Original Article

A Gene Selection Approach for Diabetic Retinopathy Microarray Data classification Using Ant Colony Optimization

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Abstract

Background: Almost all diabetic patients develop diabetic retinopathy. Interpersonal diversity contributes significantly to the susceptibility of serious manifestations of diabetic retinopathy leading to impaired vision. Further, insufficient studies have been performed on the diagnosis of molecular biomarkers for diabetic retinopathy using machine learning. Hence, this study proposed an approach for gene selection in microarray data.
Material and Methods: The proposed method involves a primary filter approach that uses the results of different gene expression analyzes, thereby reducing the primary genes and thus the complexity of space and search time. A set of genes that improve classification accuracy are then identified using the Ant Colony Optimization (ACO) method based on the heuristic approach. Selected genes in the final phase are evaluated using a ROC curve (receptor function trait) to determine the most effective while the smallest subset of traits. The classifier evaluated in the proposed framework is the K-nearest neighbor. A set of diabetic retinopathy microarrays is used to test the proposed approach.
Results: The results of the experiment reveal that the our suggested method obtained a high accuracy rate with 9 highly informative genes. Furthermore, we found four genes including ANKDD1A, ZNF786, SNORA3B and, C14orf2 as novel potential molecular biomarker in diabetic retinopathy.
Conclusion: The results showed that the other heuristic algorithms can be used in eye diseases for gene selection. Also, it is worthwhile evaluating them through biological research and experimentation because of the good discrimination power of the selected genes.
Keywords: K-nearest Neighbor Classification; Gene Selection; Microarray Data; Diabetic Retinopathy, Ant Colony Optimization.

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Introduction

Nearly all diabetes patients develop diabetic retinopathy [1]. The leading cause of blindness in workers in the United States is diabetic retinopathy. Inter-individual variation significantly contributes to the susceptibility of serious manifestations of diabetic retinopathy, resulting in impaired vision. Epidemiological studies indicate two main risk factors affecting phenotypic variation: diabetes duration,glycemia, andHbA1c of an individual [2].

However, the risk of an individual developing diabetes retinopathy is not fully explained by these two factors. Together, these observations in association with the high concordance between family members of diabetic retinopathy promote the underlying genetic mechanism. Family aggregation and twin studies are estimated to account for 25 to 50 % of an individual's risk of serious diabetic retinopathy [3, 4]. There is unfortunately little knowledge of the genetic architecture which helps make diabetes retinopathy susceptible. Genetic studies show a highly polygenic feature influenced by multiple small effect genetic variants.

However, such studies have had limited success, probably as the insufficient samples and diabetic retinopathy has a phenotypical heterogeneity.

In particular, the majority of genetic variants nominally related to diabetic retinopathy [5-7] are located in intronic or intergenic regions, as are other complex disease traits [8, 9], including age-based macular degeneration [5]. In regulating gene expression, most of these variants appear to have critical functional role [10].

In order to discover the genes involved in diabetic retinopathy, we evaluated gene expression data from three groups of people: non-diabetics, diabetics without retinopathy, and diabetics with retinopathy. We suggested a heuristic method for selecting the smallest group of genes with the best classifier performance [11]. This approach consists of two phases. In the first phase, genes that expressed differences were identified, and among them, 200 genes with smallest adjusted P value were selected and fed to the heuristic approach (second phase) which is based on the ant colony optimization [12, 13], a probabilistic technique for solving computational problems which can be reduced to finding good paths through graphs, and K nearest neighbors (KNN) [14], a supervised classification method. At the end best genes' subset identify by ROC curve, a performance measurement for the classification problems at various threshold settings.

The rest of this paper is organized as follows. Section 2 introduces the suggested approach's main materials, such as ant colony optimization and K nearest neighbors. The experimental results are summarized in Section 3. Section 4 concludes with comments and a guidance for feature works.

Material and methods

Gene Expression Dataset

The data is downloaded from gene expression omnibus (GEO), an international public repository that archives high-throughput gene expression and other functional genomics data sets [15], with accession number GSE146615 [16]. It consisted of the 144 samples from 22 individuals' gene expression [7 individuals with no diabetes (H), 7 with type 1 diabetes mellitus (T1D) with no retinopathy (DWoC) and 8 with T1D with proliferative diabetic retinopathy (DWC)] in conditions of standard glucose (11mM of glucose) and high glucose (30mM of glucose). Gene expression was assessed three biological replicates

for each individual (for three individuals it was assessed five biological replicates). All individuals were Caucasian, and 60 % were female. Table 1 summarized demographic features of individuals.

Data normalization (normalize Quantiles) has been done by the R package limma 4.0.3 [17]. After data quantile normalization [18-20], a technique for making two distributions identical in statistical properties [21]; in order to analyze the gene expression in high glucose condition, we proposed a method consisting of three main stages include: gene ranking using adjusted P value criterion, optimum gene subset selection using ant colony optimization, and final gene determination using Receiver Operating Characteristics (ROC).

Gene ranking using adjusted P value criterion

In this stage, in order to eliminate the insignificant genes, we utilized an adjusted P value as a ranking method. The present generation of biological data is massive, leading not only to an avalanche of raw data but to several hypotheses being tested [22]. Inferential statistics are applied for the test of these hypotheses, leading to further biological insights and potential findings [11, 23]. We removed genes with the P value more than 0.01.

Functional enrichment

In order to find the gene ontology and pathway terms, a Enrichr web tool (https://maayanlab.cloud/Enrichr/) was utilized [11, 24-27]. The significant terms were identified based on the adjusted P value which was less than 0.01.

Gene selection by ant colony optimization

We used the average of the adjusted P values as heuristic information (initial predictions of gene (feature) performance) and the initial amount of pheromones, which is a chemical substance produced and released into the environment by an animal, particularly a mammal or an insect, that affects the behavior or physiology of other animals of the same species. In the equation, the ant employs the probability rule [1]. to select features The number of features that each ant is allowed to select is determined at random [28]. The classifier's performance is determined by the features that each ant selects and is used to update the local pheromone.

$$P_i^k(t) = \begin{cases} \frac{[\tau_i(t)]^\alpha [\eta_i(t)]^\beta}{\sum_{u \epsilon j^k} [\tau_u(t)]^\alpha [\eta_u(t)]^\beta} & \text{if } i \epsilon j^k \\ 0 & \text{Otherwise} \end{cases} \quad 1$$

P^k_i The probability of selecting i^{th} feature by k^{th} ant in time step t.

τ_i The pheromone amount of i^{th} feature.

η_i The heuristic information of i^{th} feature.

α The relational importance of pheromone.

β The relational importance of heuristic information.

The pheromone is then globally updated. To accomplish this, the best ant must first be identified. The performance of the KNN classifier, which is directly related to the features chosen by that ant, is used to select the best ant. Following the selection of the best ant, the global pheromone is updated in accordance with equation [2].

$$\tau_i(t+1) = (1-\rho).\tau_i(t) + \sum_{k=1}^{m} \Delta\tau_i^k(t) + \Delta\tau_i^g(t) \quad 2$$

P Global pheromone evaporation rate.

M Number of ants.

$\Delta\tau^g_i(t)$ The change amount the best ant has had on the pheromone vector as equation [3].

$$\Delta\tau_i^k(t) = \begin{cases} \varphi.S^k(t) + \frac{(1-\varphi).(n-|S^k(t)|)}{n} & \text{if } i \epsilon S^k(t) \\ 0 & \text{Otherwise} \end{cases} \quad 3$$

$\Delta\tau^k_i(t)$ Pheromone of feature i of the k^{th} ant at time t.

φ Local evaporation coefficient.

$S^k(t)$ Accuracy of the cell's classifier.

|. | The number of chosen features by the k^{th} ant.

N The total number of features.

After updating the global pheromone, the current and previous iterations' information is compared, and the ant with the best performance is saved as the algorithm's final solution up to this iteration. The algorithm runs until it reaches the maximum number of iterations, denoted by T.

The ROC curve is now used to identify the final features. The sensitiveness versus specificity of the ROC curve is demonstrated.

Sensitivity shows the ratio between the correctly classified positive samples and the true positive samples.

$$\text{Sensitivity} = \frac{\text{Correctly classified positive samples}}{\text{True positive samples}} \quad (4)$$

Specificity shows the ratio between the correctly classified negative samples and the true negative samples.

$$\text{Specificity} = \frac{\text{Correctly classified negative samples}}{\text{True negative samples}} \quad (5)$$

We divided the dataset samples into two groups using the 10-fold cross validation technique: train and test. For each best feature set, we plotted the ROC curve and calculated the area under the curve (AUC). The feature with the highest AUC is in the last feature set.

Results

As mentioned before, the 144 samples from 22 individuals (i.e. 3 replicates for each individual, except 3 individuals with 5 replicates) were reported in gene expression data. Two conditions, standard glucose and high glucose, were examined for the expression of genes.

In this study, we looked at gene expression in non-diabetic people, type 1 diabetic patients without Retinopathy, and type 1 diabetic patients with Retinopathy under high-glucose (30mM) conditions. This condition is passed by 72 out of 144 samples [21 with no diabetes (H), 25 with T1D with no retinopathy (DWoC), and 26 with T1D with proliferative diabetic retinopathy (DWC)].

In the experimental study, we exclude probes with no annotated genes or with NaN values. The total number of probes falls from 47282 to 10262. Then gene expression has been transformed by log_2 *(gene expresion + 1)*.

In order to quality control, we examine the correlation of samples, samples distribution and principal component analysis (PCA). Principal component analysis (PCA) of gene expression was run with the prcomp function in R. Figure 1 shows that the first three PC can

Table 1: Data Set. Demographic features of Individuals in the study

Class Names	Number of individuals	Ethnicity	Female (%)	Age (years, std)	Mean duration of type 1 diabetes in months (years, std)	Number of samples
H	7	Caucasian	5 (71.4)	21 (6.6)	---	42
DWoC	7	Caucasian	4 (57.1)	32 (3.9)	27 (13.4)	50
DWC	8	Caucasian	5 (62.5)	31 (8.5)	53 (43.4)	52

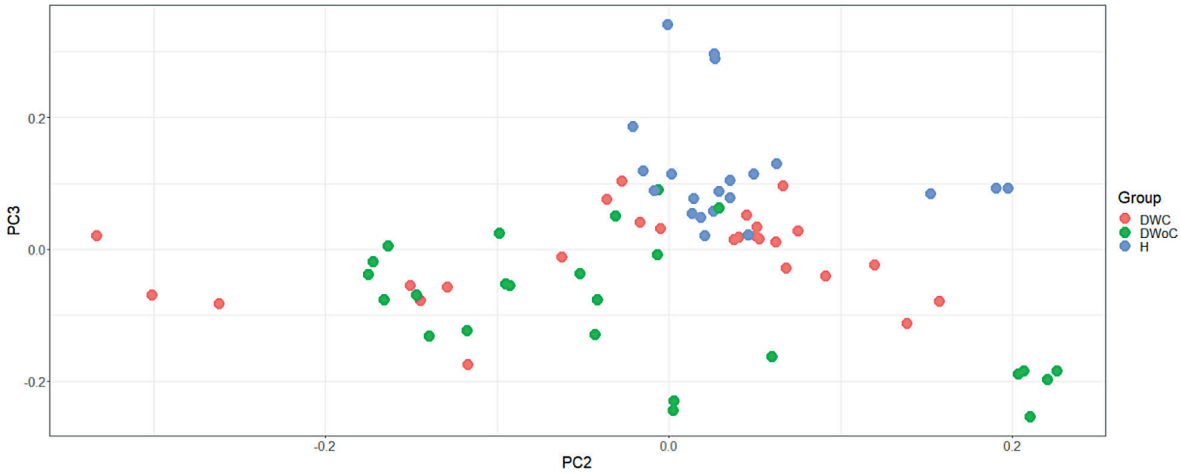

Figure 1: PCA plot. dimensional reduction by principal component analysis. red, green, and blue dots represent position of the DWC, DWoC, and H sample in the new space

model data variation.

In the second phase, we try to find differently expressed genes. The analysis was carried out using the R package limma 4.0.3 .

The design matrix was created; its dimension is equal to size of samples by size of groups. Each row of the matrix determines a sample's group. For instance, if i-th sample in dataset belong to j-th group then i*j design matrix entry is one otherwise zero. We built a design matrix using the model.matrix function. Then a linear model was fit to data using the lmFit function.

We set up contrasts of interest for each pair of groups by make Contrasts function, then recalculate model coefficients using contrasts fit function. For estimating importance of genes, we use Bayesian model (eBayes function). We assume that 1 % of genes are significant and use it as prior knowledge in Bayesian model. The Benjamini-Hochberg Procedure uses for adjusting the model. We construct table of top significant genes by applying the topTable function. At the end, the genes with adjusted P value ≤ 0.01 consider as significant genes. Only 1862 genes pass this criterion. All the functions in this part are in limma R package.

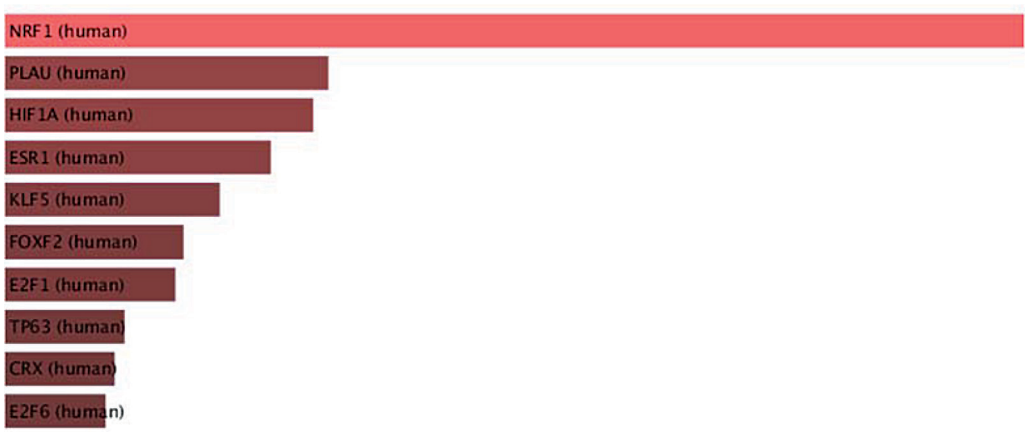

Figure 2: Transcription analysis. TRANSFAC and JASPAR PWMs analysis of differentially expressed genes

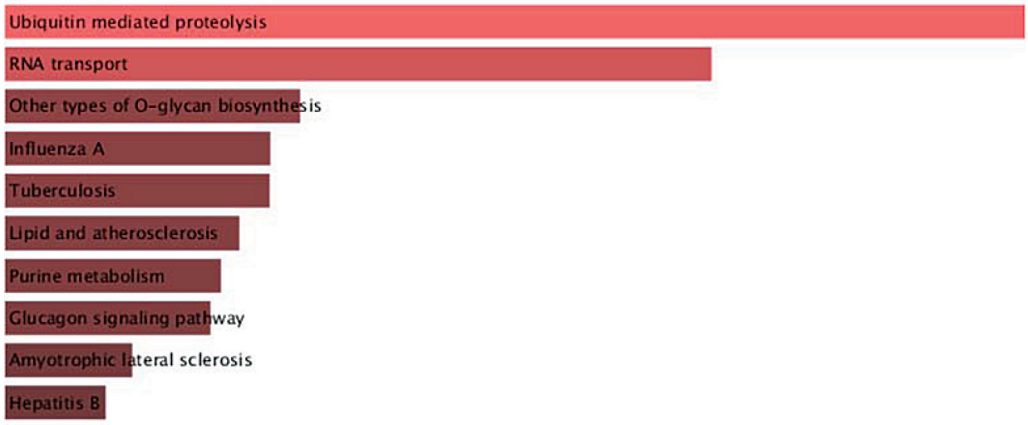

Figure 3: Pathway analysis. KEGG 2021 Human analysis of differentially expressed genes

For more investigation, we map genes to TRANSFAC and JASPAR PWMs and KEGG datasets. Using the PWM from TRANSFAC and JASPAR the binding motifs were detected at the promoter of gene. The NRF1 (adjusted P value = 2.929e-8) is the most significant transcription factor. According to the KEGG 2021 Human dataset, most of these genes are in Ubiquitin mediated proteolysis pathway or UPS (adjusted P value = 0.001269). This pathway controls cell cycles, differentiations and different signal transduction pathways in eukaryotic cells as the basis of protein quality control.

UPS is essential to normal cell physiology to timely and selective degradation of surplus or aberrant proteins. Diabetic retinopathy (DR) and diabetic nephropathy (DN) are disrupted by high blood glucose or by hyperglycemia from diabetes in various target organs including the retina and kidney (DN).

The majority of studies focused on the renal and gave insights into DN microvascular damage contribution of dysregulated UPS. The eye is one organ that separates a semi-fluid medium, the vitreous humor, from a semi-solid lens' tissue, between the neural retina and their blood vessels. For a non-diabetic vision, the complexity of the eye's cellular and molecular elements can require normal functioning and well-tuned UPS .

After finding differently expressed genes, 200 genes with the smallest adjusted P value fed to ant colony optimization. The algorithm run 30 times, then X most frequently chosen by ACO consider as a top features. At the end we calculate AUC for determining the best features. Table 2 represents the parameters of the K nearest neighbor classifier. Based on the experimental results obtained in different implementations of the algorithm, the number of neighborhoods was considered 3. In Table 3, the result of classification by 200 genes and X Top gens are shown.

For calculating mean of classification accuracy and AUC, we apply 10-fold cross validation and reaped it for 10 times. Comparing the classification accuracy and AUC in these cases shows that The best results occur when data were classified with 200 genes or 9 genes- ANKDD1A, SLC30A7, DSG2, FRMD4A, GBF1, ZNF786, SNORA3B, FOXO1 and C14orf2. The results show that while a small sub-set of gene is selected, the selected genes influence the separation of different classes highly. The experiment shows that with

Table 2: Parameters of Classifier. Parameters value for KNN classifier

Classifier	Parameters
K-nearest neighbor	Distance = Standardized Euclidean distance; number of nearest neighbors = 3

Table 3: classification results. The classification accuracy and AUC at the end of the proposed algorithm

Number of features		(gene symbols)	Mean of classification accuracy (%)	AUC
	200	-	95.0	0.99
Top Genes (Selected By ACO)	15	NR2F6, ANKDD1A, SLC30A7, DSG2, FRMD4A, GBF1, ZNF786, SNORA3B, FOXO1, C14orf2, ZNF652, USP32, RN7SL1, CHMP4B, MFSD14C	94.1	0.94
	10	NR2F6, ANKDD1A, SLC30A7, DSG2, FRMD4A, GBF1, ZNF786, SNORA3B, FOXO1, C14orf2	96.1	0.99
	9	ANKDD1A, SLC30A7, DSG2, FRMD4A, GBF1, ZNF786, SNORA3B, FOXO1, C14orf2	97.5	1
	8	NR2F6, ANKDD1A, SLC30A7, DSG2, FRMD4A, GBF1, ZNF786, SNORA3B,	94.2	0.99
	6	NR2F6, ANKDD1A, SLC30A7, DSG2, FRMD4A, GBF1	92.8	0.99
	4	NR2F6, ANKDD1A, SLC30A7, DSG2	85	0.92

9 highly informative genes, the proposed approach has achieved a high precision rate. In addition, the five selected genes (GBF1, DSG2, FRMD4A, SLC30A7 and Foxo1) have been found meaningfully in the biology texts.

Discussion

This paper proposes an approach of feature selection to find the most informative genes to select diabetic retinopathy (ACO). Diabetic retinopathy disease, the main goal of the approach proposed is to identify the smallest biomarker subset which can efficiently indicate the disease. Due to its benefits such as a higher convergence rate and computational efficiency, ACO is chosen. The ROC curve will also ensure the stability of the method to select the final subset. By stability, we mean the ability to extend this approach to datasets with far fewer samples. On a microarray dataset the proposed approach is evaluated.

Finally, 9 genes (ANKDD1A, SLC30A7, DSG2, FRMD4A, GBF1, ZNF786, SNORA3B, FOXO1 and C14orf2) that had the greatest ability in classifying diabetic, diabetic retinopathic and healthy patients were

introduced. Five of these genes have already been mentioned in the literature - GBF1, DSG2, FRMD4A, SLC30A7, Foxo1. Wang et al. 2017 claim that GBF1's selective inhibitor golgicide can prevent the delivery of rhodopsin to the cilia without damaging the photoreceptor Golgi [29]. DSG2 antibody and its epitope (named KC21) inhibits Angiogenesis and attenuates Hypoxia-Induced Retinopathy [30]. A Signal Near FRMD4A is associated with lower extremity arterial disease in patients with Type 2 diabetes [31]. SLC30A7 has anti-oxidant stress effects in high glucose-induced apoptosis via the NFE2L2/HMOX1 signal transduction pathway [32]. It is proof that in the absence of Foxo1, direct liver insulin signaling is dispensable for glucose metabolism in vivo [33].

The ANKDD1A, ZNF786, SNORA3B and, C14orf2 genes were not directly listed in the literature as genes involved in diabetic retinopathy, but were listed on the GeneCards as genes influencing diabetes, obesity, and metabolism [34]. These diseases are the underlying issue associated with diabetes retinopathy. So it is suggested that they can be further investigated in future biological research and considered as potential candidate. ANKDD1A (ankyrin repeat and death domain containing 1A), Predicted to be involved in signal transduction. ANKDD1A interacts with FIH1 directly and upregulates FIH1 to inhibit HIF1 transcriptional activity. Furthermore, by upregulating FIH1, ANKDD1A reduces the half-life of HIF1, decreases glucose uptake and lactate production, inhibits glioblastoma multiforme (GBM) autophagy, and induces apoptosis in GBM cells under hypoxia. Furthermore, ANKDD1A is frequently methylated in GBM [35]. ZNF786 ((Zinc Finger Protein 786)) is a Protein Coding gene. Gene Expression is one of its related pathways. Nucleic acid binding is among the Gene Ontology (GO) annotations for this gene [34]. SNORA3B (snoRNAs) is small noncoding RNA involved in RNA processing [36].

In addition, other heuristic algorithms can be used in future works, like artificial bee colony, for gene selection. Also, it is worthwhile evaluating them through biological research and experimentation because of the good discrimination power of the selected genes.

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References

1. Control CfD, Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: US department of health and human services, centers for disease control and prevention. 2011;201(1):2568-9.

2. Group DER. Frequency of evidence-based screening for retinopathy in type 1 diabetes. New England Journal of Medicine. 2017;376(16):1507-16.

3. Arar NH, Freedman BI, Adler SG, Iyengar SK, Chew EY, Davis MD, et al. Heritability of the severity of diabetic retinopathy: the FIND-Eye study. Investigative ophthalmology & visual science. 2008;49(9):3839-45.

4. Hietala K, Forsblom C, Summanen P, Groop P-H, Group FS. Heritability of proliferative diabetic retinopathy. Diabetes.

2008;57(8):2176-80.
5. Fritsche LG, Fariss RN, Stambolian D, Abecasis GR, Curcio CA, Swaroop A. Age-related macular degeneration: genetics and biology coming together. Annual review of genomics and human genetics. 2014;15:151-71.
6. Fritsche LG, Igl W, Bailey JNC, Grassmann F, Sengupta S, Bragg-Gresham JL, et al. A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. Nature genetics. 2016;48(2):134-43.
7. Pournoor E, Elmi N, Masoudi-Nejad A. Catbnet: A multi network analyzer for comparing and analyzing the topology of biological networks. Current Genomics. 2019;20(1):69-75.
8. Mousavian Z, Kavousi K, Masoudi-Nejad A, editors. Information theory in systems biology. Part I: Gene regulatory and metabolic networks. Seminars in cell & developmental biology; 2016: Elsevier.
9. Mousavian Z, Díaz J, Masoudi-Nejad A, editors. Information theory in systems biology. Part II: protein–protein interaction and signaling networks. Seminars in cell & developmental biology; 2016: Elsevier.
10. Skol AD, Jung SC, Sokovic AM, Chen S, Fazal S, Sosina O, et al. Mendelian randomization identifies folliculin expression as a mediator of diabetic retinopathy. bioRxiv. 2020.
11. Maghsoudloo M, Jamalkandi SA, Najafi A, Masoudi-Nejad A. An efficient hybrid feature selection method to identify potential biomarkers in common chronic lung inflammatory diseases. Genomics. 2020;112(5):3284-93.
12. Dorigo M, Gambardella LM. Ant colony system: a cooperative learning approach to the traveling salesman problem. IEEE Transactions on evolutionary computation. 1997;1(1):53-66.
13. Sharbaf FV, Mosafer S, Moattar MH. A hybrid gene selection approach for microarray data classification using cellular learning automata and ant colony optimization. Genomics. 2016;107(6):231-8.
14. Fix E, Hodges JL. Discriminatory analysis. Nonparametric discrimination: Consistency properties. International Statistical Review/ Revue Internationale de Statistique. 1989;57(3):238-47.
15. Clough E, Barrett T. The gene expression omnibus database. Statistical genomics: Springer; 2016. p. 93-110.
16. Skol AD, Jung SC, Sokovic AM, Chen S, Fazal S, Sosina O, et al. Integration of genomics and transcriptomics predicts diabetic retinopathy susceptibility genes. Elife. 2020;9:e59980.
17. Ritchie ME, Phipson B, Wu D, Hu Y, Law CW, Shi W, et al. limma powers differential expression analyses for RNA-sequencing and microarray studies. Nucleic acids research. 2015;43(7):e47-e.
18. Maghsoudloo M, Azimzadeh Jamalkandi S, Najafi A, Masoudi-Nejad A. Identification of biomarkers in common chronic lung diseases by co-expression networks and drug-target interactions analysis. Molecular Medicine. 2020;26(1):1-19.
19. Ghasemi M, Seidkhani H, Tamimi F, Rahgozar M, Masoudi-Nejad A. Centrality measures in biological networks. Current Bioinformatics. 2014;9(4):426-41.
20. Pournoor E, Elmi N, Masoudi-Sobhanzadeh Y, Masoudi-Nejad A. Disease global behavior: a systematic study of the human interactome network reveals conserved topological features among categories of diseases. Informatics in Medicine Unlocked. 2019;17:100249.
21. Bolstad BM, Irizarry RA, Åstrand M, Speed

TP. A comparison of normalization methods for high density oligonucleotide array data based on variance and bias. Bioinformatics. 2003;19(2):185-93.
22. Pournoor E, Mousavian Z, Dalini AN, Masoudi-Nejad A. Identification of key components in colon adenocarcinoma using transcriptome to interactome multilayer framework. Scientific reports. 2020;10(1):1-14.
23. Jafari M, Ansari-Pour N. Why, when and how to adjust your P values? Cell Journal (Yakhteh). 2019;20(4):604.
24. Chen EY, Tan CM, Kou Y, Duan Q, Wang Z, Meirelles GV, et al. Enrichr: interactive and collaborative HTML5 gene list enrichment analysis tool. BMC bioinformatics. 2013;14(1):1-14.
25. Kuleshov MV, Jones MR, Rouillard AD, Fernandez NF, Duan Q, Wang Z, et al. Enrichr: a comprehensive gene set enrichment analysis web server 2016 update. Nucleic acids research. 2016;44(W1):W90-W7.
26. Xie Z, Bailey A, Kuleshov MV, Clarke DJ, Evangelista JE, Jenkins SL, et al. Gene set knowledge discovery with Enrichr. Current protocols. 2021;1(3):e90.
27. Zou L, Imani S, Maghsoudloo M, Shasaltaneh MD, Gao L, Zhou J, et al. Genome-wide copy number analysis of circulating tumor cells in breast cancer patients with liver metastasis. Oncology reports. 2020;44(3):1075-93.
28. Masoudi-Sobhanzadeh Y, Omidi Y, Amanlou M, Masoudi-Nejad A. Trader as a new optimization algorithm predicts drug-target interactions efficiently. Scientific reports. 2019;9(1):1-14.
29. Wang J, Fresquez T, Kandachar V, Deretic D. The Arf GEF GBF1 and Arf4 synergize with the sensory receptor cargo, rhodopsin, to regulate ciliary membrane trafficking. Journal of Cell Science. 2017;130(23):3975-87.
30. Lu C-S, Lee Y-N, Wang S-W, Wu Y-J, Su C-H, Hsieh C-L, et al. KC21 peptide inhibits angiogenesis and attenuates hypoxia-induced retinopathy. Journal of cardiovascular translational research. 2019;12(4):366-77.
31. NSTEMI S. CARDIOVASCULAR DISEASE AND DIABETES—CLINICAL AND TRANSLATIONAL 1-OR.
32. Zhang X, Guan T, Yang B, Chi Z, Wan Q, Gu HF. SLC30A7 has anti-oxidant stress effects in high glucose-induced apoptosis via the NFE2L2/HMOX1 signal transduction pathway. Diabetes Research and Clinical Practice. 2021;172:108445.
33. Titchenell PM, Chu Q, Monks BR, Birnbaum MJ. Hepatic insulin signalling is dispensable for suppression of glucose output by insulin in vivo. Nature communications. 2015;6(1):1-9.
34. Fishilevich S, Nudel R, Rappaport N, Hadar R, Plaschkes I, Iny Stein T, et al. GeneHancer: genome-wide integration of enhancers and target genes in GeneCards. Database. 2017;2017.
35. Feng J, Zhang Y, She X, Sun Y, Fan L, Ren X, et al. Hypermethylated gene ANKDD1A is a candidate tumor suppressor that interacts with FIH1 and decreases HIF1α stability to inhibit cell autophagy in the glioblastoma multiforme hypoxia microenvironment. Oncogene. 2019;38(1):103-19.
36. Abbamonte P, Rusydi A, Smadici S, Gu G, Sawatzky G, Feng D. Spatially modulated'mottness' in La2-xBaxCuO4. Nature Physics. 2005;1(3):155-8.

Footnotes and Financial Disclosures

Conflict of interest:

The authors have no conflict of interest with the subject matter of the present manuscript.