Knowledge-driven generative subspaces for modeling multi-view dependencies in medical data

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Abstract

Early detection of Alzheimer’s disease (AD) and identification of potential risk/beneficial factors are important for planning and administering timely interventions or preventive measures. In this paper, we learn a disease model for AD that combines genotypic and phenotypic profiles, and cognitive health metrics of patients. We propose a probabilistic generative subspace that describes the correlative, complementary and domain-specific semantics of the dependencies in multi-view, multi-modality medical data. Guided by domain knowledge and using the latent consensus between abstractions of multi-view data, we model the fusion as a data generating process. We show that our approach can potentially lead to i) explainable clinical predictions and ii) improved AD diagnoses.

1 Introduction

AD is a neurodegenerative disorder that may be influenced by many factors from genetic, medical and family history, demographics and other personal attributes. An AD diagnosis is characterized by abnormalities in multiple diagnostic modalities including neuroimages such as Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET), and neuropsychological or clinical tests [Gray (2012)]. Thus, clinical data include markers from diagnostic modalities as well as protective/risk factors from the patient’s background. Each feature set provides a partial, yet different perspective to reveal the underlying cognitive health state of the study subject. With the recent progress in multi-view machine learning, combinations of markers distinguish AD patients from healthy controls with high accuracy [Weiner et al. (2017)]. However, accurate detection at the early stages, where interventions are most likely to be effective, remains challenging. Through data fusion, we seek to extract salient semantic representations of markers and background information, explain their dependencies, and improve key prediction metrics for AD diagnosis and prognosis.

We use a dataset of 589 subjects (refer to Table 1 for demography stats) from the ADNI dataset, which include their background features: demographic, genotypic (Single Nucleotide Polymorphism (SNP)) and medical history, and markers: grey matter volumes from baseline MRI and CSF biomarkers, and cognitive measures: Mini Mental State Examination (MMSE) and Clinical Status (CS) (Cognitively Normal (CN), Mild Cognitive Impairment (MCI) and AD). Each view has specific distributional properties: MRI volumes are continuous, medical history questions are categorical, clinical status is ordinal etc. Also, features within a view could structurally be composed of several smaller features. Probabilistic dependence between features could be mutual and non-directional (e.g., correlation) or conditional and directional (e.g., conditional dependence/independence, causation). Differentiating the types of probabilistic dependence makes the model more intuitive and interpretable. For instance, a person’s cognitive capability assessed...
Figure 1: Sparse Bayesian Multi-view Subject Model

by MMSE on a 30-point scale, consists of orientation, registration, recall, attention, language etc., which can be further decomposed. The marks scored by a person in two questions may be correlated, but conditionally independent given the clinical status. Therefore, background features influence the clinical condition which in turn decides the values of the markers. We learn the dependencies in multi-view clinical data by associating and generating them through their conceptual abstractions. Subspace modeling relates measurable features (e.g. MRI volumes) to abstract concepts in a probabilistic way which allows flexible and efficient statistical reasoning and inference. Shared subspaces are based on the idea of a latent consensus between views representing the same real-world entity. Zhe et al. (2015); Xu et al. (2016); Lian et al. (2015) developed generative models to model views of heterogeneous biomedical data through a shared latent subspace that represents the information shared between the views. Xue et al. (2017) recently proposed an optimization-based approach that simultaneously learns individual information in each view but also captures feature correlations among multiple views by learning the shared component. Though most of them enable supervised predictions, we require an approach that simultaneously allows: i) view-specific dependencies, ii) shared dependencies between subsets of the views iii) inclusion of domain knowledge and, iv) multiple response variables.

We propose a generative modeling of the probabilistic subspace that represents an individual’s clinical condition as a latent continuum from healthy to being sick. We use view-specific subspaces to abstract concepts from markers (e.g., brain’s structural integrity from volumetric MRI), background (e.g., genetic profile from SNP) and cognitive measures (e.g., cognitive capability from MMSE) which are not measurable directly. We assume from domain knowledge that the dependencies between abstract markers and cognitive capability are conditionally independent given the latent clinical condition, which is in turn conditioned on the background feature abstractions in a hierarchical manner. A graphical representation of our approach, Sparse Bayesian Multi-View Subject Model (SBMVSM), is depicted in Figure 1. The observed features at Level-0 comprise the views constructed from markers, background and cognitive measures (colored cells in Figure 1). Level-1 latent factors explain the view-specific correlations. Level-2 latent factors represent the subspace shared across the view-specific latent factors. Through the model, we: i) dimensionality reduction using sparse projections of the subspaces to the lower level, and ii) build the subject’s clinical profile using continuous latent variables which are more efficient at representing information, using fewer variables.

2 Model

2.1 Notation:

We consider a supervised setting, where $X^{(1)} \ldots X^{(M_{\text{mark}})}$ represent the the multi-view markers, $B^{(1)} \ldots B^{(M_{\text{bg}})}$, the background views, $R, C$ the response variables i.e., MMSE and clinical status CS respectively, $M_{\text{mark}}$ the number of marker views, $M_{\text{bg}}$ the number of background views and $N$ the number of subjects.
2.2 Knowledge-driven generative modeling of the dependency subspace

Shwe et al. [1991]; Pradhan et al. [1994]; Seixas et al. [2014] translated the biomedical knowledge bases and datasets into multi-layered Bayesian networks. Each layer corresponds to specific types of variables: i) layer 1 - predisposing (background) ii) layer 2 - diseases and iii) layer 3 - symptoms. The layering represents the probabilistic relationships between different types of variables—the variables in layer 1 influence layer 2, which in turn affect layer 3. We follow a similar hierarchy to simulate the data generation process and include the domain knowledge from the epidemiology of AD. We adopt the prior knowledge of a causal approach in which genetic variables like SNP and demographic variables such as age and sex are fixed before other variables and are not influenced by them. These should be roots in the hierarchy, which impact the distributions of the clinical condition. On the contrary, markers are dependent on the clinical condition and possibly background variables, but do not affect other variables and hence should be leaves in the hierarchy (Jin et al. [2016]). We follow a full Bayesian treatment of SBMVM which includes the following steps:

Extracting view-specific subspaces: We use Bayesian matrix factorization (Nakajima and Sugiyama [2011]) to extract latent subspaces from continuous-valued views. For categorical-valued views, we use Item Response Theory (IRT) models (Hambleton et al. [1991]) to express the observed variables as resulting from continuous latent traits, while for ordinal-valued views, we opt for the graded response model (Samejima [1969]) to quantify the latent trait. The observed continuous views of markers, $X^{(j)}$, and background variables, $B^{(k)}$, are linear transformations of uncorrelated low-rank latent factors, $L_{X^{(j)}}$ and $L_{B^{(k)}}$ with $l^{(j)}$ and $l^{(k)}$ number of latent factors respectively (i.e., $L_{X^{(j)}} \sim N(0, I_{l^{(j)}})$. In a simplified sense, $X^{(j)} = \sum_{r=1}^{l^{(j)}} L_{X^{(j)}} V^{(j)} + \epsilon_{X^{(j)}}$, where $V^{(j)}$ is the weight matrix and $\epsilon_{X^{(j)}}$ is the noise. IRT expresses the categorical views, $X^{(j)}$ (0 if ’no’/1 if ‘yes’) as resulting from a latent trait, $\theta_i^{(j)} (\theta_i \sim N(0, 1))$ of sample $i$, parameterized by the difficulty, $\delta_q$ (the slope of $P(X_{iq}^{(j)} = 1|\theta_i)$) and discrimination, $\alpha_q$ (where $P(X_{iq}^{(j)} = 1|\theta_i) = 0.5$) of the corresponding feature, $q$ from $X^{(j)}$. We have the probability of a ‘yes’ following a logistic function; $P(X_{iq}^{(j)} = 1|\theta_i, \alpha_q, \delta_q) = \frac{\exp(\alpha_q(\theta_i - \delta_q))}{1+\exp(\alpha_q(\theta_i - \delta_q))}$. Similar equations apply for background views.

Generating shared subspace: We link the vertical concatenation of Level-1 marker abstractions, $L_{X}$ through the Level-2 shared subspace, $U$, using similar sparse projections. We model $U$ to follow a multivariate normal distribution with the mean expressed as multiple linear regressions on the vertical concatenation of Level-1 background abstractions $L_{B}$.

Linking responses to shared latent subspace: The correlation between the continuous (e.g. MMSE) and ordinal (e.g. CS) response variables, $R$ and $C$ is captured using single continuous latent variable, $G$. We first follow the principle that each ordinal variable, $C$, is a chopped-up version of a hypothetical underlying continuous variable ($C^*$) with a mean of 0. Thus, $P(C_i|C^*_i) = \sum_{c=0}^{2} \eta(C_i = c) \eta(b_c \leq C^*_i < b_{c+1})$. A patient, $i$ has a CS $c$, if $C^*_i$ falls between cutpoints, $b_c$ and $b_{c+1}$. Further, we model the two continuous response variables, $R$ and $C^*$ as projections of the latent variable, $G$.

Priors for weight matrices of projections: The view-specific weight matrices from Level-1, $V^{(j)}$’s, have a horseshoe prior (Carvalho et al. [2009]), to promote sparsity and reduce number of features loading on a particular factor. Further, we use the group sparse ARD priors (Tipping [2001]) for the shared subspace, $U$, to allow subsets of views if not all to interact. We also use appropriate hyperpriors to enable hierarchical Bayesian modeling.

3 Preliminary results

We build our inference engine in Stan probabilistic programming language (Carpenter et al. [2017]; Stan Development Team [2017]) using its R interface (Stan Development Team et al. [2016]). All views share the the number of samples, $N$, as the common dimension. We represent each view as a matrix, $D^{(j)} \in R^{N \times M^{(j)}}$, where the rows correspond to the subjects and the columns to the features. We utilize the fused representation from our SBMVM model to predict the clinical status (2- AD, 1-
MCI and 0-CN (cognitively normal) and MMSE scores. Further, we decide on the dimensions of Level-1 ($L_X$, $L_B$) and Level-2 ($U$) subspaces through multiple cross-validations.

In this study, we use the data collected from the ADNI database [ADNI (2017)]. The views we consider include MRI volumes (90 features), CSF biomarkers (3 features), selected SNPs (924 features) [Zhe et al. (2014)], demographics (7 features). The resulting dataset after incomplete data imputation/removal, consists of 589 study subjects (128 AD, 174 CN, 287 MCI). We use SMOTE oversampling [Chawla et al. (2002)] to overcome class-imbalance and $z$-normalize all continuous features. We report the prediction performances over ten-fold cross-validation using the standard metrics of accuracy (Acc.), precision (Prec.) and recall (Rec.) for multi-class classification and, Root Mean Square Error (RMSE) for MMSE score prediction. We determine the dimensions of the best low-rank approximation of the MRI view to be 20 by cross-validation while predicting the clinical status. We present the weights of the Level-1 MRI factors in a heatmap (Figure 2a). Further, we extract the 10 top-weighted features from the factors. A snapshot of the salient features from the factors with a higher say in clinical status determination indicates that similar structures in the left and right brain fall under the same factor, due to their correlations (Figure 2b). e.g. AMYGDYL and AMYGDR in Factor V7.). View-specific latent trait from SNPs identify the ones in (Figure 2c) as the top 10. Many of these belong to genes salient to AD such as ABL1, MAP3K1, TOMM40 etc. We fix the dimensions of the shared latent subspace, $U$, as 20 through cross-validation.

### Table 2: Prediction performance: Comparison with state-of-the-art

| Study            | Modalities       | N   | Task                      | Prediction metrics          |
|------------------|------------------|-----|---------------------------|-----------------------------|
| Zhu et al. (2016b) | MRI, PET         | 202 | AD vs. MCI vs. CN         | Acc. 76.4, Prec. 0.79, Rec 0.77 |
| SBMVSM           | MRI, PET         | 187 | AD vs. MCI vs. CN         | Acc. 77.19, Prec. 0.77, Rec 0.74 |
| Zhu et al. (2016a) | MRI, PET, CSF, demographics | 589 | MMSE score regression    | RMSE 1.10 ± 0.41           |
| SBMVSM           | MRI, PET, CSF, demographics | 187 | MMSE score regression    | RMSE 1.44 ± 0.38           |
| SBMVSM           | MRI, PET, CSF, demographics | 589 | MMSE score regression    | RMSE 1.83 ± 0.35           |

4 Conclusion

We propose a probabilistic graphical model-based framework that takes into account the data generation and dependency semantics among the features from disparate data sources. The generative framework identifies a shared latent space between multiple marker and background views and response variables. SBMVSM serves as a multi-view multi-task disease prediction model and achieves good prediction performance in both the tasks in some preliminary studies.
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