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

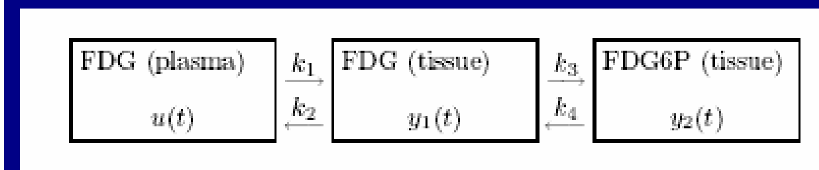
- Understand Compartmental Kinetic Model for Parameter Estimation
- Write Requirements Document and Build Shared Code Repository
- Identify Inputs/Outputs
- Identify User options
- Error Handling
- Build Prototype

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 Renaut’s Inputs to come up with initial Interface design.

Compartmental Kinetic Model Outputs: K1-K4

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



k1 = Transport rate of FDG from the blood to the Tissue

k2 = Transport rate of FDG from the tissue to the blood,

k3 = Phosphorylation rate of the intra-cellular FDG by hexokinase enzymes to FDG-6-phosphate, and

k4 =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/BigK are the local cerebral metabolic rate of glucose (FDG)
- K7 – (1-K5) Partial Volume Coefficient

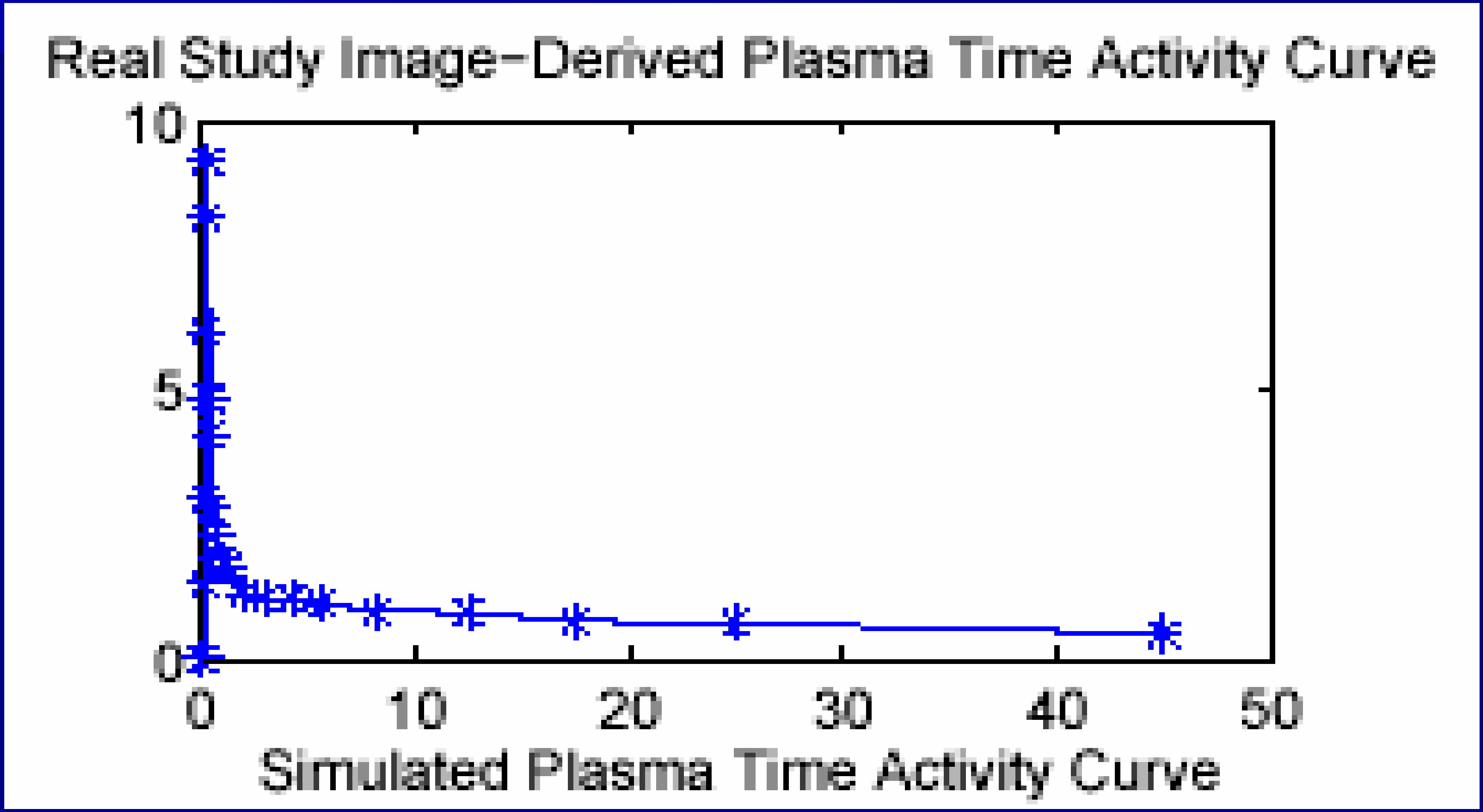
Spill-Over

- 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

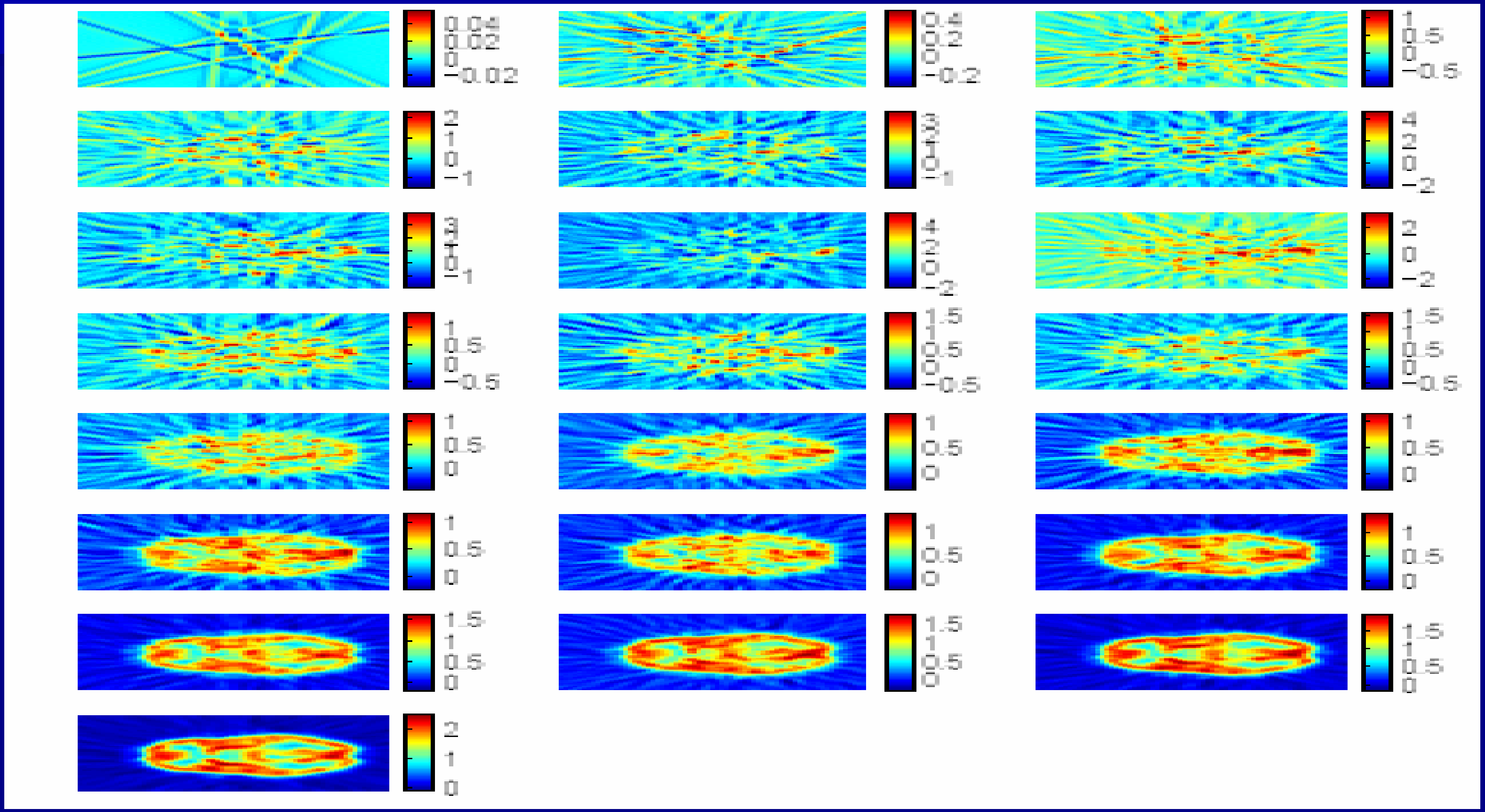
Partial Volume Effects

- 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 K7 or (1-K5)

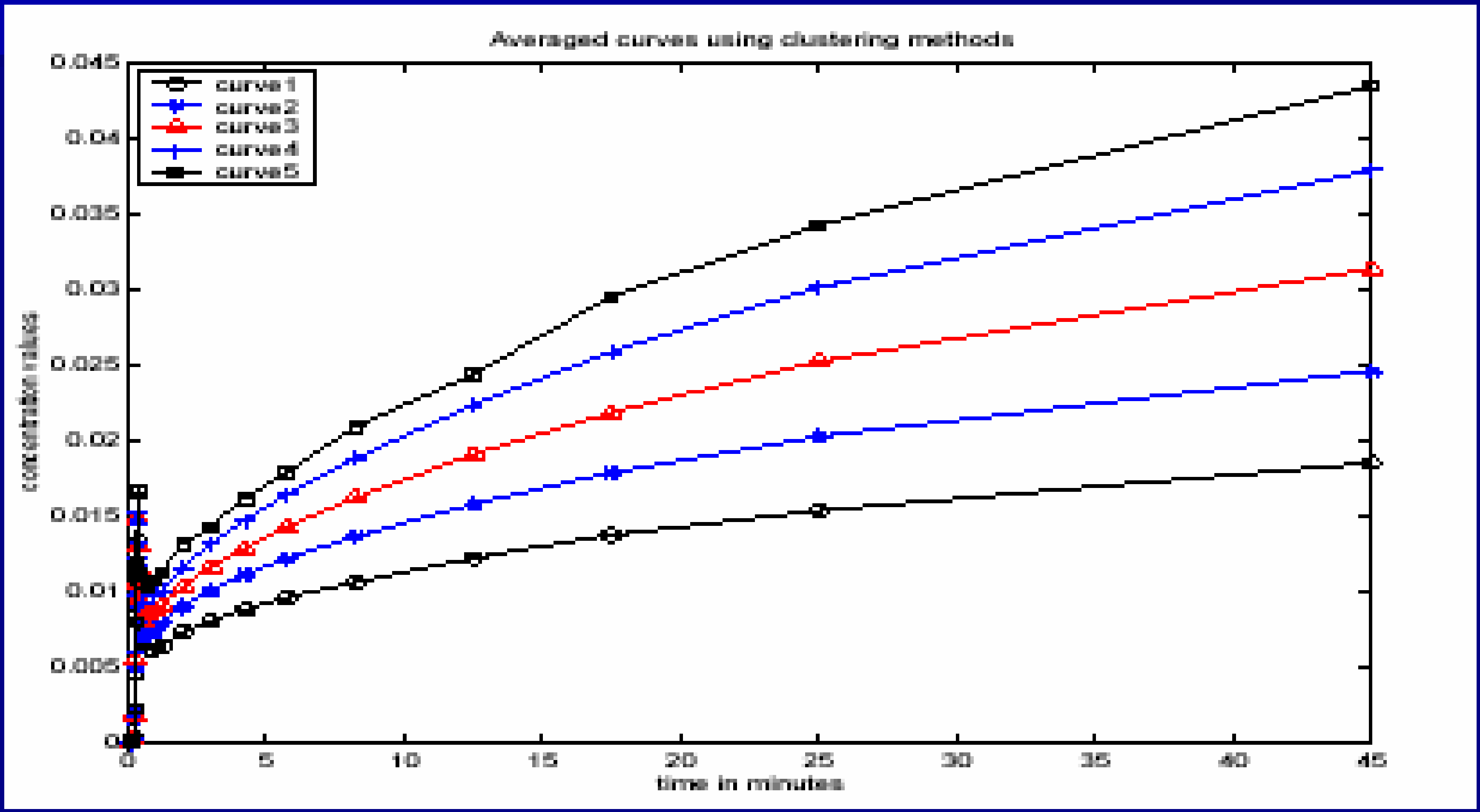
Input : PTAC “u(t)”



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.

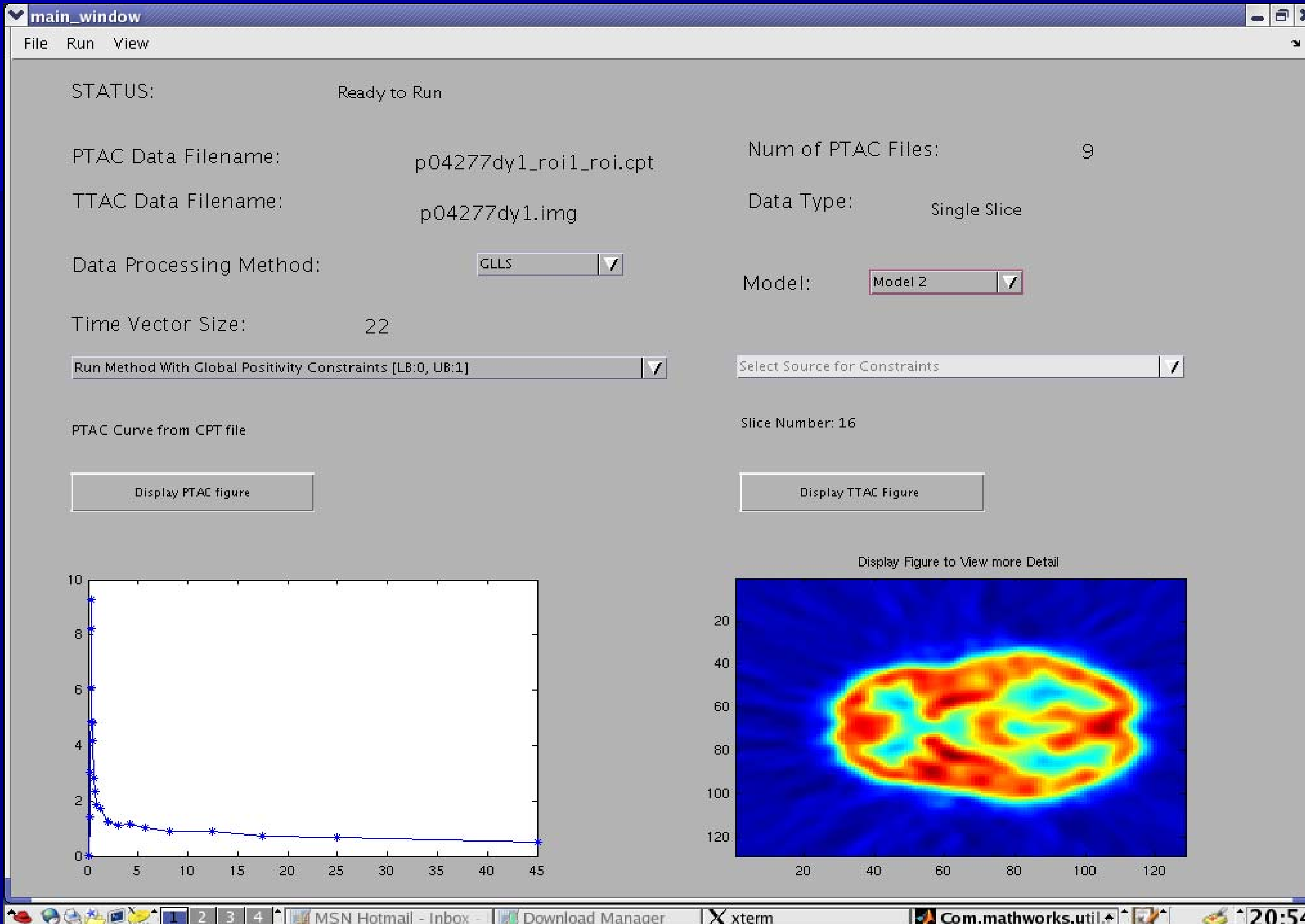
Model Descriptions
Different Estimation Approaches

- Model 1: k4=0, Spill-Over=0
- Model 2: k4=0, Spill-Over>0
- Model 3: k4=0, Spill-Over>0 with PV
- Model 4: k4>0, Spill-Over=0
- Model 5: k4>0, Spill-Over>0
- Model 6: k4>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



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

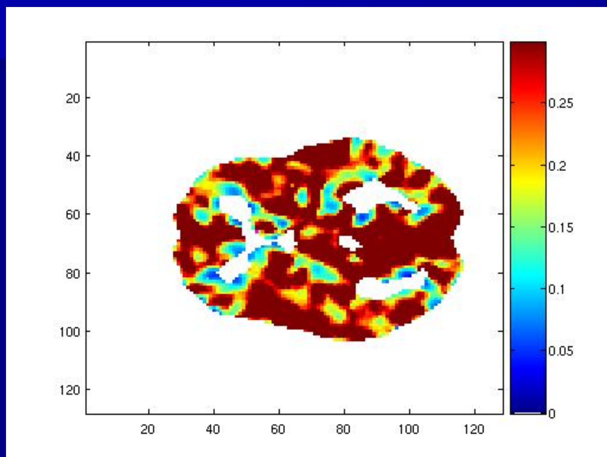
These are the Constraint Options and Constraints for K1-K5
Running Without Constraints For Kinetic Parameters K1-K5
LB_K: UB_K: LB_THETA: UB_THETA:
Filter and Spatial Segmentation Options for Reading/Running TTAC Data
0=OFF and 1=ON
Filter ON/OFF: 0
Spatial Segmentation: 0
Process CSF: 0

Results Format

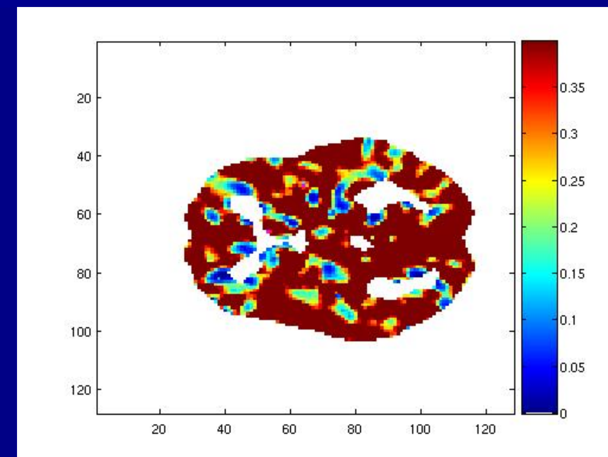
- *.tiff files (Initial Choice)– Portable, but cannot store raw results.
- *.mat –Not Portable, but can store raw results
- *.txt files= Only for cluster results

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

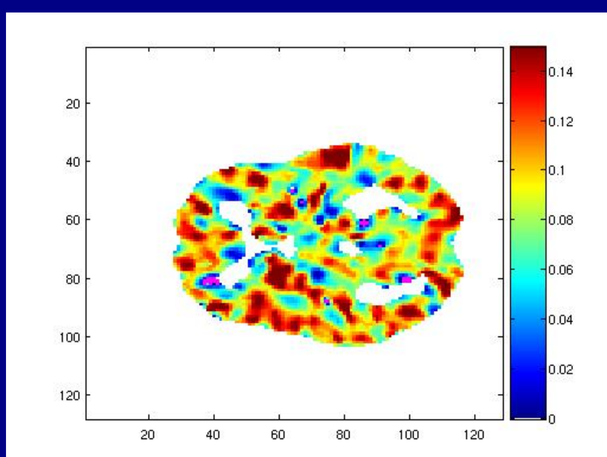
K1



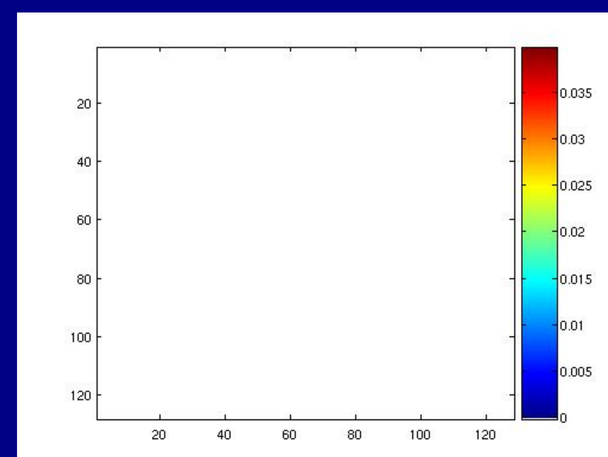
K2



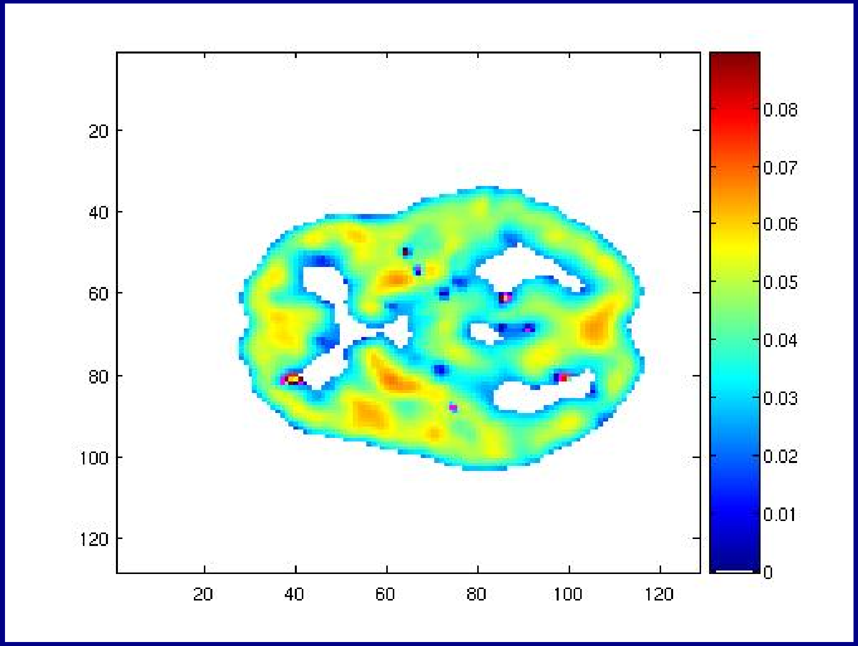
K3

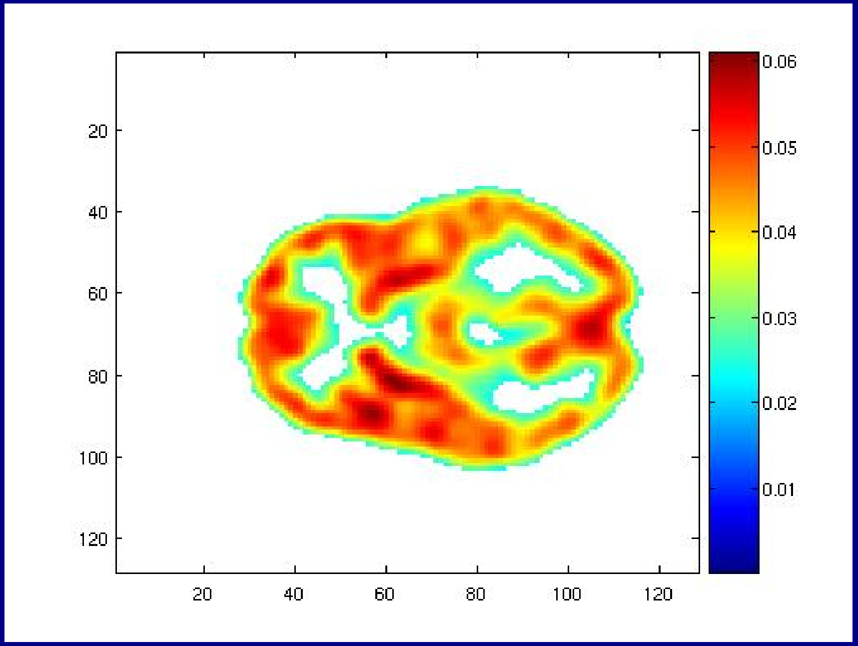


K4

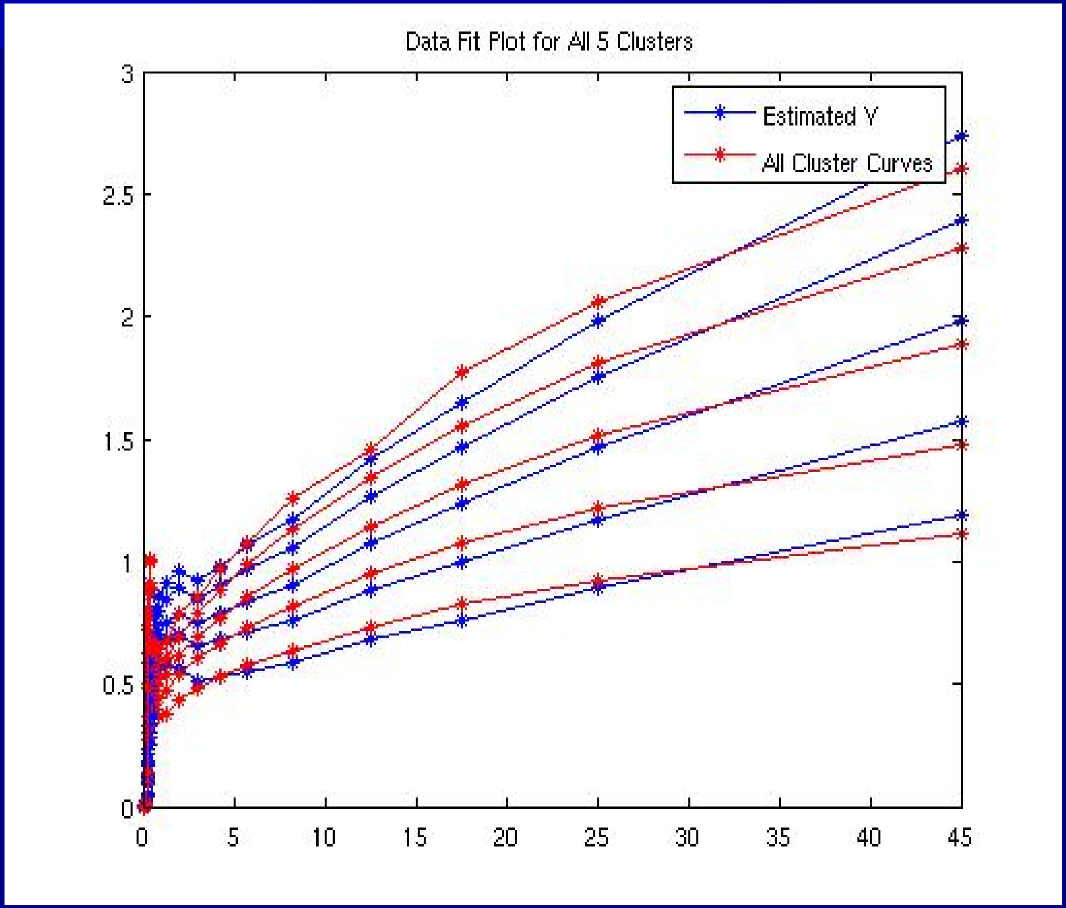


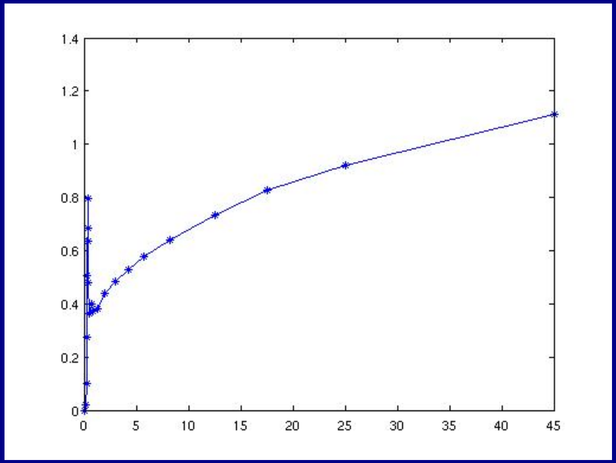
Results for Slice 16 - K6/BigK (All Results Scaled)

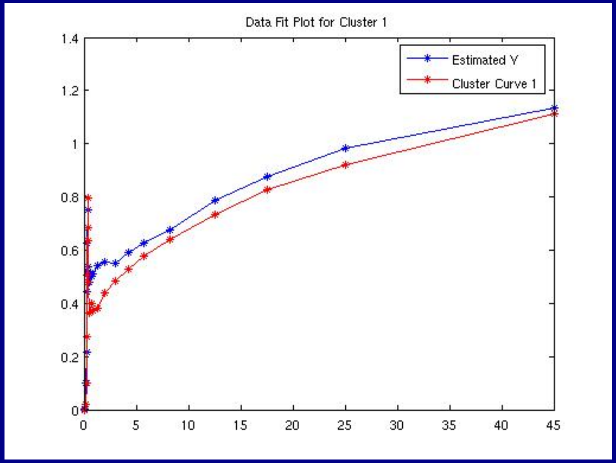




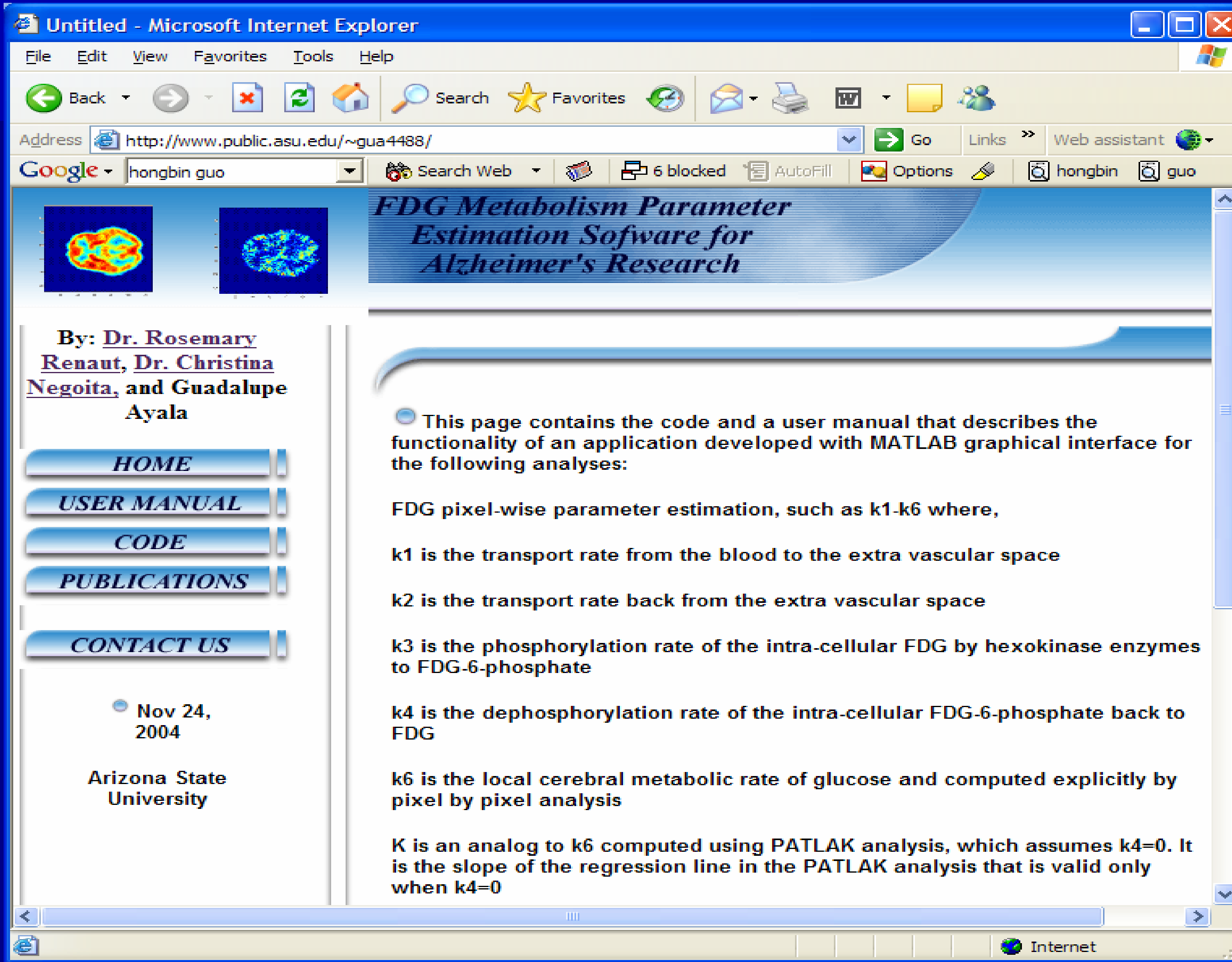
Cluster Curve Data Fit







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



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- 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.