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

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Supported by Arizona Alzheimer’s Research Center and NIH

Arizona State University

March 30, 2007 Georgia State University Colloquium
Outline

1 PET Images

2 FDG-PET Quantification
   - The Standard Model
   - Practical Difficulties - obtaining the input function
   - Possible Solution: Arterial ROI TAC
   - Review

3 Parameter Estimation
   - Modeling the input function
   - The New Input
   - Estimating Parameters of the Model
   - Results

4 Image Restoration
   - Regularized Optimization
   - Numerical Results

5 Conclusions and Future Work
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Example of typical PET scan

Typical PET Images show
- High noise content (non-Gaussian)
Example of typical PET scan

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- High blurring
- *Partial volume Effects*
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Typical PET Images show
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- Reconstruction artifacts
- Reconstruction using filtered backprojection
Example of Dynamic PET series
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Dynamic data
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Dynamic data
- Very poor initial scans
- Noise levels change across scans
- Time interval increases with scan
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- Time interval increases with scan
- Movement of patient
- Physiological Movement
**Goals/Methods of the Study**

- Improved Sensitivity for identifying features in images:
  - Identify anomalies in single images.
  - Identify changes over time: Longitudinal Studies of AD
  - Assessing disease state- AD or MCI (mild cognitive impairment)
  - Assess impact of drug treatment

- Noninvasive assistance in AD studies.

- Solve Ordinary Differential System of Equations.

- Use basic **Inverse Problems**, **Optimization** and **Statistics**.
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PET Imaging System **Input**, Response and **Output**

**Input Tracer Density in plasma**

\[ u(t) \]
PET Imaging System Input, Response and Output

Brain Tissue: Impulse Response Function (IRF)

\[ h(t, K_1, k_2, k_3, k_4) \]
Output: Tissue time activity curve

\[ y(t) \]
Convolution Solution of Differential Equation

\[ y(t) = u \otimes h \]
FDG-PET Compartmental Modelling

The diagram illustrates the metabolic pathways involving glucose and FDG (Fluorodeoxyglucose) in biological systems. Key components and processes are highlighted:

- Glucose compartments
- FDG compartments
- Metabolic fluxes indicated by arrows
- Kinetic parameters (K1, K2, K3, K4)

These pathways are crucial for understanding tissue metabolism and disease states, as inferred from PET (Positron Emission Tomography) imaging.
The Differential System of Equations

\[
\begin{align*}
\dot{y}_1 &= K_1 u(t) - (k_2 + k_3) y_1(t) + k_4 y_2(t) \\
\dot{y}_2 &= k_3 y_1(t) - k_4 y_2(t).
\end{align*}
\]

1. \(K_1\) and \(k_2\)–FDG transport rate
2. \(k_3\) and \(k_4\) phosphorylation and dephosphorylation rate.
3. \(\text{LCMRglc: } \frac{K_1 k_3}{k_2 + k_3} \frac{C_p}{LC} = K \frac{C_p}{LC}\).
4. \(y_1(t)\) is the FDG in tissue
5. \(y_2(t)\) the phosphorylated FDG in tissue.
6. \(u(t)\) is the FDG input in plasma.
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- $u(t)$ is the FDG input in plasma.
Given $u(t)$ and $y(t) = y_1(t) + y_2(t)$, estimate $K_1, k_2, k_3, k_4$ and $K$.

Let $k_4 = 0$, the solution of the system is easily found and we have

$$y(t) = u(t) \otimes h(t, K_1, k_2, k_3)$$

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

This gives the nonlinear least squares estimation

$$\min_{K_1, k_2, k_3} \| y(t) - u(t) \otimes h(t, K_1, k_2, k_3) \|_W.$$ 

Here $\| \cdot \|_W$ indicates that this is in a weighted norm.
Obtain Input Function by Blood Sampling

- **Gold Standard**: arterial sampling causes discomfort. There are potential risks, e.g., arterial thrombosis, arterial sclerosis, and ischemia to the extremity.

- **Arterialized venous sampling method**, the limb is heated to avoid discomfort, (Phelps et al., 1979). Still requires frequent blood sampling.

- **Population based input function**, (Takikawa et al., 1993 and Erberl et al., 1997). Not individual specific.

- **Challenge** Reducing/avoiding blood sampling.
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Challenge Reduce/avoid blood sampling.
Using the Region of Interest (ROI): Carotid Arterial ROI TAC and Blood Samples

Blood ROI TAC

Tissue ROI TAC

Blood samples

Avg Blood TAC (ABTAC)
Recent Representative Methods—Without blood samples

- **Image-derived input function**: no blood samples. Blood ROIs are identified by aligning MR and PET, and average blood TAC, \( v(t) \), is used. (Litton, 1997, Liptrot *et al*, 2004, Wahl *et al*, 1999).

- **Simultaneous Estimation of Input and Output (SIME)**:

  \[
  u(t) = (A_1 t - A_2 - A_3) e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t} + A_3 e^{-\lambda_3 t}
  \]

  Let \( P_m = \{k_1, \cdots, k_4\} \) for \( m^{th} \) tissue TACs, and solve (6 input parameters) (Feng *et al*, 1997).

  \[
  \min_{A_i, \lambda_j, P_m} \sum_{m=1}^{M} \sum_{n=1}^{N} w_{mn} \left\{ y_m(t_n) - (h_m(t, P_m) \otimes u(t, A_i, \lambda_j))_n \right\}^2.
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- **Difficulties**: former requires MR images and registration, latter assumes \( y \) not contaminated by partial volume or spillover.
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  $$\min_{A_i, \lambda_j, \mathcal{P}_m} \sum_{m=1}^M \sum_{n=1}^N w_{mn} \left\{ y_m(t_n) - (h_m(t, \mathcal{P}_m) \otimes u(t, A_i, \lambda_j))_n \right\}^2.$$ 

- **Difficulties:** former requires MR images and registration, latter assumes $y$ not contaminated by partial volume or spillover.
Using a Limited Number of Blood Samples

- **SIME based method**, (Sanabria-Bohorquez *et al*, 2003), Let

  \[ u(t) = sf \cdot F(t) \cdot v(t) + A \cdot te^{-Bt} \quad F(t) = a \cdot e^{-bt} + 1 - a \]

  where \( F(t) \) models the \([^{11}C]\)-FMZ fraction in plasma, \( b \) is decay, and \( sf \) and \( a \) are determined using three late blood samples. Then \( A \) and \( B \) are calculated by SIME with information from tissue TACs.

- **Linear relationship based method**: (Chen *et al*, 1998, 2007), assume \( v(t) = \alpha \cdot u(t) + \beta \cdot y(t) \). Solve for \( \alpha \) and \( \beta \) by using three late venous samples to correct partial volume and spillover effects.

- **Proposed method** (Guo *et al*). Model late portion by \( A \cdot e^{-\lambda(t-\tau)} \delta \) and early portion by correcting the partial volume of \( v(t) \). Do not use the later portion of \( v(t) \).
Real Data

- FDG-PET data from 951/31 ECAT for **18 healthy subjects**.
- Images are reconstructed by filtered back projection. Each reconstructed data set includes **31 slices** with 3.375mm 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 the frames are 0.2, 8 × 0.0333, 2 × 0.1667, 0.2, 0.5, 2 × 1, 2 × 1.5, 3.5, 2 × 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, the 5, 6, 8, 10, 12, 15, 20, 25, 30, 40, 50 and 60 minutes. We represent the blood samples by $u_{bs}(t_j), j = 1, 2, \cdots, 34$. 
Compare CA-ROI TAC with Blood Samples

Early Time curves compare

Later time curves compare
Proposed Model for the input function

Formulation

\[ u_e(t, \theta, \lambda, \delta) = \begin{cases} 
\theta \cdot v(t) & t \in [0, \tau] \\
\theta \cdot v(\tau) \cdot e^{-\lambda(t-\tau)\delta} & t \in [\tau, T] 
\end{cases} \] (Window 1)

1. \( \tau \) separates \( W_1 \) and \( W_2 \).
   - On \( W_1 \), the curve is high quality, spillover can be ignored.
   - On \( W_2 \) use the analytic formula.

\( \tau \) is a parameter that has to be determined so as to trade off between the best characteristics of the two windows.

2. \( \theta \cdot v(\tau) \) assures continuity at \( \tau \).

3. Blood samples at \( t = 10, 20 \) and 60 min. are used in fitting to obtain the model’s parameters.
Rationale

Compare the proposed formulation with two standard models

\[
\begin{align*}
  u_{\text{Phelps}} &= A_1 e^{-\lambda_1(t-\tau)} + A_2 e^{-\lambda_2(t-\tau)} + A_3 e^{-\lambda_3(t-\tau)}, \\
  u_{\text{Feng}} &= (A_1(t - \tau_0) - A_2 - A_3)e^{-\lambda_1(t-\tau_0)} + A_2 e^{-\lambda_2(t-\tau_0)} + A_3 e^{-\lambda_3(t-\tau_0)}
\end{align*}
\]

Fit blood samples on \( W_2 \) using...
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Fit blood samples on \( W_2 \) using

- all available nodes \( t_i \geq \tau \)
Rationale

Compare the proposed formulation with two standard models

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Fit blood samples on $W_2$ using

- just using nodes at $\tau$ and 10, 20, and 60 min.
Fit the proposed formula by blood samples at $t = 10, 20$ and $60$ min. to estimate parameters $\theta$, $\lambda$ and $\delta$. 
Extrapolation for Different Subjects for $t < 10$

Fit the proposed formula by blood samples at $t = 10, 20$ and $60$ min. to estimate parameters $\theta$, $\lambda$ and $\delta$.

\[ \theta = 11.19 \]
Extrapolation for Different Subjects for $t < 10$

Fit the proposed formula by blood samples at $t = 10, 20$ and $60$ min. to estimate parameters $\theta$, $\lambda$ and $\delta$.

$$\theta = 1.001$$
Fit at $t = 10, 20$ and $60$ min. and $[\tau, \theta \ast \nu(\tau)]$. 
Interpolation and Picking $\theta$

Fit at $t = 10, 20$ and $60$ min. and $[\tau, \theta \ast v(\tau)]$.

$\theta = 6$
Interpolation and Picking $\theta$

Fit at $t = 10, 20$ and $60$ min. and $[\tau, \theta \ast v(\tau)]$.

$\theta = 2.8$

$\theta$ is the only independent parameter, once a good $\theta$ is obtained, the whole curve is recovered.
Overview of fitting: The choice of $\theta$ is important

$\theta$ must be chosen to fit the measured data
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$\theta$ must be chosen to fit the measured data
θ is the Only Independent Parameter

Method

For a given value of θ, parameters λ, δ are determined by

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

where \((t_i, u_{bs}(t_i))\), \(i = 1, 2, 3\) are venous blood samples.

θ is the inverse of the recovery coefficient, and measures the ability to recover the actual blood data from the brain measurement.
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For a given value of \( \theta \), parameters \( \lambda, \delta \) are determined by

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Nonlinear Method

Method (Here using two TTAC curves obtained by clustering)

\[
\min_{\theta, P_1, P_2, \alpha_i} \sum_{i=1}^{2} \sum_{j=1}^{n} w_{ij} \left[ y_i(t_j) - \alpha_i \cdot (h_i \otimes u_e)_j - (1 - \alpha_i) \cdot u_e(t_j, \theta) \right]^2,
\]

subject to

\[
0.015 \leq K_1^{(i)} \leq 0.3, \quad 0.024 \leq k_2^{(i)} \leq 0.54, \quad 0.01 \leq k_3^{(i)} \leq 0.2,
\]

\[
0.9 \leq \alpha_i \leq 1, \quad 1.2 \leq \theta \leq 4
\]

1. Weight \( w_{ij} = \Delta t_j / y_i(t_j) \)
2. Parameter \( \alpha_i \) corrects spillover from blood to tissue
3. Tissue clusters \( y_i(t) \) are generated by a fast PET data clustering algorithm, (Guo et al, 2003).
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Representative Results
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![Graph showing counts/min vs log of time (min.)]
Table: Linear regression: $K$ calculated by the Patlak method for 50 clusters of each subject, comparing blood samples $u_{bs}$ and estimated input function $u_e$.

<table>
<thead>
<tr>
<th>Subject</th>
<th>$u_{bs}$ mean $K$ ± standard deviation</th>
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<td>−4.8e−05</td>
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<tr>
<td>4</td>
<td>2.6678e−02 ± 3.7e−03</td>
<td>2.6811e−02 ± 3.7e−03</td>
<td>9.991e−01</td>
<td>1.000</td>
<td>1.3e−04</td>
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<tr>
<td>5</td>
<td>3.0645e−02 ± 5.9e−03</td>
<td>3.0775e−02 ± 5.8e−03</td>
<td>9.9945e−01</td>
<td>0.984</td>
<td>6.1e−04</td>
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<td>6</td>
<td>3.1183e−02 ± 6.3e−03</td>
<td>3.0731e−02 ± 6.1e−03</td>
<td>9.9932e−01</td>
<td>0.958</td>
<td>8.7e−04</td>
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<tr>
<td>7</td>
<td>2.8179e−02 ± 5.0e−03</td>
<td>2.7959e−02 ± 4.9e−03</td>
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<td>2.3342e−02 ± 5.0e−03</td>
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<td>9</td>
<td>2.3579e−02 ± 5.1e−03</td>
<td>2.4315e−02 ± 5.3e−03</td>
<td>9.997e−01</td>
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<td>−2.1e−04</td>
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<tr>
<td>10</td>
<td>2.7038e−02 ± 4.7e−03</td>
<td>2.7303e−02 ± 4.8e−03</td>
<td>9.995e−01</td>
<td>1.016</td>
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<tr>
<td>11</td>
<td>2.7517e−02 ± 7.8e−03</td>
<td>2.8196e−02 ± 7.8e−03</td>
<td>9.991e−01</td>
<td>1.015</td>
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<tr>
<td>12</td>
<td>2.3044e−02 ± 4.2e−03</td>
<td>2.4276e−02 ± 4.6e−03</td>
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<td>2.5904e−02 ± 1.1e−02</td>
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<td>15</td>
<td>3.5393e−02 ± 6.7e−03</td>
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<td>16</td>
<td>2.3601e−02 ± 5.3e−03</td>
<td>2.4239e−02 ± 5.7e−03</td>
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<td>17</td>
<td>2.7052e−02 ± 4.9e−03</td>
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<td>18</td>
<td>2.5460e−02 ± 4.6e−03</td>
<td>2.5182e−02 ± 4.8e−03</td>
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Regression for $K$ Over All Subjects

Linear regression for $K$ calculated with blood samples $u_{bs}$ and estimated input function $u_e$ using the Patlak method. Correlation 0.9969, slope .9878 and intercept $7.1 \times 10^{-4}$. 
Parameters for one subject. The correlation coefficients are 0.9814, 0.9954, 0.9992 and 0.9890
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1. Solution of simple ODEs.
2. Nonlinear fit - two options, one a simple nonlinear fit.
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Observations: Very Simple Problem requiring basic mathematics

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More About PET images

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- For a small $\beta$ define

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- On the left simulated PET from blurred segmented MRI scan using **Gaussian PSF** and noise added.
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Recover real PET image

- Reconstruction done using Filtered Back Projection
- PSF estimated by a Gaussian
- TV regularization
Observations

- Image improvement is possible even with a rough estimation of the PSF (non-blind deconvolution)
- Total Variation regularization (piecewise constant solution) is appropriate: intensity levels depend on the tissue type.
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  \[ g = Hf + n \]

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- TLS assumes error in \( H \) and \( g \) i.e.
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Scaled TLS: different noise levels

- Theory (Paige and Strakos, Numerische Mathematik)

\[ \min ||E|n||_F^2 \quad \text{subject to} \quad g = (H + E)f + \frac{n}{\gamma} \]

- Minimum is obtained as the minimum singular value of \([H, \gamma g]\)
- For flexibility use Rayleigh quotient formulation

\[ \min_f \frac{||Hf - g||_2^2}{1 + \gamma^2 ||f||_2^2} \]

- \(\gamma = 0\) is the LS problem
- \(\gamma = 1\) is the standard TLS problem
- \(\gamma\) accounts for different noise levels in \(H\) and \(g\).
Scaled TLS: different noise levels

- Theory (Paige and Strakos, Numerische Mathematik)

\[ \min ||E|n||_F^2 \quad \text{subject to} \quad g = (H + E)f + \frac{n}{\gamma} \]

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Regularize scaled RQ:

$$\min_f \frac{\|Hf - g\|^2_2}{1 + \gamma^2\|f\|^2_2} + \lambda R(f)$$

- Permits careful investigation of effect of noise levels in $H$ and $g$.
- Which is greater, the error in the PSF or the error in the measured data?
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Which is greater, the error in the PSF or the error in the measured data?
Test Problem Noisy Shepp Logan Phantom

Shepp Logan Phantom
Blur with Gaussian $h(x) = \frac{1}{\sigma\sqrt{2\pi}} e^{-\frac{|x|^2}{2\sigma^2}}$ with $\sigma = 1.5$ (6mm half width)

Take forward Radon transform with 45 angles

Add Poisson Noise to sinogram

Transform back, with filtered back projection
Deconvolving the Shepp-Logan Phantom

- Gauss PSF with $\sigma = 2$ and TV regularization

$$\gamma^2 = 0 \quad \gamma^2 = 7.3 \times 10^{-9} \quad \gamma^2 = 3.7 \times 10^{-7}$$

- Scaling shows how to improve impact of badly chosen PSF.
- Scaling $\|Hf\| = \|g\| = 1$ (Notice for given image $\|g\|^2 \approx 10^9$)
- For scaled problem $\gamma^2$ is 1, 50, resp.
Deconvolving the Shepp-Logan Phantom

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\end{align*}

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Real PET data
Use a PSF with $6\text{mm}$ half width Gaussian and then restore

\[ \gamma = 0 \text{ Least Squares} \]
Use a PSF with $6\,mm$ half width Gaussian and then restore

$$\gamma = 3.7e^{-7}$$ Total Least Squares
Use a PSF with 6mm half width Gaussian and then restore

\[ \gamma = 1.5 \times 10^{-5} \]
Use a PSF with 6mm half width Gaussian and then restore

\[ \gamma = 1 \times 10^{-4} \]
Observations

- RTLS with TV handles inexact PSFs better then simple RLS
- Scaled RTVTLS with parameter $\gamma$ in
  \[
  \min_f \frac{\|Hf - g\|_2^2}{1 + \gamma^2 \|f\|_2^2} + \lambda R(f)
  \]
  allows further tuning in case of an unknown PSF
- Iterations are expensive.
Observations

- RTLS with TV handles inexact PSFs better than simple RLS
- Scaled RTVTLs with parameter $\gamma$ in
  \[
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- Scaled RTVTLS with parameter $\gamma$ in

$$\min_f \frac{\|Hf - g\|^2_2}{1 + \gamma^2 \|f\|^2_2} + \lambda R(f)$$

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Conclusions and Future Work

- Further investigation of RTVTLS and relation to RTVLS (also with scaling)
- Improve efficiency of algorithms (methods of Guo and Renaut)
- Further interaction with medical consultants for impact and direction of the work.
- What can be achieved with wavelets? This yields other interesting work!
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Acknowledgments

- Hongbin Guo (Total Least Squares)
- Haewon Nam and Kewei Chen for the data and discussions on PET imaging
- Supported by: Arizona Alzheimer’s Research Center and NIH NIBIB
THANK YOU!