Estimate the time-to-conversion for Alzheimer's Disease using neuroimaging-genomics multi-modal deep survival analysis

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Outlines

• Background / Aims
  • Predict time-to-conversion for dementia
  • Study the influence of different data modality on dementia conversion

• Study Design
  • Outcome measurement
  • Cohort Stratification
  • Independent variables

• Data processing / Feature extraction
  • Multi-type feature selection
  • Feature importance analysis – Permutation test

• Experimental setup
  • Deep Survival Model design
  • Evaluation

• Results
• Conclusion
Study Aims

• Predict time-to-conversion for Dementia of Alzheimer’s Type (DAT)
  • Using multi-modal predictor, including: MRI, Genetics, Cerebrospinal Fluid (CSF) biomarker, Cognitive tests

• Study the influence of each data modality on disease prediction
Predicting time-to-conversion - Survival analysis

- **Probability of dementia risk**
  - as a function of time

- Example:
  - APOE allele dementia risk

![The survival curve for APOE](image-url)

*Reiman et al. 2020 Nature Communication*
Survival analysis - Sensoring

**Survival Analysis:**
- Analysis of the time an individual will experience an event of interest

**Event of Interest**
- Dementia onset (DAT diagnosis confirmation)

**Left sensor**
- Event happens before the first clinical visit (baseline)

**Right Sensor**
- Event happens after last clinical visit (final timepoint)
Predicting time-to-conversion - Survival analysis

**Ground truth labels**

1. **Event indicator:**
   - 0 = Non-progressive (right censored)
   - 1 = Progressive

2. **Duration:**
   - **Non-progressive:** Duration between the first and last visit
   - **Progressive:** Duration between first visit and DAT diagnosis confirmation

![Diagram showing study start and end with different censoring and event types](image)
**Training/evaluation cohort: ADNI-1**

### Subject grouping

<table>
<thead>
<tr>
<th>Group name</th>
<th>Clinical progression</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-progressive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sNC: stable NC</td>
<td>NC → NC</td>
<td>109</td>
</tr>
<tr>
<td>uNC: unstable NC</td>
<td>NC → MCI</td>
<td>22</td>
</tr>
<tr>
<td>sMCI: stable MCI</td>
<td>MCI → MCI</td>
<td>101</td>
</tr>
<tr>
<td><strong>Progressive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pNC: progressive NC</td>
<td>NC → MCI → DAT</td>
<td>14</td>
</tr>
<tr>
<td>pMCI: progressive MCI</td>
<td>MCI → DAT</td>
<td>155</td>
</tr>
</tbody>
</table>

### Stratified Train/Valid/Test split

<table>
<thead>
<tr>
<th>Groups</th>
<th>Training set</th>
<th>Validation set</th>
<th>Testing set</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>sNC</td>
<td>70</td>
<td>17</td>
<td>22</td>
<td>109</td>
</tr>
<tr>
<td>uNC</td>
<td>14</td>
<td>4</td>
<td>4</td>
<td>22</td>
</tr>
<tr>
<td>pNC</td>
<td>9</td>
<td>2</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>sMCI</td>
<td>65</td>
<td>16</td>
<td>20</td>
<td>101</td>
</tr>
<tr>
<td>pMCI</td>
<td>99</td>
<td>25</td>
<td>31</td>
<td>155</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>257</td>
<td>64</td>
<td>80</td>
<td>401</td>
</tr>
</tbody>
</table>

*Only baseline data were used for training*
Data – Input Features

Neuroimage & Genomic Feature Selection (Within Training Data)

MRI data
(91 FreeSurfer parcellated ROI volumes)

Genetic data
(521,014 “plink” quality-checked SNPs + APOE-ε2/3/4)

Welch’s t-test

Fisher’s exact test

Sub-bagging x 10

21 MRI features

21 genetic features

Feature ranking based on selection frequency

Final 21 MRI features

Final 21 genetic features
Data modalities

- **MRI**: 21 ROI volume (Z-standardized) (21 features)
- **Genetic**: 18 SNPs + 3 APOE alleles (21 features)
- **DTC**: 21 features
  - Demographic (4 features)
  - Cognitive Tests (11 features)
  - CSF (7 features)
- Only baseline data was used for training

<table>
<thead>
<tr>
<th>MRI features</th>
<th>Genetic features</th>
<th>DTC features / #missing data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amygdala - Left</td>
<td>APOE-ε2</td>
<td>AB40 (CSF) / 41</td>
</tr>
<tr>
<td>Amygdala - Right</td>
<td>APOE-ε3</td>
<td>AB42 (CSF) / 40</td>
</tr>
<tr>
<td>Entorhinal - Left</td>
<td>APOE-ε4</td>
<td>AB (CSF) / 176</td>
</tr>
<tr>
<td>Entorhinal - Right</td>
<td>rs524410</td>
<td>ptau (CSF) / 176</td>
</tr>
<tr>
<td>Fusiform - Left</td>
<td>rs746947</td>
<td>ptau/AB (CSF) / 176</td>
</tr>
<tr>
<td>Fusiform - Right</td>
<td>rs1010616</td>
<td>Tau (CSF) / 176</td>
</tr>
<tr>
<td>Hippocampus - Left</td>
<td>rs1864036</td>
<td>tau/AB (CSF) / 176</td>
</tr>
<tr>
<td>Hippocampus - Right</td>
<td>rs2085925</td>
<td>Age (DEM) / 0</td>
</tr>
<tr>
<td>Inferior-parietal - Left</td>
<td>rs2405940</td>
<td>Education (DEM) / 0</td>
</tr>
<tr>
<td>Inferior-parietal - Right</td>
<td>rs2883782</td>
<td>Marital status (DEM) / 0</td>
</tr>
<tr>
<td>Inferior-temporal - Left</td>
<td>rs4953672</td>
<td>ADAS11 (TST) / 0</td>
</tr>
<tr>
<td>Inferior-temporal - Right</td>
<td>rs5918417</td>
<td>ADAS13 (TST) / 0</td>
</tr>
<tr>
<td>Inferior-lateral-ventricle - Left</td>
<td>rs5918419</td>
<td>CDRSB (TST) / 0</td>
</tr>
<tr>
<td>Inferior-lateral-ventricle - Right</td>
<td>rs6116375</td>
<td>FAQ (TST) / 2</td>
</tr>
<tr>
<td>Middle-temporal - Left</td>
<td>rs6773506</td>
<td>LDELTOTAL (TST) / 0</td>
</tr>
<tr>
<td>Middle-temporal - Right</td>
<td>rs7627954</td>
<td>MMSE (TST) / 0</td>
</tr>
<tr>
<td>Parahippocampal - Left</td>
<td>rs10465385</td>
<td>RAVLT-forgetting (TST) / 1</td>
</tr>
<tr>
<td>Parahippocampal - Right</td>
<td>rs10510985</td>
<td>RAVLT-immediate (TST) / 1</td>
</tr>
<tr>
<td>Precuneus - Left</td>
<td>rs10924809</td>
<td>RAVLT-learning (TST) / 1</td>
</tr>
<tr>
<td>Precuneus - Right</td>
<td>rs12522102</td>
<td>RAVLT-%forgetting (TST) / 2</td>
</tr>
<tr>
<td>Supramarginal - Left</td>
<td>rs17197559</td>
<td></td>
</tr>
</tbody>
</table>
Cox regression model
• Hazard function: \( h(t|x) = h_0(t) \exp[g(x)] \)

Deep Survival Model
• a non-linear version of the Cox model where \( g(x) \) parametrized by a neural network (Multi-Layer-Perceptron)

Loss function
• \( \text{loss} = \sum_i D_i \log(\sum_{j \in R_i} \exp[g(x_j) - g(x_i)]) \)
  • \( D_i \): event indicator for subject \( i \) (1=progressive, 0=non-progressive)
  • \( R_i \): set of all individuals at risk

\( g(x) = \beta^T x \)
6 Feature sets combination

1. Genetic data (GEN; 21 features)
2. MRI data (MRI; 21 features)
3. Demographic + Cognitive Test + CSF (DTC; 21 features)
4. MRI and genetic data (GEN+MRI; 42 features)
5. Genetic and DTC data (GEN+DTC; 42 features)
6. MRI and DTC data (MRI+DTC; 42 features)
7. All features (GEN+MRI+ DTC; 63 features)
Integrated Brier Score (IBS)

• The average squared distances between the observed \(y_i\) and predicted survival probability \(\hat{p}_i\)

\[
BS = \frac{1}{N} \sum_i (y_i - \hat{p}_i)^2
\]

• \(0 < \text{IBS} < 1\) (the smaller the better)
Evaluation Metrics 1 Results

**Same conclusion:**

- Combining MRI and GEN (MRI+GEN) improves the performance
- DTC works best amongst single modalities
- MRI + GTC improved GTC (not statistically significant)
Time-dependent Concordance Index ($C_{td}$-index)

- Compares the order of predicted survival times with true survival times for a random pair of subjects

$$0 < C_{td}$-index < 1 \text{ (the bigger the better)}$$
Combining MRI and GEN (MRI+GEN) improves the performance.

DTC works best amongst single modalities.

MRI + GTC improved GTC (not statistically significant).
Predicted vs. true time-to-conversion difference

Results
Results

Predicted vs. true time-to-conversion difference

- **Predicted time**: the time a subject's survival probability reaches 50%
  - If this doesn’t happen: Predicted time = 20 years after initial visit

- More than half of the subjects (80/150 or 53.4%) had a time difference of less than 1.5 years

- The predicted event time was earlier than the actual event time for 37 subjects (24.7%)
Feature type comparison

- Dementia onset time prediction
- DTC
  - Demographic
  - Cognitive test
  - Cerebral Spinal Fluid Biomarker

Results
Feature Importance Analysis

• Explain and compare the contributions of each feature toward the time-to-conversion prediction

• Determine feature contributions through the permutation importance analysis

• Random shuffling of each feature
Feature importance: ALL

- **27/36 features** had a positive effect on performance
  - 6 GEN
  - 9 MRI
  - 12 DTC

- **8 of the top 10 features** were from **DTC** including **7 TST** features and **1 DEM**

- The most important feature was **CDRSB** (Clinical Dementia Rating Scale)
Feature importance: GEN

- 14/21 features had a positive effect on performance
- The most important feature was APOE-ε4
- Top 10 most important features were from chromosomes 2, 3, 19, and X
Results

Feature importance: MRI

- 15/21 features had a positive effect on performance
- The most important feature was L-Hippocampus
- Other important features include: L-Amygdala, R-Hippocampus, and R-inferiorparietal
Results

Feature importance: DTC

- 19/21 features had a positive effect on performance.
- 8 of the top 10 features were from cognitive tests (TST) and the other 2 were demographic (DEM) features.
- The most important feature was the Delayed recall variable from the Logical memory test (LDEL-Total).
• Modality comparison for Alzheimer’s disease time-to-conversion prediction estimation for subjects at different stages of the disease
  • Genomic factor is better at the prodromal stage (pNC)
  • Neuroimage + CSF is better at early disease stage (pMCI)

• Novel AD-related genomic factors are discovered Explainable AI to explore feature importance
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Q&A