

Meta-review

5. Please provide your final assessment of this work, taking into account all reviews and authors' rebuttal (if available). (visible to authors and reviewers).

Some steps of the method need to be further explained. The comparison is relatively weak.

We thank the reviewers for their feedback. Reviewers agreed that the proposed DKT method is novel, robust and interpretable, and strengths and limitations are well discussed. Moreover, DKT presents new and interesting technical challenges to which the authors propose the first solutions. Specific shortcomings raised are:

1. Comparison with state-of-the-art methods (R5.5.2 R5.6.2)

~~Currently there are not~~ ~~is unclear what are the~~ state of the art methods in Alzheimer's disease future prediction, ~~as there have been~~ ~~and there are~~ no benchmarks to evaluate algorithms. ~~on this task. While~~ ~~T~~ the recently launched TADPOLE challenge is currently addressing this ~~at, ye its the~~ results have not ~~yet~~ been released ~~[maybe ignore]~~. ~~We cannot compare to~~ ~~If the reviewers were referring~~ to deep transfer learning methods, ~~these are not~~ ~~unsuitable~~ for this task ~~because~~ ~~as~~ (i) they have not yet been adapted to estimate the future evolution of subjects ~~and~~ (ii) the input data in our problem is represented by extracted features and not raw images, hence we cannot use convolutional neural networks ~~[you technically could btw, CNNs simply take local features]~~. ~~We nevertheless performed~~ ~~i~~ In Table 1 a comparison with the most up-to-date disease progression models available ~~[cite]~~ (Jedynak et al., Neuroimage, 2012) ~~as well as~~ ~~in addition to~~ other popular prediction methods (Gaussian Process regression and spline regression).

2. Use of sigmoid function when the dynamics of dysfunction scores might not always be monotonically increasing (R4.6.1)

We ~~actually~~ believe the dysfunction trajectory should ~~also~~ be monotonically increasing, as previous research in Alzheimer's disease seems to suggest the disease is irreversible in absence of treatments ~~[cite]~~ (e.g. Filley, Geriatrics, 1995). This assumption also helps with model identifiability – non-monotonic trajectories will require strong priors on subjects' disease stages.

3. How can the model be used to predict unseen data, when parameters beta and lambda are related to each subject? (R4.6)

Beta and Lambda are estimated based on ~~e.g.~~ the MRI data of the subject, and the model can then predict the other unseen multimodal biomarkers for the same subject: DTI, FDG, et ~~c~~ ... The correlations are learned from the other diseases while ~~ste~~ also considering the different spatial distribution of pathology.

4. More details on parameter estimation (R5.6.1, R5.5.1)

We agree with the [reviewerR5](#) that parameter estimation is important. ~~However,~~ due to constraints on page limit, we felt it was more important to provide further explanations of the idea behind the method, its motivations, and why the assumptions make sense. We are [also](#) not aware of similar methods ~~developed previously~~, hence the focus on explaining the overall [approach?picture](#). We will include a link to supplementary material to explain parameter estimation and will also provide the source code for reproducibility. [\[Just to say, one of our reviewers like the](#)

5. Lack of detailed interpretation of results (R4.6.2)

While we provide high-level interpretation of results in the paper, we [are constrained by space-feel that more to provide more](#) detailed clinical interpretations [is better suited for a journal paper due to MICCAI page limits and of less interest to the more technical MICCAI audience-, which will be explored in future work. \[Reason for choosing your interpretation of results, I am not sure if saying MICCAI is a technical paper is correct, ask Danny et.c\]](#) As noted in section 3 paragraph 2, our aim was to demonstrate the feasibility of inferring plausible non-MRI biomarker trajectories in a rare disease in lack of such data.

6. More details on synthetic dataset (R1.6.1) and demographics of test set (R1.6.2)

~~We agree we should have provided more information on this. Unfortunately, D~~ due to the page limit constraints, we [believed it was more important to prioritised](#) explaining the motivation for the problem and the key ideas of the method. We plan to include in the supplementary material more information regarding the synthetic dataset and the test set.-

View Reviews

Paper ID1296

Paper Title: Disease Knowledge Transfer across Neurodegenerative Diseases

Reviewer #1

Questions

1. Please confirm that you have read and understood the MICCAI 2019 Reviewers' Guide https://www.miccai2019.org/information/information-cmt_rev/information-reviewers/

Agreement accepted

2. As reviewer conflicts have been taken into consideration for the paper allocation process, there are no allowable changes of co-authorship during the paper review process and after paper acceptance. Only in exceptional circumstances, requests for late authorship changes may be made in writing to the Program Chairs, but under no circumstances may they compromise the review process conflict checking and will be denied in such cases. Please acknowledge that you have read and understood this notice.

Agreement accepted

3. Please provide a summary of the paper (a few lines)

The authors of this paper propose a new framework to transfer biomarker information from neurodegenerative disease to another related one by inferring multimodal biomarker trajectories. The method is evaluated within a synthetic dataset and two different datasets involving AD and PCA patients. Moreover, the method shows for the first time a multimodal signature derived for PCA.

4. Please list the major strengths of the paper (bulleted list)

1. The paper is well structured.
2. The proposed method to infer the trajectory of multimodal biomarkers within longitudinal studies is novel and promising.
3. The evaluations are pertinent and the proposed technique — that is compared with state-of-the-art methods — shows promising results.
4. The strength and limitations of the method are well discussed.

5. Please list the major weaknesses of the paper (bulleted list).

1. The description of demography of the subjects involved in the validation datasets is missing.
2. Since the proposed technique is designed for longitudinal studies, it would be interesting to see the impact of the number of visits and the time of follow up.

6. Please provide detailed and constructive comments for the authors. Please also refer to our Reviewer's guide on what makes a good review:

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1. A better description of the generation of synthetic dataset would help to appreciate the validation.
2. How many time visits and how long the follow up of each subject is provided (is it homogeneous?)

7. Please rate the clarity and organisation of this paper

Very Good

8. Please rate whether the paper introduces significant scientific innovation.

Moderately likely

10. Please rate whether this work is likely to make a significant impact (clinical, scientific, algorithmic, biomedical, mathematical, etc.).

Moderately likely

Reviewer #4

Questions

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Agreement accepted

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Agreement accepted

3. Please provide a summary of the paper (a few lines)

Authors introduced Disease Knowledge transfer (DKT) for transferring biomarker information between related neurodegenerative diseases.

4. Please list the major strengths of the paper (bulleted list)

- DKT infers robust multimodal biomarker trajectories in rare neurodegenerative disease
- DKT is a joint-disease generative model of biomarker progression, which allows understanding underlying disease mechanisms and also predicting the future evolution of subjects at risk of disease.

5. Please list the major weaknesses of the paper (bulleted list).

- It is not generally convincing to use sigmoid function to model two functions
- Some errors
- Lack of the detailed interpretation for the results

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In Method section, authors model both two functions using sigmoid function. It might be reasonable for the disease stage to a dysfunction score with the assumption that the function is a smooth monotonic. However, the trajectory of biomarker within agnostic unit is a function of mapping dysfunctionality score to biomarker value.

It might not always be monotonically increasing.

This also relates to the motivation of better interpretation than existing transfer learning methods. Unfortunately, authors did not show the detailed interpretation of the obtained results, but leave it as the future work. Hence, the motivation of the good interpretation of this method is not verified by the experiments.

In equation (1) and (2), the subscript j for the j th visit is missing. This confuses the understanding of this model on how it works. From the model, the model parameter β and λ should be related to each subject, so how is the model possible for the prediction of unseen data?

7. Please rate the clarity and organisation of this paper

Satisfactory

8. Please rate whether the paper introduces significant scientific innovation.

Neutral

10. Please rate whether this work is likely to make a significant impact (clinical, scientific, algorithmic, biomedical, mathematical, etc.).

Neutral

Reviewer #5

Questions

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Agreement accepted

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Agreement accepted

3. Please provide a summary of the paper (a few lines)

1. This paper introduces Disease Knowledge Transfer (DKT) to transfer biomarker information between related neurodegenerative diseases. It is a joint-disease generative model of biomarker regressions.

2. The proposed method is claimed to be the first work to estimate plausible multimodal biomarker trajectories in Posterior Cortical Artrophy (PCA).

3. Experiments have validated on synthetic data and two patients datasets.

4. Please list the major strengths of the paper (bulleted list)

1. The proposed DKT is interpretable and can also predict the future evolution of subjects at risk of diseases.

2. DKT can model the dynamics of some biomarkers disease-agnostic.

5. Please list the major weaknesses of the paper (bulleted list).

1. Missing details in method section which will make readers difficult to follow and re-implement.

2. It seems the authors didn't compare with state-of-the-art methods.

6. Please provide detailed and constructive comments for the authors. Please also refer to our Reviewer's guide on what makes a good review:
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1. Solving the full model likelihood (3) is also very important for readers. However, not much details are given which will not help readers understand how model parameters are estimated. It is recommended to include a detailed algorithm here.

2. It is important to compare with other state-of-the-art models as authors claimed the contribution of the proposed DKT. Discussions with other transfer learning methods [4, 5] can be included in experiments to better see their limitations.

7. Please rate the clarity and organisation of this paper

Very Good

8. Please rate whether the paper introduces significant scientific innovation.

Moderately likely

10. Please rate whether this work is likely to make a significant impact (clinical, scientific, algorithmic, biomedical, mathematical, etc.).

Moderately likely