Disease Knowledge Transfer across Neurodegenerative Diseases

Răzvan Marinescu[1,2], Marco Lorenzi[3], Stefano Blumberg[1], Alexandra Young[1], Pere Morell[1], Neil Oxtoby[1], Arman Eshaghi[1,4], Keir Young[5], Sebastian Crutch[5], Polina Golland[2], Daniel Alexander[1]

[1]Centre for Medical Image Computing, UCL, UK
[2]Computer Science and Artificial Intelligence Laboratory, MIT, USA
[3]University of Côte d'Azur, Inria Sophia Antipolis, France
[4]Queen Square MS Centre, UCL Institute of Neurology, UK
[5]Dementia Research Centre, UCL, UK

Aim Infer progression of non-MRI biomarkers in rare neurodegenerative diseases (NDs) by leveraging larger datasets of common NDs.

Why Posterior Cortical Atrophy (PCA): progression of non-MRI biomarkers not known → Identify outcome measures and suitable subjects for PCA clinical trials

Challenges

Typical Neurodeg. Diseases	Rare Neurodeg. Diseases
• Large datasets ✓	• Small datasets ✗
• Multimodal imaging ✓	• MRI only ✗
• Longitudinal ✓	• Cross-sectional ✗

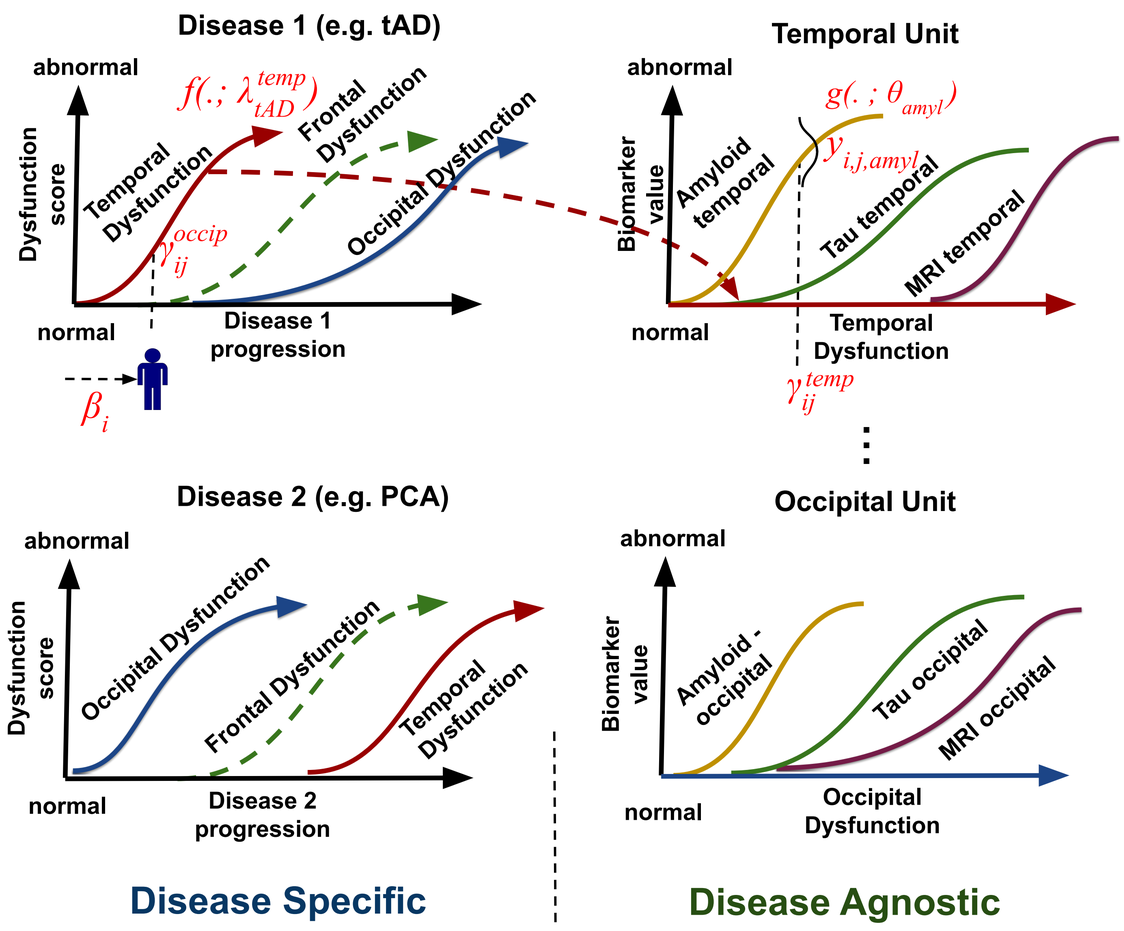
Method

1. Each disease characterised by region-specific dysfunction profile

$$\gamma_{ij}^{l} = f(\beta_i + m_{ij}; \lambda_{d_i}^{l})$$

2. Dysfunction score modelled using region-specific biomarkers

$$y_{ijk} = g(\gamma_{ij}^{\psi(k)}; \theta_k) + N(0, \epsilon_k)$$



3. Extend to multiple subjects, biomarkers and diseases

$$p(\boldsymbol{y}|\theta, \lambda, \beta, \epsilon) = \prod_{(i,j,k)\in\Omega} p(y_{ijk}|\theta_k, \lambda_{d_i}^{\psi(k)}, \beta_i)$$

Inference: Loopy belief propagation

Initialise $\boldsymbol{\theta}^{(0)}$, $\boldsymbol{\lambda}^{(0)}$, $\boldsymbol{\beta}^{(0)}$

while $\boldsymbol{\theta}$, $\boldsymbol{\lambda}$, $\boldsymbol{\beta}$ *not converged* **do**

; // Estimate biomarker trajectories (disease agnostic)

$$\theta_k^{(u)} = \arg\min_{\theta_k} \sum_{(i,j)\in\Omega_k} \left[y_{ijk} - g\left(f(\beta_i^{(u-1)} + m_{ij}; \lambda_{d_i}^{\psi(k),(u-1)}); \theta_k \right) \right]^2$$

; // Estimate dysfunction trajectories (disease specific)

$$\lambda_d^{l,(u)} = \arg\min_{\lambda_d^l} \sum_{(i,j,k)\in\Omega_{d,l}} \left[y_{ijk} - g\left(f(\beta_i^{(u-1)} + m_{ij}; \lambda_d^l); \theta_k^{(u)} \right) \right]^2$$

; // Estimate subject-specific time shifts

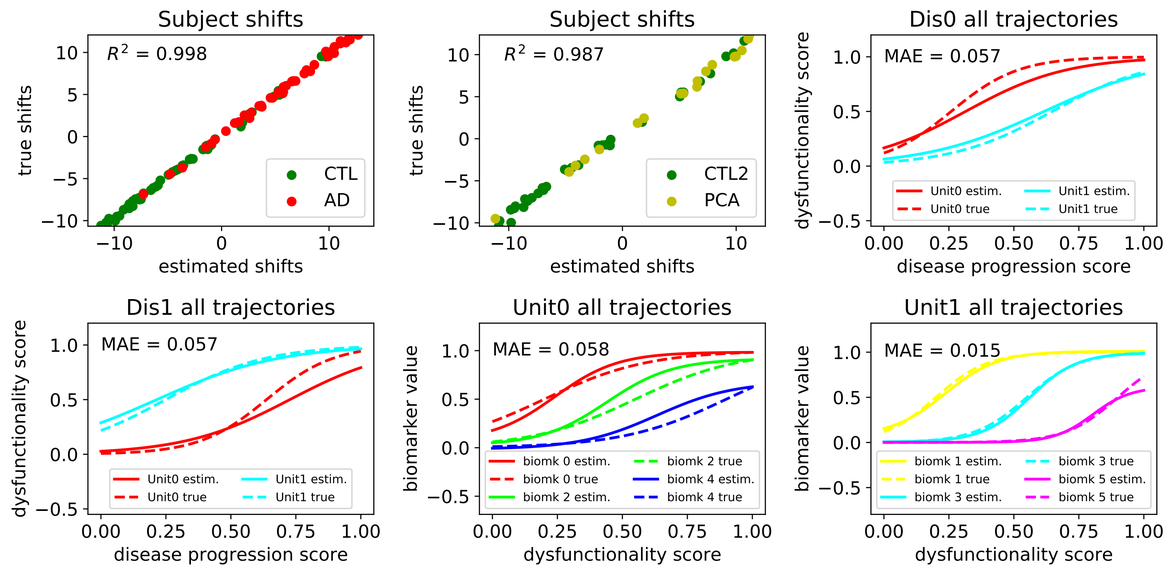
$$\beta_i^{(u)} = \arg\min_{\beta_i} \sum_{(j,k)\in\Omega_i} \left[y_{ijk} - g\left(f(\beta_i + m_{ij}; \lambda_{d_i}^{\psi(k),(u)}); \theta_k^{(u)} \right) \right]^2$$

Demographics

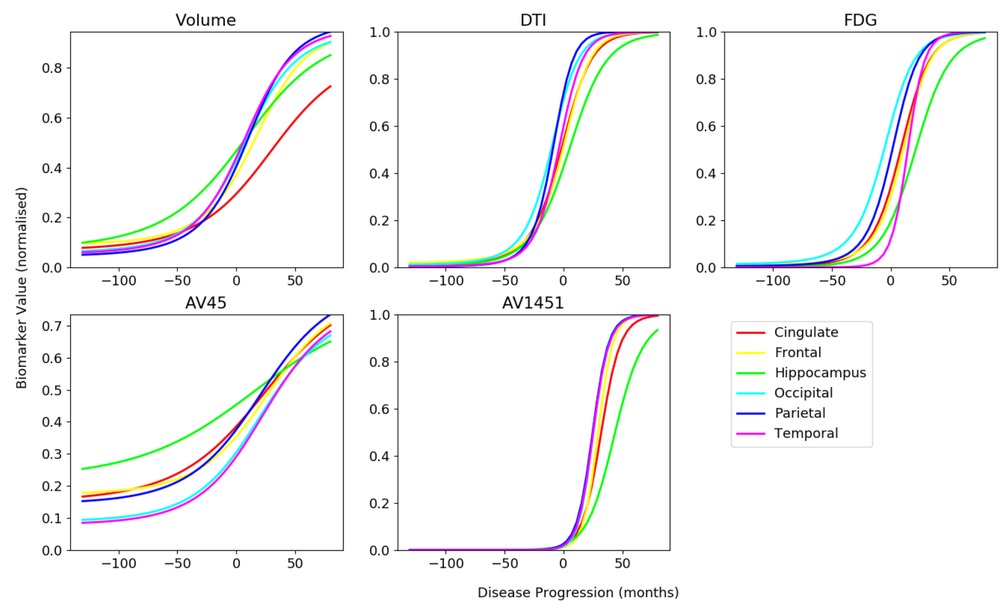
- Dementia Research Center cohort: 76 PCA, 67 tAD, 87 age-matched controls for training, 10 PCA with DTI for validation
- TADPOLE Challenge dataset split into three subgroups with different progressions: 21 hippocampal, 35 cortical, 27 subcortical.
- Synthetic dataset mimicking the DRC cohort: 50 subjects with "synthetic PCA", 100 subjects with "synthetic AD".

Results

In synthetic experiment, the estimated parameters are close to the true parameters



Inferred multimodal trajectories for Posterior Cortical Atrophy are plausible, suggesting late-stage parietal and occipital damage.



Our model has favourable performance compared to other models, on two different datasets

Model	Cingulate	Frontal	Hippocam.	Occipital	Parietal	Temporal
	TADPOLE: Hippocampal subgroup to Cortical subgroup					
DKT (ours)	0.56 ± 0.23	**0.35 ± 0.17**	**0.58 ± 0.14**	-0.10 ± 0.29	**0.71 ± 0.11**	**0.34 ± 0.26**
Latent stage	0.44 ± 0.25	0.34 ± 0.21	0.34 ± 0.24*	**-0.07 ± 0.22**	0.64 ± 0.16	0.08 ± 0.24*
Multivariate	**0.60 ± 0.18**	0.11 ± 0.22*	0.12 ± 0.29*	-0.22 ± 0.22	-0.44 ± 0.14*	-0.32 ± 0.29*
Spline	-0.24 ± 0.25*	-0.06 ± 0.27*	0.58 ± 0.17	-0.16 ± 0.27	0.23 ± 0.25*	0.10 ± 0.25*
Linear	-0.24 ± 0.25*	0.20 ± 0.25*	0.58 ± 0.17	-0.16 ± 0.27	0.23 ± 0.25*	0.13 ± 0.23*
	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*
Spline	0.52 ± 0.20*	-0.03 ± 0.35*	0.66 ± 0.11*	0.09 ± 0.25*	0.53 ± 0.20	0.30 ± 0.21*
Linear	0.52 ± 0.20*	0.34 ± 0.27	0.66 ± 0.11*	**0.64 ± 0.17**	0.54 ± 0.22	0.30 ± 0.21*

Conclusion

- Developed a novel methodology and model for transfer learning across different diseases
- Inferred multimodal trajectories for Posterior Cortical Atrophy

Weblinks

- Source code: https://github.com/mrazvan22/dkt
- Website: https://people.csail.mit.edu/razvan/

Funders

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