Transfer Learning from typical Alzheimer’s disease to rare dementias using Disease Knowledge Transfer

Razvan Marinescu
Alzheimer’s disease is a devastating disease

- Currently no treatment available that can stop, or at least slow down, cognitive decline
Neurodegenerative diseases other than Alzheimer’s also affect many worldwide

- **Posterior Cortical Atrophy > 1 million**
- Frontotemporal dementia > 6 million
  - All tauopathies …
- Dementia with Lewy bodies > 1.6 million
- Vascular dementia > 8 million
- Creutzfeld-Jacobs disease > 7000/year
- Parkinson’s disease
- Huntington’s disease
Progression of Alzheimer’s disease is known.
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Lack of datasets that are:
- Large
- Longitudinal
- Multimodal

Progression of less common neurodegenerative diseases is not known
Progression of Alzheimer’s disease is known

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Transfer learning provides a key solution towards characterizing rare diseases
Previous literature on Transfer Learning for neurodegenerative diseases

- Hon and Khan 2017, Nanni et. al. 2020 - transfer from computer vision datasets to medical datasets
- Cheng, Zhang and Shen 2012, Wachinger and Reuter, 2017, Guerrero et. al. 2014, Hofer et. al. 2017 - transfer learning across Alzheimer’s disease diagnoses (e.g. CN vs MCI -> MCI vs AD)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Topic</th>
<th>Task</th>
<th>Domain</th>
<th>Transfer type</th>
</tr>
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<td>Zhang and Shen (2012)</td>
<td>MCI conversion prediction</td>
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<td>feature, multi-task</td>
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Methods are supervised on clinical diagnosis, which is **unreliable without post-mortem neuropathology**

- No work tried to use transfer learning to improve predictions on **rarer** neurodegenerative diseases

Survey of transfer learning in Alzheimer’s research (Cheplygina et. al., 2019)
Transfer Learning intuition: sharing the disease progression template but not the extent of damage

- Two diseases such as typical AD and Posterior Cortical Atrophy (PCA) affect the brain at different spatial locations.
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- Each region, e.g. occipital lobe, is believed to follow a certain cascade of events.
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- We propose that each region follows the same multimodal trajectories for both typical AD and PCA.

- Difference between typical AD vs PCA is the extent of pathology along the trajectory.

Marinescu et al., MICCAI, 2019
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- Current understanding: PCA, as a different syndrome, is modeled separately from tAD.

Marinescu et al., MICCAI, 2019
The Disease Knowledge Transfer (DKT) framework
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- Model disease as progression of composite dysfunction scores for each brain region:
  - Typical AD: temporal first
  - PCA: occipital first

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  - Typical AD: temporal first
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- Model dysfunction scores as “aggregate pathology” from multiple modalities (e.g. amyloid + tau + atrophy)
- Extend dysfunction modeling to all brain regions
- A new disease, e.g. Posterior Cortical Atrophy (PCA) will have **different** dysfunction progression across the brain (disease specific), but **similar** progression within individual regions (disease agnostic)

Marinescu et al., MICCAI, 2019
DKT is a bayesian hierarchical model
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- Define subject disease stage:

![Diagram of disease progression](image)
DKT is a bayesian hierarchical model

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  \[ \beta_i + m_{ij} \]
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- Estimate value of a biomarker of a particular modality given the dysfunction score:

![Growth curve diagram](image)
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- Functions \( f \) and \( g \) are parameterized using sigmoidal curves
Outline of Results

- Results on simulated data
- Results on patient data from ADNI and the Dementia Research Center UK
- Quantitative evaluation
DKT works well on simulated data

- Simulated 100 subjects with two diseases: synAD & synPCA

- To simulate lack of multimodal data in synPCA, we discarded 4/6 biomarkers
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Marinescu et al., MICCAI, 2019

Disease Knowledge Transfer

DTI → MRI
Common Diseases (AD)
→ FDG PET

 Ürün estim. Ürün estim. Ürün true Ürün true Ürün true Ürün true

Unit0 all trajectories

MAE = 0.057

0.00 0.25 0.50 0.75 1.00
disease progression score

−0.5 0.0 0.5 1.0
dysfunctionality score

biomark 0 estm.
biomark 0 true
biomark 2 estm.
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On real data, DKT can estimate *multimodal* trajectories of Posterior Cortical Atrophy only using structural MRI

- Ran on 76 PCA subjects from the Dementia Research Center UK

- Given structural MRI, DKT was able to infer missing DTI, FDG, Tau PET and Amyloid PET in PCA, in lack of such data.
  - We subsequently validate the DTI trajectories

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Marinescu et al., MICCAI, 2019
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- Split ADNI into three different subgroups with different disease progressions (using SuStaIn)
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- Transferred information from Cortical to Hippocampal subgroups

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TADPOLE: Hippocampal subgroup to Cortical subgroup

**typical Alzheimer's to Posterior Cortical Atrophy**

- DKT (ours)  | 0.77 ± 0.11 | 0.39 ± 0.26 | 0.75 ± 0.09 | 0.60 ± 0.14 | **0.55 ± 0.24** | **0.35 ± 0.22** |
| Latent stage | **0.80 ± 0.09** | **0.53 ± 0.17** | **0.80 ± 0.12** | 0.56 ± 0.18 | 0.50 ± 0.21 | 0.32 ± 0.24 |
| Multivariate | 0.73 ± 0.09 | 0.45 ± 0.22 | 0.71 ± 0.08 | -0.28 ± 0.21* | 0.53 ± 0.22 | 0.25 ± 0.23* |
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Summary and future work

• Proposed a model to perform transfer learning across different neurodegenerative diseases

• Transfer learning is done through sharing the underpinning disease mechanisms

• Model evaluated and validated in simulations as well as real data (ADNI & Dementia Research Center UK) on the largest PCA cohort to date

• Future work: transfer learning using deep-learning approaches, by synthesizing PET/DTI/CT scans for rarer neurodegenerative diseases where such data is very limited

• Such synthesis will enable characterizing their progression, which can help identify novel drug targets, stratify cohorts for clinical trials and identify suitable endpoints.