Design and parametrization of a population-based causal model for Alzheimer’s Disease using Multidimensional Biomarkers

ADITHI RAO
NCSSM
Background: Causes

- Amyloid Plaque Buildup
- Neurofibrillary Tangles
- Final stage of several etiopathogenic mechanisms with similar final phenotype

![Normal vs. Alzheimer's Diseased Brain](image)

© 2000 by BrightFocus Foundation
Background

- Alzheimer’s Disease (AD) diagnosis current methods:
  - Mini Mental State Examination
  - AD Assessment Scale
- Stages of AD: Normal (NL), Mild Cognitive Impairment (MCI), AD
- Most relevant biomarkers
  - Cerebrospinal Fluid (CSF) ABeta
  - Cerebrospinal Fluid (CSF) Tau
  - Fluorodeoxyglucose PET
  - Structural MRI (brain volumes)
Goal

- Integrate systems biology approach to model the predominant driving mechanisms of cognitive decline in an individual and suggest a personalized optimum therapeutic strategy
  - Individual genetic, cognitive and biomarker fingerprints.
  - Express cognitive decline as a function of the biomarker levels

Specific Aims

1) Refine and test for predictive accuracy of the current qualitative population-based causal model using the trajectory of biomarkers in ADNI data

2) Add computational complexity to the model using multidimensional biomarkers to determine whether this increases predictive value.

3) Simulate the effects of various single and combination therapies on the population-based and personalized models.
Background: Biomarkers

- **CSF Abeta**
  - Abeta 42: peptides with 36-43 amino acids that cause Abeta deposition
  - Varies inversely with Abeta deposition
- **CSF P-tau**
  - Hyperphosphorylated tau
- **Hippocampal volume**
  - Measured with MRI (ml)
- **FDG**
  - Measures ratio of glucose uptake in the cortex to uptake in cerebellum (SUV)
<table>
<thead>
<tr>
<th>RID</th>
<th>P TEDUC</th>
<th>APOE4</th>
<th>FDG</th>
<th>PIB</th>
<th>ADAS11</th>
<th>MMSE</th>
<th>Ventic</th>
<th>Hippoca</th>
<th>Whole3</th>
<th>ICV</th>
<th>DX</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>16</td>
<td>0</td>
<td>1.36926</td>
<td>0</td>
<td>10.67</td>
<td>28</td>
<td>118233</td>
<td>8336</td>
<td>1229740</td>
<td>1984660</td>
<td>NL</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>1</td>
<td>1.09079</td>
<td>22</td>
<td>10.67</td>
<td>28</td>
<td>118233</td>
<td>8336</td>
<td>1229740</td>
<td>1984660</td>
<td>Dementia</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>1</td>
<td>1.0636</td>
<td>24</td>
<td>10.67</td>
<td>28</td>
<td>118233</td>
<td>8336</td>
<td>1229740</td>
<td>1984660</td>
<td>Dementia</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>1</td>
<td>1.10384</td>
<td>24</td>
<td>10.67</td>
<td>28</td>
<td>118233</td>
<td>8336</td>
<td>1229740</td>
<td>1984660</td>
<td>Dementia</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>1</td>
<td>1.03871</td>
<td>25.67</td>
<td>10.67</td>
<td>28</td>
<td>118233</td>
<td>8336</td>
<td>1229740</td>
<td>1984660</td>
<td>Dementia</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>0</td>
<td>14.33</td>
<td>27</td>
<td>10.67</td>
<td>28</td>
<td>118233</td>
<td>8336</td>
<td>1229740</td>
<td>1984660</td>
<td>MCI</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>0</td>
<td>17.33</td>
<td>27</td>
<td>10.67</td>
<td>28</td>
<td>118233</td>
<td>8336</td>
<td>1229740</td>
<td>1984660</td>
<td>MCI</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>20.33</td>
<td>27</td>
<td>10.67</td>
<td>28</td>
<td>118233</td>
<td>8336</td>
<td>1229740</td>
<td>1984660</td>
<td>MCI</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>18</td>
<td>27</td>
<td>10.67</td>
<td>28</td>
<td>118233</td>
<td>8336</td>
<td>1229740</td>
<td>1984660</td>
<td>MCI</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>0</td>
<td>1.29799</td>
<td>8.67</td>
<td>30.84</td>
<td>29</td>
<td>118233</td>
<td>8336</td>
<td>1229740</td>
<td>1984660</td>
<td>NL</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>0</td>
<td>1.30617</td>
<td>8.67</td>
<td>30.84</td>
<td>29</td>
<td>118233</td>
<td>8336</td>
<td>1229740</td>
<td>1984660</td>
<td>NL</td>
</tr>
</tbody>
</table>
Biomarker Model for MCI and AD subjects (AD Clinical Phenotype)

\[ N_D = C - N \]

\[ Cl = f(N_D, E4, Edu, b, t) \]

Based on Jack et al., Neuron 2013 Biomarker Modeling in AD
Method

- 2 broad major steps coded using Matlab
  - Generalized model based off average data and literature values for degradation using patients whose diagnosis changed
  - Personalized model
    - Patient-specific data values from ADNI file
    - Specific parameters from pulled values

paras.lambda_betaR=0.05743;
paras.d_Abeta=0.4077;
paras.lambda_tau=1.2275;
paras.d_tau=0.0578;
paras.d_Ntau=16.5*10^(-1);
paras.K_tau=2.99317;
paras.d_NAbeta=16.5*10^(-2);
paras.K_Abeta=0.994255;
paras.d_Nf=3*10^(-1);
paras.K_Abeta=0.994255;
paras.alpha=1;
Major Variables

$A_\beta$: Amyloid $\beta$

$N$: neuron concentration

$A_O$: A$\beta$-opathy

$\tau_O$: tau-opathy

$\tau$: hyperphosphorylated tau protein

$N_d$: dead neuron concentration

$S$: SNAP

$CI$: Cognition Impairment
Equation for Tau

\[
\frac{d\tau}{dt} = \lambda_T \tau_o + \lambda_{TAB} \frac{A_\beta}{A_\beta + K_{A_\beta}} - d_\tau \tau
\]

\(\lambda_T\) and \(\lambda_{TAB}\) = Rate constants
\(T_o\) = Tau-opathy
Michaelis-Menten Enzyme Kinetics
Equation for Amyloid Beta

\[
\frac{dA_\beta}{dt} = \lambda_\beta A_O A_\beta (K_{A_\beta} - A_\beta) - (1 + h) \frac{dA_\beta}{A_O} A_\beta
\]

\[
\begin{align*}
\lambda_\beta &= \text{Rate constants} \\
h &= \text{proportional to dosing level} \\
A_O &= \text{Abeta-opathy} \\
K_{A_\beta} &= \text{Max possible Abeta concentration}
\end{align*}
\]
Equation for Neurodegeneration

\[
\frac{dN}{dt} = -d_N \tau \frac{\tau}{\tau + K_\tau} N - d_{NS} SN - d_{NA} \text{Age}(t) N,
\]

**Neurodegeneration**

\[
S = \text{Suspected Non-Alzheimer’s Pathology}
\]

\[
\text{Age}(t) = \text{Age as a linear function of time}
\]

\[
N = \text{Healthy neurons}
\]
Other Significant Equations

\[ N_d = C - N \]

\[ CI = aN_d(t - Edu/E4) \]

- **a** = scaling factor
- **Edu** = Years in education
- **E4** = Copies of the E4 allele + 1
- **C** = Intracranial Volume
Generalized Solution

1) Abeta
2) Tau
3) Neurodegenerative neurons
Parameterization: Method 1

- Green: Average FDG and Hippocampal levels at different time points

- Black and red: Bottom and top parameters

- Assuming $d_F = 5e^{-2}$ -> black line
  $d_F = 1e^{-2}$ -> red line

- Assuming $d_F = 5e^{-2}$
  $d_H = 1e^{-1}$ -> black line
  $d_H = 5e^{-2}$ -> red line
Parameterization: Method 2

Steady state of differential equations:

- Assumption: Normal patients will be at steady state
- ABeta and Tau

Degradation rates: obtained from literature values
Parameterized General Solution
Patient Specific Parameterization

- Abeta: 94.42%
- Tau: 89.98%
- Neurons: 92.17%
Conclusion

• High predictive accuracy for longitudinal patient data
• Currently unable to predict patient data given short term data
  • Refinement of model will allow for the usage of fewer time points
Future Steps

- Reparametrize model using more patient data
  - Generalized solution
  - Personalized solution
- Refine cognitive impairment equation to fit MMSE or ADAS scores
- Drug effectiveness
- Examine the 8 different base cases
- CT image analysis by converting to partial differential equations
  - Abeta, Tau and FDG
<table>
<thead>
<tr>
<th>Series Description</th>
<th>Manufacturer</th>
<th>Radiopharmaceutical</th>
<th>Slice Thickness</th>
<th>Radioisotope</th>
<th>View</th>
<th>Select All</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADNI Brain PET: Raw FDG</td>
<td>Philips Medical Systems</td>
<td>18F-FDG</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw AV45</td>
<td>Philips Medical Systems</td>
<td>18F-AV45</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw FDG</td>
<td>Philips Medical Systems</td>
<td>18F-FDG</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw AV45</td>
<td>Philips Medical Systems</td>
<td>18F-AV45</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw FDG</td>
<td>Philips Medical Systems</td>
<td>18F-FDG</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw AV45</td>
<td>Philips Medical Systems</td>
<td>18F-AV45</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw FDG</td>
<td>Philips Medical Systems</td>
<td>18F-FDG</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw AV45</td>
<td>Philips Medical Systems</td>
<td>18F-AV45</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw FDG</td>
<td>Philips Medical Systems</td>
<td>18F-FDG</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw AV45</td>
<td>Philips Medical Systems</td>
<td>18F-AV45</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw FDG</td>
<td>Philips Medical Systems</td>
<td>18F-FDG</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw AV45</td>
<td>Philips Medical Systems</td>
<td>18F-AV45</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw FDG</td>
<td>Philips Medical Systems</td>
<td>18F-FDG</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw AV45</td>
<td>Philips Medical Systems</td>
<td>18F-AV45</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw FDG</td>
<td>Philips Medical Systems</td>
<td>18F-FDG</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw AV45</td>
<td>Philips Medical Systems</td>
<td>18F-AV45</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw FDG</td>
<td>Philips Medical Systems</td>
<td>18F-FDG</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw AV45</td>
<td>Philips Medical Systems</td>
<td>18F-AV45</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw FDG</td>
<td>Philips Medical Systems</td>
<td>18F-FDG</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw AV45</td>
<td>Philips Medical Systems</td>
<td>18F-AV45</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw FDG</td>
<td>Philips Medical Systems</td>
<td>18F-FDG</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw AV45</td>
<td>Philips Medical Systems</td>
<td>18F-AV45</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw FDG</td>
<td>Philips Medical Systems</td>
<td>18F-FDG</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw AV45</td>
<td>Philips Medical Systems</td>
<td>18F-AV45</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw FDG</td>
<td>Philips Medical Systems</td>
<td>18F-FDG</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw AV45</td>
<td>Philips Medical Systems</td>
<td>18F-AV45</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw FDG</td>
<td>Philips Medical Systems</td>
<td>18F-FDG</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
<tr>
<td>ADNI Brain PET: Raw AV45</td>
<td>Philips Medical Systems</td>
<td>18F-AV45</td>
<td>2.0</td>
<td>F-18</td>
<td>VIEW</td>
<td></td>
</tr>
</tbody>
</table>
Acknowledgements

Dr. Jeffrey Petrella, Duke University
Dr. Wenrui Hao, Pennsylvania State University
Chris Calixte
NCSSM Foundation
Mr. Robert Gotwals
Dr. Bruno
Dr. Shoemaker
UNC General Admission Undergraduate Research Award
Citations

Thank you for your time! Any questions?
Appendix: Michaelis-Menten Kinetics

• One of the best known models for enzyme kinetics
Appendix: ADAS/MMSE

ADAS:

• Word recall task, Naming Objects and Fingers, Following Commands, Constructional Praxis, Ideational Praxis, Orientation, Word Recognition Task, Remembering Test Directions, Spoken Language, Word-Finding Difficulty

• Greater the dysfunction, higher the score

MMSE:

30-point questionnaire used to screen for dementia
Appendix: Amyloid Plaque and Neurofibrillary Tangles

• Neurofibrillary tangles consist primarily of the tau protein
  • Normal cases: the tau protein is part of a structure called a microtubule
  • AD: tau protein is abnormal, and as a result, the microtubule structures do not function correctly.

• Amyloid Fibrils:
  • Protein aggregates linked to several degenerative diseases.
  • Amyloid precursor protein (APP), a normally soluble protein, undergoes proteolysis to form beta amyloid (Aβ) when cleaved by beta secretase and gamma secretase.
  • Contribute to Alzheimer’s by blocking cell-to-cell communication and activating immune system cells that cause inflammation and destroy disabled cells.
Appendix: Partial Differential Equations

• FEniCS: popular open-source computing platform for differential equations

• Mimics: advanced segmentation toolbox used for medical image-based research and development
Appendix: Pathology

• Pure AD pathology
• Mixed types of dementia
• Alternative pathologies with no relation to AD dementia: AB negative but Tau positive

• Tauopathies: class of diseases characterized by misfolding of the Tau protein
  • Not directly linked to AD dementia
  • Tau proteins increases rate at which other tau proteins misfold, eventually leading to AD dementia
• AB-opathy: only occurs in patients with the AD form of dementia
## Appendix: MRI and PET

<table>
<thead>
<tr>
<th>Magnetic Resonance Imaging</th>
<th>Positron Emission Tomography</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Noninvasive medical test used to diagnose various medical conditions</td>
<td>• Involves injecting radioactive tracers to check for diseases</td>
</tr>
</tbody>
</table>
Appendix: SNAP

• Suspected Non-Alzheimer’s Pathology

• Cognitively normal elderly adults who have one of several markers of neurodegeneration but test negative for brain amyloid

• Linked to Neurodegeneration
Appendix: General Model Parameterization

```c
1 function dudt=Right_hand_side(t,u,paras)
2 Abeta=u(1);
3 tau=u(2);
4 N=u(3);
5 Nd=u(4);
6 paras.A_O=paras.A_O1*(paras.A_Ou+paras.A_Ob*t^3/(10+t^3));
7 paras.Age=60+t;
8 paras.tau0=paras.tau01*(1+9*t^3/(10+t^3));
10 (paras.lambda_tau*paras.tau0+paras.lambda_tauAb*Abeta/(paras.K_Abeta+Abeta)-paras.d_tau*tau);
11 paras.alpha1=-(paras.d_Ntau*(tau-1.272)/t+paras.K_tau)*N-paras.d_NS*paras.S*N-paras.d_NA
12 paras.alpha1=(paras.d_Ntau*(tau-1.272)/t+paras.K_tau)*N+paras.d_NS*paras.S*N+paras.d_NA*paras.Age*N);
```
Parameters $A_0$ and $T_0$ are calculated through an iterative optimization function
Appendix: Drug Testing

• Primarily focused on reducing AB aggregation
• Reducing Tau aggregation and reducing inflammation
• For example: Aducanumab
Appendix: Equation for Tau

\[
\frac{d \tau}{dt} = \lambda_\tau \tau_o + \lambda_{\tau A\beta} \frac{A\beta}{A\beta + K_{A\beta}} - d_\tau \tau
\]

- Hyperphosphorylated tau: constitutively released from amyloid beta and Tau-opathy at a rate of $\lambda_\tau$
- Degraded at a rate of $d_\tau$
Appendix: Equation for Amyloid Beta

\[ \frac{dA_\beta}{dt} = \lambda_\beta A_0 A_\beta (K_{A_\beta} - A_\beta) - (1 + h) \frac{dA_\beta}{A_0} A_\beta \]

- Production and degradation: affected by AB-opathy
- \( h \) is proportional to dosing level: \( h(t) \) would more aptly display its effect overtime
- Degraded at a rate of \( d_{AB} \)
Appendix: Equation for Neurodegeneration

Active neurons degrade because of:
- Tau proteins
- Patient’s age
- SNAP

Where \( \text{Age}(t) = A_0 + t \)

\[
\frac{dN}{dt} = -d_{N\tau} \frac{\tau}{\tau + K_{\tau}} N - d_{NS} SN - d_{NA} \text{Age}(t) N,
\]

Neurodegeneration
Appendix: Other Significant Equations

\[ N_d = C - N \]

\[ CI = aN_d(t - Edu/E4) \]

- Damaged Neuron: formed from dysfunctional neuronal injury via amyloid beta

  - Cognitive impairment:
    - Shift to the left is increased by dead neurons and E4 gene, decreased by education
    - \( a \): scaling factor
Impact of Jack et al

• Jack et al: AD Biomarkers evolve in a sequential but temporally overlapping manner

• Has caused shift from focusing on symptomatic impairment to biomarker levels