ADNI Progress report

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Part I

Using HMMs to predict disease progression

1 Using PET scans as features for the HMMs

First, we use the 5-dimensional feature vectors derived from PET scans (mean tracer retention in five expert defined regions) to train a HMM and observe the correlation of the Viterbi states with the clinical labels and the clinical tests.

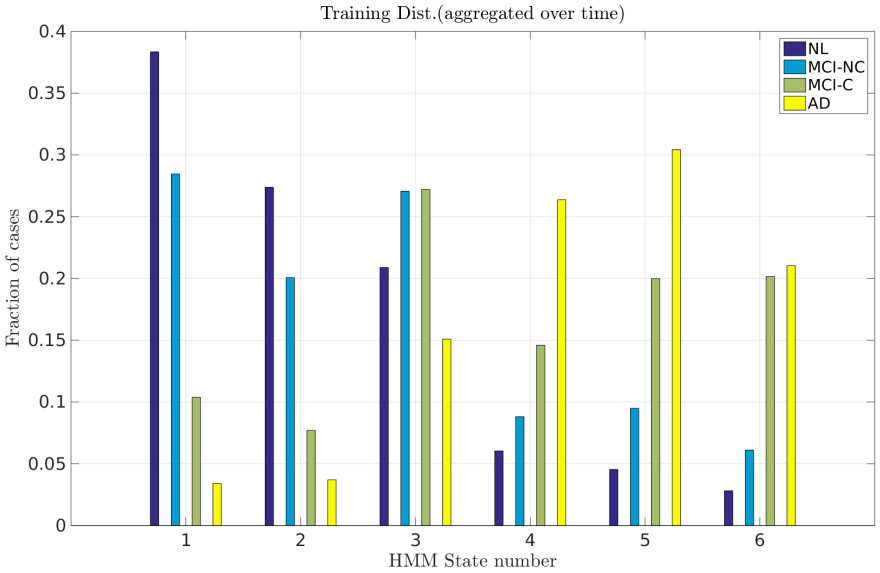

Figure 1: Distribution of labels given HMM state (Training set)

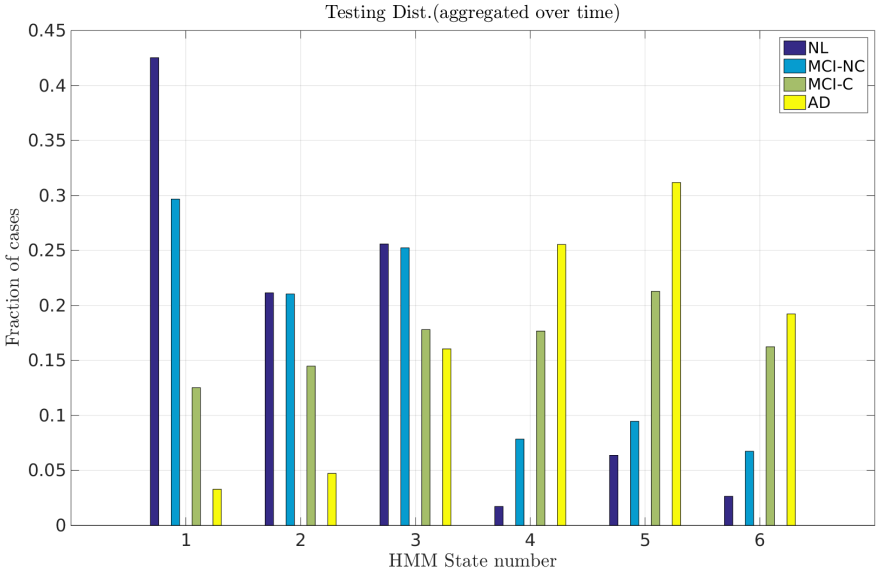

Figure 2: Distribution of labels given HMM state (Test set)

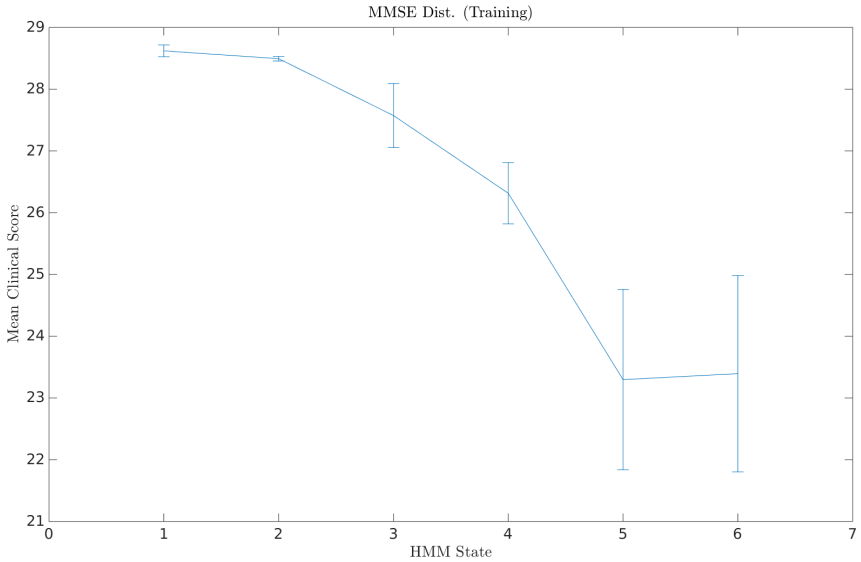

Figure 3: Mean MMSE score given Viterbi state (Training set)

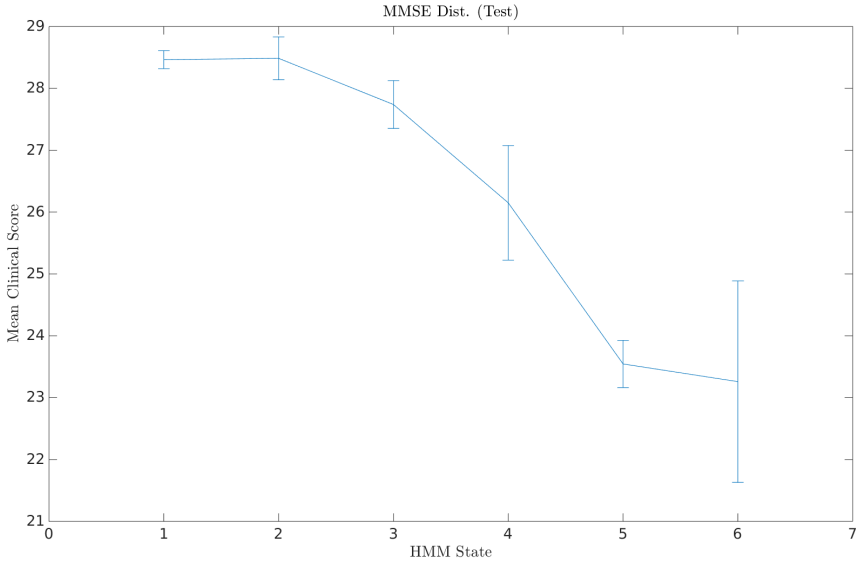

Figure 4: Mean MMSE score given Viterbi state (Test set)

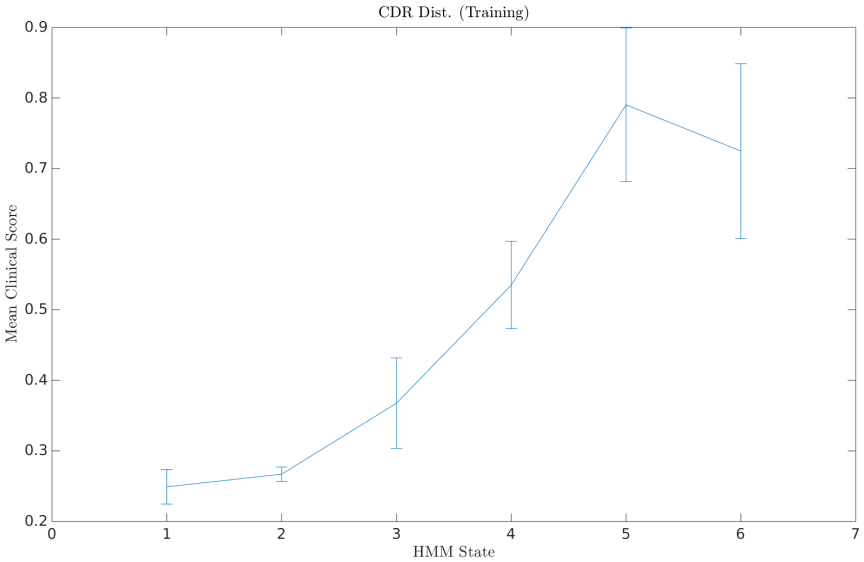

Figure 5: Mean CDR score given Viterbi state (Training set)

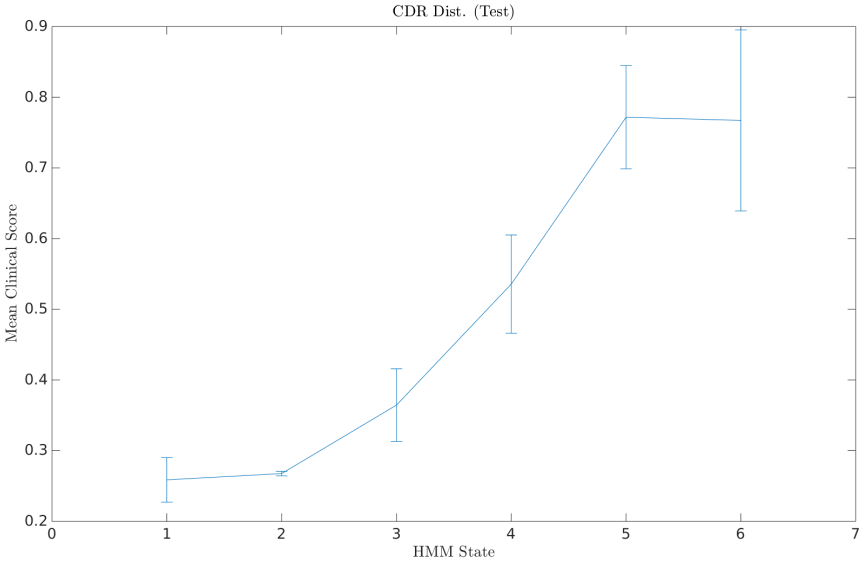

Figure 6: Mean CDR score given Viterbi state (Test set)

2 Using the Viterbi probabilities for a discriminative classifier

We use the Viterbi lattice probability vectors to predict the clinical labels of the patients.

Using the K-dimensional vector of probabilites as a feature vector for a linear classifier, the accuracies are 42%, with a roughly uniform probability being assigned to each of the three states. If the feature vector is appended with the argmax of the probability vector, the accuracy increases to 49%.

As a possible explanation for this, we observe the figure below which shows the distribution of probabilities at each state of the HMM as calculated by the forward-backward algorithm.

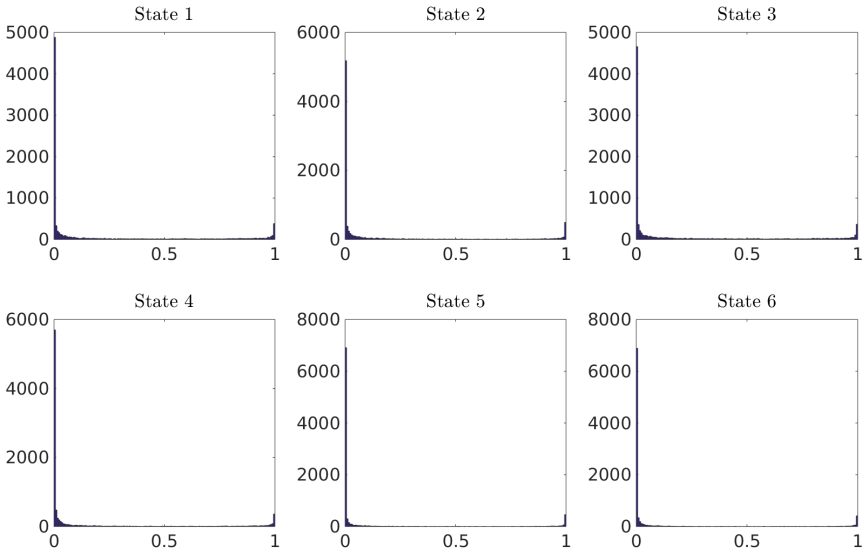

Figure 7: Distribution of probabilities at each state of the HMM as calculated by forward-backward algorithm

The overwhelmingly bi-modal distribution of probabilities likely provides very little information to the discriminative classifier.

3 Using MMSEs as features for the HMM

We use the MMSE scores from patients as observations for the HMM.

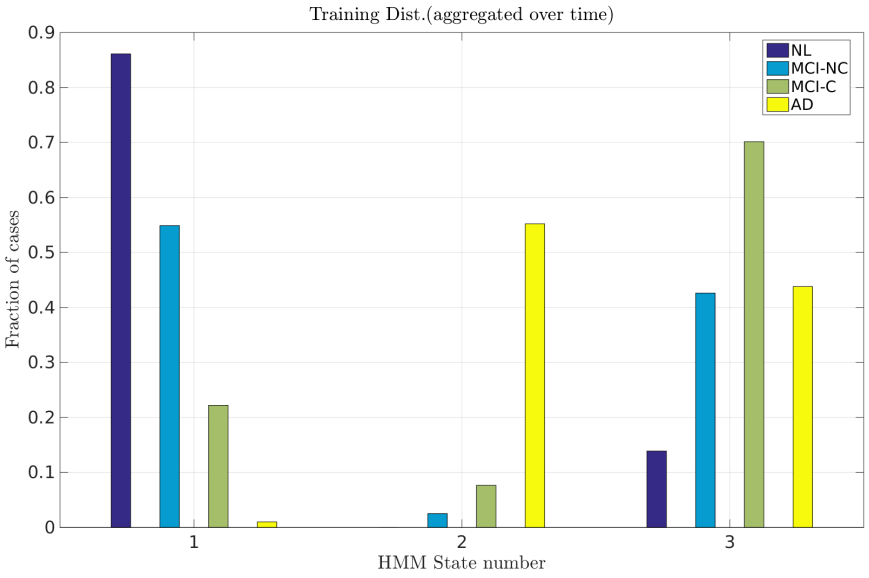

Figure 8: Distribution of labels given HMM state using MMSE (Training set)

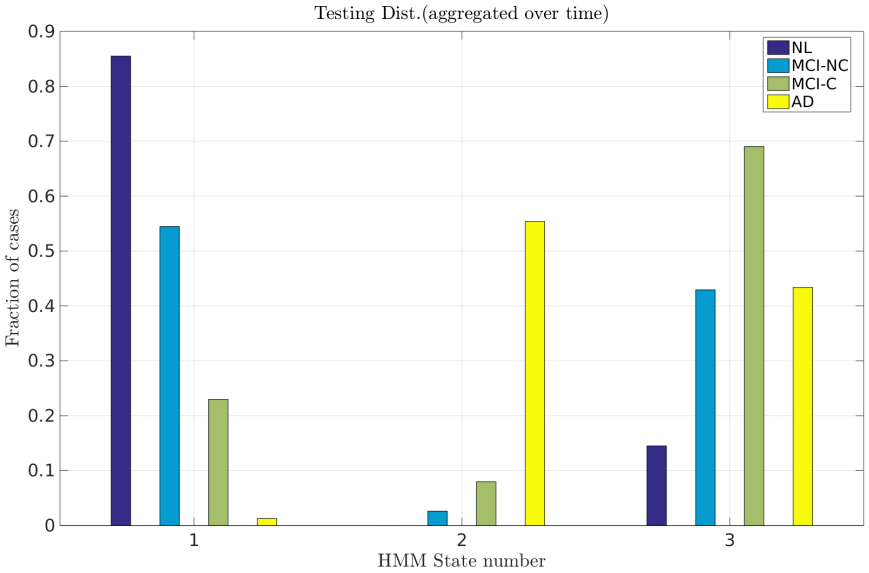

Figure 9: Distribution of labels given HMM state using MMSE (Testing set)

However, training a traditional HMM using MMSE scores is problematic and susceptible to singular covariance matrices in the observation models due to the non-Gaussian nature of the distribution of the MMSE scores. Consider the following figure:

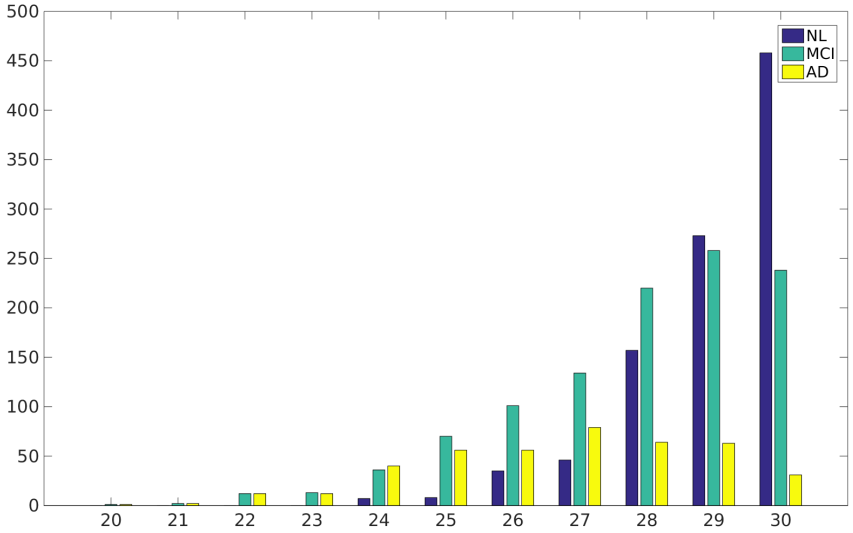

Figure 10: Distribution of MMSE scores over clinical labels

4 Comparison of HMMs

We compare the states assigned by the HMM using PET scans with those assigned by the HMM using MMSE scores.

Three states each for both HMMS,

	State 1 (MMSE)	State 2 (MMSE)	State 3 (MMSE)
State 1 (PET)	0.73 ± 0.03	0.01 ± 0.01	0.26 ± 0.03
State 2 (PET)	0.42 ± 0.05	0.12 ± 0.02	0.46 ± 0.04
State 3 (PET)	0.13 ± 0.04	0.46 ± 0.03	0.41 ± 0.03

Six states for the HMM using PET scans and three states for the HMM using MMSE,

	State 1 (MMSE)	State 2 (MMSE)	State 3 (MMSE)
State 1 (PET)	0.76 ± 0.06	0.01 ± 0.01	0.23 ± 0.06
State 2 (PET)	0.70 ± 0.03	0.02 ± 0.01	0.30 ± 0.03
State 3 (PET)	0.55 ± 0.04	0.06 ± 0.03	0.40 ± 0.03
State 4 (PET)	0.21 ± 0.17	0.32 ± 0.15	0.47 ± 0.03
State 5 (PET)	0.23 ± 0.12	0.32 ± 0.17	0.45 ± 0.08
State 6 (PET)	0.20 ± 0.10	0.35 ± 0.17	0.46 ± 0.08

5 Comparison with related work

The most similar work to ours is Disease Progression modeling using Hidden Markov Models, where the authors use a similar approach to stage patients using HMMs. Some differences are:

- The above work uses **longitudinal** MRI-based features as compared to our **cross-sectional** PET-based features
- They only analyze the distributions of {NL, MCI, AD} over each HMM state as compared to our analysis of {NL, MCI-stable, MCI-converters, AD}

A more reputable but only somewhat similar work appears in Event-based model of Alzheimer's Disease.

The main idea here is to fit Gaussian mixture models to 14 biomarkers (combination of CSF, MRI and clinical tests such as the MMSE, ADAS-cog, etc.) with the two mixture components representing 'controls' or 'patients'.

The hypothesis states that there is a natural ordering of these 14 biomarkers, and using a maximum-likelihood approach we are able to find the most likely current position of the patient in the 'event' space, where an event represents the control/patient status of a biomarker. Thus, being in state k of the event-space signifies that events $1 - k$ have occured (their levels are abnormal as observed in patients) and events $k - 14$ have not occured (their levels are normal as observed in controls).

The natural ordering of the 14 biomarkers is retrieved using a greedy approach that maximizes the joint likelihood of that data. Furthermore, using MCMC sampling, the authors are able to provide a notion of uncertainty associated with the ordering of the events.

Using the above natural ordering a patient can be assigned to a particular stage k in the natural ordering such that the likelihood of the data is maximized. Furthermore, they simply threshold on an event stage to predict conversion from NL→MCI or MCI→AD. This stage is picked such that the prediction accuracy is maximized.

Some key difference of this paper with our work are:

- Works with just one visit of the patient (cross-sectional data) as opposed to our reliance on a sequence of visits. The caveat to this is that it does not exploit the temporal information in the data

- Makes use of a several modalities (three different sources), some of which are invasive (CSF)
- Prediction of conversion is not state of the art given the range of modalities used, however it is more interpretable from a clinical standpoint and completely unsupervised

6 Conclusions/Future Work

One possible use for our model is to deploy it as an 'assistant' to clinicians. In particular, all diagnostic labels in the ADNI cohort are assigned based purely on clinical tests such as the MMSE, ADAS-Cog, RVLT, etc. However, the final diagnostic label is assigned to the patient at the discretion of the clinician - there are no hard-coded boundaries/guidelines available.

It might be useful to have a mathematical model of the correlation between all of these scores and the final clinical label, that the clinician can refer to as a second opinion. While the current results for this task are only mildly positive, it could be worthwhile to retrain the model with a non-Gaussian observation model/using a combination of several clinical tests.