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Machine Learning in Image-omics

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Disclosures

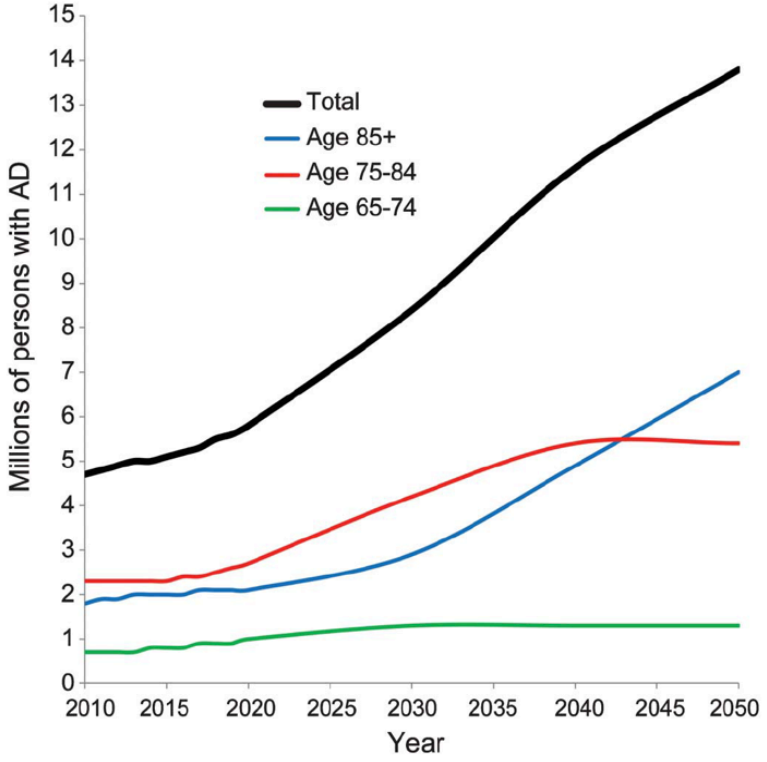
- Nothing to declare.

Goals

- Appreciate the potential of combining quantitative imaging with quantitative genetics
- Basic understanding of a typical machine learning framework for an 'image-omics' study
- Gain insight into the acceleration potential of publicly shared data and software in 'image-omics'

Alzheimer's Disease

- Most common type of dementia
- Nearly 5.2 million people in United States in 2013 have AD
- Prevalence expected to approximately triple by 2050



Estimated number of people with Alzheimer's disease in the United States in 2010 and projections through 2050[1]

[1]Hebert et al., "Alzheimer disease in the United States (2010–2050) estimated using the 2010 census," *Neurology*, Feb. 2013.

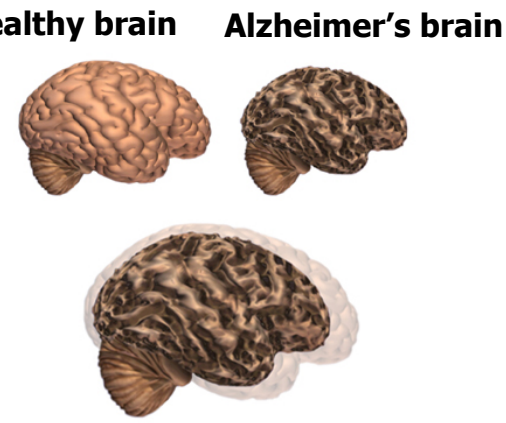
Alzheimer's Disease

- No treatment exists to slow down or prevent neurodegeneration
- Several disease-modifying treatments are currently undergoing clinical trials
  - But, outcome measures are insensitive
- Substantial neuronal loss has already occurred by the time Alzheimer's disease can be diagnosed
  - **Early detection at the prodromal stage of mild cognitive impairment (MCI) is essential**

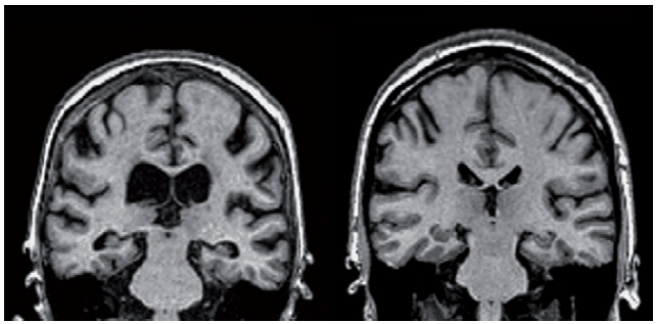
Imaging Biomarkers

- Biomarker that tracks disease progression with high precision

- Neuronal loss manifests as progressive cerebral atrophy
  - Structural magnetic resonance imaging (MRI)
  - High sensitivity in detecting structural changes in brain



Illustrations from Alzheimer's Disease research, American Health Assistance Foundation



MRI slices corresponding to a patient suffering from Alzheimer's disease and normal control.

Imaging Biomarkers

- Cerebral atrophy promising for tracking Alzheimer's disease progression
- CAD system based on cerebral atrophy quantified on MRI images could help in early detection of Alzheimer's disease
- Perhaps genetic risk factors could also be included in such a CAD system?

Imaging Biomarkers

- Cerebral atrophy can also be used as quantitative phenotype for investigating genetic risk factors

- Network of genes found significant can help in identifying biochemical processes that play important roles in neurodegeneration due to Alzheimer's disease

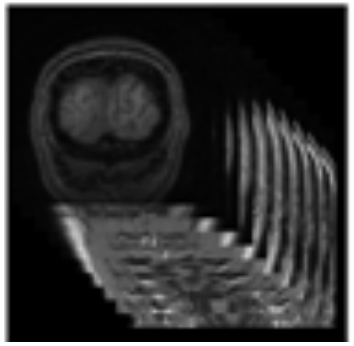
Data

- Alzheimer's Disease Neuroimaging Initiative (ADNI)

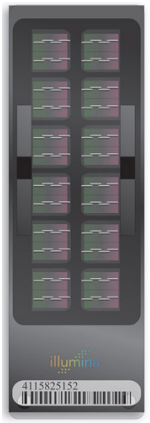
- Participants:
  - 217 normal controls, 361 mild cognitively impaired patients, and 179 Alzheimer's disease patients
  - Longitudinal data: 0, 6, 12, 18, 24, and 36 months

Data

- Imaging: Structural MRI volumes
- Genetic: Illumina Human610-Quad BeadChip data (620,901 SNP and CNV markers)
- Cognitive assessment: Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog)
- Demographics: Patient age and gender



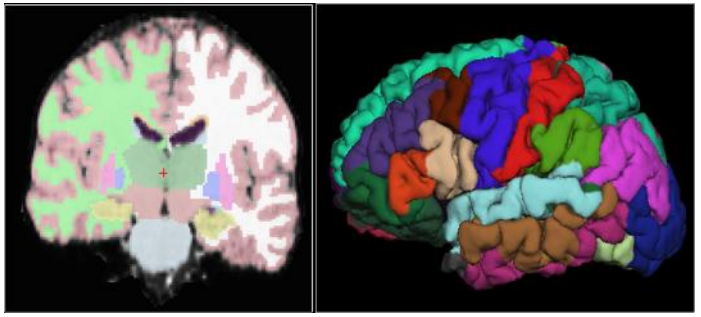
MRI Images



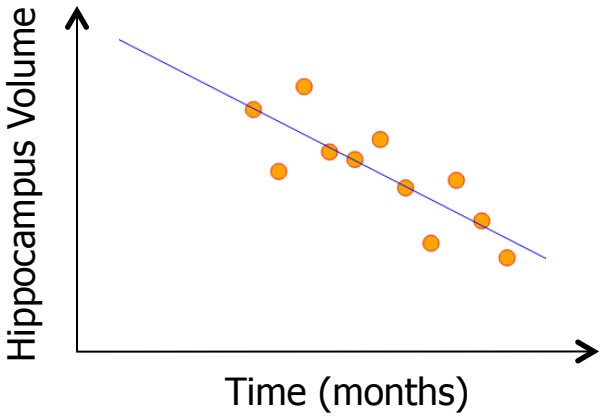
Illumina Human610-Quad BeadChip

MRI Analysis

- FreeSurfer Suite
  - Preprocessing
  - Tissue and subcortical structure segmentations
  - Structural measurements
    - Cortical thickness, structure volumes
  - Atrophy quantification
    - Linear regression over longitudinal measurements



FreeSurfer segmentation

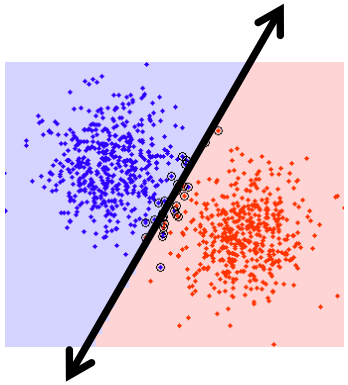


Atrophy quantification

Imaging Feature Selection

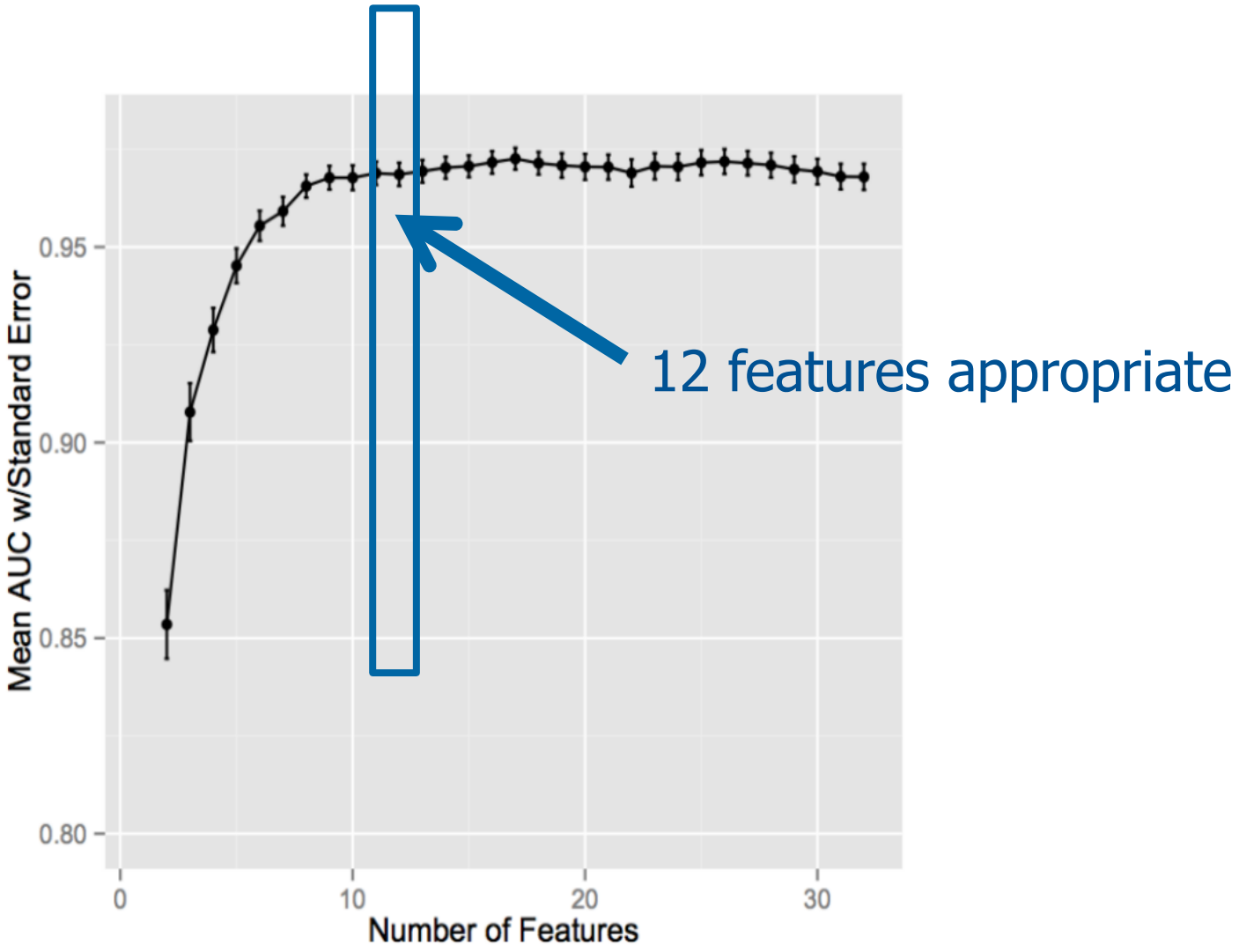
- Reduce dimensionality
- Identify highly informative quantitative traits
- Maximum-relevance minimum-redundancy (mRMR) algorithm

Healthy controls



Alzheimer's patients

Imaging Feature Selection



Testing SNP Associations

- To minimize effects of multiple comparisons, 66 candidate genes selected
  - Based on literature search from the Online Mendelian Inheritance in Man and the AlzGene databases

- 599 SNPs within the 66 genes considered for investigation

Testing SNP Associations

- For testing association between j^{th} imaging feature and m^{th} SNP, linear regression model

$$y_{ij} = \beta_{0,j} + \sum_{m=1}^{M} \beta_{1,j}^{m} X_i^m + \beta_{2,j} \left(\frac{1}{n_i} \sum_{k=1}^{n_i} ADAS_{i,k} \right) + \beta_{3,j} \left(\frac{1}{n_i} \sum_{k=1}^{n_i} Age_{i,k} \right)$$

Covariate terms of M SNPs

Controlling for variability in Alzheimer's severity

Controlling for variability in patient age

- Gender and its interactions with SNPs were tested, but were not found to be significant predictors in the model

Testing SNP Associations

- 53 SNPs were found to be significantly associated with the 12 imaging features

Variation	Gene	Gene Description	Imaging Feature	P-Value
rs9341052	ESR1	Estrogen receptor 1	Left Lateral Ventricular Enlargement	2.513×10^{-5}
rs4726618	EPHA1	EPH receptor A1	Left Inferior Lateral Ventricular Enlargement	2.985×10^{-4}
rs9341052	ESR1	Estrogen receptor 1	Right Lateral Ventricular Enlargement	1.186×10^{-3}
rs17014923	BIN1	Bridging integrator 1	Third Ventricular Enlargement	2.449×10^{-3}
rs6584777	SORCS1	Sortilin-related VPS10 domain containing receptor 1	Left Inferior Lateral Ventricular Enlargement	4.407×10^{-4}
rs749008	BIN1	Bridging integrator 1	Third Ventricular Enlargement	5.694×10^{-3}

All p-values are corrected using the false-discovery rate control

Estrogen treatment affecting ESR1 modulates risk of developing AD in women

Genetic variations on SORSC1 alter Aβ protein processing

Testing SNP Associations

Imaging Feature	Gene	Unique SNPs
Lateral Ventricular Enlargement	ESR1	6
	BIN1	1
	LDLR	1
Inferior Lateral Ventricular Enlargement	SORCS1	10
	ESR1	3
	APP	2
Hippocampal Atrophy	ESR1	18
	LRAT	3
	APP	1
Cortical Atrophy	TF	4
	APP	2
	SORCS1	2

Future Work

- Pathway analysis involving interactions between genes against imaging phenotypes
  - Will provide more insight into biochemical processes affecting atrophy in brain regions

Concluding Remarks

- Exciting potential for combining imaging and genetic analysis
- Sharing data and software accelerates discovery

Acknowledgements

- Data analyzed from Alzheimer's Disease Neuroimaging Initiative (ADNI)
  - http://www.adni-info.org
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- FreeSurfer: http://surfer.nmr.mgh.harvard.edu
- PLINK: http://pngu.mgh.harvard.edu/~purcell/plink/
- NeuroTexas Institute Research Foundation

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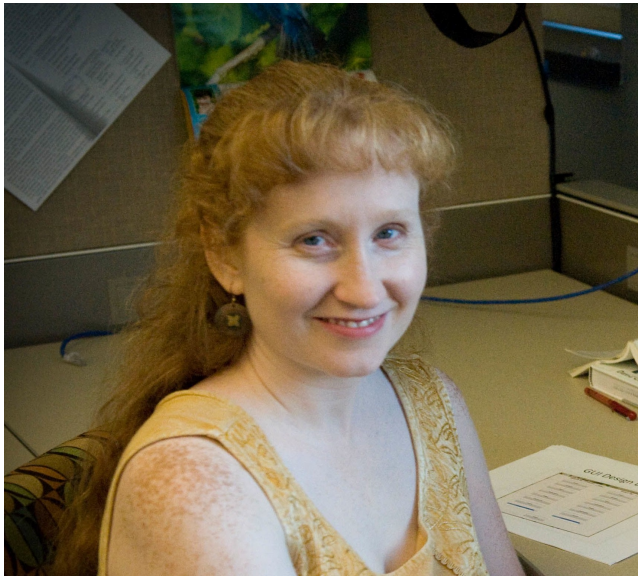

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