Model-based Clustering of Ischemic Stroke Patients

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Abstract: The objective of our study is to find meaningful groups in the data of ischemic stroke patients using unsupervised clustering. The data are modeled using Gaussian mixture models with a variety of covariance structures. Cluster parameters in each of these models are estimated by maximum likelihood via the Expectation-Maximization algorithm. The best models are then selected by relying on information-theoretic criteria. It is observed that the stroke patients can be grouped into a small number of medically relevant clusters that are defined primarily by the presence of diabetes and atrial fibrillation. Characteristics of the clusters found are discussed, using statistical comparisons and data visualization.

1 INTRODUCTION

Stroke is the rapid loss of brain function due to disturbance in the blood supply to the brain. It is one of the leading causes of death worldwide (Donnan et al., 2008). Stroke can be broadly classified into two types: Ischemic, which occurs due to lack of blood flow; and hemorrhagic, which is caused by internal bleeding. In this study we deal with data from patients with ischemic stroke, the more prevalent of the two types. The data comprises of demographic information, medical history, laboratory test results and treatment records of 501 patients collected retrospectively from the University of Massachusetts Medical School, Worcester.

Clustering is the unsupervised classification of a set of objects into groups in such a way that objects within a group are similar to each other based on some perceived measure of similarity (Jain, 2010). Clustering has been applied in many contexts and in varied disciplines. In the field of data mining, it is one of the major techniques for exploratory data analysis. There are different types of clustering algorithms. Based on the relationship between clusters, clustering algorithms may be partitional or hierarchical; and based on the nature of clusters they can be centroid-based, model-based or density-based (Pang-Ning et al., 2005).

1.1 Scope of this Paper

In this study, we attempt to find natural clusters among stroke patients using a model-based partitional clustering approach. Model-based clustering is used here for its ability to produce stable clusters along with complex models for the clusters that can also capture correlation and dependence of attributes (Jain and Maheswari, 2012). Finding clusters among stroke patients can be helpful from the medical perspective as it may lead to the discovery of new patterns and more effective ways to manage stroke. The technique used in our study produces two suitable clustering models – one with two clusters and the other with three – that can be described primarily using only two attributes: antidiabetic medication and atrial fibrillation. Study of the cluster assignments also revealed that there is a clear hierarchical relation between the clusters of the two models. The characteristics of the clusters are analyzed by observing the attributes that have significant differences in values between different clusters.

1.2 Related Work

There have been numerous works that use the technique of clustering in medical related data. One of the studies (Bruehl et al., 1999) used cluster analysis to validate the established diagnostic

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criteria for migraine and tension-type headache, finding two clusters that are consistent with existing classification. K-means clustering was used to provide a novel approach for identifying asthma phenotypes (Haldar et al., 2008). Later, hierarchical clustering was used for the same purpose (Moore et al., 2010) on a different set of patients achieving a set of clusters with different characteristics. A comparison of the performances of four different clustering algorithms on clinical datasets has also been published (Hirano et al., 2004).

Clustering has been used specifically in the field of stroke research as well. While analyzing the effect of stroke type on patients' quality of life (QL), cluster analysis was performed to identify homogeneous subgroups of patients with specific QL patterns (De Haan et al., 1995). The gait patterns of patients recovering from stroke were classified using clustering (Mulroy et al., 2003). Density-based clustering was applied to Computed Tomography perfusion maps to diagnose acute stroke (Baumgartner et al., 2005). More recently, cluster analysis has been used in stroke brainwave classification (Omar et al., 2013) and to stratify patients based on their motor abilities during post-stroke recovery (Aluru et al., 2014). The aforementioned studies apply clustering on some specific aspects related to stroke, or in solving some subproblems as part of a wider research. However, to the best of our knowledge, no attempt has been made to group stroke patients as a whole based on a wide range of data that span from the patients' past medical records to medication and recovery after stroke.

1.3 Plan of the Paper

Data preparation and clustering methodology are described in section 2. Section 3 presents and analyzes the results of this study. Section 4 concludes with a summary of findings and directions for future work.

2 METHODOLOGY

2.1 Data Preparation

Our study is conducted on retrospective data extracted from 501 records of Ischemic stroke patients admitted at the University of Massachusetts Medical School, Worcester, MA, USA between 2011 and 2013. Relevant information from the medical records was extracted and collected into a dataset after appropriate preprocessing.

2.1.1 Selection of Attributes

The attributes selected for analysis were determined by one of the co-authors, a neurologist who specializes in stroke medicine. The attributes include demographic information (such as age and gender), medical history and risk factors (such as personal and family history of diabetes, and hypertension), laboratory test results, and prescribed medication. A measure of stroke severity determined by the National Institutes of Health Stroke Scale (NIHSS) score (Brott et al., 1989) and a measure of stroke recovery determined by a binary categorization (see Table 2) of the modified Rankin Scale at 90 days after stroke (mRS-90) score (Rankin, 1957) are also included. Among the attributes, 9 are continuous and 32 are categorical. Of the categorical attributes, only two are multi-class and the rest are binary. A complete list of attributes used in the study along with summary statistics is shown in Table 1 (continuous attributes) and Table 2 (categorical attributes).

Table 1: Summary statistics of the continuous attributes of the stroke dataset.

	Range of values	Mean	Standard deviation
Age	23 - 104	69.47	14.91
HbA1c	4.6 - 15	6.28	1.32
Cholesterol	85 - 400	172.76	46.26
HDL	21 - 107	46.99	14.04
LDL	11 - 415	100.93	42.30
Triglycerides	21 - 1020	130.92	93.56
BP Systolic	82 - 238	131.18	18.43
BP Diastolic	36 - 117	71.89	12.30
NIHSS score	0 - 37	6.62	7.86

2.1.2 Data Cleaning

The extraction of data from the medical records involved a mixture of manual and automated processing. Values of some attributes, such as lab test results, were readily available and required no further translation. For some other attributes, the medical doctors co-authors of this study interpreted the patients' records to transform them to a suitable value in the dataset. For example, the Infarct size of the patient was categorized into small, medium and large by inspecting the patients' MRI reports. Various commercial names of medications were converted to their generic names. In some cases, several attributes were aggregated into one attribute. As an example, father, mother and sibling's stroke histories were combined into family history of stroke. Spelling and abbreviation variations were

also eliminated. For example, tPA, TPA, tpa and Tissue plasminogen activator were all converted to 'tPA'. Records with high occurrences of missing values were omitted. Among the 501 records included in this study, some numeric values that remained missing (<1% overall) were replaced by the median.

Table 2: Summary statistics of the categorical attributes of the stroke dataset. For binary attributes, only the percentages of TRUE values are shown. "Fam Hx" is short for Family history; "Pre med" means medication being used prior to stroke; and "Discharge med" are medications present at the time of discharge from hospital.

Attribute	Distribution of values
Race	White: 88.4%, Others: 11.6%
Gender	Male: 53.3%, Female: 46.7%
Lipid Profile	Abnormal: 65.1%
Infarct Size	Small: 39.5%, Medium: 14.6% Large: 8.2%, None: 37.3%
INR	Abnormal: 55.9%
Hypertension	81.0%
Diabetes	30.1%
Overweight	21.4%
Smoking	19.4%
Alcohol	18.0%
Fam Hx of Stroke	13.2%
Fam Hx of Heart Disease	20.6%
Fam Hx of Cholesterol	2.6%
Fam Hx of Diabetes	8.8%
Fam Hx of Hypertension	7.4%
Previous stroke	22.4%
Coma on admission	19.0%
Atrial Fibrilation	27.7%
Active Cancer	8.6%
tPA	17.8%
Etiology of stroke	Small vessel: 15.4%, Large vessel: 14.8%, Cardioembolic: 31.3% Cryptogenic: 24.2%, Others: 6.8%
Pre med Antiplatelets	49.5%
Pre med Anticoagulants	9.2%
Pre med Statins	43.7%
Pre med Antidiabetics	22.0%
Pre med Antihypertension	66.7%
Discharge med Antiplatelets	84.8%
Discharge med Anticoagulants	18.2%
Discharge med Statins	83.2%
Discharge med Antidiabetics	23.0%
Discharge med Antihypertension	65.3%
mRS-90	Low (<3): 62.3%, High (≥3): 37.7%

2.1.3 Attribute Preprocessing for Clustering

Since the stroke data contains attributes of different types and ranges, steps to normalize the values were taken. The continuous attributes were scaled to values in the range of 0 to 1 inclusive. For each value x in attribute A, its scaled value n_x was calculated by

$$n_x = \frac{x - min_A}{max_A - min_A} \quad (1)$$

where min_A and max_A are respectively the minimum and maximum values for attribute A. For the binary categorical attributes with true/false values, 0 and 1 were assigned to the FALSE and TRUE values respectively. For attributes that have two possible values *Normal* and *Abnormal*, 0 was assigned to *Normal* and 1 to *Abnormal*. In other cases such as gender, binary values were assigned arbitrarily to the attribute values (0 for male, 1 for female). In the case of multivalued categorical attributes, we took different approaches for ordinal and non-ordinal attributes. For the attribute *infarct size*, where we have small/medium/large values with an ordinal relationship, we assigned 0 to No infarction, 0.33 to small, 0.66 to medium and 1 to large infarctions respectively. For the other multivalued attribute *etiology of stroke,* five binary attributes for the five possible values were created, with each attribute value specifying whether (1) or not (0) that particular etiology is present in that data instance.

2.2 Clustering

Because of its simplicity, K-means (MacQueen, 1967) is often the initial technique of choice for clustering. But K-means suffers from several drawbacks including the requirement of pre-selecting the number of clusters, the variability of results for different initializations, and the assumption of spherical equal-size clusters (Jain, 2010). As part of our study, we used K-means with different random seeds to cluster the data with values of k=2, 3, and 4; but the assignment of data points to clusters varied greatly. Hence, K-means was deemed too unstable for clustering our data.

Expectation-Maximization (EM) (Dempster et al., 1977; Neal and Hinton, 1998) is a powerful clustering method that uses iterative search to find parameterized families of probabilistic models that locally maximize the likelihood of a given set of data. In this paper, we use the EM algorithm initialized by hierarchical clustering for parameterized Gaussian mixture models. We select the clustering model by maximizing the Bayesian Information Criterion (BIC), which provides an optimal tradeoff between model complexity and goodness of fit (Schwarz, 1978). To implement the

proposed method, we wrote scripts in the R programming language utilizing the contributed package MCLUST (Fraley and Raftery, 2006). The algorithm assumes a Gaussian mixture model where the likelihood of data consisting of n observations is:

$$\prod_{i=1}^{n}\sum_{k=1}^{G}\tau_k\varphi_k(x_i \mid \mu_k, \Sigma_k) \quad (2)$$

where x represents the data instances with i subscript denoting an individual observation; G is the number of components or clusters with k subscript representing a particular component; τ_k is the probability that an observation belongs to the kth component (or cluster); and

$$\varphi_k(x \mid \mu_k, \Sigma_k) = (2\pi)^{-\frac{p}{2}}|\Sigma_k|^{-\frac{1}{2}} exp\left\{-\frac{1}{2}(x-\mu_k)^T\Sigma_k^{-1}(x-\Sigma_k)\right\} \quad (3)$$

Here p is the spatial dimension (i.e., number of attributes used for clustering); the components are ellipsoidal, centered at the means μ_k with covariance matrices Σ_k determining their other geometric features; and each covariance matrix Σ_k is parameterized by eigenvalue decomposition of the form

$$\Sigma_k = \lambda_k D_k A_k D_k^T \quad (4)$$

where D_k is the orthogonal matrix of eigenvectors, A_k is a diagonal matrix with its elements proportional to the eigenvalues of Σ_k, and λ_k is a scalar (Banfield and Raftery, 1993). D_k determines the orientation of the principal components of Σ_k, while A_k determines the shape of the density contours. λ_k controls the volume of the corresponding ellipsoid.

Table 3: Parameterizations of the covariance matrix Σ_k. The three letters of the identifiers denote the volume, shape and orientation of the distribution respectively. E, V and I stand for Equal, Variable and Identity respectively. For example, VEI denotes a model in which the volumes of the clusters may vary (V), the shapes of all the clusters are equal (E), and the orientation is the identity (I).

ID	Model	Distribution	Volume	Shape	Orientation
EII	λI	Spherical	equal	equal	NA
VII	$\lambda_k I$	Spherical	variable	equal	NA
EEI	λA	Diagonal	equal	equal	coord. axes
VEI	$\lambda_k A$	Diagonal	variable	equal	coord. axes
EVI	λA_k	Diagonal	equal	variable	coord. axes
VVI	$\lambda_k A_k$	Diagonal	variable	variable	coord. axes
EEE	λDAD^T	Ellipsoid	equal	equal	equal
EEV	$\lambda D_k A D_k^T$	Ellipsoid	equal	equal	variable
VEV	$\lambda_k D_k A D_k^T$	Ellipsoid	variable	equal	variable
VVV	$\lambda_k D_k A_k D_k^T$	Ellipsoid	variable	variable	variable

Orientation, volume and shape of distributions are estimated from the data, and can be allowed to vary between clusters, or kept the same for all clusters. Table 3 presents the characteristics of different mixture models achievable by the algorithm along with their MCLUST identifier and corresponding equation for Σ_k (Fraley and Raftery, 2006).

In our study, k clusters are created at each stage starting with $k = 2$ and incrementing the value of k to 9. For each value of k, we try to fit ten different clustering models as specified in Table 3. The BIC values of all the models (including all values of k) are compared, and the ones with highest BIC values are chosen as our desired clustering models.

2.3 Statistical Significance of the Differences among Clusters

Statistical hypothesis tests are used to identify significant differences among clusters of the distributions of individual attributes. For categorical attributes, statistical significance is assessed by using the χ^2 test for independence. For continuous attributes, cluster means or medians are compared. In the case of normally distributed attributes, a standard ANOVA test is used for assessing significance of differences in means. Otherwise, a Kruskal-Wallis test (Kruskal and Wallis, 1952) is used to assess significance of differences in medians. The Shapiro-Wilk method (Shapiro and Wilk, 1965) is used to test for normality.

We use the Benjamini-Hochberg method (Benjamini and Hochberg, 1995) to control the increased risk of false positives that is associated with simultaneous multiple tests of significance. Given n individual findings with corresponding sorted p-values $p_1 < p_2 < \cdots < p_n$, and given a desired overall level of significance α, the Benjamini-Hochberg method considers as significant only the first k findings, where k is the largest index i, $1 \le i \le n$, for which $p_i n/i < \alpha$. In this study, the standard value of α=0.05 is our desired level of significance. The Benjamini-Hochberg method controls the false discovery rate (FDR), the portion of findings that are predicted to be positives but are actually negatives. The procedure described here guarantees an overall FDR below the desired level α (Benjamini and Hochberg, 1995).

3 RESULTS

3.1 Selection of Clustering Models

Based on the methodology described in Section 2, a variety of Gaussian mixture models are applied to the dataset for different numbers (k) of clusters where values of k are between 2 and 9. The Bayesian Information Criterion (BIC) for each model that could be fitted to the data is recorded, the results of which are shown in Figure 1. The best BIC value is achieved with the VEV model (BIC = -15047.50) followed closely by the EEV model (BIC = -15143.54), both of which are ellipsoid distributions with equal shape, but differing only in that while the former has variable volume, the latter has same volumes. Both these models divide the dataset into two clusters. A three-cluster VEV model also achieves fairly good BIC value (BIC = -15563.68). Both the spherical models EII and VII show steady rises in BIC values as the number of components is increased before becoming almost constant after around k=6. We inspect the clusters for the two-cluster VEV and EEV models and observe that the cluster assignments are almost identical with the exception of only two data points. Hence for further analysis we select the VEV models with 2 and 3 clusters respectively.

3.2 Salient Properties of the Two-cluster Model

The two-cluster VEV mixture model creates clusters of sizes 395 and 106 respectively. Table 4 shows the mean and standard deviations of the continuous attributes for each of the clusters along with their level of significance (p-value) as determined from a Kruskal-Wallis test which was used since all the continuous attributes were deemed to be non-normally distributed based on the Shapiro-Wilk test. Table 5 shows the probability distribution of each categorical attribute for different clusters along with p-values computed from the χ^2 test.

Among the continuous attributes of Table 4, HbA1c, cholesterol, HDL, LDL and Triglycerides all have significant differences between clusters. The first is a measure of average blood glucose level for a prolonged period of time, while the other four are measures of different types of fat found in the body. What is noticeable is that the patients in Cluster 2 exhibit lower levels of healthiness than those of Cluster 1. On an average, Cluster 2 patients have higher HbA1c, lower HDL (the "good" cholesterol), higher LDL (the "bad" cholesterol) and higher Triglyceride levels than Cluster 1 patients, which correspond to the worse conditions for each of these laboratory test results.

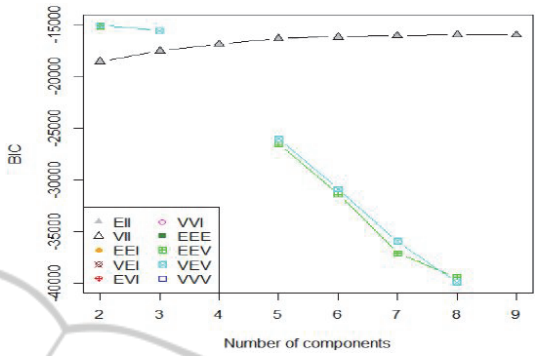


Figure 1: Comparison of BIC values for different numbers and variations of Gaussian mixture components. Missing points in this plot correspond to experiments that yielded no clustering models.

Table 4: Differences in means of each continuous attribute between clusters. The p-values that are significant after the Benjamini-Hochberg correction at the level FDR < 0.05 are marked with an asterisk.

Attribute	Cluster 1 (395 instances)	Cluster 2 (106 instances)	Kruskal-Wallis test statistic	p-value
Age	69.47 ± 15.53	69.47 ± 12.29	0.065	0.7995
HbA1c	5.86 ± 0.63	7.86 ± 1.90	169.526	0.0000 *
Cholesterol	175.42 ± 44.31	162.87 ± 51.71	11.375	0.0007 *
HDL	48.14 ± 14.42	42.68 ± 11.55	13.587	0.0002 *
LDL	103.73 ± 41.82	90.48 ± 42.42	13.415	0.0002 *
Triglycerides	123.88 ± 90.33	157.15 ± 100.47	17.115	0.0000 *
BP Systolic	130.64 ± 18.06	133.16 ± 19.62	1.373	0.2413
BP Diastolic	72.30 ± 12.21	70.36 ± 12.53	1.373	0.2412
NIHSS score	6.92 ± 8.28	5.51 ± 5.93	0.016	0.9010

From Table 5, the attributes with significant differences are in race, patients' history of hypertension and diabetes, and several of the medications administered on the patient before admission or during the time of discharge. Cluster 2 patients are more likely to be non-White, more likely to be hypertensive and diabetic, and more likely to be administered all of the medications than Cluster 1 patients. The conspicuous differences occur in the case of diabetic history and the intake of antidiabetic medication where the probabilities for Cluster 2 are significantly higher than Cluster 1 with very large values of the χ^2 statistic.

Worthy of mention are some attributes that are empirically known to be important factors for stroke (Dyken, 1991), but exhibit no significant difference between clusters, such as age, gender, blood pressure, and previous history of stroke. There is

also no significant difference in terms of stroke severity (NIHSS score) and stroke recovery rate (mRS-90 score).

Table 5: Differences in probabilities of each categorical attribute between clusters. For Boolean attributes, the probability of the TRUE value is given. The p-values that are significant after the Benjamini-Hochberg correction at the level FDR < 0.05 are marked with an asterisk.

Attribute	Cluster 1 (395 instances)	Cluster 2 (106 instances)	χ^2	p-value
Race (Non-White)	0.084	0.217	13.674	0.0002*
Gender (Female)	0.466	0.443	0.130	0.7188
Lipid Profile (Abnormal)	0.648	0.660	0.452	0.7979
Infarct Size (small/medium/ large)	0.397/ 0.137/ 0.068	0.406/ 0.179/ 0.132	8.131	0.0434
INR (Abnormal)	0.547	0.613	1.1028	0.5762
Hypertension	0.772	0.953	16.598	0.0000*
Diabetes	0.119	0.981	290.943	0.0000*
Overweight	0.192	0.292	4.4027	0.0359
Smoking	0.210	0.132	2.780	0.0954
Alcohol	0.195	0.123	2.494	0.1143
Fam Hx of Stroke	0.119	0.179	2.152	0.1424
Fam Hx of Heart Disease	0.187	0.274	3.296	0.0694
Fam Hx of Cholesterol	0.030	0.009	0.740	0.3896
Fam Hx of Diabetes	0.076	0.132	2.623	0.1053
Fam Hx of Hypertension	0.076	0.066	0.019	0.8908
Previous stroke	0215	0.255	0.542	0.4617
Coma on admission	0.203	0.142	1.647	0.1993
Atrial Fibrillation	0.286	0.245	0.505	0.4772
Active Cancer	0.096	0.047	1.974	0.1600
tPA	0.195	0.113	3.282	0.0700
Etiology of stroke (Sm ves/ Lg ves/ Card. /Crypt. / Others)	0.144/ 0.139/ 0.327/ 0.241/ 0.063	0.189/ 0.179/ 0.264/ 0.245/ 0.085	6.1737	0.2897
Pre med Antiplatelets	0.448	0.670	15.559	0.0000*
Pre med Anticoagulants	0.101	0.057	1.499	0.2208
Pre med Statins	0.380	0.651	23.891	0.0000*
Pre med Antidiabetics	0.048	0.858	315.589	0.0000*
Pre med Antihypertensives	0.613	0.868	23.370	0.0000*
Discharge med Antiplatelets	0.841	0.877	0.619	0.4315
Discharge med Anticoagulants	0.182	0.179	0.000	1.0000
Discharge med Statins	0.803	0.943	10.895	0.0010*
Discharge med Antidiabetics	0.025	0.991	434.845	0.0000*
Discharge med Antihypertensives	0.592	0.877	28.692	0.0000*
mRS-90 (High, ≥ 3)	0.352	0.472	4.608	0.0318

However, it is noteworthy that Cluster 1 patients have slightly more severe stroke on average but are more likely to have a better recovery rate. This goes to show that the proposed clustering technique uncovers a group of patients who are characterized primarily by diabetes and secondarily by higher levels of cholesterol and hypertension who are at higher risk of poor recovery from stroke.

3.3 The Three-cluster Model and Hierarchical Structure of Clusters

The three-cluster VEV model creates clusters consisting of 233, 161 and 107 instances respectively. There is a clear hierarchical structure of clusters since the first cluster of the two-cluster VEV model splits almost perfectly into the first two clusters of the three-cluster model; whereas the other cluster remains intact with the exception of only three data points, two of which are added to and one removed from this cluster in the three-cluster model compared to the two-cluster model. For convenience of understanding, we call the first two clusters 1a and 1b and the other intact cluster 2c. We compare the differences first between the clusters 1a and 1b and then between all the three clusters for different continuous (Table 6) and categorical (Table 7) attributes. Once again the statistically significant differences after applying Benjamini-Hochberg correction are marked with asterisks.

In terms of the continuous attributes, the newly formed clusters exhibit some differences in HbA1c and some cholesterol values. The major differences, however, are exhibited in age and stroke severity. Patients of Cluster 1b are on an average significantly older and suffer from more severe strokes than the patients in Cluster 1a.

As far as the categorical attributes (Table 7) are concerned, significant difference between the clusters can be found in quite a few attributes. Hypertension plays an important role in separating these clusters as patients' own and family history of hypertension along with use of antihypertensive medication are all significantly different. Interestingly, Cluster 1a patients are more likely to have a family history of hypertension, but are less likely to be hypertensive themselves. Cluster 1a is also characterized by worse health habits (more smoking and alcohol consumption) but better comorbid conditions (less chance of coma or atrial fibrillation at the time of stroke). The difference between the likelihood of atrial fibrillation in particular is highly significant. There are also significant differences in the use of medication, while Cluster 1b patients have higher probability of getting anticoagulants (blood-clot removing agents), Cluster 1a patients are more likely to be treated with Statins and antiplatelets during their stay at the

Table 6: Differences in means for continuous attributes among clusters 1a, 1b and 2c.

Attribute	Cluster 1a (233 instances)	Cluster 1b (161 instances)	Cluster 2c (107 instances)	Clusters 1a and 1b		All 3 clusters	
				Kruskal-Wallis statistic	p-value	Kruskal-Wallis statistic	p-value
Age	64.27 ± 15.17	76.99 ± 12.77	69.49 ± 12.23	64.255	0.0000 *	69.939	0.0000 *
HbA1c	5.78 ± 0.60	5.96 ± 0.66	7.86 ± 1.88	7.086	0.0078 *	181.748	0.0000 *
Cholesterol	182.64 ± 43.79	164.45 ± 42.90	163.78 ± 51.76	18.630	0.0000 *	27.627	0.0000 *
HDL	48.43 ± 14.36	47.71 ± 14.53	42.75 ± 11.53	0.540	0.4623	13.647	0.0011 *
LDL	107.48 ±38.96	97.77 ± 44.96	91.41 ± 42.77	9.571	0.0020 *	20.942	0.0000 *
Triglycerides	137.69 ± 104.10	104.06 ± 60.50	156.60 ± 100.16	15.340	0.0000 *	32.474	0.0000 *
BP Systolic	129.00 ± 16.46	133.07 ± 19.99	133.06 ± 19.51	2.948	0.0860	4.198	0.1226
BP Diastolic	73.10 ± 11.60	70.86 ± 12.98	70.79 ± 12.48	2.994	0.0836	3.600	0.1653
NIHSS score	4.39 ± 5.72	10.45 ± 9.76	5.73 ± 6.41	38.503	0.0000 *	40.5951	0.0000 *

Table 7: Differences in probabilities for continuous attributes among clusters 1a, 1b and 2c.

Attribute	Cluster 1a (233 instances)	Cluster 1b (161 instances)	Cluster 2c (107 instances)	Clusters 1a and 1b		All 3 clusters	
				$\chi 2$	p-value	$\chi 2$	p-value
Race (Non-White)	0.099	0.062	0.215	1.219	0.2695	15.873	0.0004 *
Gender (Female)	0.451	0.484	0.449	0.569	0.4505	0.860	0.6505
Lipid Profile (Abnormal)	0.661	0.627	0.664	2.234	0.3272	2.719	0.6058
Infarct Size (small/medium/large)	0.412 / 0.150 / 0.52	0.373/0.118 / 0.093	0.411 / 0.178 /0.131	3.718	0.2936	11.429	0.076
INR (Abnormal)	0.524	0.578	0.607	1.156	0.561	2.471	0.6499
Hypertension	0.717	0.851	0.953	8.9815	0.0027 *	29.236	0.0000 *
Diabetes	0.086	0.161	0.981	4.576	0.0324	301.305	0.0000 *
Overweight	0.227	0.143	0.290	3.852	0.0497	8.755	0.0126 *
Smoking	0.270	0.118	0.140	12.505	0.0004 *	16.646	0.0002 *
Alcohol	0.245	0.124	0.121	8.030	0.0046 *	12.4887	0.0019 *
Fam Hx of Stroke	0.142	0.087	0.178	2.214	0.1368	4.987	0.0826
Fam Hx of Heart Disease	0.249	0.093	0.280	14.288	0.0002 *	18.802	0.0000 *
Fam Hx of Cholesterol	0.047	0.006	0.009	4.120	0.0424	7.8159	0.0201 *
Fam Hx of Diabetes	0.099	0.043	0.131	3.381	0.0659	6.789	0.0339 *
Fam Hx of Hypertension	0.124	0.006	0.065	17.283	0.0000 *	19.607	0.0000 *
Previous stroke	0.215	0.211	0.262	0.000	1.0000	1.146	0.5638
Coma on admission	0.137	0.292	0.150	13.245	0.0003 *	16.230	0.0003 *
Atrial Fibrilation	0.013	0.683	0.243	205.907	0.0000 *	214.231	0.0000 *
Active Cancer	0.107	0.081	0.047	0.496	0.4814	3.506	0.1732
tPA	0.137	0.267	0.131	9.574	0.0020 *	13.011	0.0015 *
Etiology of stroke (Sm ves/ Lg ves/ Card. /Crypt. / Others)	0.227/0.210/ 0.043/ 0.399/ 0.107	0.025/0.037/ 0.733/0.006/ 0.000	0.187/0.178/ 0.271/ 0.252/ 0.084	302.895	0.000*	317.047	0.0000 *
Pre med Antiplatelets	0.408	0.509	0.664	3.572	0.0588	19.392	0.0000 *
Pre med Anticoagulants	0.030	0.199	0.065	28.525	0.0000 *	33.638	0.0000 *
Pre med Statins	0.365	0.410	0.636	0.6406	0.4235	22.552	0.0000 *
Pre med Antidiabetics	0.017	0.099	0.841	11.703	0.0006 *	310.515	0.0000 *
Pre med Antihypertensives	0.528	0.745	0.850	18.137	0.0000 *	40.942	0.0000 *
Discharge med Antiplatelets	0.944	0.689	0.879	44.126	0.0000 *	48.986	0.0000 *
Discharge med Anticoagulants	0.039	0.391	0.178	76.951	0.0000 *	79.685	0.0000 *
Discharge med Statins	0.893	0.671	0.944	28.145	0.0000 *	45.733	0.0000 *
Discharge med Antidiabetics	0.034	0.000	1.000	4.0484	0.0442	457.318	0.0000 *
Discharge med Antihypertensives	0.567	0.634	0.869	1.506	0.2197	30.010	0.0000 *
mRS-90 (High, ≥ 3)	0.219	0.547	0.467	43.355	0.0000 *	48.216	0.0000 *

hospital. Etiology (cause) of stroke also shows an interesting pattern: Cardioembolic strokes are prevalent in Cluster 1b while all other etiologies are more associated with Cluster 1a. A striking

difference between the two clusters is in stroke recovery rate where Cluster 1a patients are much more likely to recover well from stroke.

If we compare all the three clusters together, many attributes show significant differences between clusters. The ones that stand out are diabetes along with pre and discharge med antidiabetics, atrial fibrillation, and etiology of stroke. Age, NIHSS score, mRS-90 score, and discharge medications of antiplatelets, anticoagulants and Statins also display highly significant differences.

3.4 Decision Tree to Predict Clusters

From the three-cluster model, we build a decision tree where all the attributes of the dataset are used as the predicting variables and the assigned cluster for each record is used as the target (prediction) attribute. The C4.5 algorithm (Quinlan, 1996) is used, as implemented in the J4.8 function in Weka (Witten et al., 2011), with a pruning confidence factor of 0.01 and a minimum of 40 instances per leaf to achieve a minimalist tree with only two inner nodes and three leaves. The resulting tree, shown in Figure 2, has accuracy = 87.62%, precision = 0.890, recall = 0.876 and area under the ROC curve = 0.887 evaluated by 10-fold cross-validation. Using only two attributes - discharge medication of antidiabetics and comorbid condition of atrial fibrillation - the three clusters can be defined reasonably accurately.

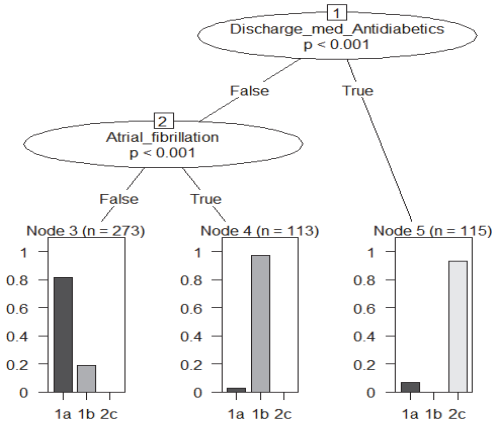


Figure 2: Decision tree to predict cluster assignments.

3.5 Cluster Visualization

We now present a series of plots visualizing the data clusters created by our proposed methods. In each plot a pair of attributes with significant differences across clusters are chosen, and their cluster assignments are shown. Figure 3 shows the cluster assignments with respect to the risk factors diabetes and hypertension for both the two-cluster and three-cluster models. The ellipses show the cluster centers with the axes representing the within cluster covariance. A small amount of random noise (jitter) was added to the attribute values to separate the data points that would otherwise be in the same coordinate. In Figure 3(a), there is clear separation between clusters 1 and 2 based on diabetes. In Figure 3(b), Cluster 2c stays in the same place as Cluster 2, whereas Cluster 1 breaks into overlapping clusters 1a and 1b based on hypertension.

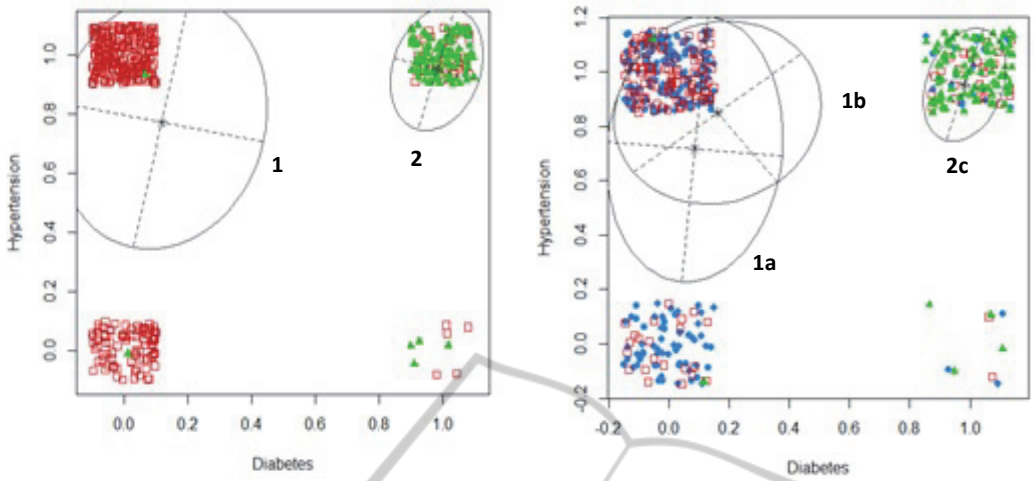
If we take a look at a pair of continuous attributes Age and HbA1c in Figure 4, we see a similar structure where Clusters 1 and 2 are separated by HbA1c and not Age (Figure 4a), but in the split clusters 1a and 1b show significant differences in age. The values of both the attributes are normalized to a [0,1] range.

The hand-picked dimensions selected in Figures 3 and 4 to project the clustered data onto provide a good visual separation of the clusters. Interestingly, the two dimensions suggested by the decision tree in Section 3.4, Discharge Med Antidiabetics and Atrial fibrillation, provided a much better projection space to discern the three clusters. The jitter-added data points for these attributes are shown in Figure 5, and clearly demonstrate well-defined clusters described by these two attributes.

4 CONCLUSIONS

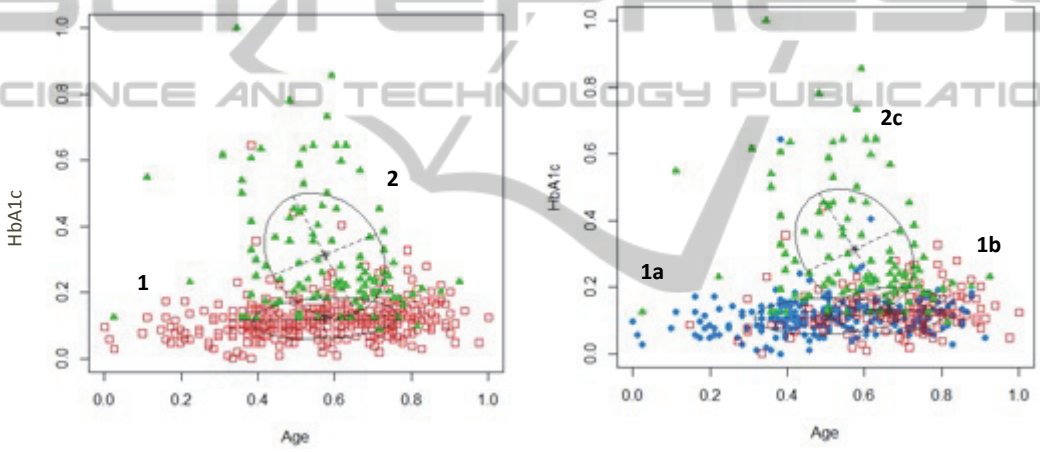
This paper has presented the results of clustering stroke patients based on the data consisting of demographics, medical history, test results and medication records. Using the EM algorithm to estimate the parameters of Gaussian mixture models, two suitable clustering schemes are found that suggest the division of the stroke patients into two and three clusters respectively. With two attributes - antidiabetic medication at discharge and atrial fibrillation – selected by a decision tree constructed over the clustered data, the clusters can be well discerned. A hierarchical structure between the two-cluster and three-cluster structure is observed and the nature of the relationship among clusters uncovered. Statistically significant differences in the values of various attributes across clusters are found and examined.

The clusters present very interesting patterns from a medical perspective. In the two-cluster model, the clusters can be described almost entirely



(a) (b)

Figure 3: Clustered data projected onto Diabetes and Hypertension for a) Two-cluster and b) Three-cluster models.



(a) (b)

Figure 4: Clustered data projected onto Age and HbA1c for a) Two-cluster and b) Three-cluster models.

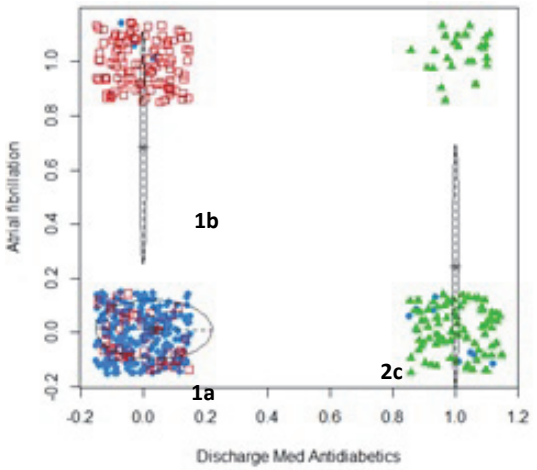


Figure 5: Clustered data projected onto Discharge Med Antidiabetics and Atrial Fibrillation.

by the history of diabetes and use of antidiabetic medicine.

The cluster characterized by the high presence of diabetes also exhibits poor conditions of hypertension and body fat levels. In the three-cluster model, this cluster stays almost unchanged while the other cluster splits into two new clusters which are separated primarily by atrial fibrillation. One of these clusters represent older patients with more severe conditions at the time of stroke, and significantly lower rate of recovery. The other cluster is characterized by younger patients with poorer health habits (more smoking and alcohol consumption), but nevertheless exhibiting less severe strokes and more favorable outcomes after stroke. Interestingly the mRS-90 score, a medical outcome measuring stroke recovery after 90 days of

stroke onset, varies significantly among the three clusters. This provides additional evidence that further thorough analysis of these clusters from a medical point of view may lead to better understanding of stroke physiology and more informed management of stroke patients. Furthermore, the information from these clusters may be utilized to address other research problems, such as the construction of computational models for identifying people at risk of stroke, and for predicting the outcome of patients after stroke.

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