Ranking of Cancer Mediating Genes: A Novel Approach Using Genetic Algorithm in DNA Microarray Gene Expression Dataset

Sujay Saha[1](✉), Priyojit Das[2], Anupam Ghosh[3], and Kashi Nath Dey[4]

[1] Department of CSE, Heritage Institute of Technology, Kolkata 700107, West Bengal, India
sujay.saha@heritageit.edu

[2] Department of CSE, National Institute of Technology Calicut, Kattangal 673601, Kerala, India
priyodas3@gmail.com

[3] Department of CSE, Netaji Subhash Engineering College, Kolkata 700152, West Bengal, India
anupam.ghosh@rediffmail.com

[4] Department of CSE, University of Calcutta, Kolkata 700073, West Bengal, India
kndey55@gmail.com

Abstract. Genes need to be investigated either in Gene Interaction Network or in a DNA microarray gene expression data to understand the role they play in complex diseases like cancer. The prioritized genes can help us to know the molecular mechanism, as well as to discover the promising candidates of cancer. Several gene ranking algorithms already have been proposed that produces the top ranked genes according to their importance with respect to a particular disease. In this work, we have developed one Genetic Algorithm (GA) based algorithm, MicroarrayGA, to rank the genes responsible for a particular cancer to occur. The whole research works on six datasets like Colorectal Cancer, Diffuse Large B-Cell Lymphoma, Pediatric Immune Thrombocytopenia (ITP), Small Cell Lung Cancer (SCLC), Breast Cancer and Prostate Cancer, publicly available from NCBI (National Center for Biotechnology Information) online repository. We have validated the outcome of the proposed algorithm by classification step using Support Vector Machine (SVM) classifier and we have also compared the results of MicroarrayGA with three existing methods on the basis of percentage of accuracy, precision, recall, F1-Score and G-Mean metrics.

Keywords: Gene ranking · Gene interaction · Microarray · Genetic algorithm SVM classifier

1 Introduction

Uncontrollable growth of cells in an unusual fashion is the primary basis of cancer, which is often classified as a group of diseases [1]. Thousands of several genes are responsible for a particular cancer to occur. But all those genes may not be equally

M. Singh et al. (Eds.): ICACDS 2018, CCIS 906, pp. 129–137, 2018.
https://doi.org/10.1007/978-981-13-1813-9_13

significant in this case. Due to this reason, selection of genes based on their ranks for a specific cancer is highly important [2]. In this work, we try to find the significant mediating genes of six various human cancer datasets and to prioritize them as well.

The algorithm used in this paper to rank the genes is primarily constructed by analyzing the expression change of the genes between a diseased and a normal sample. The Genetic Algorithm (GA) based implementations, namely MicroarryGA is applied on microarray gene expression datasets of different cancers to rank genes. Genetic Algorithm can be considered as one of the popular evolutionary algorithms [3, 4]. Later, these ranks are validated by classification step using SVM classifiers [5, 6]. The workflow of the proposed MicroarrayGA method is given in Fig. 1.

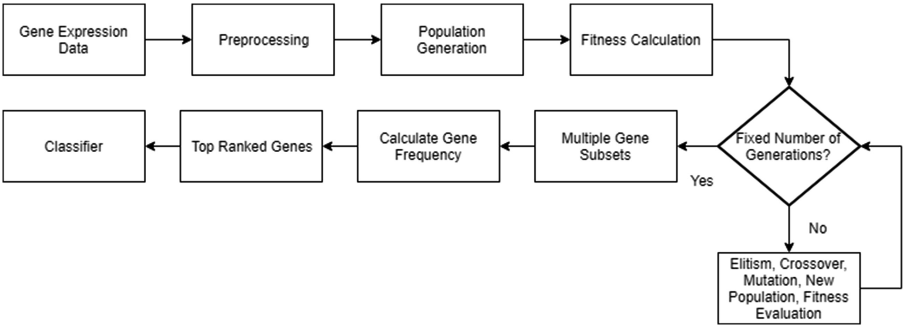


Fig. 1. Workflow of the proposed MicroarrayGA method

2 Related Earlier Works

Ranking genes based on the information from several DNA microarray gene expression data is of fundamental importance [7]. Since data sources contain thousands of several genes, so to determine the set of prioritized genes according to their significance order is an important task. Some of methods from current literature are mentioned briefly as follows:

A soft clustering based microarray expression analysis algorithm is proposed in [8] to analyze genes responsible for acute leukemia. Another method mentioned in [9] uses non-parametric statistical tests - Mann-Whitney U test and k-sample Kruskal-Wallis H test to rank genes. A statistical gene subset selection algorithm using Wilcoxon rank sum test is presented in [10].

Huerta et al. [13] analyzed Leukemia [12] and Colon cancer [14] datasets using their proposed genetic algorithm based gene selection method along with SVM classifier. Mondal et al. presented a multi-objective GA based gene ranking approach in [15]. Another method proposed in [16], selects significant features using genetic algorithms (GAs) and then uses Constructive Neural Networks (CNN) [17], C-Mantec [18] based classification methods to validate the results. A neuro-fuzzy approach is proposed in [19] to select those genes responsible for a particular type of cancers. Another method presented in [20] uses graph theory based approach to identify most significant as well as most non-redundant genes from a DNA gene expression dataset. Dragon Wrapper Feature Selection (DWFS), a web based tool, proposed in [21], is used to select significant features for a various types of problems efficiently.

Another new approach was proposed in [22] to rank the genes of microarray gene expression data using squared Pearson correlation coefficient. Another work presented in [23] developed a fuzzy set theory based index, named as Gaussian Fuzzy Index (GFI) to select a set of cancer mediating genes. GeneRank developed by Morrison et al. [24], is a straightforward generalization of PageRank [25] algorithm used by Google.

3 Methodology

We have developed following GA based approach named as MicroarrayGA. This method initially begins with pre-selection based on filtering, and then generates gene subset G_P of P genes, where P is problem dependent. A small set of the most important genes are selected from this reduced subset of genes, which give the highest accuracy when used with classification task. Detailed steps of this approach are given below:

1. In the first step, genes/features form the microarray are sorted using Fisher's Discriminant Criteria [26] in decreasing order. Then from the sorted genes, top P genes are selected for our calculation.
2. Then N different gene subsets are generated randomly from selected P genes and they are used as initial GA population. To encode each of the gene subsets of the population, binary chromosome representation is used, given in Fig. 2. If a particular gene is present in the gene subset, then the corresponding bit is set to 1, otherwise set to 0 in that chromosome representation.

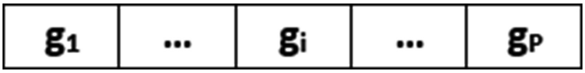


Fig. 2. Chromosome representation

3. After obtaining the initial population, a minimizing fitness function is applied on each of the chromosomes to find the individual fitness value. For each gene present in chromosome, p-value is calculated from Student's two-tailed t test between the two types of sample corresponding to that gene (normal and cancerous). After calculating the p-values of each of the genes present in the chromosome, the average p-value is calculated, which is the fitness value of the chromosome.
4. In this step, a temporary population N' is created which will be used as a population N in the next generation. The new population N', is filled up in three steps. In the first step, the top 40% individuals (based on fitness value; in this method from lower to higher) of N are copied to N' (elitism). In the next two steps, genetic operators: uniform crossover and binary mutation operators are applied respectively to obtain new chromosomes (child solutions).

5. A random pair of solutions are selected from N and uniform crossover operator is applied on these two individuals. The resulting new child solution is inserted in N'. This step is repeated for $0.4 * |N|$ times, where 0.4 is crossover probability (P_c).
6. In this step, mutation operator is applied on individual solution selected randomly from N. This step is repeated for $0.2 * |N|$ times, where 0.2 is mutation probability (P_m).
7. Replace N with N' and repeat the steps from 3 to 7 until fixed number of generations are completed.
8. After the completion of all the generations, each gene is assigned an importance value depending on the frequency of selection among all the N gene subsets. A gene having higher frequency of appearance gets high importance value and vice versa. Their significance is tested by the classification performance using SVM classifier.

4 Experimental Results

MicroarrayGA based approach is applied on microarray gene expression dataset of six various types of cancers, like Breast Cancer, Prostate Cancer, Pediatric Immune Thrombocytopenia (ITP), Small Cell Lung Cancer, Diffuse Large B-Cell Lymphoma (DLBCL) and Colorectal Cancer available at NCBI online repository.

4.1 Dataset Used

Colorectal Cancer tumor (GDS4382) [27, 32] dataset contains 17 samples are of type normal and 17 are of type diseased. Small Cell Lung Cancer (GDS4794) [28, 32] dataset is divided into diseased and normal sample subsets of size 23 and 42 respectively. For DLBCL-FL (GDS4236) [29, 32] dataset, 8 samples are rapamycin sensitive and 6 are rapamycin resistant. In Prostate Cancer (GDS4824) [30, 32] Dataset, 13 diseased samples and 8 normal samples are present. Breast Cancer (GDS4056) [11, 32] contains 32 diseased samples and 29 normal samples. Pediatric Immune Thrombocytopenia (ITP) [31, 32] dataset has total 13 samples out of which 7 are of type newly diagnosed immune thrombocytopenia samples and 6 are of type chronic immune thrombocytopenia samples.

4.2 Parameter Settings

The parameters of the GA applied on microarray gene expression dataset are represented in Table 1 below:

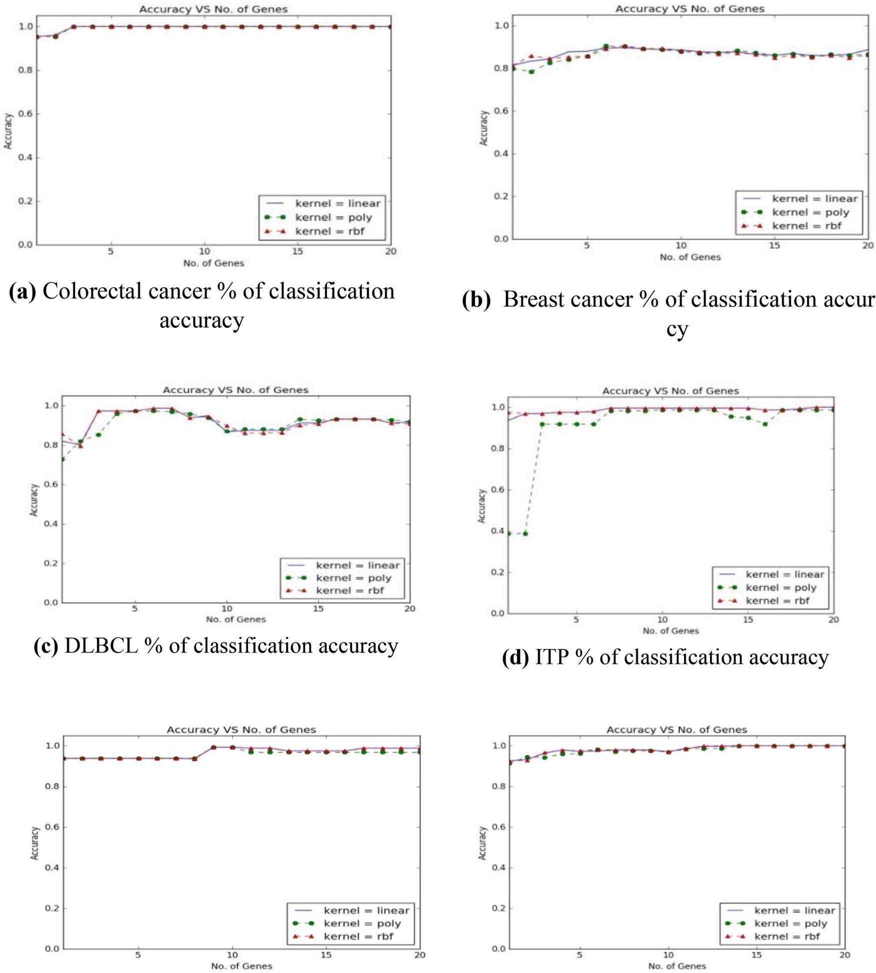
Table 1. GA parameters for MicroarrayGA

N	No. of generations	P	Genes selected	P_c	P_m
100	100	1000	490–500	0.4	0.2

4.3 Results and Comparison with Other Methods

Classification algorithm is used to validate the proposed GA based algorithm's effectiveness in gene ranking. The proposed method's efficiency is compared with some existing ranking methods on the basis of percentage of classification accuracy along with some other metrics.

We take top 20 genes from the ranked set of 1000 genes. These ranking is validated again by the classification process using SVM method with three kernels. Before the classification process starts, we divide the whole sample space into 60:40 ratio. Following Fig. 3 shows how the MicroarrayGA's performance varies on the basis of



(a) Colorectal cancer % of classification accuracy

(b) Breast cancer % of classification accuracy

(c) DLBCL % of classification accuracy

(d) ITP % of classification accuracy

(e) Prostate cancer % of classification accuracy

(j) SCLC % of classification accuracy

Fig. 3. Performance of MicroarrayGA method for six cancer dataset on two metrics

percentage of accuracy using only top most 20 genes for six cancer datasets. From that figure it is clear that for which dataset what is the percentage of classification accuracy proposed algorithm achieves by using how many genes. Although we have done our experiment on six publicly available cancer datasets, but to compare our GA based method's performance with three state-of-the art methods, like Particle Swarm Optimization (PSO) based Graph Theoretic Approach [20], DWFS using K-Nearest Neighbor (KNN) classifier and DWFS using Naïve Bayes (NBC) classifier [21] only two datasets, Prostate Cancer and DLBCL-FL are used. Table 2 shows this comparative study on the basis of percentage of classification accuracy, F1 Score, G-Mean, Recall, Precision [33].

Table 2. Performance comparison of MicroarrayGA with existing works

Algorithm used	Performance metrics	Dataset (No. of genes)	
		Prostate cancer (9)	DLBCL-FL (3)
Proposed approach (MicroarrayGA)	Accuracy	0.9931972	0.97278911
	F1 Score	0.9948169	0.97993197
	G-Mean	0.9954079	0.98388373
	Recall	0.9948979	1.0
	Precision	0.9959183	0.96802721
PSO based graph theoretic approach	Accuracy	0.91	0.94
	F1 Score	0.91	0.89
	G-Mean	0.91	0.94
	Recall	0.91	0.95
	Precision	0.92	0.94
DWFS using KNN classifier	Accuracy	0.86	0.91
	F1 Score	0.86	0.94
	G-Mean	0.86	0.9
	Recall	0.87	0.97
	Precision	0.85	0.85
DWFS using NBC classifier	Accuracy	0.80	0.96
	F1 Score	0.8	0.9
	G-Mean	0.78	0.94
	Recall	0.76	1
	Precision	0.85	0.9

Following Table 3 shows top 15 genes returned by MicroarrayGA algorithm.

Table 3. Top-most 15 genes from all six cancer datasets

Rank	Colorectal cancer	DLBCL-FL	ITP	SCLC	Breast cancer	Prostate cancer
1	LPAR1	C16orf45	CHST2	FANCI	CRIP1	CALM3
2	FAM60A	AAK1	BE670797	SRSF1	C9orf116	SIN3A
3	ABCA8	OR7D4	NR1D2	SPAST	TSPAN13	PRKAA2
4	UTP23	CSPG4P5	KMT2A	HAUS1	MREG	ZNF697
5	BRWD3	SRR	MYBL2	SUMO1	MCCC2	LOC100287413
6	MYC	RFESD	SNX5	NUSAP1	GFRA1	GAL
7	AJUBA	PLPP2	SEC31B	BUB3	TPBG	TIMM8A
8	MGA	chr7:43234021-43234081	SFPQ	RSRC1	ARMT1	RAB17
9	FAM214A	RFC1	GOLGA1	NUP133	PNPLA4	CRISPLD2
10	MRE11A	RHOBTB3	ATPAF1	SRP9	FBP1	FNDC3A
11	SYNCRIP	NIPSNAP3B	OAS2	TMEM258	AGR2	MMGT1
12	GART	GALR1	SLC30A5	SUB1	TFF3	OR7E14P
13	CASZ1	AKR7A2P1	237398_at	UBE2V2	P2RX4	STARD4
14	PPM1H	HIVEP2	FBXO38	SNRPG	TBC1D9	PTRF
15	MMP28	TRPT1	DZIP3	DYNLT1	GATA3	MAGI2

5 Conclusion and Future Scope

In the proposed approach, a genetic algorithm based implementation, MicroarrayGA is used to rank the genes causing various cancers. Ranking is validated by SVM classifier method with three kernels. From Fig. 3 it is clear that for which dataset what is the percentage of classification accuracy proposed algorithm achieves by using how many genes. Three different existing methods from current literature are used in this paper along with MicroarrayGA method for the performance comparison purpose. From the performance scores given in Table 2, it can be concluded that our GA based approach surpasses the other methods. Since MicroarrayGA uses gene expression dataset, the results shows that this approach uses top most 3 genes to top most 9 genes for various cancer datasets to achieve percentage of classification accuracy close to 100%.

We have used only microarray dataset to rank genes. But it is quite possible that gene dataset is obtained in terms of gene interaction network. In that case we need to think about new ways to rank the genes involved in the network. Another modification that can be done is the generation of multiple gene subsets (non-dominated solutions) rather than a single gene subset, which can be used for further biological analysis. For that we can think about multi-objective genetic algorithm. That may improve our results further.

References

1. Defining Cancer: National Cancer Institute, June 2014
2. Zhang, C., Lu, X., Zhang, X.: Significance of gene ranking for classification of microarray samples. IEEE/ACM Trans. Comput. Biol. Bioinform. (TCBB) **3**(3), 312–320 (2006)
3. Goldberg, D.E.: Genetic Algorithms in Search, Optimization and Machine Learning. Addison-Wesley, Boston (1989)
4. Holland, J.H.: Adaptation in Natural and Artificial Systems, 2nd edn. MIT Press, Cambridge (1975)
5. Boser, B.E., Guyon, I., Vapnik, V.: A training algorithm for optimal margin classifiers. In: Proceedings of 5th Annual Workshop on Computational Learning Theory, pp. 144–152. ACM Press (1992)
6. Zisserman, A.: The SVM Classifier. Lecture Notes (2015)
7. Wang, Y., et al.: Gene selection from microarray data for cancer classification—a machine learning approach. Comput. Biol. Chem. **29**(1), 37–46 (2005)
8. Yoo, C.K., Leeb, I.B., Vanrolleghema, P.A.: Interpreting patterns and analysis of acute leukemia gene expression data by multivariate fuzzy statistical analysis. In: Proceedings of 14th European Symposium on Computer Aided Process Engineering. ESCAPE-14, vol. 29, no. 6, pp. 1345–1356 (2005)
9. Peterson, L.E., Coleman, M.A.: Comparison of gene identification based on artificial neural network pre-processing with k-means cluster and principal component analysis. In: Bloch, I., Petrosino, A., Tettamanzi, A.G.B. (eds.) WILF 2005. LNCS (LNAI), vol. 3849, pp. 267–276. Springer, Heidelberg (2006). https://doi.org/10.1007/11676935_33
10. Liao, C., Li, S., Luo, Z.: Gene selection using Wilcoxon rank sum test and support vector machine for cancer classification. In: Wang, Y., Cheung, Y.-M., Liu, H. (eds.) CIS 2006. LNCS (LNAI), vol. 4456, pp. 57–66. Springer, Heidelberg (2007). https://doi.org/10.1007/978-3-540-74377-4_7
11. West, M., Blanchette, C., Dressman, H., et al.: Predicting the clinical status of human breast cancer using gene expression profiles. Proc. Natl. Acad. Sci. **98**, 11462–11467 (2001)
12. Golub, T.R., Slonim, D.K., Tamayo, P., Huard, C., Gaasenbeek, M., et al.: Molecular classification of cancer: class discovery and class prediction by gene expression monitoring. Science **286**(1999), 531–537 (1999)
13. Huerta, E.B., Duval, B., Hao, J.-K.: A Hybrid GA/SVM approach for gene selection and classification of microarray data. In: Rothlauf, F., et al. (eds.) EvoWorkshops 2006. LNCS, vol. 3907, pp. 34–44. Springer, Heidelberg (2006). https://doi.org/10.1007/11732242_4
14. Alon, U., Barkai, N., Notterman, D.A., Gish, K., Ybarra, S., et al.: Broad patterns of gene expression revealed by clustering analysis of tumor and normal colon tissues probed by oligonucleotide arrays. Proc. Natl. Acad. Sci. USA **96**, 6745–6750 (1999)
15. Mondal, K.C., Mukhopadhyay, A., Maulik, U., Bandhyapadhyay, S., Pasquier, N.: MOSCFRA: a multi-objective genetic approach for simultaneous clustering and gene ranking. In: Rizzo, R., Lisboa, P.J.G. (eds.) CIBB 2010. LNCS, vol. 6685, pp. 174–187. Springer, Heidelberg (2011). https://doi.org/10.1007/978-3-642-21946-7_14
16. Luque-Baena, R.M., Urda, D., Subirats, J.L., Franco, L., Jerez, J.M.: Analysis of cancer microarray data using constructive neural networks and genetic algorithms. In: 1st International Work-Conference on Bioinformatics and Biomedical Engineering-IWBBIO, Granada, Spain (2013)
17. Parekh, R., Yang, J., Honavar, V.: Constructive neural-network learning algorithms for pattern classification. IEEE Trans. Neural Netw. **11**(2), 436–451 (2000)

18. Subirats, J.L., Franco, L., Jerez, J.M.: C-Mantec: a novel constructive neural network algorithm incorporating competition between neurons. Neural Netw. **26**, 130–140 (2012)
19. Ghosh, A., Dhara, B.C., De, R.K.: Selection of genes mediating certain cancers, using neuro-fuzzy approach. Neurocomputing **133**, 122–140 (2014)
20. Mandal, M., Mukhopadhyay, A.: A novel PSO-based graph-theoretic approach for identifying most relevant and non-redundant gene markers from gene expression data. Int. J. Parallel Emerg. Distrib. Syst. **30**(3), 175–192 (2015)
21. Soufan, O., Kleftogiannis, D., Kalnis, P., Bajic, V.B.: DWFS: a wrapper feature selection tool based on a parallel genetic algorithm. PLoS One (2015). https://doi.org/10.1371/journal.pone.0117988
22. Demidenko, E.: Microarray enriched gene rank. BioData Min. **8**, 2 (2015). https://doi.org/10.1186/s13040-014-0033-1
23. Ghosh, A., De, R.K.: Identification of certain cancer mediating genes using Gaussian Fuzzy cluster validity index (GFI). J. Biosci. **40**, 741–754 (2015)
24. Morrison, J.L., Breitling, R., Higham, D.J., Gilbert, D.R.: GeneRank: using search-engine technology for the analysis of microarray experiments. BMC Bioinform. **6**(2015), 233–247 (2015)
25. Page, L., Brin, S., Motwani, R., Winograd, T.: The PageRank Citation Ranking: Bringing Order to the Web. Stanford InfoLab, Stanford (1999)
26. Iatan, I.F.: The fisher's linear discriminant. In: Borgelt, C., et al. (eds.) Combining Soft Computing and Statistical Methods in Data Analysis, vol. 77, pp. 345–352. Springer, Heidelberg (2010). https://doi.org/10.1007/978-3-642-14746-3_43
27. Khamas, A., Ishikawa, T., Shimokawa, K., Mogushi, K., et al.: Screening for epigenetically masked genes in colorectal cancer using 5-Aza-2′-deoxycytidine, microarray and gene expression profile. Cancer Genom. Proteom. **9**(2), 67–75 (2012)
28. Sato, T., Kaneda, A., Tsuji, S., Isagawa, T., et al.: PRC2 over-expression and PRC2-target gene repression relating to poorer prognosis in small cell lung cancer. Sci. Rep. **3**, 1911 (2013)
29. Singh, D., et al.: Gene expression correlates of clinical prostate cancer behavior. Cancer Cell **1**(2002), 203–209 (2002)
30. Hans, C.P., Weisenburger, D.D., Greiner, T.C., Gascoyne, R.D., Delabie, J., et al.: Confirmation of the molecular classification of diffuse large B-cell lymphoma by immune histo-chemistry using a tissue microarray. Blood **103**(2004), 275–282 (2004)
31. Shad, A.T., Gonzalez, C.E., Sandler, S.G.: Treatment of immune thrombocytopenic purpura in children: current concepts. Paediatr. Drugs **7**(5), 325–336 (2005)
32. Seal, D.B., Saha, S., Mukherjee, P., Chatterjee, M., Mukherjee, A., Dey, K.N.: Gene ranking: an entropy & decision tree based approach. In: IEEE 7th Annual Ubiquitous Computing, Electronics & Mobile Communication Conference (UEMCON), New York City, NY, USA, pp. 1–5 (2016). https://doi.org/10.1109/UEMCON.2016.7777837
33. Powers, D.M.W.: Evaluation: from precision, recall and F-measure to ROC, informedness, markedness & correlation. J. Mach. Learn. Technol. **2**(1), 37–63 (2011)