Data-driven Autism Biomarkers Selection by using Signal Processing and Machine Learning Techniques

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Abstract: To analyze microarray gene expression data from homogeneous group of children diagnosed with classic autism, a synergy of signal processing and machine learning techniques is proposed. The main focus of the paper is the gene expression preprocessing, which relies on Fractional Fourier Transformation, and the obtained data is further used for biomarker selection using an entropy-based method. This is a crucial step needed to obtain knowledge of the most informative genes (biomarkers) in terms of their discriminative power between the autistic and the control (healthy) group. The relevance of the selected biomarkers is tested using discriminative and generative machine learning classification algorithms. Furthermore, a data-driven approach is used to evaluate the performance of the classifiers by using a set of two performance measures (sensitivity and specificity). The evaluation showed that the model learned by Naive Bayes provides best results. Finally, a reliable biomarkers set is obtained and each gene is analyzed in terms of its chromosomal location and accordingly compared to the critical chromosomes published in the literature.

1 INTRODUCTION

Autism is considered to be neurodevelopmental disorder, emerging from the early childhood. It is often manifested by an impediment in personal, social, academic, or professional functioning. (Azizi, 2015)

Autism Spectrum Disorder (ASD) is characterized by troubles with social interaction and communication, as well as by restricted and repetitive behavior. The first signs of ASD occur in the first 18-30 months of the child's life (Baron-Cohen et al., 1992), and they are of progressive nature. Globally, in 2015, the number of people who have been diagnosed with autism is 24.8 million (Wikipedia, 2016).

Autism reflects on the brain information processing and thus, on the way the neurons and the synapses are linked between. However, there are not sufficient number of research papers to confirm this hypothesis. By now, it is confirmed that the autism has a strong genetic basis that is complex and vague since this disorder comes out of rare mutations with big effects and/or out of rare multigenomic interactions of common gene variants (Yuen et al., 2017).

The enormous progress of the DNA microarrays allowed the researchers to analyze the expression levels of thousands of genes simultaneously. There is a correlation between the different genes regulation, meaning we have to consider the co-operability among the genes in order to find the true characteristics of a genome. In the literature, there is variety of microarrays researches that usually include various Machine Learning (ML) techniques to discover the differences and characteristics of cancers, disorders and/or diseases. However, the diagnosis of the specific type of autism remains a challenge, since the autism is represented by spectrum of disorders, including Asperger's syndrome, Pervasive developmental disorder, and Childhood disintegrative disorder.

In this paper, signal processing and ML methods are fused to analyze microarray gene expression data from homogeneous group of children diagnosed with classic autism, excluding the autism with regression and Asperger's syndrome (Alter et al., 2011). The focus of the paper is on the gene expression prepro-

cessing as crucial step needed to obtain knowledge of the most informative genes (biomarkers) in terms of their discriminative power between the autistic and the control (healthy) group. The biomarkers selection procedure relies on Fractional Fourier Transformation (FRFT) and on an Entropy - based method. The relevance of the biomarkers is tested by several discriminative and generative ML classification algorithms. Furthermore, the performance of the classifiers is ranked by a specific ranking approach that enables the inclusion of multiple metrics when evaluating the classifier. At the end of the process, a reliable biomarkers set is obtained and each gene is analyzed in terms of its chromosomal location and accordingly compared to the critical chromosomes published in the literature.

The major contributions of the work presented in this paper are multifold:

- Signal processing technique is shown to be applicative for gene expression data normalization;

- The preprocessing methods used allow proposition of multiple candidate biomarkers sets;

- The ML methods are used to find the most promising biomarkers set;

- Multiple ML discriminative and generative models are built for autism prediction and the generative approach is chosen as best (Naive Bayes), achieving high sensitivity and specificity;

- Data-driven analysis is done to obtain reliable choice for suitable biomarkers set;

- The biomarkers set is further analyzed and compared to the literature.

The rest of the paper is organized as follows. In Section 2 we present the published work related to our problem. Sections 3 and 4 present the data used and the methodology developed. The experiments and the results are explained in Section 5. Finally, the conclusion is given in the last Section 6.

2 RELATED WORK

ASD shows an extreme clinical heterogeneity, and thus, it is very interesting for the researchers to investigate the disorders at genomic level.

Copy Number Variants (CNVs) are considered as one of the main reasons for ASD. The triplication of chromosome 15q11-q13, deletion on chromosome 9p24, and deletion on chromosome 3q29, are some of the CNVs published in (Nava et al., 2014). Besides these variants, the researchers succeeded in finding

the critical regions related to ASD. The work published in (Philippi et al., 2005) summarize multiple related research papers and finds *chromosome 16p* to be commonly discussed along with the *PRKCB1 gene*, which is considered to be involved in the etiology of the autism, but still cannot be proved.

As the connection between the CNVs and the chromosomal alterations with the ASD is confirmed, the genetic mutations often cover multiple genes, single genes isomorphs, as well as regulatory elements, e.g. the *ASD - risk gene, PTCHD1-AS* and combinations of its mutations (Yuen et al., 2017).

Some other research papers refer to other genes that might be related to the ASD, e.g. duplication and/or deletion of the genes that are on the *22q11.2 chromosome*. Also, there are new CNVs included, obtained with deletion in the *18q22* region (Ceylan et al., 2018).

A connection between the mitochondrial disfunction and ASD has been discovered by finding the common mutations while investigating the patients' *mtDNA*. Even though it has been concluded that the mtDNA mutations are more common at ASD patients rather than the controls, the mtDNA deletions are not always related only to ASD, but there are other cases where they are associated with alterations in genes responsible for intergenomic communication (Varga et al., 2018).

3 MATERIALS

The dataset used in this paper is obtained from the NCBI database, identified as **GSE25507** (Alter et al., 2011). This dataset consists of 54613 probes and 146 samples in total, from which 82 refer to patients diagnosed with autism, and 64 controls, i.e. healthy samples. The platform for the initial execution of the experiment is *Affymetrix Human Genome U133 Plus 2 Array*.

4 METHODOLOGY

The methodology proposed in this paper was inspired by the work of Guo et al. (Guo et al., 2017) and adapted to the problem at hand. The idea of applying signal processing technique on autism gene expression data was challenging, since up to our knowledge, none of the papers reported in the literature has applied such techniques on the autism problem before.

The methodology was developed by following the classical ML procedure and fused with data-driven

ranking method to find the best model and biomarkers set. We used Matlab for calculating FRFT coefficients and ranking the FRFT coefficients. For generating and evaluating the ML models we used Python. Each step of the methodology is explained in the following subsections and depicted in Figure 1.
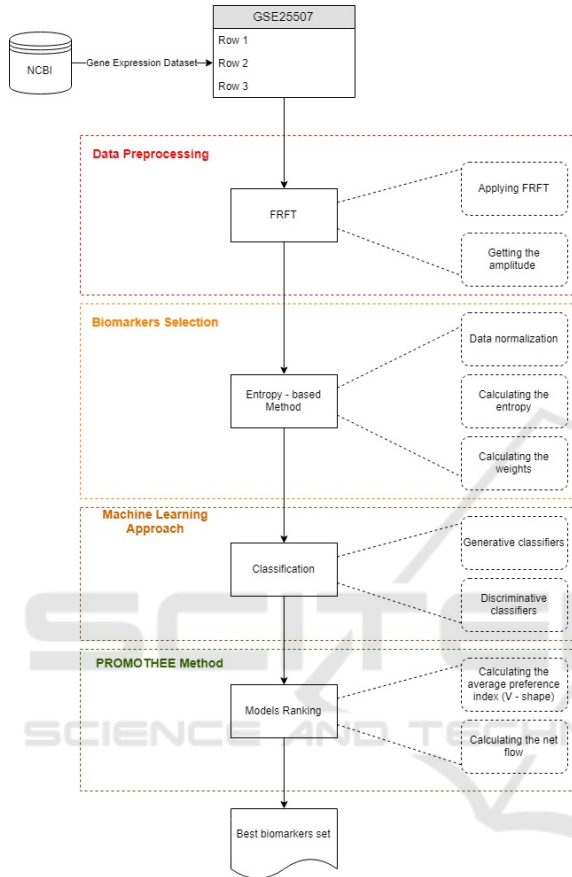

Figure 1: The methodology.

4.1 Data Preprocessing

Gene expression data are characterized with high dimensionality. In our case we are able to observe 54613 probes simultaneously. Choosing the representative features is crucial when building the classification model, (Boulesteix et al., 2008), however, when reducing the dimensionality, we have to be careful not to lose any significant information that would lead to a poor classification of new patients' gene expression data (Alkoot and Alqallaf, 2016).

Noise is a common issue when analyzing gene expression data and can be either of biological or technical nature. Therefore, normalizing the gene expression data before applying methods for knowledge extraction is an essential step for reliable biomarkers set selection. In this paper we use the application of the

Fractional Fourier Transformation (FRFT) as a generalized form of the standard Fourier Transformation (FT) as proposed by Guo et al.(Guo et al., 2017). With the FRFT we map the data from a spatial, or time domain into a frequency domain, obtaining the gene's amplitude and phase. FRFT can be thought of as a linear operator defined with the following Equation 1:

$$f_p(u) = \int_{-\infty}^{+\infty} f(t)K_p(t,u)dt \qquad (1)$$

where $K_p(t,u)$ represents a kernel function defined as:

$$K_p(t,u) = \begin{cases} A_\alpha exp[j\pi(\cot\alpha - 2ut\csc\alpha + t^2)], & \alpha \neq n\pi \\ \delta(u-t), & \alpha = 2n\pi \\ \delta(u+t), & \alpha = (2n\pm 1)\pi \end{cases}$$

and $A_\alpha = \dfrac{exp[-\frac{-j\pi sgn(\sin\alpha)}{4+j\alpha}]}{|\sin\alpha|^{\frac{1}{2}}}$, $\alpha = \frac{pn}{2}$, $n \in \mathbb{Z}$, $\delta(t)$ is the Dirac function.

If $\alpha = 2n\pi + \frac{\pi}{2}$, FRFT is the standard FT, whereas for each value $0 < \alpha < \frac{\pi}{2}$ a rotated time series is produced, i.e., frequency representation of the signal.

The result of this transformation is a complex number which can be plot on an Argand diagram. From the Argand diagram, we then have the polar coordinates of the complex number (modulus and argument), where the modulus matches the amplitude of the complex number and the argument is the phase of the complex number.

Let $z = x + iy$, where $x, y \in \mathbb{R}$ and $i = \sqrt{-1}$. The amplitude can be obtained from the complex number by using the following Equation 2:

$$|z| = \sqrt{Real(z)^2 + Imag(z)^2} \qquad (2)$$

where x is the real part of the complex number and y is the imaginary part.

Some of the FRFT parameters are fixed, some are calculated by equations, and some can accept a range of real values that change the overall results. Considering the equation $\alpha = \frac{pn}{2}$, it can be noticed that there is a parameter p that does not have a predefined value. Choosing different values for p affects the rotation of the signal. Thus, we experiment with different values for p and do FRFT for each probe of the gene expression dataset, mapping it in a vector of complex values and hereupon calculate the amplitudes. The parameter p differs from the p used in statistics.

4.2 Biomarkers Selection

As we obtained a normalized gene expression dataset, we are interested in finding the most significant

probes (genes). For this purpose we use the entropy as a measure of randomness or disruption of a system. This method is very useful in cases where we want to add weights on some coefficients, or parameters. The benefit of using the entropy is in its objectivity. Considered to be fixed, it weights the specified parameter by using its quantity of information.

In this research, the entropy-based method is used to estimate, i.e., to give specific weights to the obtained FRFT coefficients, in order to find the ones with the biggest quantity of information. The coefficients with the biggest quantity of information are selected to be biomarkers upon which an intelligent model is built.

Let us have i samples and j FRFT coefficients, where x_{ij} is the j-th amplitude of the FRFT coefficient of the i-th sample. To eliminate the influence among the coefficients, we normalize them by using Equation 3:

$$r_{ij}^{`} = \frac{x_{ij}}{max\{x_{ij}\}}, (i = 1, ..., m; j = 1, ..., n) \quad (3)$$

and map them in range [0, 1] (Equation 4).

$$f_{ij} = \frac{r_{ij}^{`}}{\sum_{i=1}^{m} r_{ij}^{`}}, (i = 1, ..., m; j = 1, ..., n) \quad (4)$$

Hereupon, the entropy is calculated for each of the coefficients by using the Equation 5:

$$H_j = -\frac{\sum_{i=1}^{m} f_{ij} \ln f_{ij}}{\ln m}, (i = 1, ..., m; j = 1, ..., n) \quad (5)$$

Finally, the weight of each coefficient is calculated by using Equation 6:

$$w_j = \frac{1 - H_j}{n - \sum_{j=1}^{n} H_j}, (\sum_{j=1}^{n} w_j = 1; j = 1, ..., n) \quad (6)$$

Following the advice of Guo et al. (Guo et al., 2017), we ranked the probes according to their weights and chose the top 300 (0.55% of all) to be the most significant, referred to as biomarkers.

4.3 Machine Learning Approach

In order to test the relevance of the chosen biomarkers, we tested their discriminative power between healthy and autistic patient's gene expression data by applying different machine learning methods. In order to model the problem from different aspects, we chose representative methods from both discriminative and generative approaches. All the classifiers used the default parameters values. Three discriminative classifiers were used as follows.

- Support Vector Machine (SVM). Two different types of the SVM classifiers were used, LinearSVM and NuSVM. The difference between LinearSVM and NuSVM classifiers is in the type of function used to separate the feature space. LinearSVM uses linear function, and the NuSVM classifier uses the radial basis kernel function.

- K - Nearest Neighbors (KNN). KNN is a non-parametric method whose input consists of the k closest training examples in the feature space. The class of the new samples will be the same as the class of the majority of its neighbors.

- Random Forest (RF). RF is an ensemble classification method that uses multiple decision trees for classifying a given sample. The advantage over the decision trees is that the RF classifier avoids overfitting over the training data.

Naive Bayes is used as a representative from the generative approach. It is a probabilistic classifier based on the Bayes' Theorem.

Each of the classifiers was evaluated by using 10-fold cross-validation method. This method groups the data in 10 sets. In every step, one of these sets, that hasn't been chosen before, is chosen to be the testing set and the others are used for training the model. The overall result, for sensitivity, specificity and accuracy, for every classifier represents the average of the results obtained in every step of the 10-fold cross-validation method.

The performance of the models was measured by using the standard evaluation metrics for medical problems. Sensitivity is used to evaluate how many of the positive (autistic) samples were truly classified as such. Specificity measures the model's ability to recognize truly negative (healthy) samples. Eventually, the overall accuracy for each classifier is obtained. The calculation for each metric is given by the equations 7, 8 and 9, correspondingly,

$$sensitivity = \frac{TP}{TP + FN} \quad (7)$$

$$specificity = \frac{TN}{TN + FP} \quad (8)$$

$$accuracy = \frac{TP + TN}{TP + TN + FP + FN} \quad (9)$$

where TP is the number of true positive predictions, TN is the number of true negative predictions, FP is the number of false positive predictions and FN is the number of false negative predictions.

Table 1: Decision matrix.

	Sensitivity (q_1)	Specificity (q_2)
C_0	$q_1(C_0)$	$q_2(C_0)$
$C_{0.05}$	$q_1(C_{0.05})$	$q_2(C_{0.05})$
$\vdots$	$\vdots$	
C_1	$q_1(C_1)$	$q_2(C_1)$

4.4 PROMETHEE Method

To find the best value of p, which means to find the best biomarkers set within each classifier, the conclusion is made by fusing the result obtained for sensitivity and specificity. The fusion is made following the idea of PROMETHEE methods (Brans and Mareschal, 2005). To compare the results obtained for all p values within each classifier, and to select the best p value, their results are organized into a decision matrix (Table 1). The rows of the decision matrix correspond to the same classifier trained with different value of p, and the columns correspond to the values obtained for the sensitivity and specificity. First, a generalized preference function (Brans and Mareschal, 2005) should be selected for each performance measure. In our case, the V-shape generalized preference function is used for each performance measure, where the threshold of strict preference is set to the maximum difference that exists for each preference measure from all pairwise comparisons according to that performance measure (Brans and Mareschal, 2005). After that, the average preference index for each pair of meta-models should be calculated, which gives information of global comparison between them using all performance measures. To rank the classifiers obtained for different values of p, a net flow for each one needs to be calculated. It is a difference between a positive preference flow and a negative preference flow of the classifier. The positive preference flow gives information how a given classifier is globally better than the other classifiers, while the negative preference flow gives the information about how a given classifier is outranked by all the other classifiers. This approach has been already used for evaluation of multi-objective meta-heuristic stochastic optimization algorithms regarding a set of performance measures. More details about the ranking approach and the equations for the net, positive, and negative flow, can be find in (Brans and Mareschal, 2005).

5 EXPERIMENTS AND RESULTS

Considering the data preprocessing explained in Section 4.1, it can be noticed that the rotation of the probes' values in the FRFT method depends on the parameter p. Providing different values for p, results in different weights for the probes in Section 4.2, meaning different probes might be ranked as top 300 and thus, different biomarkers sets will be chosen. The best biomarker set is chosen according to best results obtained as explained in Sections 4.3 and 4.4, and therefore, the best value for p.

For p, values are taken from the interval [0, 1] in an ascending order with step of 0.05. Figures below depict the sensitivity and the specificity metrics, whereas the accuracy is omitted from the figures since its information is included in the previous two.
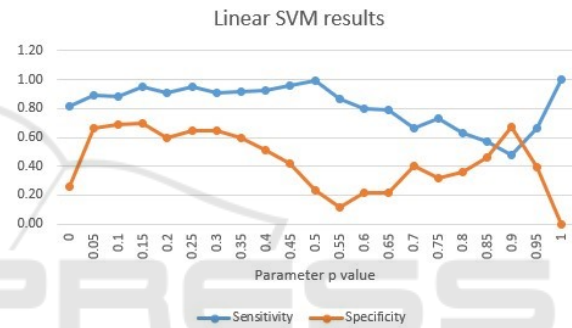

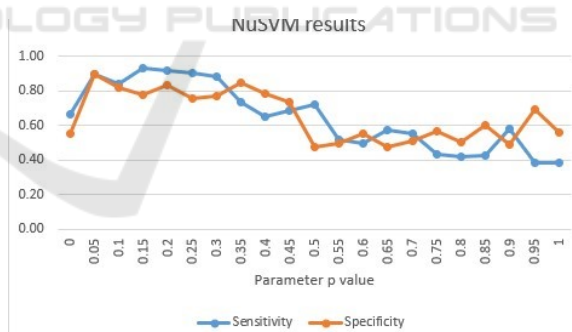
Figure 2: LinearSVM Classifier.

Figure 3: NuSVM Classifier.

Figure 2 shows the sensitivity and specificity results obtained from the LinearSVM classifier. Considering the intention for obtaining both as close and as high as possible sensitivity and specificity values that explain the models ability to perform well on both autistic and healthy samples, the most promising values for the parameter p regarding the LinearSVM model are in range [0.05-0.3]. For the other values of the parameter p there is a decrease at both metrics, especially at the specificity.

The most promising values for the parameter p at the NuSVM model (figure 3) are shown to be from
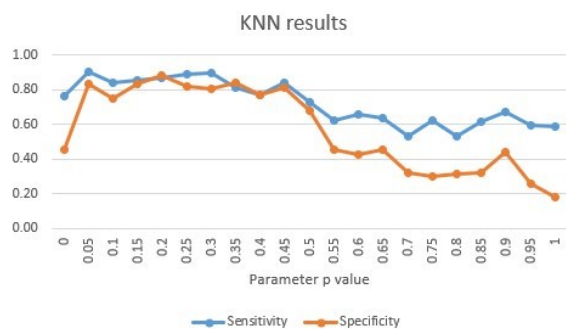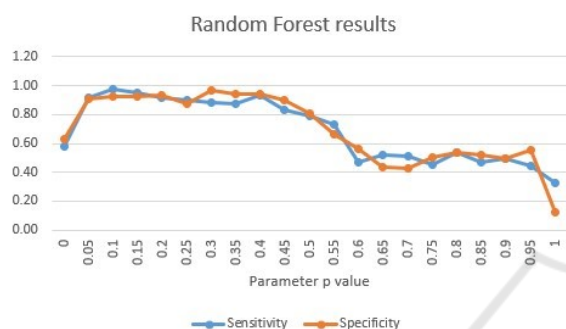
Figure 4: KNN Classifier.
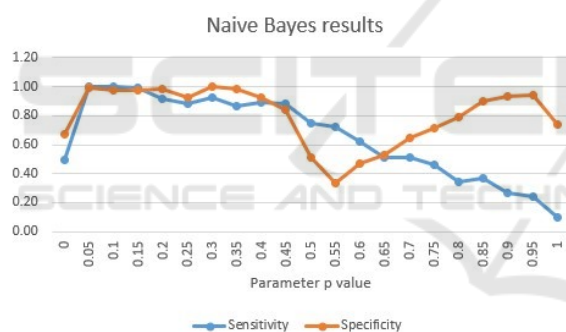

Figure 5: Random Forest Classifier.

Figure 6: NaiveBayes Classifier.

0.05, up to 0.25. For the other values of the parameter p the models classification ability significantly decreases and in some cases the specificity performs better than the sensitivity which we find unfavorable for our problem, meaning we prefer false positives (autistic) rather than false negative (healthy) classifications.

Figure 4 depicts the most promising values for the parameter p at the KNN case to be all from 0.05, up to 0.5. For values above 0.5, the model's performance decreases.

Figure 5 hows that RF behaves similarly to KNN, again performing best for p in range [0.05-0.5]. However, when compared to all previously used discriminative classifiers, it shows highest sensitivity and specificity values.

Considering the generative Naive Bayes model,

the most promising values for the parameter p are from 0.05, up to 0.45. For values above 0.45, the model's behavior is completely destabilized.

Given the figures, we have come to a conclusion that at almost all models, the sensitivity and specificity is stable and satisfying when p varies in range [0.05-0.5]. This conclusion, however, cannot tell on a single best p value, meaning to find the best biomarkers set, and even more, on a single best classifier. For that purpose, we propose the application of the data-driven approach explained in Section 4.4 for finding the best p value within a model, and afterwards finding the best model that explains the relations in the biomarkers set.

Table 3 presents the sensitivity and specificity for all parameter values of p for each of the classifiers. The bold values are found to be the best within each classifier by using the PROMETHEE method. The results provided in Table 2 present the best p parameter results within each model. Eventually, the models are ranked and their status is shown in the last column. From the results it can be concluded that best biomarkers set is obtained when parameter p is set to 0.05, for which the generative Naive Bayes method achieved highest sensitivity and specificity values. From the discriminative methods applied, RF performed best when trained on biomarkers obtained for p parameter set to 0.1.

Table 2: Ranking the classifiers.

Classifier	Best p	Sensitivity	Specificity	Rank
LinearSVM	0.15	0.95	0.70	4
NuSVM	0.05	0.90	0.90	3
KNN	0.05	0.90	0.84	5
RF	0.1	0.98	0.92	2
Naive Bayes	0.05	1	0.99	1

The biomarkers set relation to autism is further inspected by performing gene analysis to find their particular chromosomes locations. Table 4 presents the chromosomes sorted by the number of biomarkers inside each of them.

When compared to the biomarker genes discovered in the published literature, the following overlapping is found with four of the biomarkers we have discovered:

- **CD274 chromosome 9 location 9p24.1**
- **KMT2C chromosome 7 location 7q36.1**
- **KLF13 chromosome 15 location 15q13.3**
- **DOCK4 chromosome 7 location 7q31.1**

Autism relation with chromosome 7 is already proven before (Scherer et al., 2003; Cukier et al., 2009; Ashley-Koch et al., 1999) and in the recent

Table 3: Ranking the best biomarker sets within each classifier.

	LinearSVM		NuSVM		KNN		RF		Naïve Bayes	
p	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
0	0.81	0.26	0.67	0.55	0.77	0.46	0.58	0.63	0.50	0.67
0.05	0.89	0.66	**0.90**	**0.90**	**0.90**	**0.84**	0.91	0.91	**1.00**	**0.99**
0.1	0.88	0.69	0.84	0.82	0.84	0.75	**0.98**	**0.92**	1.00	0.97
0.15	**0.95**	**0.70**	0.93	0.78	0.85	0.84	0.95	0.93	0.99	0.98
0.2	0.90	0.60	0.92	0.83	0.87	0.89	0.92	0.94	0.92	0.98
0.25	0.95	0.65	0.90	0.76	0.89	0.82	0.90	0.88	0.89	0.93
0.3	0.91	0.65	0.89	0.77	0.90	0.81	0.88	0.96	0.92	1.00
0.35	0.91	0.59	0.74	0.85	0.82	0.84	0.87	0.94	0.87	0.98
0.4	0.92	0.51	0.65	0.78	0.77	0.77	0.93	0.94	0.89	0.92
0.45	0.96	0.42	0.68	0.74	0.84	0.82	0.83	0.90	0.88	0.84
0.5	0.99	0.24	0.72	0.48	0.73	0.68	0.79	0.81	0.75	0.51
0.55	0.86	0.12	0.52	0.50	0.63	0.45	0.73	0.67	0.72	0.34
0.6	0.80	0.21	0.49	0.56	0.66	0.43	0.47	0.56	0.62	0.47
0.65	0.79	0.22	0.58	0.48	0.64	0.46	0.52	0.43	0.51	0.53
0.7	0.66	0.40	0.55	0.51	0.53	0.32	0.51	0.43	0.51	0.65
0.75	0.73	0.32	0.44	0.57	0.62	0.30	0.45	0.50	0.46	0.72
0.8	0.63	0.36	0.42	0.50	0.54	0.31	0.54	0.54	0.34	0.79
0.85	0.57	0.46	0.43	0.60	0.61	0.32	0.47	0.52	0.37	0.90
0.9	0.48	0.67	0.58	0.49	0.67	0.44	0.50	0.49	0.27	0.94
0.95	0.66	0.39	0.38	0.70	0.60	0.26	0.44	0.55	0.24	0.94
1	1.00	0.00	0.39	0.56	0.59	0.18	0.32	0.12	0.10	0.74

Table 4: Number of biomarker genes in each chromosome.

Chromosome	Number of genes	Genes
1	31	GBP1, ISG15, GBP5, ADAMTSL4, ASPM, CDC20, C1QB, C4BPA, IFI44, THRAP3, DTL, UTS2, IFI44L, PTGS2, ATF3, C1QA, G0S2, TACSTD2, IFI6, RAVER2, C1QC, GBP5, FCGR1B, CCL3L3
14	16	IFI27, EIF5, DLGAP5, RNASE3, RNASE2, IGHV3-9, FOS, IGHV4-61, IGHD, IGHV3-7, IGHV4-61, IGHV1-69, IGHV3-23, IGHEP1, IGHV3-72, IGHD
11	15	TRIM6, BATF2, NUMA1, MALAT1, FOLR3, SERPING1, SF1, HBG2, CD3E, MMP8, NEAT1
17	15	TOP2A, EIF1, RP11-798G7.6, SOCS3, MXRA7, CCL8, CCL2, RNF213, CCL23, CD7, XAF1, CDC6, SEPT4
10	13	SMC3, ANKRD22, KIF11, IFIT1, CDK1, CEP55, NEBL, ZWINT, MCM10, IFIT3, IFIT2
2	13	SPATS2L, NR4A2, PLEKHB2, MXD1, RSAD2, RRM2, CMPK2, RP11-373D23.2, CYP26B1
4	11	CXCL10, IL8, SPP1, EREG, BOD1L1, HERC5, ANXA3, RAPGEF2, CXCL5, CXCL1
19	10	CEACAM8, UHRF1, TINCR, CD22, RETN, CD177, FOSB, FCAR, LENG8
6	9	RNU6-1016P, HLA-DQA1, SOD2, PHACTR2, CRISP3, TREML4, ETV7, ATXN1
5	8	FST, HBEGF, AC008964.1, EGR1, CD74, CENPK, DUSP1
7	8	PSPH, KMT2C, AOC1, DOCK4, SAMD9L, NAMPT, IFRD1, TMEM176B
8	8	ERG3, NKX3-1, DEFA4, ERICH1-AS1, MYOM2, LY6E, PBK, IDO1
12	7	OAS3, OSBPL8, OASL, RP11-476D10.1, A2M-AS1, C12ORF79
15	7	PKM, IGF1R, THBS1, CCNB2, IQGAP1, KIAA0101, KLF13
22	7	IGLV3-10, IGLV4-60, IGLV3-25, FAM118A, APOBEC3B, IGLV7-43, OSM
20	6	TPX2, PI3, TUBB1, RBM39, SIGLEC1
3	6	LAMP3, KIF15, GPR128, LTF, MBNL1, CPA3
9	5	CD274, TLN1, ORM1, ORM2, LCN2
18	4	TYMS, MBP, ZCCHC2
13	3	EPSTI1, OLFM4
21	3	MX1, ITGB2, SON
16	2	CYB5B, PRSS33

literature (Klein-Tasman and Mervis, 2018), as well as the chromosome 15 (Cooper et al., 2011; Sanders et al., 2011; Sieg and Karl, 1990; Battaglia, 2008).

6 CONCLUSIONS

This paper proposes a methodology that is a fusion of multiple different techniques with the aim to discover a reliable biomarker set for autism recognition. Signal processing technique is used to normalize the gene expression dataset, and a combination with the entropy-based method is used to obtain different biomarkers sets. The reliability of the biomarkers sets is measured by following standard ML approach including discriminative and generative classification methods. In order to find the best model, and therefore, the best biomarkers set, a specific ranking method is applied. The biomarkers set is further analyzed and compared with the published literature. The results confirm a relation between the biomarkers and the disorder investigated.

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