Trajectory Based Predictive Modeling of Conversion from Mild Cognitive Impairment to Alzheimer's Disease

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***Abstract*— Accurate prediction of clinical changes of Mild Cognitive Impairment (MCI) patients at future time points is important for early diagnosis and possible prevention of Alzheimer's disease (AD). In this paper, future clinical changes in Neuropsychological Measures (NM) of MCI patients are estimated via three different predictive models employing linear regression and extrapolation. The completed time domain trajectories are processed in the Euclidean space to extract features encompassing clinical change in the biomarker values. These features are then fed to an optimized SVM classifier to predict conversion of an MCI patient to AD. A wrapper based biomarker subset selection is adopted to analyze the effect of single and combined NM biomarkers. The proposed predictive modelling techniques were validated on 186 MCI subjects with the selected NM readings available at baseline and 3 annual follow-up visits. 1 and 2 year ahead conversion prediction was made using the current and at least 1 year old biomarker reading. Maximum accuracy of 77.87% and 73.24% is achieved for 1 and 2 year ahead conversion prediction respectively.**

I. Introduction

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder mostly associated with the elderly. Along with increase in life expectancy, the size of population suffering from AD is on the rise. Currently, around 30 million people around the world suffer from AD; this number is expected to triple by 2050 [1]. AD is categorized with significant memory loss, cognitive decline and inability to perform daily routine tasks. It was established in 1990s [2] that the AD causing neuropathological changes in the brain occurs decades before the symptoms of the disease become visible. The initial symptoms of the disease are mild memory impairment and a little cognitive decline [3]. This stage is called Mild Cognitive Impairment (MCI). At this stage, dementia has not set in and the patient is able to carry out routine activities. Manly et al [4] concluded that 10-15 percent of the MCI patients progress to AD in the future (MCIp) while other retain the stable diagnosis of MCI (MCIs). If MCIp patients are accurately distinguished from the MCI patients, better disease management can be provided to them. Furthermore clinical trials can be conducted to slow down or stop the progression of MCI to AD.

MCI diagnostic tools are the same as those for AD. These include Cerebrospinal Fluid (CSF) sampling, Positron Emission Tomography (PET), Magnetic Resonance Imaging (MRI) of the brain and paper based Neuropsychological Testing. Jack et al. [5] presented a concise summary of biomarkers and their variability in relation to AD progression. It was identified that CSF and PET are best for detecting pathological changes at pre-symptomatic stage of AD. Structural MRI is used to capture neurodegeneration which continues throughout the disease span. However, cognitive function captured via Neuropsychological Measures (NM) deteriorate when the disease is progressing from MCI to AD.

The multimodal, multivariate biomarkers have repeatedly been used in the literature for segregating MCIp and MCIs patients which is a binary classification problem. In numerous studies including [6] – [9] single modality biomarkers have been employed for the said classification. Contrarily, a plethora of studies exists which utilized a combination of multimodal biomarkers for the MCIp vs. MCIs classification. These include [10] – [13]. Yet the classification performance stayed limited and [14] along with many others concluded that classification performance using single modality biomarkers is as good as that obtained by multimodality biomarkers.

Further efforts for improving classification accuracy were made in [15] – [19] where longitudinal biomarker data were used instead of single time point data for recognizing the incipient disease. Even tough better generalizability is achieved by using time sampled data, more detailed efforts are required in order to obtain a dependable clinical decision support system. In this paper we present a classification framework leveraging the latent information in pateints' longitudinal NM trajectories for predicting the disease course. The main contributions of our work are as follows:

1. Forecasting future biomarker values using baseline and first follow-up readings. For this we propose three different techniques based on linear and piecewise linear modelling of the longitudinal biomarker trajectories.

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2. Mapping of time domain trajectories to feature space using Euclidean geometry to extract instance specific features.
3. Classification of individual instances into MCIp or MCIs using optimized Support Vector Machine (SVM) classifier.
4. Validation of the proposed technique using the most widely used publically available dataset.

The proposed method is used to make 1 year and 2 year ahead MCI-to-AD conversion predictions. Rest of this paper is organized as follows. Section II describes the material used and the methods adopted in this study. Section III details the results while Section IV concludes the work done.

II. Materials and Methods

A. Materials

The data used in this study were extracted from the Alzheimer's Disease Neuroimaging Initiative (ADNI) website (adni.loni.edu) on 30th May, 2015. ADNI is a five year public-private partnership engaged in gathering AD related biomarkers from Neuropsychological Measures (NM), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) scans, biochemical readings via lumbar puncture and genetic alleles. For up-to-date information about ADNI procedures and sample sizes please see www.adni-info.org.

The AD NM biomarkers selected for this study are the AD Assessment Scale (ADAS), Rey's Auditory Verbal and Learning Test (RAVLT), Clock Drawing Test (CDT), Clock Copy Test (CCT), Immediate Recall Total Score (LIMM), Mini Mental State Examination (MMSE), Trail Making Test A (TRAA) and Trail Making Test B (TRAB). The detailed description of the tests conducted and the scoring criteria of these NM is presented in ADNI General Procedures Manual [20]. MCI patients in ADNI dataset were followed up biannually for the first two years, and annually later on. For the predictive modelling framework presented in this paper, readings recorded at regular annual intervals after the baseline reading were considered i.e. 12th month, 24th month and 36th month. The participants with one or more missed follow-up readings for any of the eight biomarkers were dropped from this study so as to obtain the most accurate model. Consequently, the dataset consisted of 98 cases of MCIp and 86 cases of MCIs when 1 year ahead prediction (l=1) was considered and the sample sizes dropped to 85 cases of MCIp and 76 cases of MCIs when 2 year ahead prediction (l=2) was required.

B. Methods

The overview of the proposed MCI-to-AD conversion prediction methodology is presented in Fig. 1. Individual modules are detailed in the following paragraphs.

1) Biomarker Ranking:

The first step in the proposed method is to sift the biomarkers according to their ranks in contribution towards MCIp vs MCIs segregation. For this, the two sampled student's t-test is performed on baseline biomarker readings whose p-values indicated about significance of a particular biomarkers towards effective diagnostics. The ranked

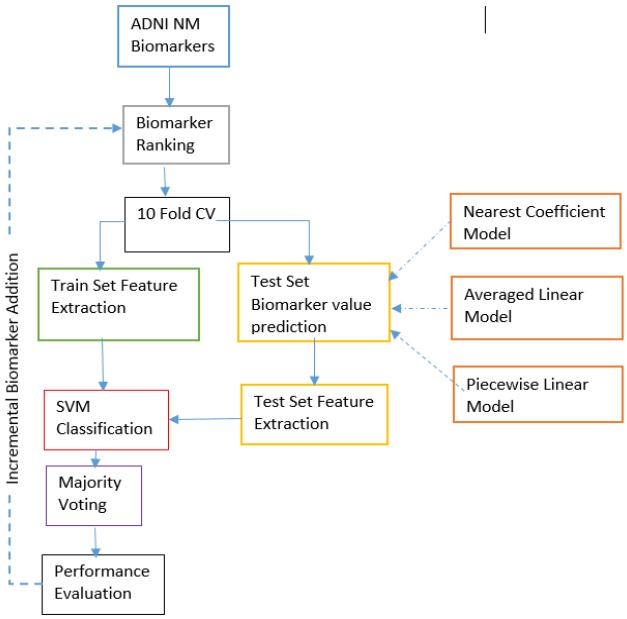

Figure 1. Proposed method

biomarkers are then passed through a wrapper system for biomarker subset selection where the biomarkers are added incrementally in the biomarker subset and the effect on classification performance is noted. The number of biomarkers considered correspond to the model rank.

2) Classification Setup

While depicting a real world situation, an MCI subject is to be classified as MCIp (c=1) or MCIs (c=0) based on the current (t=0) and at least one past (t= −1) biomarker value. In this study, the first annual follow-up biomarker readings are taken as current and the baseline biomarker readings are taken as the past values. A 10 fold cross validation setup is adopted, in which the longitudinal train set is represented by $X_m(t)$ for t= −1…l−1 and the corresponding test set is represented by $Y_m(t)$ for t= −1…l−1 only. 'm' indexes to the biomarker under consideration. A model is generated using X_m which is later employed to find future time point values for Y_m. The complete trajectories are then used to generate the final class label for the test instances. The steps are detailed below.

a) Future Biomarker Value Estimation

The following three modelling techniques are adopted and validated for prediction of future biomarker readings for the test instances (i.e. at t = l):

(1) Nearest Coefficient Model (NCM):

In this estimation method, the gradient of change in the biomarker value over the previous years is linearly modelled for each training instance of both groups. For this linear regression using (1) is performed.

$$X_{m_c} = \beta_0 + \beta_1(t) + \epsilon, \quad for\ m = 1 - N, t = -1 \ldots l - 1, c = 0/1 \tag{1}$$

Here, β_0 is the y-intercept and β_1 is the regression coefficient for the training instances in X_m belonging to class c. ϵ is the error term measured as the difference between actual value and the modeled value and is reduced in a least squares sense to obtain best estimates for β_0 and β_1. The

regression coefficient for test instances are also obtained in a similar fashion. A *k* nearest coefficient classifier is trained using the regression coefficients of the training instances. This classifier is then employed to classify the individual test instances as c=0 or c=1 based on the regression coefficients. If a test instance is classified as MCIp, the biomarker value at t=*l* was estimated by linear extrapolation using the mean regression coefficient of MCIp group over the interval t= *l*−1…*l* and vice versa. The candidate set for *k* is varied from k = 1 – 7 to obtain the optimal solution.

(2) Averaged Linear Model (ALM):

In this case, the MCIp and MCIs groups are stratified according to their diagnosis at the end of l^{th} year. Biomarker measurements of each group are linearly modelled in the interval t= −1…*l*, to find the respective regression coefficients using least squares estimation. Equation (1) is used again first with the training instances of MCIp group and later with training instances of MCIs group to obtain β_{1_1} and β_{1_0} respectively.

Two sets of possible future values for the j^{th} test instance are calculated using both β_{1_1} and β_{1_0} regression coefficients. A cross comparison measure *s* is devised to assess the degree of correspondence between the generated test values and the training data used to generate those values. *'s'* is calculated using (2).

$$s_c\left(y'_{mj}(\beta_{1_c}), X_{m_c}\right) = \frac{\sum_{i=1}^{n(c)} \sum_{t=-1}^{l} y'_{jm}(t) - x_{im}(t)}{n(c)}, \quad \text{for m} = 1 - \text{N}, \text{j} = 1 - \text{k}, c = 0/1 \tag{2}$$

where $y'_{mj}(\beta_{1_c})$ is the completed test trajectory for m^{th} biomarker of j^{th} test instance using respective regression coefficient and X_{m_c} is the set of train trajectories belonging to respective class *c*. $n(c)$ is the number of training instances belonging to class c. If the absolute value of s_1 is lower than s_0, the values of y_{mj} resulting from β_{1_1} regression coefficient are kept for further processing and vice versa.

(3) Piecewise Linear Model (PLM):

It is common medical practice to assume linear progression of biomarkers between consecutive follow-up visits. Hence, a piecewise linear model is also designed for future biomarker value prediction. The training set is again stratified into two groups: MCIp and MCIs, and the mean annual change in m^{th} biomarker values ΔX_m on consecutive follow-up visits is noted using (3).

$$\Delta X_{m_c} = \frac{\sum_{i=1}^{n(c)} X_{m_c i}(t+1) - X_{m_c i}(t)}{n(c)}, \quad for\ m = 1 - N, t = -1 \ldots l - 1, c = 0/1 \tag{3}$$

where n(c) is the number of instances in the train set of the respective group. Likewise, the annual change in m^{th} biomarker values for the j^{th} test instance, ΔY_{mj}, is computed by (4).

$$\Delta Y_{mj} = y_{mj}(t+1) - y_{mj}(t), \quad for\ m = 1 - N, t = 0, j = 1 - k, t = -1 \tag{4}$$

Next, based on minimum absolute difference of ΔY_{mj} from ΔX_{m_0} and ΔX_{m_1}, a test instance is assigned to either of the two classes. An offset value between the annual change of the test instance and the mean annual of the selected class for the m^{th} biomarker is generated using (5).

$$offset_m = \Delta X_{m_c} - \Delta Y_{mj}, for\ m = 1 - N, j = 1 - k \tag{5}$$

Here, ΔX_{m_c} is the mean annual change observed for the class to which a test instance belonged. For forecasting one year ahead biomarker value, the mean annual change of the selected group over the next interval and the offset value are added to the current value of the test instance according to (6).

$$y_{mj}(t+1) = y_{mj}(t) + \Delta X_{m_c} + offset_m, \quad for\ m = 1 - N, j = 1 - k, t = 0 - 2 \tag{6}$$

b) Feature Extraction

In order to attenuate the effect of inexact biomarker values, the time domain biomarker trajectories are mapped to feature space by extracting the following information.

- Y Intercept: This feature corresponds to the biomarker value at baseline visit.
- Difference: This is the measure of change of biomarker values between the baseline and the l^{th} follow-up visit.
- Variance: This feature captures the variance of the biomarker values over time
- Annual change: Instead of discrete time point biomarker readings, the annual change in biomarker values is used during classification
- Overall change: A best fit line is modelled from every instance's biomarker trajectory. The slope of this best fit line is then taken as one of the features.

c) Classification

The features extracted from the train and test trajectories are fed to an optimized Support Vector Machine classifier. The SVM classifier is trained with the Radial Basis Kernel Function and the candidate set for soft margin value is varied from 0 – 1 in steps of 0.2. For each test instance, this classification results in a class label and a likelihood score that the instance came from that particular class.

For determining the final conversion prediction label for a test instance, the class labels and classification scores resulting from each of the N biomarkers are stored. A test case is classified as MCIp (c=1) if more biomarkers indicated progression and MCIs otherwise. In cases where a tie between MCIp and MCIs occurs, the final label is given based on maximum likelihood value resulting from the classification scores.

III. RESULTS

First of all we detail the results of our biomarker ranking step. The observed order of biomarkers in decreasing segregating power is RAVLT, ADAS, MMSE, CDT, LIMM, CCT, TRAA and lastly TRAB. These ranked biomarkers are incrementally added in the biomarker set to be considered for future MCI-to-AD conversion predictions.

The classification performance is encapsulated by Accuracy, Precision and Area Under ROC curve (AUC). For benchmarking, the original observed test trajectories provided by ADNI are passed through the system to obtain ground truth performance measures. Later, the estimated biomarker trajectories are used for classification and performance measures are reported. Error between the ground truth measures and obtained measures is also stated.

Highest ground truth accuracy of 81.52% for 1 year ahead prediction was achieved by using only four top ranked biomarkers. The corresponding measures for AUC and

precision were 88.81% and 81.32%. Table I entails a comparison amongst the three proposed future value forecasting techniques and the ground truth results for 1 year ahead AD conversion prediction. It can be seen that the ALM modelling of the train data for future biomarker value forecasting outperforms the other techniques in terms accuracy with a minimal error of 3.27% using a model of top three biomarkers. PLM also delivered comparable accuracy (77.87%) but the AUC and precision values achieved by PLM were higher than those resulting from ALM using the same biomarker model.

Similar analysis was performed for 2 year ahead conversion prediction. The maximum ground truth accuracy of 75.11% was achieved by utilizing only the top most biomarker. Table II presents a comparison of the ground truth and the forecasting techniques performance metrics. For long tern conversion prediction, ALM delivered least error in both accuracy and AUC using a model of rank 6. Maximum accuracy of 73.24% and AUC of 78.85% was achieved. Presence of observer variances is also evident from the ground truth results as the performance metrics are recorded to be less than 100%.

TABLE 1: COMPARISON FOR 1 YEAR CONVERSION PREDICTION

	GT	NCM		ALM		PLM	
		O	E	O	E	O	E
Rank	4	3	-	3	-	3	-
Acc	81.52	72.75	8.77	78.25	3.27	77.87	3.65
AUC	88.81	71.68	17.13	80.36	8.45	84.1	4.71
Pre	81.32	71.63	9.69	77.06	4.26	81.06	-0.28

TABLE II: PERFORMANCE COMPARISON FOR 2 YEAR AHEAD CONVERSION PREDICTION

	GT	NCM		ALM		PLM	
		O	E	O	E	O	E
Rank	1	4	-	6	-	3	
Acc	75.11	72.68	2.43	73.24	1.87	70.07	5.04
AUC	84.33	72.33	12	78.85	5.48	77.8	6.53
Pre	74.82	72.7	2.12	67.74	7.08	73.51	1.31

GT: Ground truth, O: observed value, E: Error = GT-Observed, Acc: Accuracy, Pre: Precision, Rank: No. of biomarkers in the model delivering highest Accuracy

IV. CONCLUSION

Early detection of AD amongst the MCI patients is a vital step towards effective disease management and finding the cure. In this paper we predicted the neuropsychological performance of the MCI patients over the coming years to judge if the patients will develop AD or not. 2 year ahead prediction was found to be less accurate than 1 year ahead prediction due to propagation of uncertainty in the values calculated. Even though PLM emerges as the most accurate model for short term future conversion prediction, the ALM model for predicting values proves to be the most robust for long term ahead prediction as it employed population averages instead of individual instances hence suppressing the noisy values. Even though we have presented promising modelling methods for the longitudinal data, this study can benefit a lot from the use of multimodal data recorded over a longer period of time.

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