**Study:** ASD-002

**Document:** Primary Manuscript

**Target Journal****:**  Statistics in Biopharmaceutical Research, Special Nonclinical Issue

http://tandfonline.com/action/authorSubmission?journalCode=usbr20&page=instructions

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**Data References:** ASD-002, data generated by Davit

**Version:** Submission Draft

**Date:** 14 Nov 2017

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Abstract: 175 words

Text: 2923 words

References:15

Tables: 2

Figures: 4

**Feature Selection with Weighted Importance Index in an Autism Spectrum Disorder Study**

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# **Abstract**

Elastic net regularization is a popular statistical tool for variable selection that combines lasso and ridge regression penalties. When used in combination with ensemble methods, it improves stability of the estimates and increases confidence in the results. We proposed and tested a version of this method that considers a measure of models’ goodness of fit and gives estimates of importance for each feature weighted on this measure. The method was applied to an autism spectrum disorder (ASD) study to select a subset of biosensor-based features that can be used to predict clinical scores of study participants. In this study, the participants’ responses to visual and audio stimuli were captured by the Janssen Autism Knowledge Engine (JAKE®) biosensors and used to construct approximately 50,000 features. We examined how well changes in these features mirrored changes in the Social Responsiveness Scale (SRS), a quantitative assessment of ASD patients by clinicians. As a result, we isolated the top 20 features most associated with SRS and built models to predict changes in SRS based on changes in the features.

**Key Words:** data mining, elastic net, ensemble methods, JAKE, lasso, ridge regression

# **1. Introduction**

ASD is a variety of neurological conditions manifested through communication deficits such as inappropriate responses in conversations, misreading nonverbal messages, or difficulties in forming relationships with their peers, accompanied by repetitive or obsessive behavior and high sensitivity to changes in their environment (American Psychiatric Association 2013). Janssen Autism Knowledge Engine (JAKE®), a multimodal data capture system in individuals with autism spectrum disorder (ASD), was developed by Janssen Pharmaceutical Research and Development to optimize the ability to identify subpopulations for research and sensitively measure treatment outcomes(Ness et al. 2017). JAKE is a 3-part investigational system consisting of: My JAKE, a web-based and mobile application tool to collect clinical data and monitor symptoms and progress of the study participants; JAKE Sense, a group of biosensors and tasks designed to assess physiological characteristics and behaviors related to core ASD symptoms; and JAKE Stream, a system designed to capture and process data from both My JAKE and JAKE Sense. JAKE Sense periodic biosensors recorded electroencephalography (EEG), electrocardiography (ECG), electrodermal activity (EDA), eye movement, and facial expressions (FACET) of the participants as they responded to visual and audio stimuli throughout series of tests given during clinical visits; additionally, continuous measurements for daytime activity and nighttime sleep patterns were recorded daily. Combining clinical data from multiple sources, such as JAKE Sense data, often leads to situations where a large number (*p*) of explanatory variables, or features, exists for a relatively small number (*N*) of participants, i.e. *p >> N*. Here we explored a landscape of 48,036 features constructed with biosensors data collected from 129 ASD participants over three clinical visits. We examined how changes in these features correlated with changes in clinical scores for assessing ASD severity - the Social Responsiveness Scale (SRS).

SRS is a quantitative measure of autistic traits in 4- to 18-year-olds that aggregates responses to a 65-item questionnaire. Clinicians evaluate each question on a scale between 0 (not true) and 3 (almost always true). The questions focus on participant’s behavior in the past 6 months (Bölte et al. 2008). Total scores are then transformed into *T-scores* that are standardized to mean of 50 and standard deviation of 10. Participants with T-score of 76 or higher are strongly associated with severe ASD; participants with scores between 60 and 75 are considered mild (Aldridge et al. 2010).

The primary goal of this analysis was to identify a subset of biosensor-based features that mirrored longitudinal trend in SRS (differences between first and last visits, in this case), and therefore could be used to assess ASD participants’ progress without relying on subjective measurements, i.e. clinical scales.

# **2. Methods**

To select subsets of biosensor-based features associated with clinical scores, we employed *enriched ensembles* (*EnrE*) method (Amaratunga et al. 2012), combined with *elastic-net-penalized generalized linear regression models* (Friedman et al. 2010). We subsequently improved this combined method by weighting on goodness of fit of each model.

## **2.1 Elastic Net**

*Lasso* minimizes the residual sum of squares (where residuals are the differences between the observed values and values predicted by a model) while constraining the sum of the absolute values of regression coefficients to less than a constant (Tibshirani 1996). This allows shrinking of some coefficients to zero, i.e. lasso effectively performs feature selection by removing features that are not strongly associated with the response by estimating their contribution to the model as zero. Regarding a group of highly correlated features, lasso normally picks up one while shrinking the rest of the coefficients for the group to zero. This creates a possibility of multiple or unstable solutions.

In contrast, *ridge regression* pulls coefficients of a group of highly correlated features closer together by constraining the sum of squares of these coefficients to less than a constant while minimizing the sum of squares of residuals. As a result of this procedure, the obtained estimates of regression coefficients are corrected for nonorthogonality of the features’ space. Although solutions here are stable, ridge regression does not reduce the number of features.

*Elastic net* is a compromise between the *lasso* (L1) and *ridge regression* (L2) penalties. This mixed approach is especially useful for datasets with highly correlated features. To illustrate the method, we adopt the following notations:

Given a vector of response variable

and matrix of features

we want to estimate a vector of coefficients

, with .

By balancing the two aforementioned regularization techniques, it is then possible to minimize the following expression:

where is a function of L1 and L2 penalties, and is the balance between them:

When is zero, a ridge regression is performed; on the other extreme, when is one, the method is equivalent to lasso. By adjusting in the range between 0 and 1, a solution can be found such that only a subset of features is kept (i.e. has non-zero coefficients) while the procedure simultaneously corrects for features’ correlations.

One must note that opinions are divided regarding the optimization, or “tuning” the parameter . In our opinion, this should never be done; rather, the balance between the two penalties should be decided by trying a handful of values of based on the desirable magnitude of shrinkage as it is highly dependent on the correlation structure of the data

## **2.2 Enriched Ensembles (EnrE)**

*EnrE* method is largely an improvement on *bagging-only ensembles* (*BagE*) and *simple ensembles* (*SimE*) methods. The data is initially divided into a training and a testing sets (usually at the 80%/20% rate by participants). Low signal in the data is amplified by weighted sampling of of number of features for of the participants from training set (the coefficient 0.63 here mimics bootstrap sampling effect). The sampling weights’ vector is a function of p-values calculated for each feature in relationship to the response, individually. An argument was made for using false discovery rate (FDR)-adjusted p-values instead of row p-values to reduce overfitting (Amaratunga et al. 2012). The sampling is done repeatedly several hundred to several thousand times, creating a new subset of subject and features every time. A model is fitted to each sample, and the results of each fit are recorded. The results are aggregated at the end and the final model applied to the testing set.

Generally, when *p* is much larger than *N* (as a rule of thumb, when the ration *N/log(p)* is less than 20), the number of linear combinations becomes so large that it overwhelms the model resulting in poor performance. By repeatedly sampling the data and using small subsets to fit the model, we reduce the chance of overfitting. Similar philosophy employed in gene sequencing, for example, where instead of trying to process large chunks of material at once, long sequences are broken into much smaller pieces, processed, and reassembled at the end.

In our study, we applied this technique to compute importance of each feature in relationship to the response. *Feature importance index* (*FII*) was defined as the ratio of times a feature was selected by the model over the number of times that feature was sampled:

where and are respective indicators of *j*-th feature being present in the *k*-th sample (***s***ampled) and subsequently being selected by the model (***c***hosen, i.e. having a non-zero coefficient as estimated by elastic net), with values of 0 or 1. is the total number of samples taken.

One immediate consequence of this calculation is that the contribution of each sample is equivalent, hence simply being selected by the model is the only metric that matters for FII. In reality, samples can vary vastly which will be reflected in the way data fits to the models.

## **2.3 Weighted Index of Feature Importance**

To correct for the fact that not all samples will be a good representation of the data, we proposed and implemented a weighted version of importance index. For each sample, a goodness of fit measure was collected along with the list of features sampled and selected (i.e. with non-zero regression coefficients). The *weighted index of feature importance* (*WIFI*) was then calculated for each feature (*j = 1, …, p*) as following:

where is a function of goodness of fit in the model applied to the sample.

## **2.4 Elastic Net Within Enriched Ensembles Framework**

Applying the methods described above to our data set, we broke the analysis into several steps as described below.

### Step 1. Data pre-processing

Raw data containing a total of 54,287 features constructed from biosensor records of 184 participants was processed by removing all typically developed participants, ASD participants who did not complete all three visits, and features that were constructed using data from only a part of an experiment. The remaining data contained 48,036 features for 129 ASD participants.

Next, we separated the data by the experiments (see Table1 for details). Within each experiment, we computed first-to-last visit differences for each feature and each subject. Features with near-zero variance, defined by default as features with less than 10% unique values and more than 95/5 ration of frequencies of the most common value and the second most common value (Kuhn 2008), were removed. Additionally, features with more than 30% missing data, and participants with more than 80% missing data were excluded. The data was then centered and scaled, and the remaining missing values were imputed using k-nearest neighbors (*KNN*) algorithm (Altman 1992).

### **Table1.** Number of features and participants analyzed in each experiment.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Experiment | Number of features | Missing  >30% | Number of features analyzed | Number of participants analyzed |
| Activity Monitoring | 287 | 161 | 126 | 120 |
| Biomotion | 11,853 | 11,747 | 106 | 120 |
| Chawarska | 804 | 708 | 96 | 123 |
| ERP | 2,247 | 1,874 | 373 | 121 |
| Facial Expression Production | 342 | 0 | 342 | 99 |
| Funny Videos | 684 | 627 | 57 | 103 |
| HourGlass | 84 | 0 | 84 | 120 |
| Kanwisher | 14,624 | 14,326 | 298 | 119 |
| NIMSTIM | 12,536 | 12,440 | 96 | 121 |
| VET | 607 | 417 | 190 | 114 |
| TOTAL | 48,036 |  |  |  |

NOTE: ERP = event related potentials; VET = visual exploration task

To identify and address potential outliers, we used principal component analysis (*PCA*) followed by the *modified z-score* (*MedMAD*) test (Iglewicz and Hoaglin 1993). Using first two principal components, MedMAD test flagged participants with z-scores beyond the 3.5 threshold recommended by Iglewicz and Hoaglin and excluded them from the analysis (see Figure 1 for graphical representation of data before and after outlier removal).

### Step 2. Separate training and testing sets

The data was divided into a training set and a testing set, with roughly 80% of participants selected into the training set at random and without replacement.

### Step 3. Elastic net

Figure 1: Principal component plots of features based on the Activity Monitoring experiments: (upper left) before (upper right) and after removal of outliers; (lower) biplot of the first two principal components, outliers removed. Ft1 to F126 is shortened for Feature 1 through 126.

a. Linear regression models were fitted for the response (differences in SRS between first and last visits, *dSRS*) versus each feature in the training set. The weight for each feature was then calculated as a function of these univariate p-values as following:

where is the p-value for the *j*-th feature adjusted for multiplicity following the false discovery rate (*FDR*) method (Benjamini and Hochberg 1995).

b. A random sample of 0.63of the training set’s participants and of number of features was taken without replacement.

c. Generalized linear model (GLM) with elastic net penalties was fitted to the subset using 10-fold cross-validation (Picard and Cook 1984). Multiple values of the mixing parameter were tested before deciding on 0.5 (i.e. a 50/50 mix of lasso and ridge regression) rather than searching formally for an optimal balance. At this stage, an optimal value of the parameter was determined as the smallest that minimized the cross-validation error.

d. Given the optimal value of , we extracted the list of features present in the sample and the list of features with non-zero coefficients as estimated by the model, as well as the goodness of fit estimates. We used the deviance ratio: the fraction of deviance explained by the saturated model compared to the null (intercept-only) model, as an assessment of goodness of fit:

, hence

e. We repeated Step 3 to Step 5 10,000 times (given the high number of features, we set the number of samples to 10,000 to allow more features a chance to appear in the models).

f. The output from all iterations was aggregated using the *WIFI* index described above. The features were then sorted by importance corresponding to their WIFI values.

g. Sequential selection of features in the order of the estimated importance was used to assess the final models on the testing set. Based on the model comparison results, top 20 features were selected and recommended as a subset that best reflects the changes in clinical scores.

# **3. Results**

Elastic net within enriched ensemble was applied to the recombined data set with 1,768 features across 10 experiments and 83 participants using the algorithm described in the

Figure 2. Importance indices of 1,768 biosensor-based features (10 experiments combined)

methods section. Sixty-four participants were selected at random into the training set, with 43 participants sampled without replacement at each iteration. The weighted and unweighted importance indices were calculated for each feature. The indices in decreasing order are presented in Figure 2.

Generally, weighed importance indices were higher than corresponding unweighted indices. Table 2 shows top 10 features by the weighted importance index.

### **Table 2.** Feature importance

|  |  |  |  |
| --- | --- | --- | --- |
| Feature | Univariable Coefficient | Unweighted Importance | Weighted Importance |
| bm | average AU23 Evidence | baseline not corrected | -2.08 | 0.88 | 0.98 |
| Activity monitoring | all videos together | % furniture (to total stimulation time) [%] | -2.36 | 0.90 | 0.97 |
| Facial expression production | sad | area under fear evidence curve | 1.99 | 0.86 | 0.96 |
| bm | average AU23 evidence | baseline corrected | -2.29 | 0.83 | 0.95 |
| Activity monitoring | all videos together | % furniture (to total valid time) [%] | -2.41 | 0.85 | 0.95 |
| Facial expression production | happy | sum variance neutral evidence | -1.94 | 0.84 | 0.94 |
| Kanwisher\_face | average AU7 evidence | baseline corrected | 1.67 | 0.67 | 0.91 |
| Kanwisher\_obj | average negative evidence | baseline corrected | -1.83 | 0.74 | 0.90 |
| Facial expression production | surprised | average surprise evidence | -1.78 | 0.72 | 0.89 |
| Kanwisher\_face | average negative evidence | baseline corrected | -2.02 | 0.67 | 0.88 |

NOTE: bm = biomotion

Using the training data set, features were added to regression models sequentially, in order of decreasing weighted importance, and the models compared using ANOVA. Fit improved significantly for the first three features, increasing R-squared from 0.137 in a model with a single feature (biomotion, average AU23 evidence without baseline correction) as a predictor of change in SRS, to 0.361 in a model with top three features. This final model was further validated with the testing set using data from the remaining 19 participants. Changes in SRS predicted by the final model using the testing set were compared against the observed SRS changes in the testing set. The correlation between the predicted and the observed SRS changes was low C:\git_local\mentis\tmp\srs_test_pred_vs_obs.tiff(0.12) as shown in Figure 3. These results were not unexpected, the methodology was looking for meaningful changes over time. However, the study was observational in nature, i.e. there was no study-specific intervention. The changes in SRS measure, therefore, carried large amount of noise. The method, however, was able to pick up features that were most likely to be associated with changes in SRS. C:\git_local\mentis\tmp\top3_train.tiffFurther validation of the method using data from more studies as well as simulations is necessary to definitively show the improvement in feature selection using WIFI.

Figure 3. Change in SRS, observed vs. predicted using testing set

# **4. Discussion**

The use of objective sensor-based data obtained via JAKE in individuals with ASD has the potential to transform the understanding of the pathophysiology of ASD, enhance assessments, aid in subtype identification, individualize treatments, and track developmental outcomes. In this study, we were able to identify a subset of biosensor-based features with changes that mirrored trends in clinical scores by applying data mining techniques that combined penalized regression with enriched ensembles sampling method, and goodness of fit measures of to give higher weights to features selected from models that better described the observations.

Figure 4: Changes in top three features vs changes in SRS, first to last visit

As an emerging field, there is a limited number of reports on the use of biosensors to help identify diagnostic features in individuals with ASD. Recent studies have demonstrated the usefulness of eye-tracking measures for classification and aspects of social interaction performance (Hanley et al. 2015, Frazier et al. 2016). Use of an eye tracking-based autism risk index demonstrated that this index had substantial diagnostic accuracy, outperformed the SRS, and showed strong relationships with a gold-standard measure of autism symptom severity (Frazier et al. 2016). In a study using a different objective measurement, it was found that pupil dilation metrics correlated with individual differences measured by the SRS (DiCriscio and Troiani 2017).

Extracting meaningful information form such complex data requires understanding of the data structure and thorough examination of relationships that exist between individual components. Statistical methods used in this analysis generally perform better when the data comes from a single source, e.g. gene expression data. We grouped features by experiments to make data more homogeneous within each group but disregarded biosensors that were involved in capturing the data. However, since data quality varied for different biosensors, with, for example, eye-tracker, sleep monitor, and electrocardiogram capturing higher quality signals compared to electroencephalography (Ness et al. 2017), more in-depth analysis might be necessary. One possibility is to add a grouping variable for biosensor and either incorporate it into the models or perform a subgroup analysis for each biosensor separately. Another potential direction is to use models that are robust for outliers. Although we excluded participants that were revealed by PCA as influential points, there are still questions about the distributions and outliers on the level of individual features. In such cases, downweighing of outliers might be used as an alternative to exclusion.

**Acknowledgements**

We would like to thank Stacey E. Shehin, PhD (PRA Health Sciences) and Ellen Baum, PhD (Janssen Research & Development, LLC) for writing and editorial assistance, respectively. This study was funded by Janssen Research & Development, LLC. Davit Sargsyan, Shyla Jagannatha, Nikolay V. Manyakov, Andrew Skalkin, Abigail Bangerter, Seth Ness, Kathryn Durham, and Gahan Pandina are employees of Janssen Research & Development, LLC, and may hold stock options or shares in the company. Dhammika Amaratunga and Javier Cabrera report no conflicts of interest. All authors meet ICMJE criteria, had full access to the study data, and take responsibility for integrity of the data. All authors have approved the final manuscript. Portions of this study have been presented at the ASA Biopharmaceutical Section Nonclinical Biostatistics Conference, June 12th – 14th, 2017, Rutgers University, Piscataway, New Jersey.

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