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

Guadalupe Ayala
Advisor: Dr. Rosemary Renaut
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

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

\[\begin{array}{c|c|c}
\text{FDG (plasma)} & u(t) & \text{FDG (tissue)} \\
\hline
k_1 & k_2 & y_1(t) \\
\hline
k_3 & k_4 & y_2(t) \\
\end{array}\]

\[k_1 = \text{Transport rate of FDG from the blood to the Tissue}\]
\[k_2 = \text{Transport rate of FDG from the tissue to the blood,}\]
\[k_3 = \text{Phosphorylation rate of the intra-cellular FDG by hexokinase enzymes to FDG-6-phosphate, and}\]
\[k_4 = \text{de-phosphorylation rate of the intra-cellular FDG-6-phosphate back to FDG.}\]
Other Implicit Kinetic Parameters

- **K5** - Spill – Over Coefficient
- **K6** = Computed explicitly using Kinetic Parameters = \( \frac{K1 \times K3}{K2 + K3} \)
- **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
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 $K_5$
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 “\( u(t) \)"
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
<table>
<thead>
<tr>
<th>Status</th>
<th>Ready to Run</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTAC Data Filename</td>
<td>p04277dy1_roi1_roi.cpt</td>
</tr>
<tr>
<td>TTAC Data Filename</td>
<td>p04277dy1.cpt</td>
</tr>
<tr>
<td>Data Processing Method</td>
<td>GLLS</td>
</tr>
<tr>
<td>Time Vector Size</td>
<td>22</td>
</tr>
<tr>
<td>Num of PTAC Files</td>
<td>9</td>
</tr>
<tr>
<td>Data Type</td>
<td>Single Slice</td>
</tr>
<tr>
<td>Model</td>
<td>Model 2</td>
</tr>
<tr>
<td>Slice Number</td>
<td>16</td>
</tr>
</tbody>
</table>

```
Display PTAC Figure
```

```
Display TTAC Figure
```

![Graph and Image]
Sample Header File

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)
Results for Slice 16 - K6/BigK (All Results Scaled)
Cluster Curve Data Fit

Data Fit Plot for All 5 Clusters

- Estimated V
- All Cluster Curves
Website - For more info go to:
http://www.public.asu.edu/~gua4488
Special Thanks

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

- http://www.alz.org/AboutAD/statistics.asp


- Cristina Negoita and Rosemary A Renaut, On the convergence of the generalized linear least squares algorithm, BIT (2004), accepted.