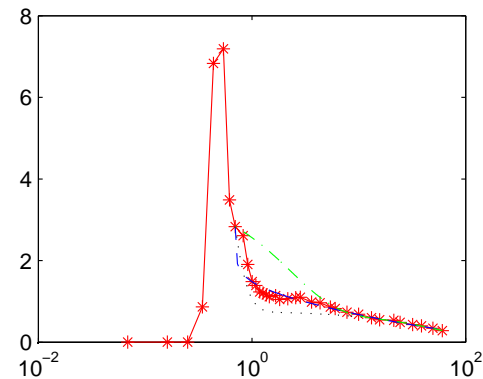
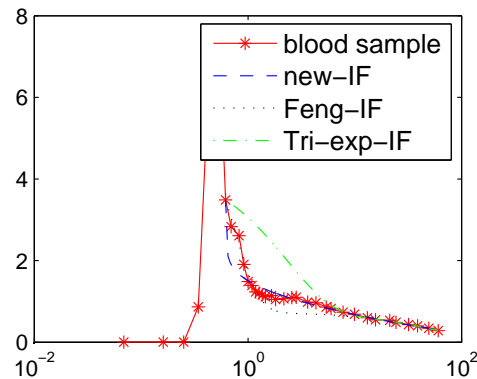
Note parameters that define input θ , λ and δ and the time points τ , τ_0 , τ_p .
 θ accounts for the partial volume, equivalently the low PET resolution

Validation of the Analytic Formulation

The mean and standard deviation of the root mean square error for nonlinear least squares data fitting over all subjects for different proposed input functions

	Analytic Input Function			
τ	u_{Phelps}	u_{Feng}	u_{Exp}	u_{PExp}
1	1.53(-2)(8.0(-3))	5.23(-2)(1.0(-2))	3.65(-1)(1.1(-1))	1.79(-2)(1.1(-2))
2	1.44(-2)(6.2(-3))	1.59(-2)(7.3(-3))	2.75(-1)(9.7(-2))	1.69(-2)(9.9(-3))
3	1.48(-2)(7.4(-3))	1.51(-2)(7.7(-3))	2.42(-1)(8.3(-2))	1.67(-2)(1.0(-2))
4	1.49(-2)(6.5(-3))	1.44(-2)(7.4(-3))	2.50(-1)(8.7(-2))	1.68(-2)(1.0(-2))

Do numbers tell everything?



Notice for one example how the fit is not good except for larger t other than using the new formulation: here these results show impact of different point of continuity τ .

3. Simultaneous Estimate Algorithm (SIME)

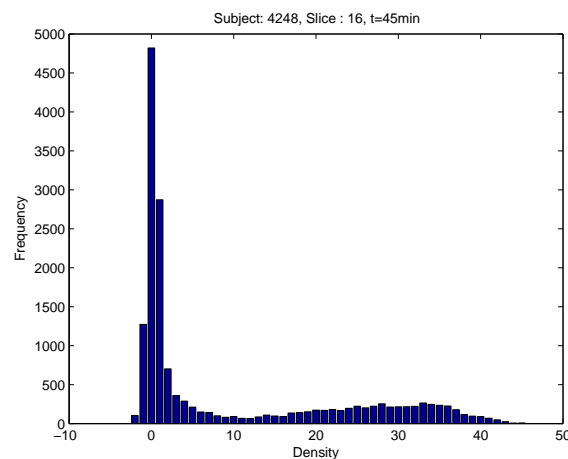
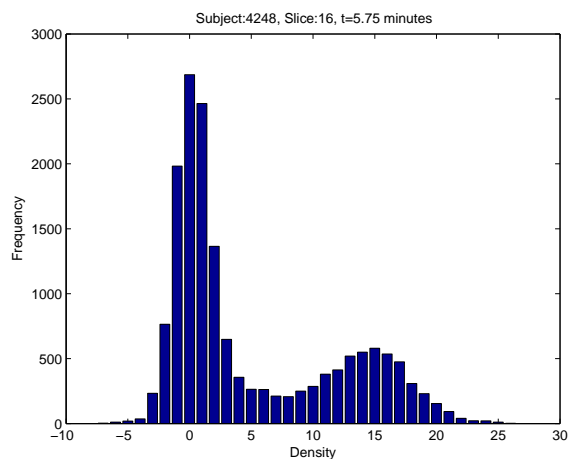
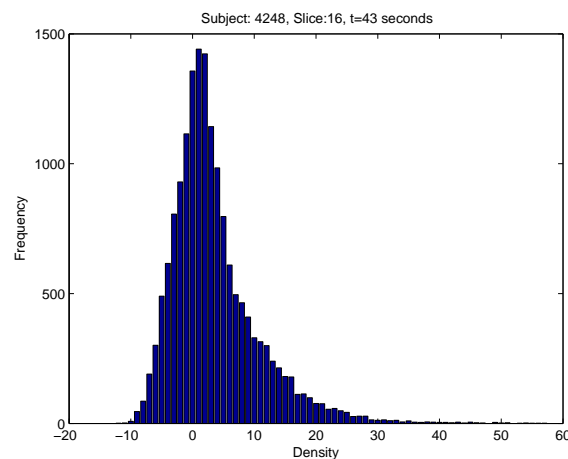
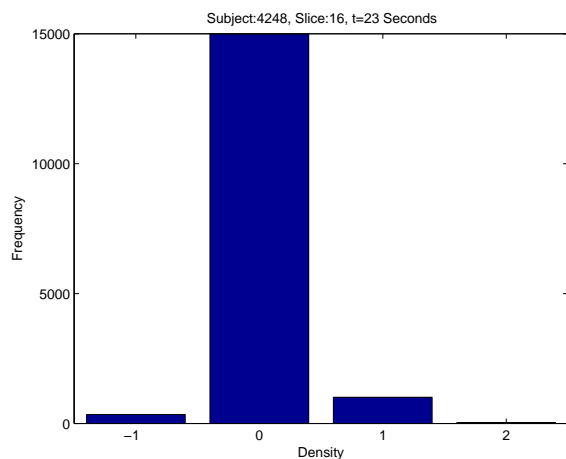
Cost Functional is Minimized:

$$\min_{\mathbf{x}, \alpha} \Phi(\mathbf{x}, \alpha) = \sum_{i=1}^3 \sum_{j=1}^n w_j \left[y_i^{\text{TAC}}(t_j) - \alpha_i \cdot y_i(t_j) - (1 - \alpha_i) \cdot u_e(t_j, \theta) \right]^2 .$$

- α_i account for spillover from blood to tissue (low value indicates high spill)
- Here to reduce the error and increase accuracy, y_i are output curves obtained from clustering.
- Observe also that Φ depends implicitly on parameters of u_e

$$\min_{\lambda, \delta} \sum_{i=1}^3 \left[\theta v(\tau) e^{-\lambda(\tilde{t}_i - \tau)^\delta} - u_{\text{bs}}(\tilde{t}_i) \right]^2 .$$

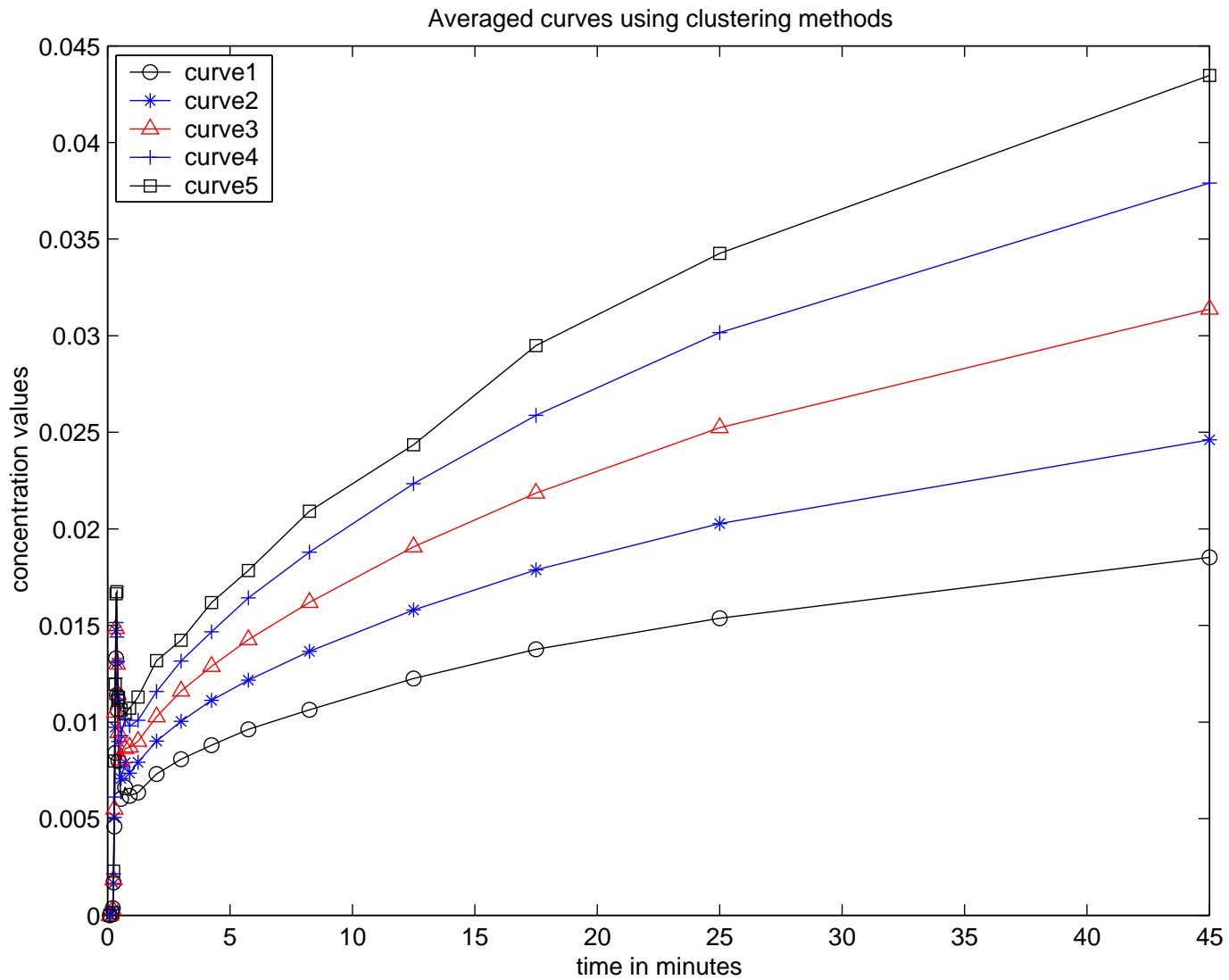
Intelligent Clustering of Voxel Data to Remove Noise



Histograms of densities summed over all three spatial dimensions for time frames with $t = 23$ seconds, 43 seconds, 5.75 minutes and the last frame at time 45 min

Threshold on Last Frame

Cluster curves: An Example



Validating Clustering of Voxel Data

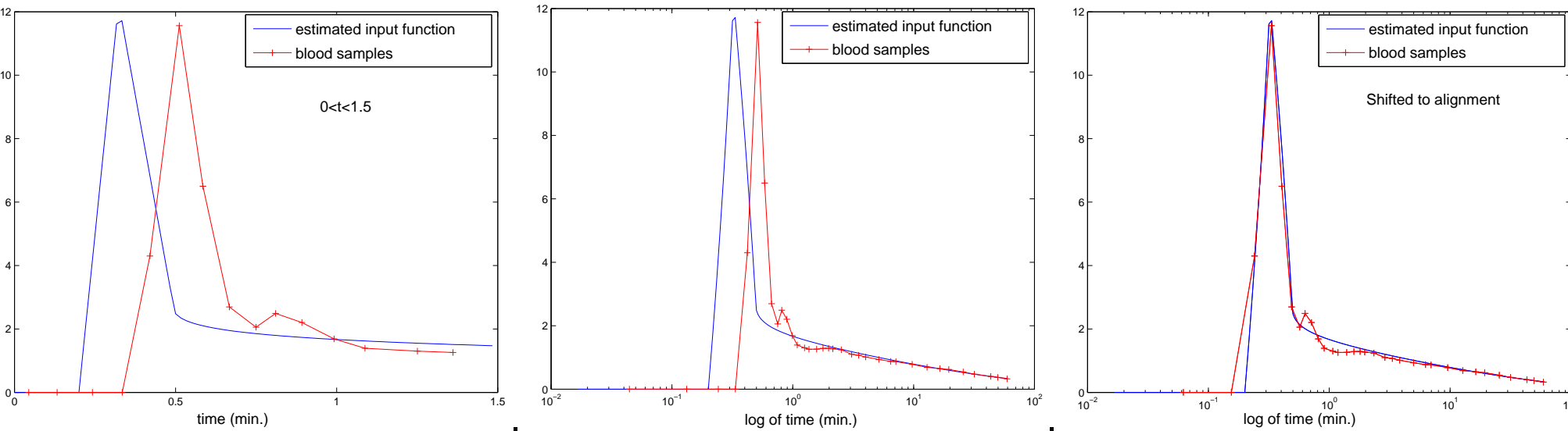
Premise

- Clustering must be cheap as possible
- Clustering results only used to obtain input and then for bounds.
- Validate using standard inter-intra cluster measures: separation, diameter, silhouette etc
- Clustering Algorithms considered, optimized hierarchical (Guo et al), hierarchical, and k-means (with weighted frame data).

Conclusions

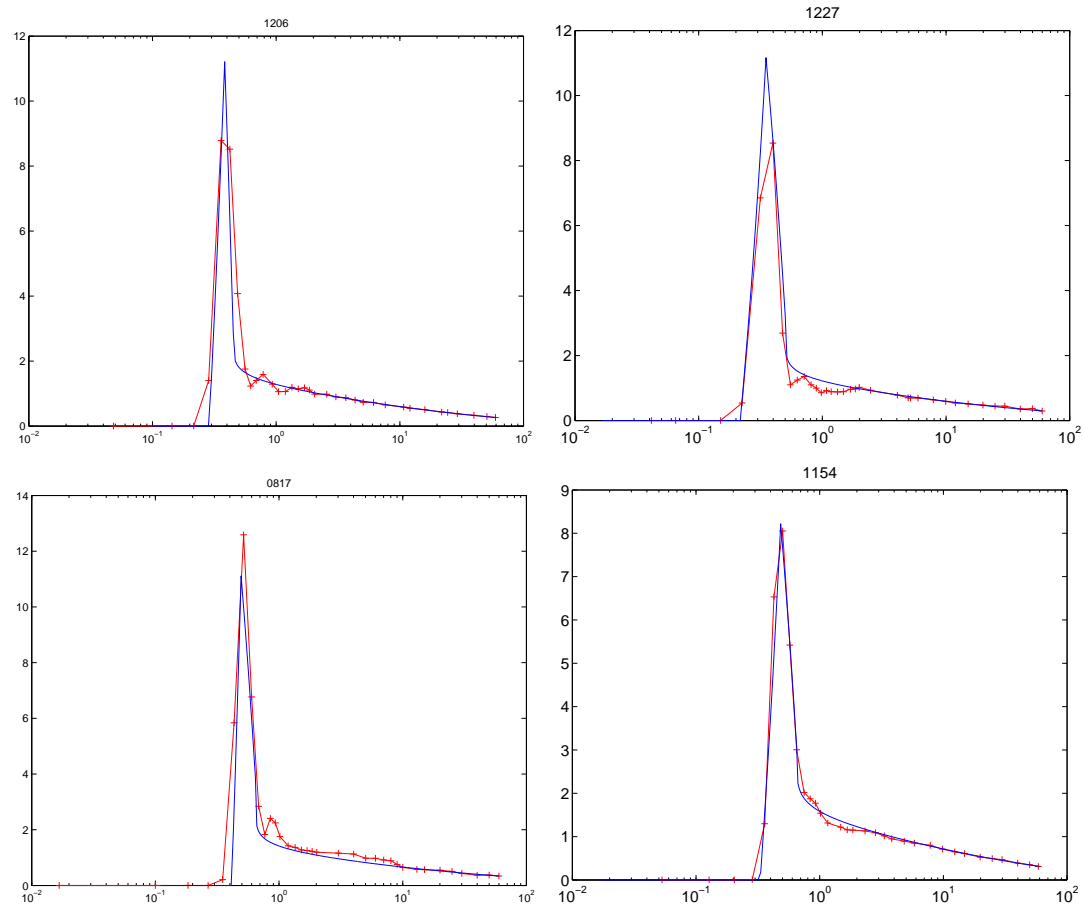
- Sufficient to use cheap cluster algorithms
- Also just use the final frame for clustering

Comparison of Recovered Input and Measured Data



The input function estimated by proposed method compared with arterial blood samples. Illustrated are the data focused on the initial window (top), the whole time window given on logarithm scale (middle), and the same data with the estimated input shifted to account for the time delay relative to the arterial blood samples (bottom).

Representative Shifted Comparisons



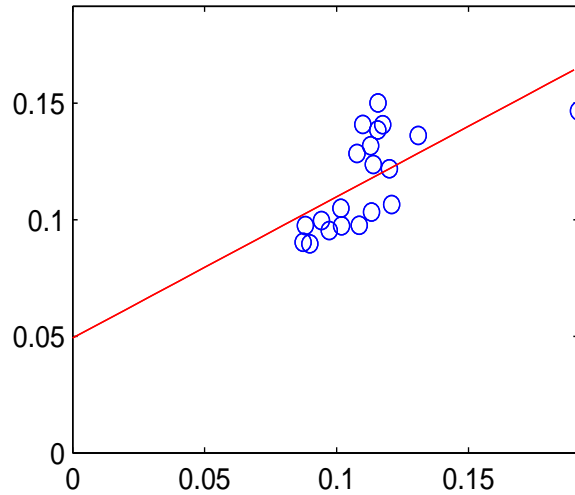
Comparison of estimated input u_e , continuous line, and arterial blood-sampled input u_{bs} , solid line with crosses, for representative subjects.

Parameters obtained in SIME procedures

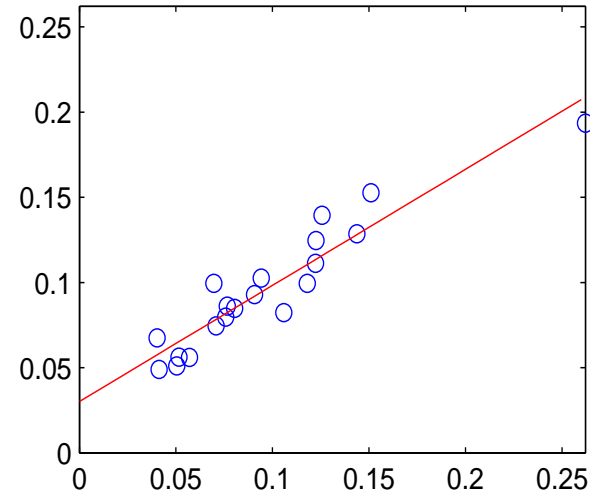
Subject	θ	λ	δ	α_1	α_2	α_3
1206	2.049	0.923	0.233	0.930	0.931	0.926
1227	4.000	1.438	0.158	0.952	0.956	0.953
817	2.843	0.691	0.241	0.935	0.935	0.919
1154	2.730	0.872	0.237	0.958	0.957	0.960
1208	1.790	0.518	0.318	0.912	0.915	0.912
1231	2.294	0.828	0.265	0.938	0.932	0.929
1245	2.287	0.350	0.364	0.928	0.929	0.922
827	3.190	0.797	0.257	0.935	0.934	0.928
1264	3.000	1.558	0.152	0.939	0.952	0.934
1078	4.000	0.889	0.260	0.961	0.963	0.963
1188	2.246	0.628	0.247	0.930	0.925	0.914
1234	3.543	0.781	0.277	0.941	0.941	0.943
1086	4.000	1.121	0.189	0.961	0.960	0.958
1191	3.781	0.792	0.257	0.942	0.940	0.941
Average	3.100	0.89	0.239	0.941	0.939	0.936

Validation by Quantification

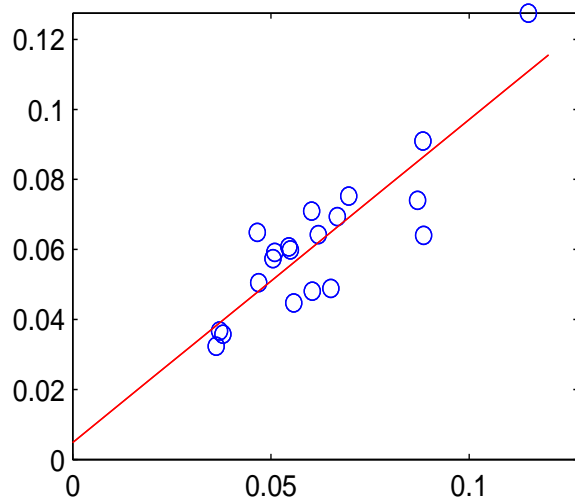
K_1 , $y=0.61x+0.049$ ($r=0.64774$, $p=0.0019$)



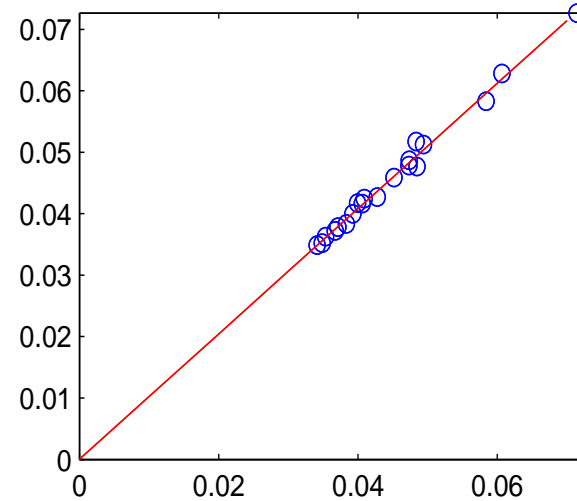
k_2 , $y=0.68x+0.03$ ($r=0.94$, $p=3.25e-9$)



k_3 , $y=0.92x+0.005$ ($r=0.87$, $p=3.48e-7$)



K , $y=1.02x+5.5e-05$ ($r=0.996$, $p<1.2e-16$)



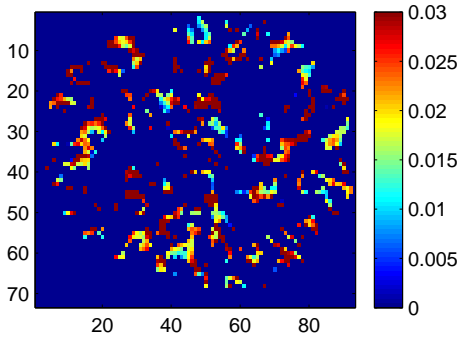
4. Observations from Results

- **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.
- **consistency of the decay** of the input across subjects to power nearer 0.25 on average.
- **spillover** is consistent across most subjects, from blood to tissue is actually quite low

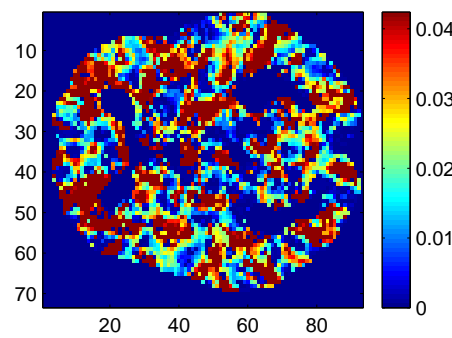
Additional Comments on the Optimization

- **Constraints** It is essential to use constraints for the minimization.
- **Cluster curves** Clustering provides subject dependent constraints

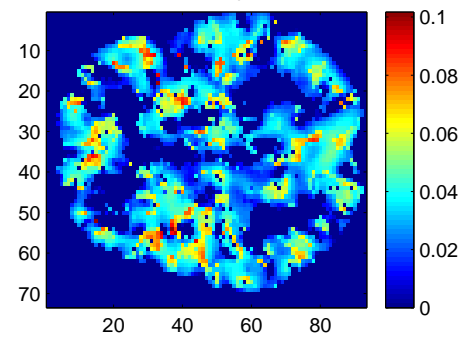
k_4 – no bounds imposed FLS



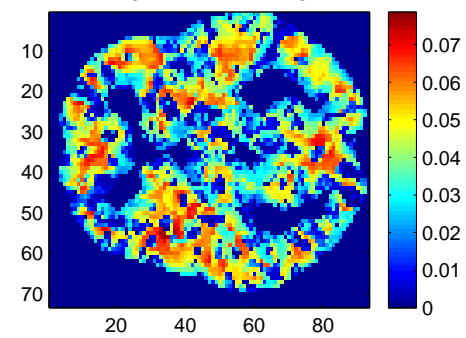
k_4 – using bounds from Feng, 1995



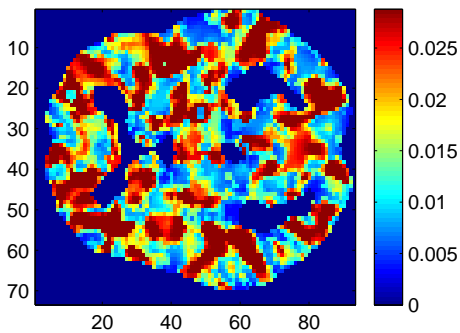
K – no bounds imposed FLS



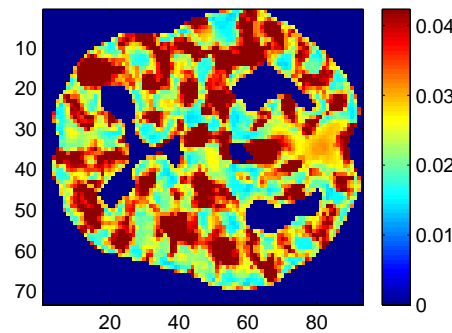
K – using bounds from Feng, 1995



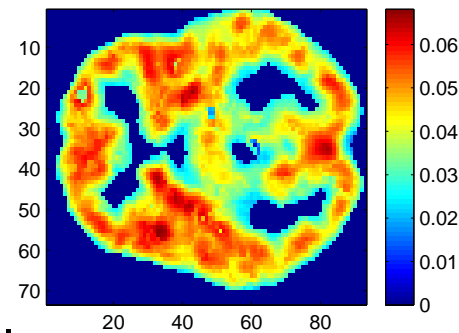
k_4 – using bounds from Piert, 1996



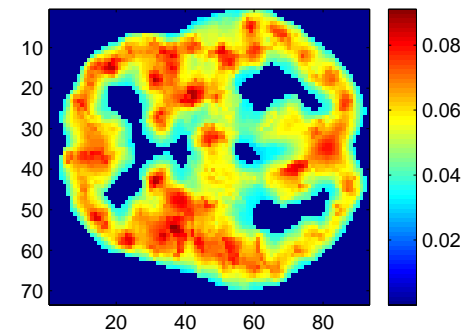
k_4 – using bounds derived from clustering



K – using bounds from Piert, 1996



K – using bounds derived from clustering

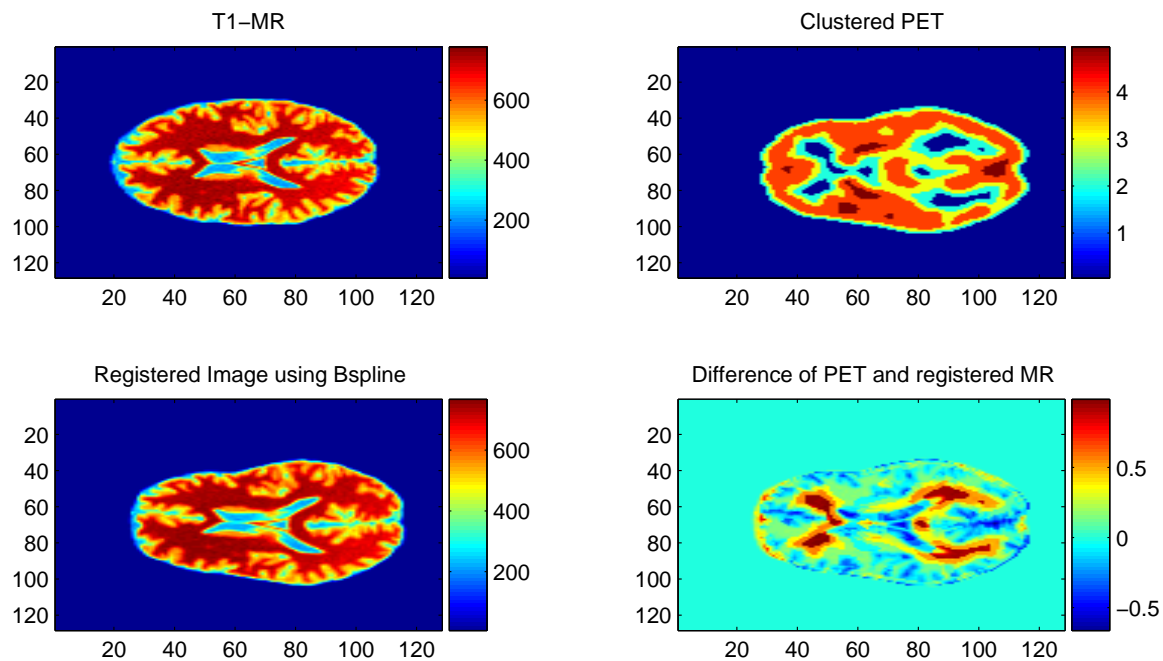


Some Remaining Issues

- **Postestimation** Use the recovered input to do parameter estimation comparison?
- **Remove blood sampling:** can input be recovered entirely without blood samples?
 - **Additional Image Analysis** automate completely identifying CA region.
 - **MR to PET registration** map MR structure to identify Carotid Artery on PET
 - **Independent Component Analysis** to identify CA in PET.

5. MR -PET Image Registration: Initial Work

- **Multi-modal registration** PET and MR are different modalities, with different distributions of image intensities
- **Mutual Information** maximize the MI between images to obtain an elastic match.



Example of PET/MR matching using MI and B-spline
joint work with Professor Farin

6. 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], 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], 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

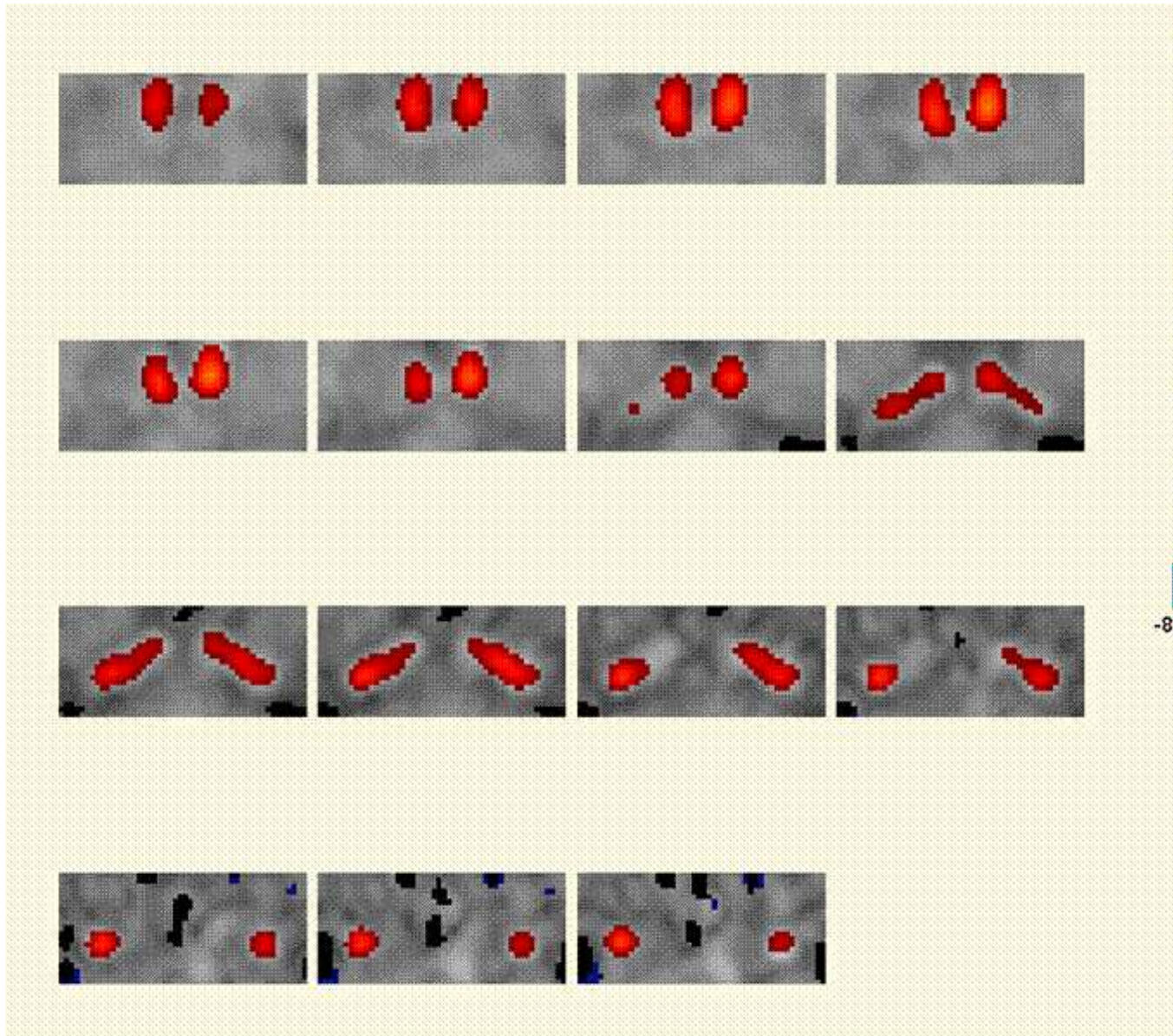
Software adopted: FMRLAB www.sccn.ucsd.edu/fmrlab (Duann, et al., 2002)

- 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 20 seconds - to identify that for blood vessel.
- Correct the partial volume and spillover effects.

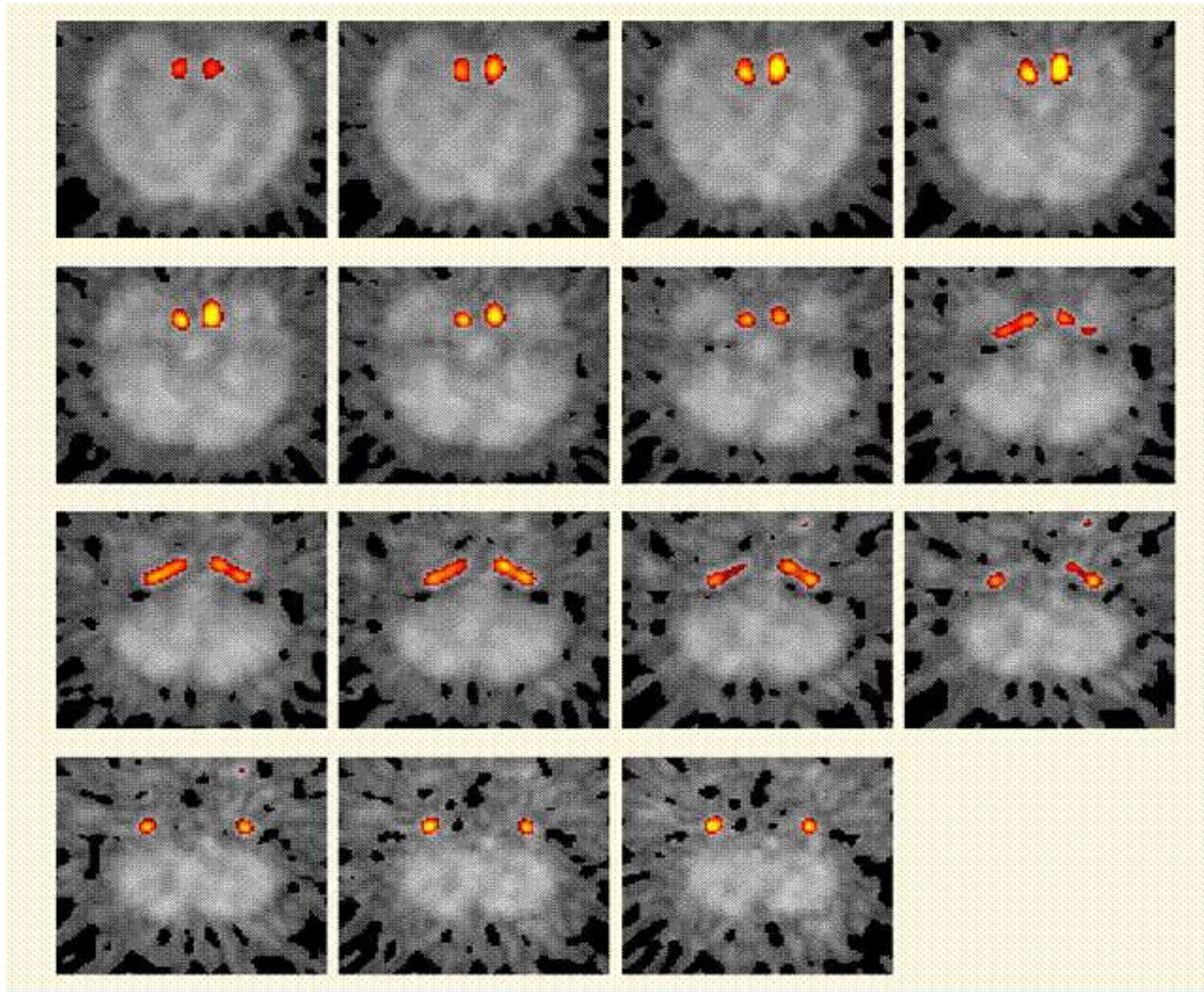
ICA Setting Determination and Validation

- Evaluate robustness of the sub-brain volume size, shape and location.
- Determine the z-threshold (Z_{input}) for carotid artery region definition.
- Determine the z-threshold (Z_{output}) 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.

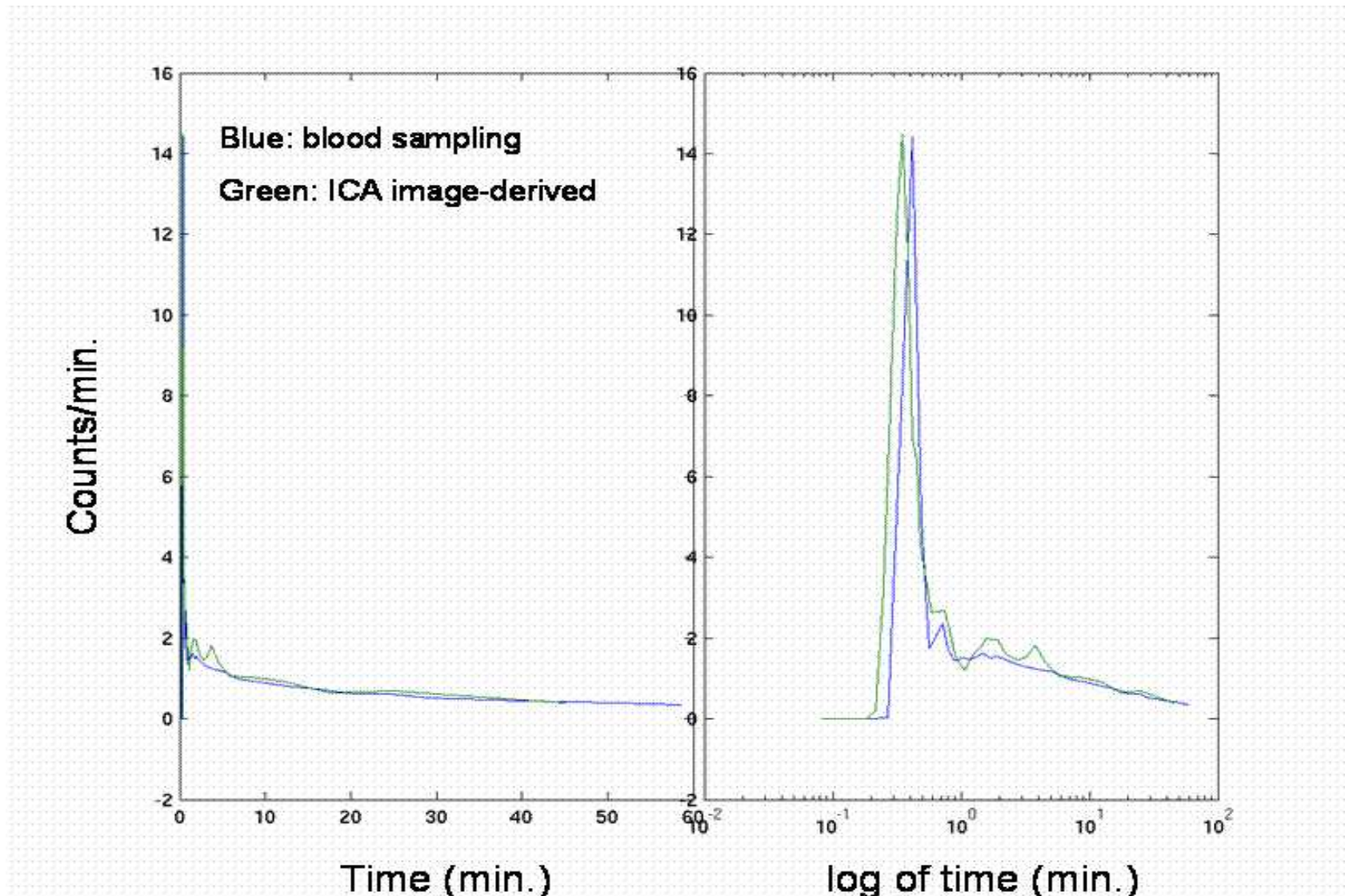
7. Results of ICA defined ROI : Subvolume



ICA Determined Carotid Artery Region: Whole Brain

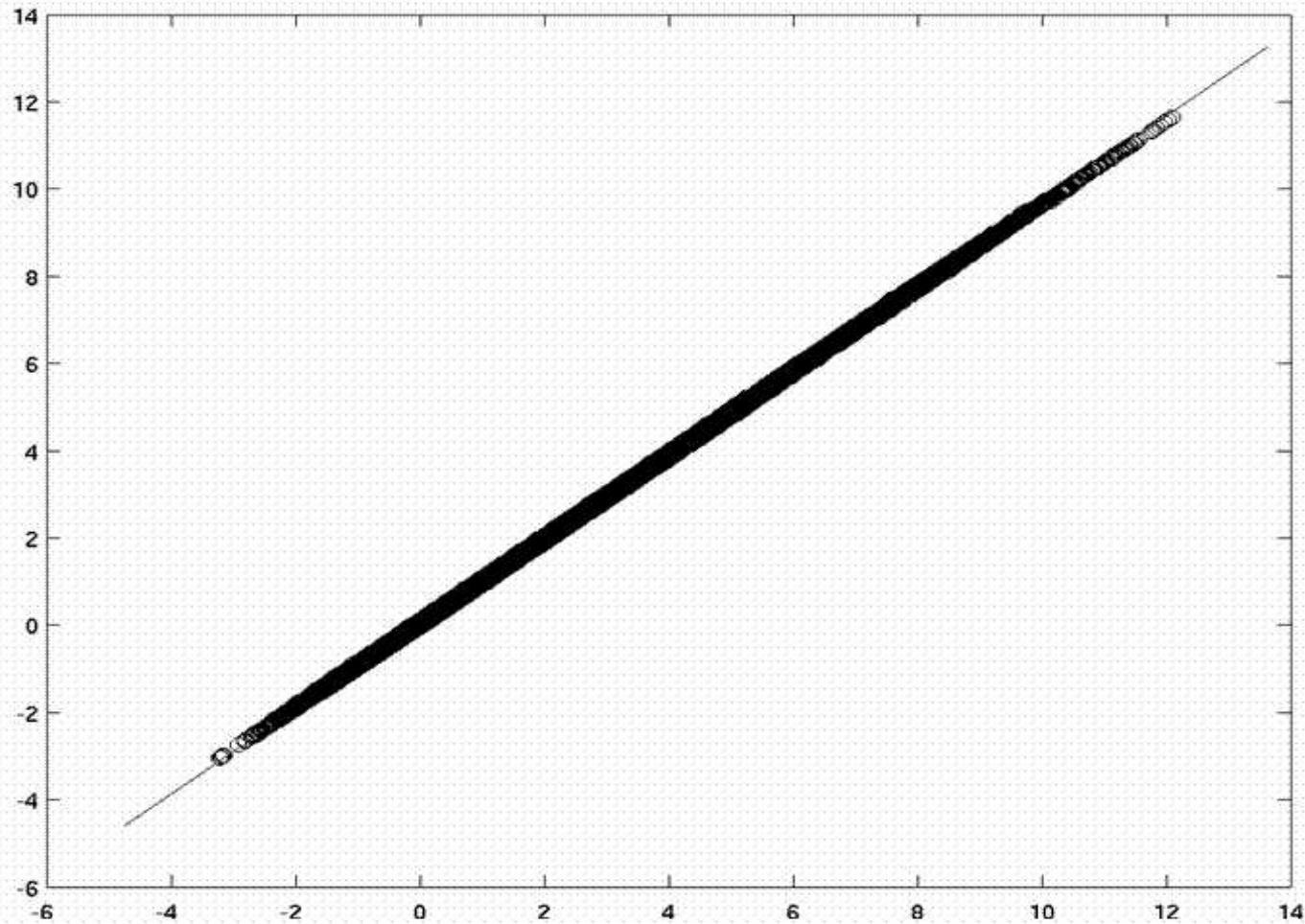


Blood-sampled and ICA image-derived input functions



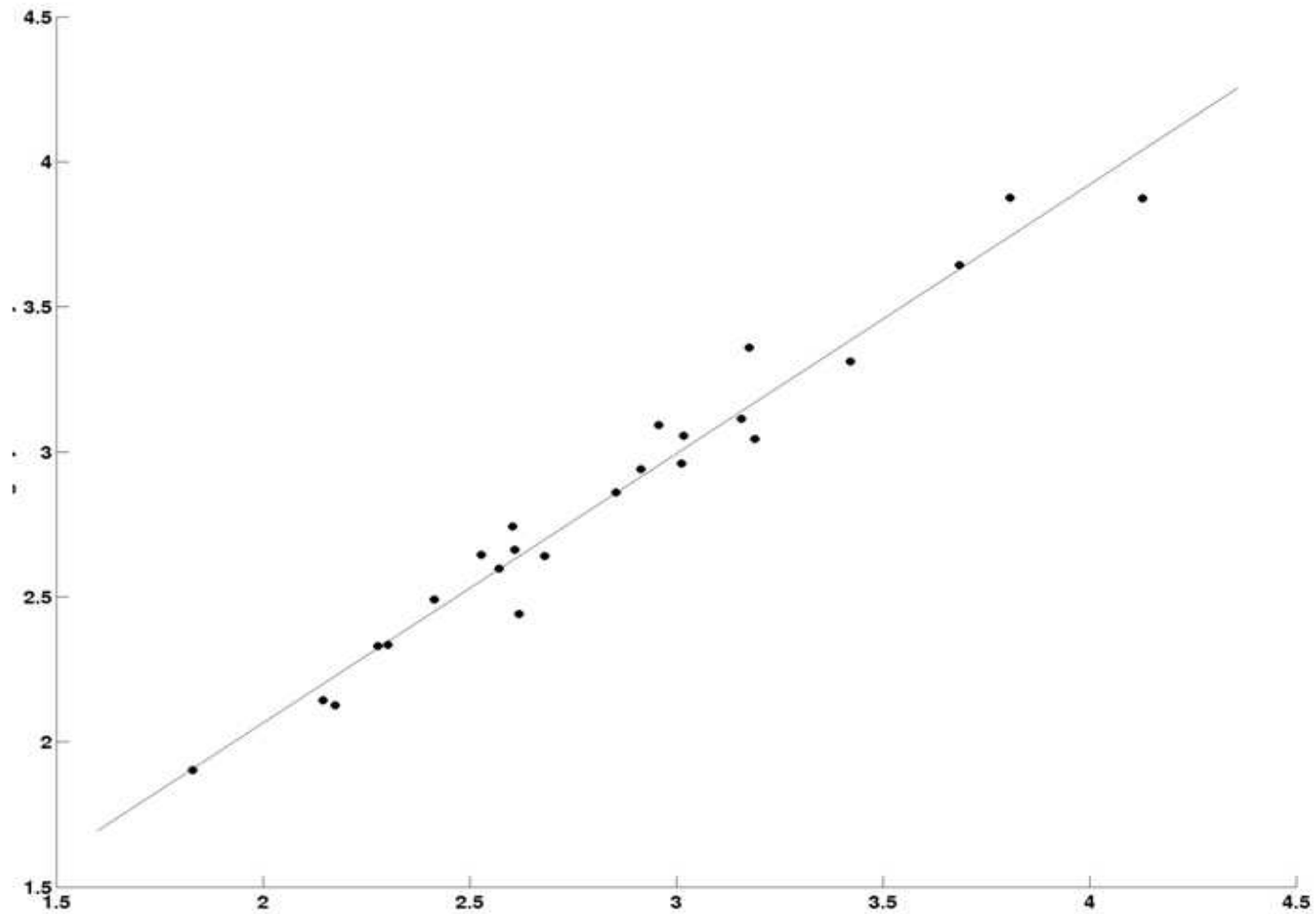
Notice again the shift between two curves

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



x-axis: blood samples; **y-axis:** CMRgl ICA derived. Calculations use Patlak not nonlinear fit.

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.

References

- [Huet] S.-C. Huang and M. E. Phelps and E. J. Hoffman and K. Sideris and C. J. Selin and D. E. Kuhl, "Noninvasive determination of local cerebral metabolic rate of glucose in man", *Am. J. Physiol.*, vol. **238 E**, pp. 69-82, 1980.
- [Phel] M. E. Phelps and S. C. Huang and E. J. Hoffman and C. E. Selin and D.E. Kuhl, "Tomographic measurement of local cerebral glucose metabolic rate in man with (^{18}F) fluorodeoxyglucose: Validation of method", *Ann. Neurol.*, vol. **6**, pp. 371-388, 1979.
- [Taki] S. Takikawa and V. Dhawan and P. Spetsieris and W. Robeson and T. Chaly and R. Dahl and D. Margouleff and D. Eidelberg, "Noninvasive quantitative fluorodeoxyglucose PET studies with an estimated input function derived from a population-based arterial blood curve", *Radiology*, vol. **188**, pp. 131-136, 1993.
- [Eberl] S. Eberl and A. R. Anayat and R. R. Fulton and P. K. Hooper and M. J. Fulham, "Evaluation of two population based input functions for quantitative neurological FDG PET studies", *Eur. J. Nucl. Med.*, vol. **24**, pp. 299-304, 1997.

References

- [Litt] J.-E. Litton, “Input function in PET brain-studies using MRI defined arteries”, *J. Comp. Ass. Tom.*, vol. 21, no. 6, pp. 907-909, 1997.
- [Lipt] M. Liptrot and K. H. Adams and L. Martiny and L. H. Pinborg and M. N. Lonsdale and N. V. Olsen and S. Holm and C. Svarer and G. M. Knudsen, “Cluster analysis in kinetic modelling of the brain: a noninvasive alternative to arterial sampling”, *Neuroimage*, vol. 21, no. 2, pp. 483-493, 2004.
- [Chen] K. Chen and D. Bandy and E. Reiman and S.-C. Huang and M. Lawson and D. Feng and L.-S. Yun and A. Palant, “Noninvasive quantification of the cerebral metabolic rate for glucose using positron emission tomography, ^{18}F -fluorodeoxyglucose, the Patlak method, and an image-derived input function”, *J. Cereb. Blood Flow Metab.*, vol. 18, pp. 716-723, 1998.
- [Feng] D. G. Feng and K.-P. Wong and C.-M. Wu and W.-C. Siu, “A technique for extracting physiological parameters and the required input function simultaneously from PET image measurements: Theory and simulation study”, *IEEE Trans. Inform. Technol. Biomed.*, vol. 1, no. 4, pp. 243-254, 1997.

References

[SanBo]

S. M. Sanabria-Bohorquez and A. Maes and P. Dupont and G. Bormans and T. de Groot and A. Coimbra and W. Eng and T. Laethem and I. De Lepeleire and J. Gambale and J. M. Vega and H. D. Burns, “Image-derived input function for [^{11}C] flumazenil kinetic analysis in human brain”, *Mol. Imag. Biol.*, vol. 5, no. 2, pp. 72-78, 2003.

[Wong]

K.-P. Wong and D. Feng and S. R. Meikle and M. J. Fulham, “Simultaneous estimation of physiological parameters and the input function - In vivo PET data”, *IEEE Trans. Inform. Technol. Biomed.*, vol. 5, no. 1, pp. 67-76, 2001.