

A Computational Tool for FDG Kinetic
Parameter Estimation using Dynamic
Positron Emission Tomography
(PET) Data to Aid in Alzheimer's Research

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Why an analysis tool for Alzheimer's Disease (AD)?

- Causes the gradual loss of brain cells
- Estimated 4.5 million Americans have AD. (doubled since 1980)
- Difficult to Diagnose at an Early Stage
- PET scans could show a consistent diagnostic pattern for Alzheimer's disease

How can Positron Emission Tomography Help Diagnose AD

- Helps to assess the level of metabolic, biochemical, and functional activity in regions of brain
- Flouro-Deoxy-Glucose (FDG) , detectable radioactive substance is injected into the body.
- Radiation detectors are placed inside the PET camera to capture signals.
- Reconstruction methods use these signals to create an image of brain and track FDG

Goals of Project

- Build an application to estimate individual kinetic parameters which describe FDG dynamics
- Evaluate Different Estimation Methods for these parameters
- Design User Friendly Interface to Explore Different Parameter Estimation Options
- Write User Manual
- Publish Application and Manual on Website

Great Opportunity to Acquire Technical Skills and Work in an Interdisciplinary Team

- Learn MATLAB GUIDE
- Learn How to Use CVS
- Learn Latex
- Communications Skills in a
Interdisciplinary Team
 - Mathematician/Computer Scientist

Challenges

- Understand Estimation Techniques
- Early Noise in Data - Major
- What to do when estimated values go out of range
- How to Handle Spill Over
- Understand Initial Code

Interface Implementation Plan

- Understand Compartmental Kinetic Model for Parameter Estimation
- Write Requirements Document and Build Shared Code Repository
- Identify Inputs/Outputs
- Identify User options
- Error Handling
- Build Prototype

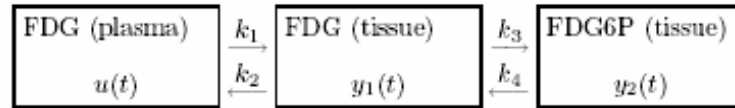
Requirements Document and Code Repository

- Requirements document
 - Helped analyze the problem to come up with the initial design.
 - Met several times to get Christina's and Renault's Inputs to come up with initial Interface design.

Compartmental Kinetic Model

Outputs: K1-K4

$$\begin{aligned}\frac{dy_1}{dt} &= k_1 u(t) - (k_2 + k_3)y_1(t) + k_4 y_2(t), \\ \frac{dy_2}{dt} &= k_3 y_1(t) - k_4 y_2(t), \\ y_1(0) &= 0, \quad y_2(0) = 0, \\ k_i &\geq 0, \quad i = 1, \dots, 4.\end{aligned}$$



k_1 = Transport rate of FDG from the blood to the Tissue

k_2 = Transport rate of FDG from the tissue to the blood,

k_3 = Phosphorylation rate of the intra-cellular FDG by hexokinase enzymes to FDG-6-phosphate, and

k_4 = de-phosphorylation rate of the intra-cellular FDG-6-phosphate back to FDG.

Other Implicit Kinetic Parameters

- K5 - Spill – Over Coefficient
- K6 = Computed explicitly using Kinetic Parameters = $(K1 * K3) / (K2 + K3)$
- BigK = Analogous to K6, and Computed Using PATLAK which Assumes $K4 = 0$
 - Biological Significance is $K6 / \text{BigK}$ are the local cerebral metabolic rate of glucose (FDG)
- K7 – $(1 - K5)$ Partial Volume Coefficient

Spill-Over

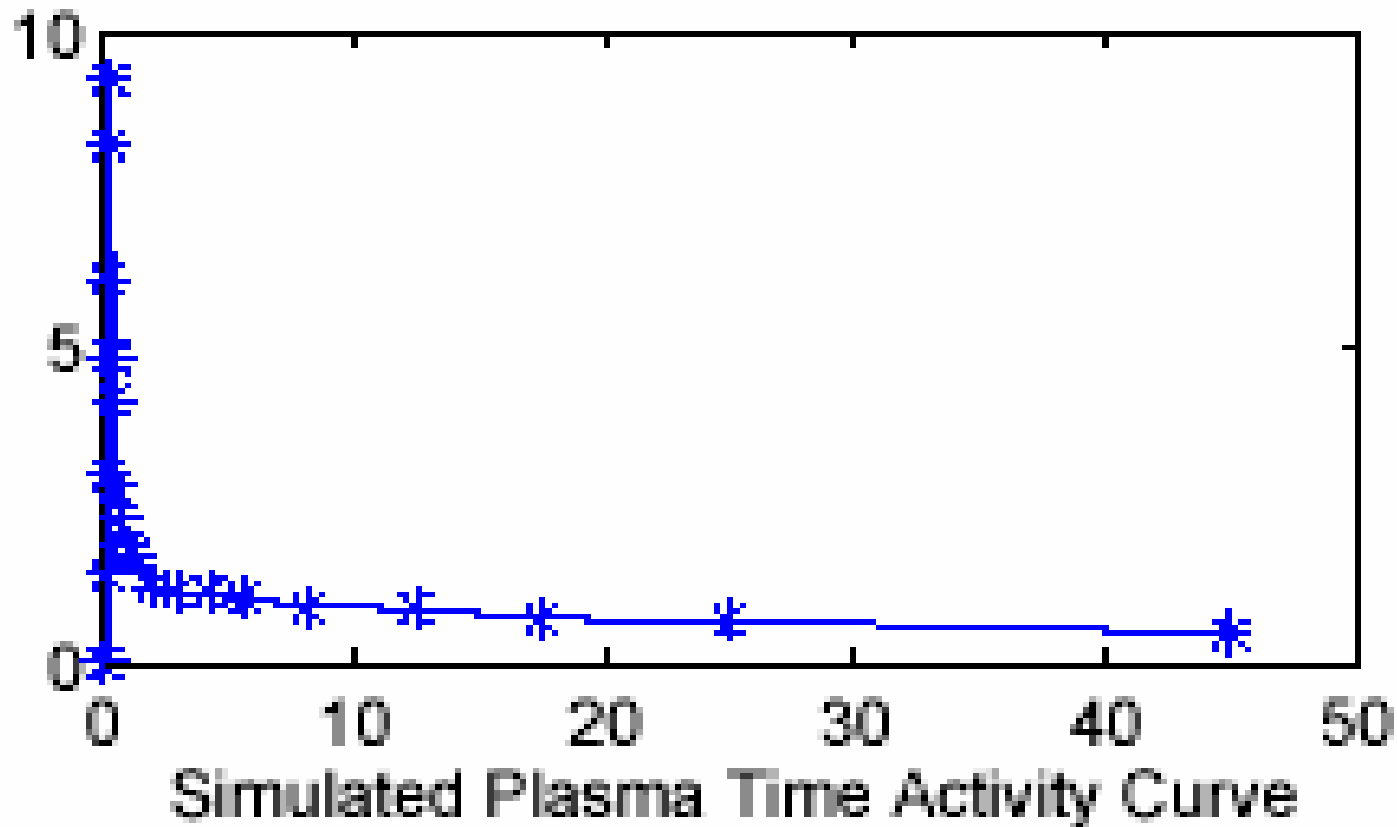
- Bi-directional, as it accounts for a percentage of the tracer in plasma being counted as total tissue-tracer, as well as for some of the tracer in tissue being counted as plasma-tracer.
- Alternatively incorporated in the model as K5

Partial Volume Effects

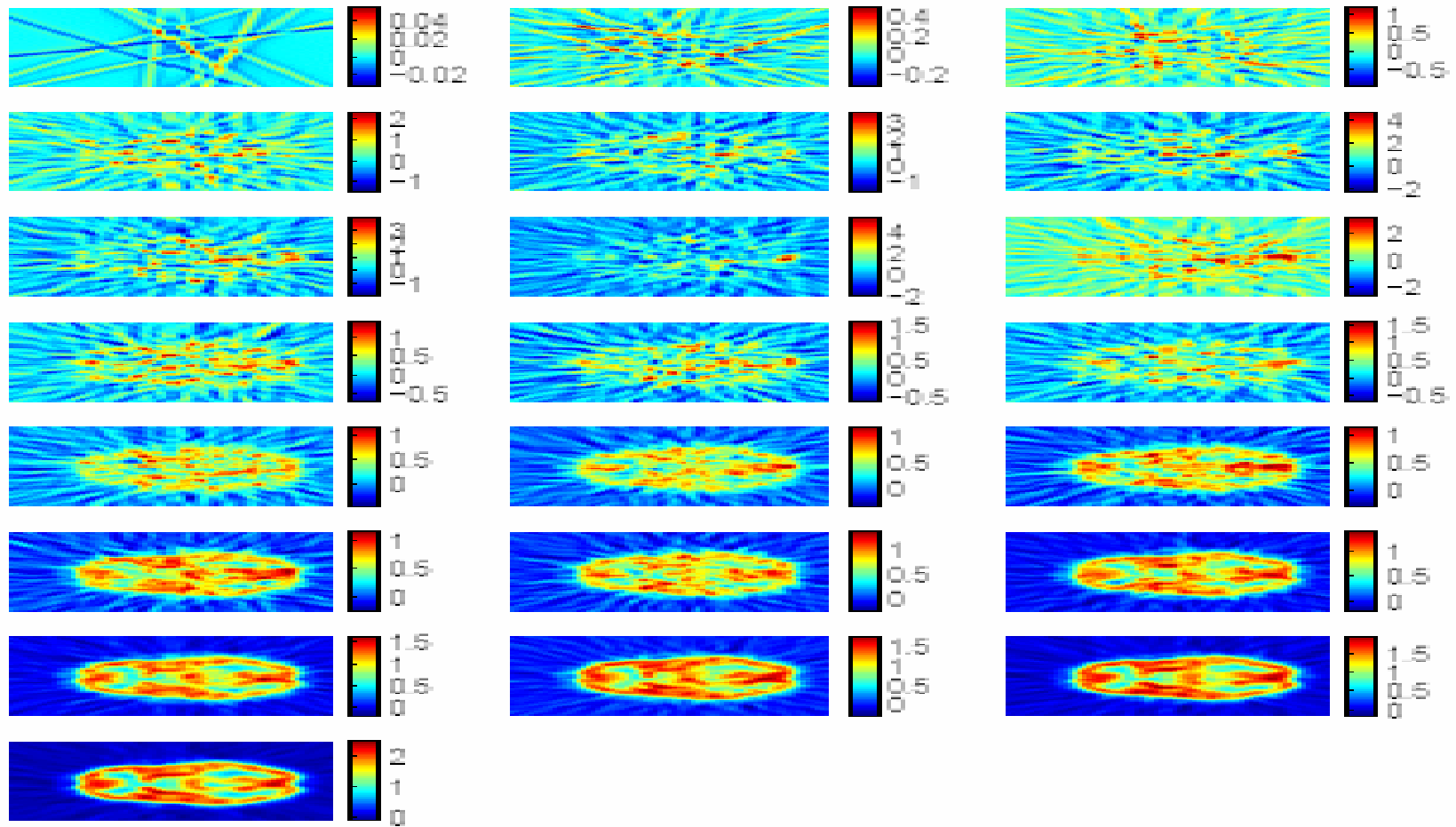
- Partial Volume Effects: Limited spatial resolution of PET scanners do not allow an exact measurement of the FDG in brain tissue
- Underestimate FDG concentration in small structures in the brain.
- Alternatively, PV is incorporated in the model as K_7 or $(1-K_5)$

Input : PTAC "u(t)"

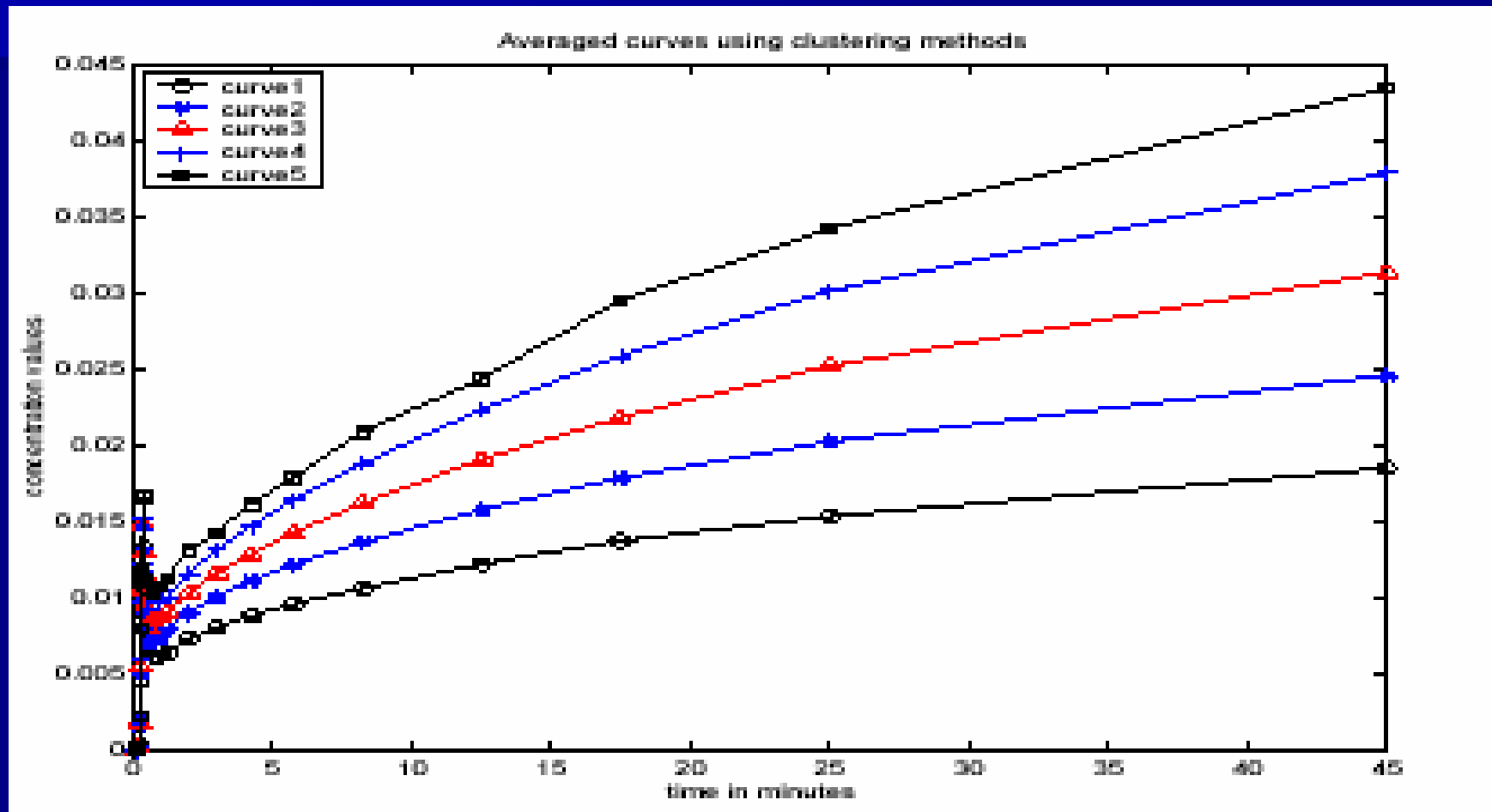
Real Study Image-Derived Plasma Time Activity Curve



Input = TTAC "y1(t)+y2(t)"



Alternative Input for TTAC: Cluster Curves



Options

- Process CSF Region?
 - User is prompted to choose at run time.
 - What to use as a threshold to segment CSF and save computation time.
- Filter Images?
 - How to reduce Noise – Clustering??
 - Anisotropic Filtering
- Segment Image?
 - Cut outer pixels in the image

More Options

- Apply Constraints during Kinetic Parameter Estimation?
 - Global, by Cluster, Positivity?
 - Automatic/User?
- What to run?
 - Entire Volume, Single Slice, Multiple Slices, Cluster Curves.
- Method Choice?
 - GLLS, Other – Currently only GLLS available

Generalized Linear Least Square (GLLS) Method

- Unbiased algorithm for parameter estimation of non-uniformly sampled data
- Eliminates the Computational burden of nonlinear least square regression
- Achieves a comparable estimation Quality in terms of the estimates' bias and standard deviation.
- Useful in pixel-by-pixel based parameter estimation for FDG dynamic studies with PET.
- Whitens Noise

Accounting for Spill-Over/Partial Volume Effect

- User can choose a specific estimation model to account for spill over or partial volume effects.
 - 6 Models available
- User is able to pick a model for each run.

Model Descriptions

Different Estimation Approaches

- Model 1: $k_4=0$, Spill-Over=0
- Model 2: $k_4=0$, Spill-Over>0
- Model 3: $k_4=0$, Spill-Over>0 with PV
- Model 4: $k_4>0$, Spill-Over=0
- Model 5: $k_4>0$, Spill-Over>0
- Model 6: $k_4>0$, Spill-Over>0 with PV

Error Handling

- Direct User enter all Required inputs
- Do not allow user to run without entering all required inputs
- Prompt User with Error Dialogs

Application Interface

main_window

File Run View

STATUS: Ready to Run

PTAC Data Filename: p04277dy1_roi1_roi.cpt Num of PTAC Files: 9

TTAC Data Filename: p04277dy1.img Data Type: Single Slice

Data Processing Method: CLLS Model: Model 2

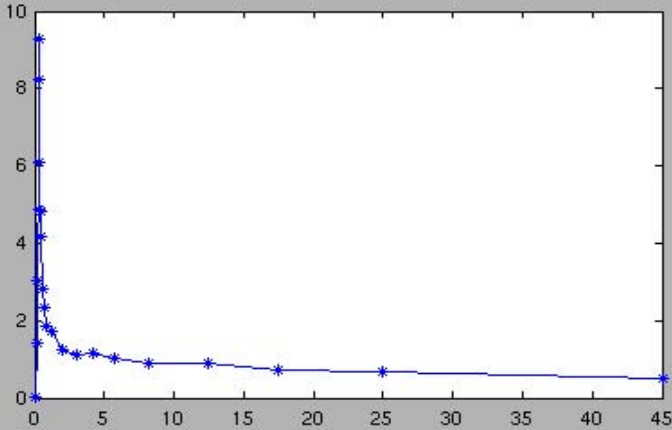
Time Vector Size: 22

Run Method With Global Positivity Constraints [LB:0, UB:1] Select Source for Constraints

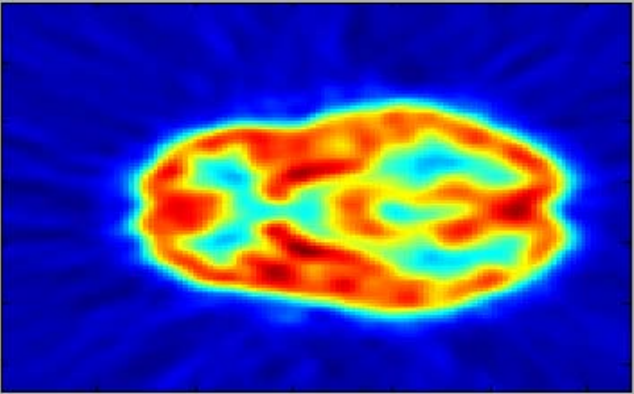
PTAC Curve from CPT file Slice Number: 16

Display PTAC figure Display TTAC Figure

Display Figure to View more Detail



| Time Step | Value |
|-----------|-------|
| 0 | 0.0 |
| 1 | 9.5 |
| 2 | 8.2 |
| 3 | 6.1 |
| 4 | 4.8 |
| 5 | 3.2 |
| 10 | 1.2 |
| 20 | 0.8 |
| 45 | 0.5 |



MSN Hotmail - Inbox - Download Manager xterm Com.mathworks.util 20:54

Sample Header File

Header Files - *.txt files

This header file contains run information

Data Type: Single Slice

TTAC Filename: p04277dy1.img

PTAC Filename 1: p04277dy1_roi1_roi.cpt

PTAC Filename 2: p04277dy1_roi2_roi.cpt

PTAC Filename 3: p04277dy1_roi3_roi.cpt

PTAC Filename 4: p04277dy1_roi4_roi.cpt

PTAC Filename 5: p04277dy1_roi5_roi.cpt

PTAC Filename 6: p04277dy1_roi6_roi.cpt

PTAC Filename 7: p04277dy1_roi7_roi.cpt

PTAC Filename 8: p04277dy1_roi8_roi.cpt

PTAC Filename 9: p04277dy1_roi9_roi.cpt

Time Vector Size: 22

Time Vector: 0.1, 0.216667, 0.25, 0.283333, 0.316667, 0.35, 0.383333, 0.416667, 0.45, 0.55, 0.716667, 0.9,
1.25, 2, 3, 4.25, 5.75, 8.25, 12.5, 17.5, 25, 45,

Processing Method: GLLS

Model: 4

Number of PTAC Files: 9

Number of Slices: 1

Slice Number: 16

These are the Constraint Options and Constraints for K1-K5

Running Without Constraints For Kinetic Parameters K1-K5

LB_K: UB_K: LB_THETA: UB_THETA:

Filter and Spatial Segmentation Options for Reading/Running TTAC Data

0=OFF and 1=ON

Filter ON/OFF: 0

Spatial Segmentation: 0

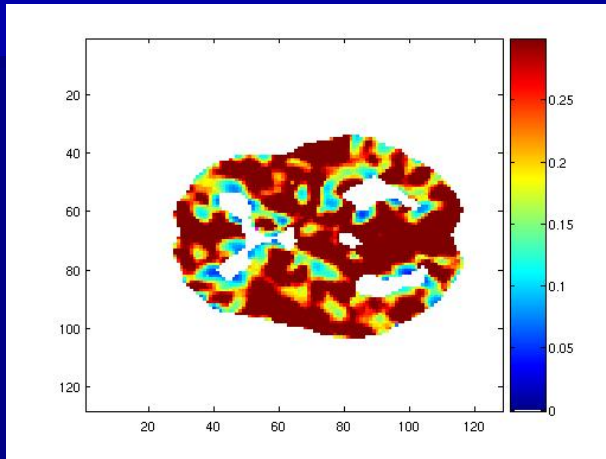
Process CSF: 0

Results Format

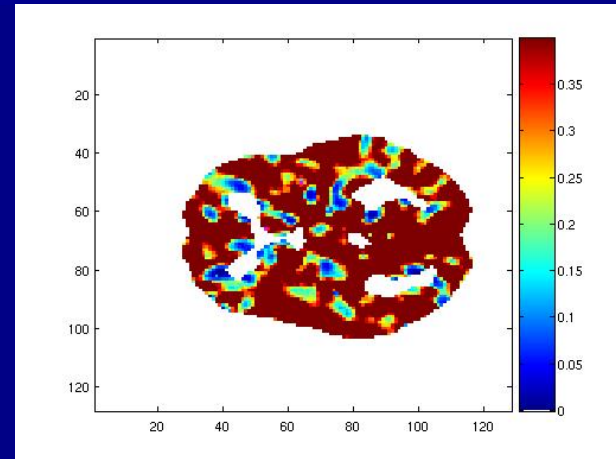
- *.tiff files (Initial Choice)– Portable, but cannot store raw results.
- *.mat –Not Portable, but can store raw results
- *.txt files= Only for cluster results

Results from Slice 16 Test Runs (No constraints, Model1, k1-k4)

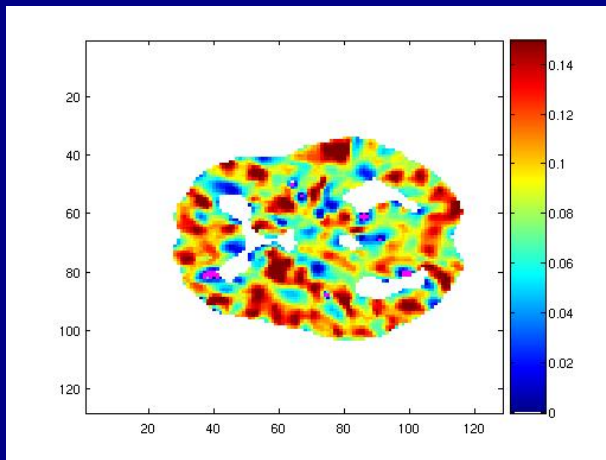
K1



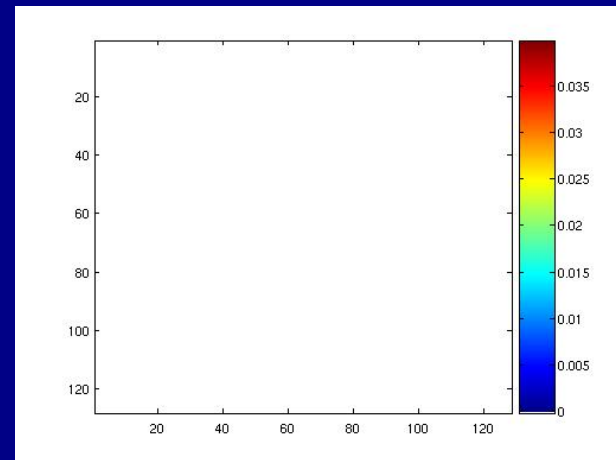
K2



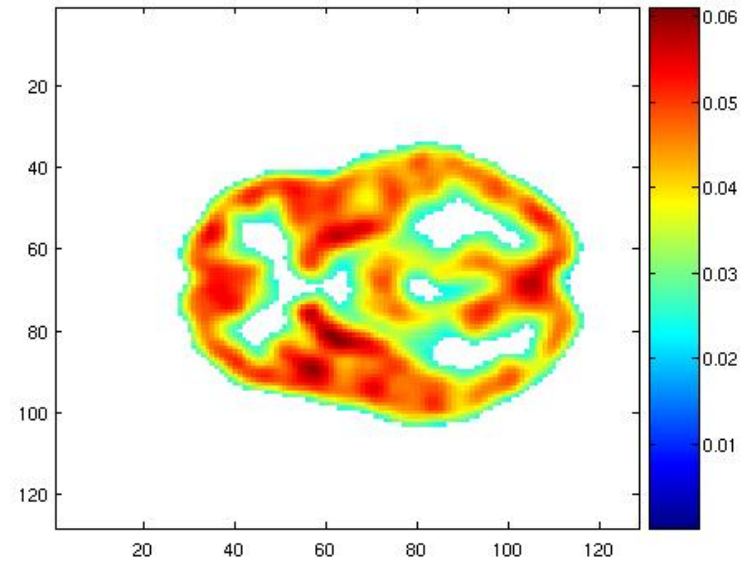
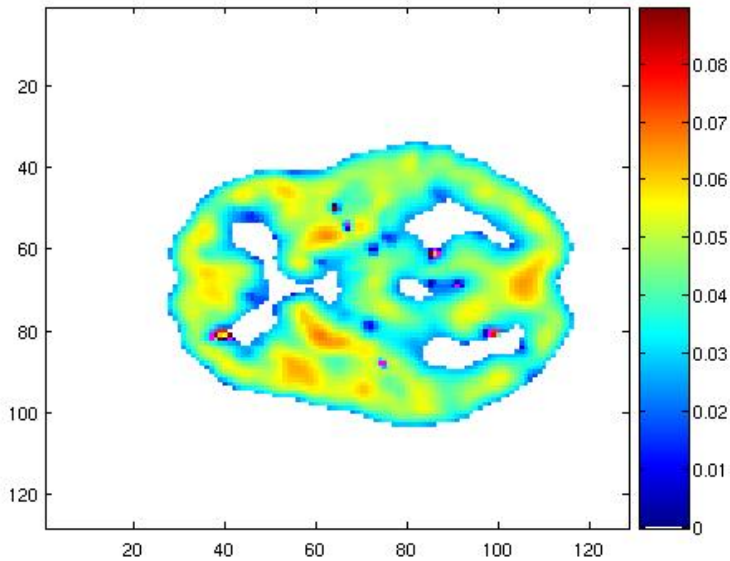
K3



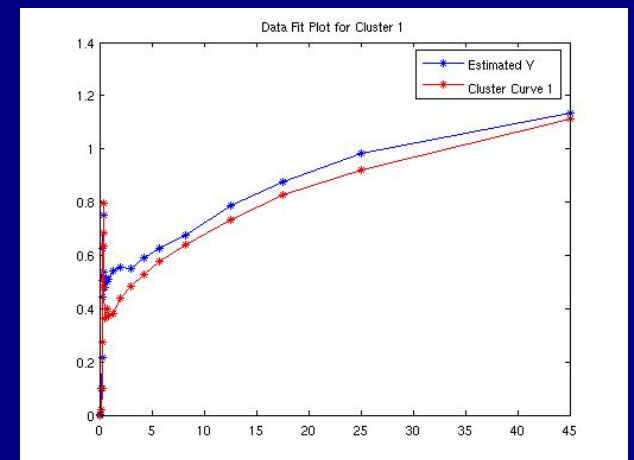
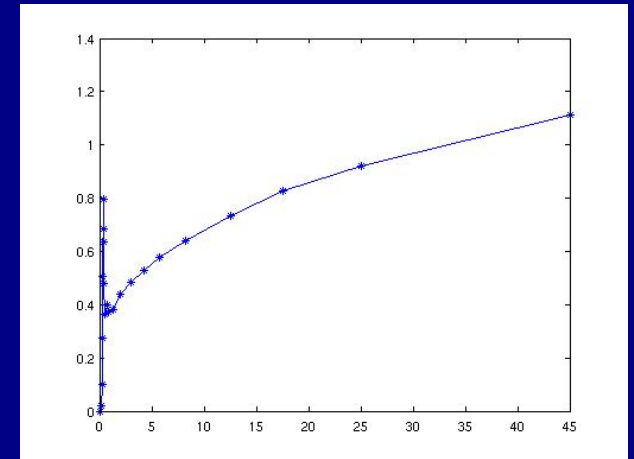
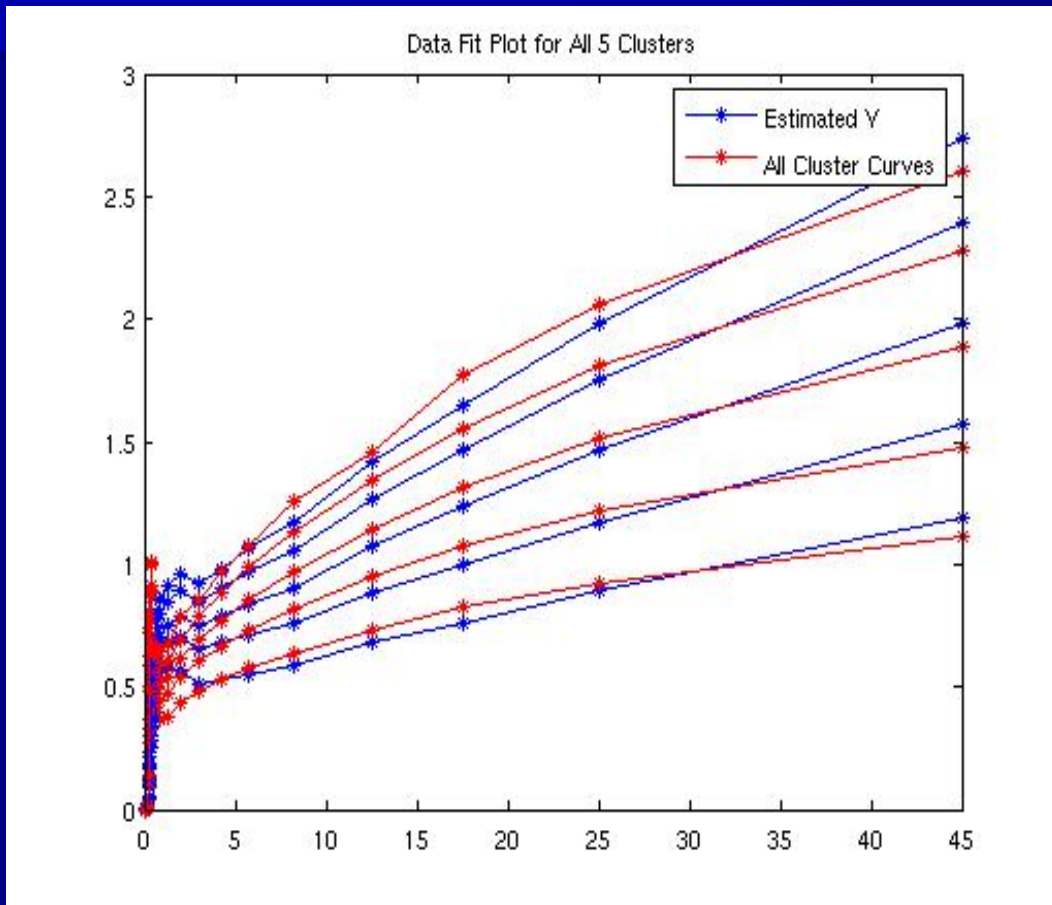
K4



Results for Slice 16 - K6/BigK (All Results Scaled)



Cluster Curve Data Fit



Website-For more info go to:
<http://www.public.asu.edu/~gua4488>

The screenshot shows a Microsoft Internet Explorer browser window. The title bar reads "Untitled - Microsoft Internet Explorer". The address bar contains "http://www.public.asu.edu/~gua4488/". The search bar shows "Google" and "hongbin guo". The main content area features a header with two brain scan images and the text "FDG Metabolism Parameter Estimation Software for Alzheimer's Research". Below the header, there is a list of authors: "By: Dr. Rosemary Renault, Dr. Christina Negoita, and Guadalupe Ayala". A navigation menu includes buttons for "HOME", "USER MANUAL", "CODE", "PUBLICATIONS", and "CONTACT US". A date stamp indicates "Nov 24, 2004" and "Arizona State University". The main text describes the software's functionality and lists parameters: k_1 (transport rate from blood to extra vascular space), k_2 (transport rate back from the extra vascular space), k_3 (phosphorylation rate of the intra-cellular FDG by hexokinase enzymes to FDG-6-phosphate), k_4 (dephosphorylation rate of the intra-cellular FDG-6-phosphate back to FDG), k_6 (local cerebral metabolic rate of glucose and computed explicitly by pixel by pixel analysis), and K (analog to k_6 computed using PATLAK analysis, which assumes $k_4=0$). The browser's status bar at the bottom shows "Internet".

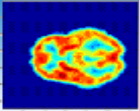
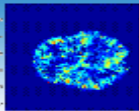
Untitled - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Forward Stop Refresh Home Search Favorites

Address <http://www.public.asu.edu/~gua4488/> Go Links Web assistant

Google hongbin guo Search Web 6 blocked AutoFill Options hongbin guo

  **FDG Metabolism Parameter Estimation Software for Alzheimer's Research**

By: Dr. Rosemary Renault, Dr. Christina Negoita, and Guadalupe Ayala

[HOME](#)
[USER MANUAL](#)
[CODE](#)
[PUBLICATIONS](#)
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Nov 24, 2004

Arizona State University

This page contains the code and a user manual that describes the functionality of an application developed with MATLAB graphical interface for the following analyses:

FDG pixel-wise parameter estimation, such as k_1 - k_6 where,

k_1 is the transport rate from the blood to the extra vascular space

k_2 is the transport rate back from the extra vascular space

k_3 is the phosphorylation rate of the intra-cellular FDG by hexokinase enzymes to FDG-6-phosphate

k_4 is the dephosphorylation rate of the intra-cellular FDG-6-phosphate back to FDG

k_6 is the local cerebral metabolic rate of glucose and computed explicitly by pixel by pixel analysis

K is an analog to k_6 computed using PATLAK analysis, which assumes $k_4=0$. It is the slope of the regression line in the PATLAK analysis that is valid only when $k_4=0$

Internet

Special Thanks

- Dr. Rosemary Renaut
- Dr. Christina Negoita
- Dr. Bradford Kirkman-Liff
- Dr. Hongbin Guo

Questions

Reference

- <http://www.alz.org/AboutAD/statistics.asp>
- Hongbin Guo, Rosemary Renaut, and Kewei Chen, Improved imaged-derived input function for study of human brain FDG-PET, submitted, 2004.
- C. Negoita, Global kinetic imaging using dynamic positron tomography data, Ph.D. thesis, Arizona State University, 2003.
- Cristina Negoita and Rosemary A Renaut, On the convergence of the generalized linear least squares algorithm, BIT (2004), accepted.