IDENTIFICATION OF PATHWAY AND GENE MARKERS USING ENHANCED DIRECTED RANDOM WALK FOR MULTICLASS CANCER EXPRESSION DATA

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DEDICATION

This thesis is dedicated to my parents, brother, supervisors, godparents, friends, and late grandma, who taught me that “learning from mistakes”, “don’t speak unless you can improve on the silence”, “self-control is a key to achieve success”, and “always remember who lent you a helping hand before”.

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ABSTRACT

Cancer markers play a significant role in the diagnosis of the origin of cancers and in the detection of cancers from initial treatments. This is a challenging task owing to the heterogeneity nature of cancers. Identification of these markers could help in improving the survival rate of cancer patients, in which dedicated treatment can be provided according to the diagnosis or even prevention. Previous investigations show that the use of pathway topology information could help in the detection of cancer markers from gene expression. Such analysis reduces its complexity from thousands of genes to a few hundreds of pathways. However, most of the existing methods group different cancer subtypes into just disease samples, and consider all pathways contribute equally in the analysis process. Meanwhile, the interaction between multiple genes and the genes with missing edges has been ignored in several other methods, and hence could lead to the poor performance of the identification of cancer markers from gene expression. Thus, this research proposes enhanced directed random walk to identify pathway and gene markers for multiclass cancer gene expression data. Firstly, an improved pathway selection with analysis of variances (ANOVA) that enables the consideration of multiple cancer subtypes is performed, and subsequently the integration of k-mean clustering and average silhouette method in the directed random walk that considers the interaction of multiple genes is also conducted. The proposed methods are tested on benchmark gene expression datasets (breast, lung, and skin cancers) and biological pathways. The performance of the proposed methods is then measured and compared in terms of classification accuracy and area under the receiver operating characteristics curve (AUC). The results indicate that the proposed methods are able to identify a list of pathway and gene markers from the datasets with better classification accuracy and AUC. The proposed methods have improved the classification performance in the range of between 1% and 35% compared with existing methods. Cell cycle and p53 signaling pathway were found significantly associated with breast, lung, and skin cancers, while the cell cycle was highly enriched with squamous cell carcinoma and adenocarcinoma.

ABSTRAK

Penanda kanser memainkan peranan penting dalam mengesan tanda-tanda penyakit kanser dan membolehkan rawatan dilakukan pada peringkat awal. Tugas ini mencabar disebabkan oleh keunikan sifat kanser itu sendiri. Pengenalpastian penanda ini boleh membantu meningkatkan kadar survival pesakit kanser apabila rawatan bersesuaian dapat diberikan dan usaha pencegahan dipertingkatkan. Kajian terdahulu menunjukkan bahawa penggunaan maklumat topologi dan laluan dapat membantu dalam mengesan penanda kanser dari ekspresi gen. Analisis ini dapat mengurangkan kerumitan sumber maklumatnya dari ribuan gen kepada ratusan laluan. Walau bagaimanapun, kebanyakan kaedah sedia ada mengkelaskan semua jenis kanser yang berbeza kepada satu petunjuk penyakit sahaja dan menganggap semua laluan adalah sama. Manakala dalam beberapa kaedah lain, interaksi antara gen dan gen yang terpisah daripada rangkaian telah diabaikan. Ini boleh menyebabkan kemerosotan prestasi pengenalpastian penanda kanser daripada ekspresi gen. Justeru, kajian ini mencadangkan kaedah yang dipertingkatkan bagi perjalanan rawak terarah untuk mengenalpasti gen dan laluan bermaklumat dari data ekspresi gen yang berasaskan pelbagai kelas kanser. Pertama, pemilihan laluan yang bertambah baik dilakukan dengan menggunakan analisis varians yang membolehkan pertimbangan pelbagai kelas kanser. Kedua, pengintegrasian pengelompokan k-means dan kaedah siluet purata dalam perjalanan rawak terarah yang mempertimbangkan interaksi pelbagai gen pula dilakukan. Kaedah yang dicadangkan telah diuji pada kumpulan data penanda aras iaitu ekspresi gen (kanser payudara, paru-paru, dan kulit) dan laluan biologi. Prestasi pengkelasan dari segi ketepatan dan luas di bawah lengkung berasaskan penerima operasi sifat yang dapat dicapai oleh kaedah yang dicadangkan ini telah diukur dan dibandingkan. Dapatan kajian menunjukkan bahawa kaedah yang dicadangkan dapat mengenalpasti senarai penanda laluan dan gen dengan ketepatan pengkelasan dan AUC yang lebih baik. Kaedah yang dicadangkan telah meningkatkan prestasi pengelasan dalam julat antara 1% hingga 35% berbanding dengan kaedah lain. Kitaran sel dan laluan isyarat p53 telah didapati secara ketara berkaitan dengan kanser payudara, paru-paru, dan kulit, sementara kitaran sel diperkayakan dengan karsinoma sel skuamus dan adenokarsinoma.

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LIST OF ABBREVIATIONS

AC	-	Adenocarcinoma
AFS	-	ANOVA-based Feature Set
AGNES	-	Agglomerative Nesting
AHC	-	Agglomerative Hierarchical Clustering
ANOVA	-	Analysis of Variance
AUC	-	Area Under the Receiver Operating Characteristics Curve
AVA	-	All-Versus-All
CCND1	-	Cyclin D1
CePa	-	Centrality-Based Pathway Enrichment
CLARANS	-	Clustering Large Applications Based on Randomized Search
CLDN3	-	Claudin 3
CLIQUE	-	Clustering in Quest
DAVID	-	Database for Annotation, Visualization, and Integrated Discovery
DB	-	Davies and Bouldin
DBSCAN	-	Density-Based Spatial Clustering of Applications with Noise
DEGs	-	Differentially Expressed Genes
DIANA	-	Divisive Analysis
DRW	-	Directed Random Walk
dwgLASSO	-	Differentially Weighted Graphical Least Absolute Shrinkage and Selection Operator
ECOC	-	Error Correcting Output Codes

eDRW+	-	An Enhanced Directed Random Walk
ERBB2	-	Receptor Tyrosine-Protein Kinase Erythroblastic Oncogene B-2
ESEA	-	Edge Set Enrichment Analysis
expO	-	Expression Project for Oncology
FCM	-	Fuzzy C Means
FCS	-	Functional Class Scoring
GANPA	-	Network-based Gene Weights
GAT	-	Gene-Set Activity Toolbox
GCHL	-	Grid-Clustering Technique for High-Dimensional and Large Spatial Databases
GCS	-	Gene Expression Change Score
GEO	-	Gene Expression Omnibus
GO	-	Gene Ontology
GRIDEN	-	Grid-based and Density-based Spatial Clustering
GRPDBCAN	-	Grid-based DBSCAN Technique with Referential Parameters
GWAS	-	Genome-Wide Association Studies
HCI	-	High-order Correlation Integration
HPRD	-	Human Protein Reference Database
ID	-	Identifier
K-NN	-	K-Nearest Neighbours
KEGG	-	Kyoto Encyclopaedia of Genes and Genomes
LCC	-	Large Cell Carcinoma
MCWalk	-	Monte Carlo Simulations with Directed Random Walk

MSE	-	Mean Square Error
NCFS	-	Negatively Correlated Feature Sets
NCFS-CORG	-	Negatively Correlated Feature Sets with Condition-Responsive Genes
NCFS-i	-	Negatively Correlated Feature Sets with Ideal Markers
NSCLC	-	Non-Small Cell Lung Cancer
OMIM	-	Online Mendelian Inheritance in Man
ORA	-	Overrepresentation Analysis
OVA	-	One-Versus-All
OVO	-	One-Versus-One
PAM	-	Partitioning Around Medoids
PARADIGM	-	Pathway Recognition Algorithm using Data Integration on Genomic Models
PCA	-	Principal Component Analysis
PCC	-	Pearson Correlation Coefficients
PerPAS	-	Personalized Pathway Alteration Analysis
PMIDs	-	PubMed Identifiers
RMA	-	Robust Multichip Average
ROC	-	Receiver Operating Characteristic
RRFE	-	Reweighted Recursive Feature Elimination
SAM	-	Significance Analysis of Microarray
SCC	-	Squamous Cell Carcinoma
skeDRW+	-	Integration of K-Means Clustering and Average Silhouette Method into Enhanced Directed Random Walk
SOM	-	Self-Organizing Maps
SPIA	-	Signalling Pathway Impact Analysis

STING	-	Statistical Information Grid
SVM	-	Support Vector Machine
SVM-RFE	-	Support Vector Machine-Recursive Feature Elimination
TP53	-	Tumor protein p53
TPEA	-	Topology-Based Pathway Enrichment Analysis
UTM	-	Universiti Teknologi Malaysia
VIF	-	Variance Inflation Factor
Weighted-SAMGSR	-	Weighted-Significance Analysis of Microarray-Gene Set Reduction
WEKA	-	Waikato Environment for Knowledge Analysis
wgLASSO	-	Weighted Graphical Least Absolute Shrinkage and Selection Operator
WHO	-	World Health Organization

LIST OF SYMBOLS

$absolute\ F_{test}$	-	Absolute Values of F-test statistic
C	-	Row-Normalized Adjacency Matrix of the Selected Gene Clusters with Silhouette Width Values in the range of 0 and 1
$F_{test}(g_i)$	-	F-test statistics of Gene i from One-Way ANOVA on Expression Values between Multiple Classes of Samples
$F_{test}(P)$	-	F-test statistics of P from One-Way ANOVA on Pathway Activities between Multiple Classes of Samples
$gene$	-	Gene Expression Values for Gene over All the Samples
$maximum\ F_{test}$	-	Maximum Values of F-test statistic
$\bar{X}$	-	Mean of Gene Expression Values for Gene
$minimum\ F_{test}$	-	Minimum Values of F-test statistic
M^T	-	Row-Normalized Adjacency Matrix of a Directed Graph
P_j	-	Pathway Activity in Row j
r	-	Restart Probability
$sgn()$	-	Sign Function
S	-	Standard Deviation of Gene Expression Values for Gene

W_0	-	Initial Weight of Gene
W_t	-	A vector that Holds the Probability at the Specific Node at Time Step t
W_∞	-	Weight of Gene
$\lvert X'X \rvert$	-	Determinant
$z(g_i)$	-	Normalized Gene Expression Values for Gene over All the Samples

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CHAPTER 1

INTRODUCTION

1.1 Introduction

Cancer is caused by cells which grow uncontrollably (Makropoulou, 2016). This disease is associated with abnormal alterations that lead to the dysregulation of the cellular system (Vaske *et al.*, 2010). According to the report of World Health Organization (WHO) in 2012, cancer contributes to approximately 14 million new cases and 8.2 million deaths. Bioinformatics develops computational methods to understand the molecular basis of disease (Napier and Limogiannis, 2016). The improved understanding of molecular biology and cellular biology has led to new cancer treatments since Richard Nixon (United States President) declared the "War on Cancer" in 1971. The cancer death rate was then declined by five percent between 1950 and 2005. Accurate classification of diseases and treatment responses is helpful in clinical and cancer research (Vaske *et al.*, 2010; Liu *et al.*, 2013a; Mohapatra *et al.*, 2016). The classification can identify groups of patients who share similar clinical features (characteristics) for the identification and implementation of suitable treatment (Macher and Crocq, 2004). Integrating pathway and topology information into microarray analysis can reduce the complexity of analysis from thousands of genes to a few hundreds of pathways (AlAjlan and Badr, 2015). This analysis is also aimed to identify more robust cancer markers to the disease of interest (Shi *et al.*, 2018).

1.2 Problem Background

Figure 1.1 presented an overview of the computational method to use in cancer classification. The common problem of cancer classification is the nature of cancer datasets, which have thousands of genes and characterized by small sample sizes based on different conditions (Su *et al.*, 2010; Jia *et al.*, 2011). In the literature, the use of microarray is different from macroarray, especially in term of probe density. Microarray contained a higher number of probes and such higher density of probes than macroarray (Vrana *et al.*, 2003). Macroarray was unique because it used radioactive target labelling for detection (Gammill and Lee, 2008). Since each picked clone must be sequenced to identify its identity, macroarray poorly annotated for potential novel genes. In the field of bioinformatics, microarray analysis is useful to measure the change of gene expression level in cancer datasets (Grewal and Das, 2013; Rajkumar *et al.*, 2013; Chandra and Babu, 2014). It is insufficient to use gene expression data only for microarray analysis, such as principal component analysis (PCA) in combination with agglomerative hierarchical clustering (AHC), mean-centering and magnitude normalization (Yasrebi *et al.*, 2009; Karn *et al.*, 2010).

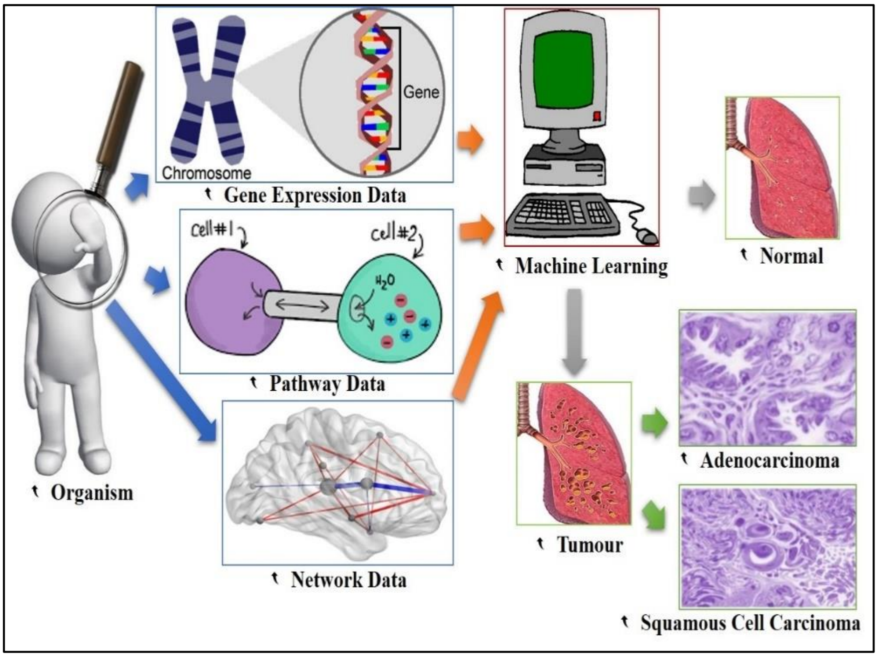


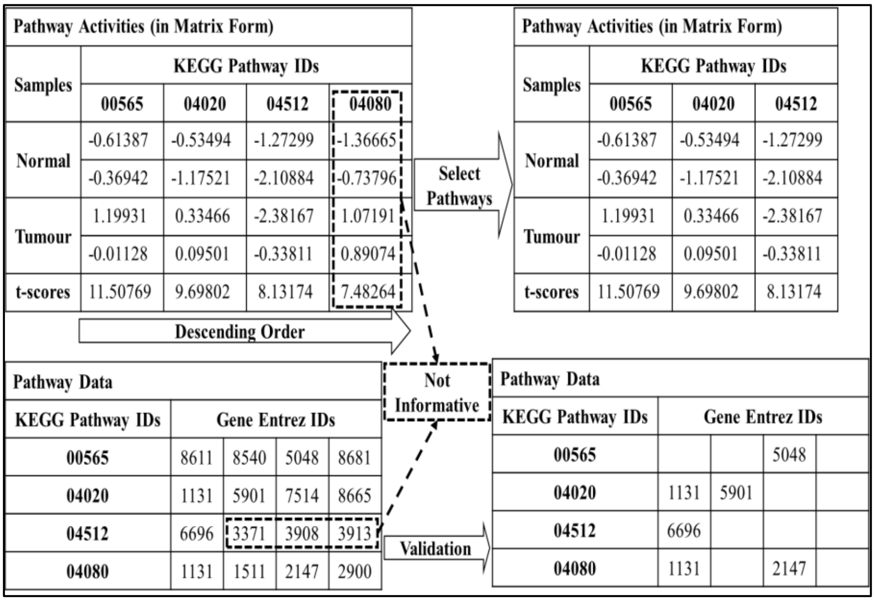
Figure 1.1 An overview of the pathway topology-based microarray analysis.

Pathway topology-based microarray analysis (e.g., Directed Random Walk [DRW]) is one of the categories for pathway-based microarray analysis, which can map genes on the precompiled pathways to visualize the whole chain of events in gene expression data (Grewal and Das, 2013). Since pathway topology-based microarray analysis can interpret pathways from the gene expression levels, pathway marker was more reliable than gene marker. The pathways were functionally related to the specified member genes with similar molecular mechanisms based on cancer subtypes (Zhao *et al.*, 2011; Hung and Chiu, 2017). Since tumour profiling of patients annotated in clinical practice, cancer markers were potentially further studied for new drug development and decision making in oncology to increase cancer survival (Wang *et al.*, 2015). DRW used weighting strategy to create weights for each gene in the directed graph based on the pathway knowledge to infer a higher reproducibility power of pathway activity (Liu *et al*., 2013a; Tian *et al.*, 2016). This method can reduce the effect of noise measurements and a correlation between genes in the same pathway (Su *et al.*, 2010). Besides, restart probability ($r = 0.7$) was the only parameter of DRW to characterize the level of strongly connected genes (e.g., a neighbourhood can be influenced by a seed gene to its neighbour gene) in the directed graph (Liu *et al*., 2013a; Wang *et al.*, 2017). The process of DRW with restart probability was iterated until all genes were visited.

In general, pathway activity is the formation of gene expression data and pathway data (with directed graph) by pathway topology-based microarray analysis. The analysis of the directed graph can reflect the functional robustness of topology in vital biochemical processes (Zhao *et al*., 2011; Roy *et al*., 2019). All the pathways used in the research were converted to a directed graph using *SubpathwayMiner* in R software package and its information was retrieved from the pathway database (e.g., Kyoto Encyclopaedia of Genes and Genomes [KEGG]) (Liu *et al*., 2013a; Dimitrakopoulos and Beerenwinkel, 2017). The topological information of the directed graph included types of interaction between two genes (direction of the edges), the weight of genes, and such position of genes. The interaction types between two genes showed how the two genes interacted and regulated each other in the processes of inhibition or activation.

The most common cancer deaths are caused in lung, breast, liver, colon, oesophagus, and stomach. Breast cancer is the most common cancer in women across every single ethnic group in Malaysia (Beshir and Hanipah, 2012; Nies *et al.*, 2017b). The breast cancer molecular subtypes are luminal A, luminal B, basal, ERBB2, and normal. The main subtypes of lung cancer are adenocarcinoma, large cell carcinoma, and squamous cell carcinoma. Some existing methods of pathway-based microarray analysis are restricted to classify the datasets between normal and tumour samples with the use of t-test, such as negatively correlated feature sets with ideal markers (NCFS-i), negatively correlated feature sets with condition-responsive genes (NCFS-CORG), and DRW (Chan *et al.*, 2011; Chandra and Gupta, 2011; Sootanan *et al.*, 2011; Liu *et al.*, 2013a; Yang *et al.*, 2014; Phongwattana *et al.*, 2015; Ross and Willson, 2017). Besides, some methods modify t-test and ANOVA to deal with multiclass issues, such as weighted-significance analysis of microarray-gene set reduction (Weighted-SAMGSR), negatively correlated feature sets (NCFS), gene-set activity toolbox, and ANOVA-based feature set (AFS) (Chen *et al.*, 2005; Engchuan and Chan, 2012, 2015; Engchuan *et al.*, 2016; Kar *et al.*, 2016; Tian *et al.*, 2016; Ortiz-Ramón *et al.*, 2018). Multiclass classification methods can be divided into two types. First, this involves extending the binary classification to deal with the multiclass problems directly (Li *et al.*, 2004; Ferdowsi *et al.*, 2014). Another type involves decomposing multiclass issues into binary problems. One-versus-one and one-versus-the-rest are common strategies for dealing with multiclass problems, but some are not extensible to multiclass approaches (Gu *et al.*, 2014; Ferdowsi *et al.*, 2014). To date, recent medical studies reported the necessity to diagnose more than two classes of disease (Engchuan and Chan, 2012, 2015; Yang and Naiman, 2014; Yang *et al.*, 2014). Clinical experiments can produce multiclass gene expression data in the detection of tumours based on their stage, grade, survival time, and drug sensitivity that are further studied for cancer treatments (Yang and Naiman, 2014; Wang *et al.*, 2015). For example, stages of such disease depend on the thickness of tumour at the time of surgical treatment.

Several studies in pathway-based microarray analysis do not select pathways, including DRW. Since pathways were commonly curated from the literature, non-informative genes can be included and affect the accuracy of the methods (Evangeline *et al.*, 2013; Zhe *et al.*, 2013; Creixell *et al.*, 2015; Li *et al.*, 2017). If a gene (e.g., tumor protein p53) is chosen, all the pathways (e.g., cell cycle and MAPK signaling pathway) consist of such gene will also be selected. Figure 1.2 illustrated the presence of non-informative genes in a pathway. Pathway selection can reduce the dimension and select informative pathways in all the examples (Zhe *et al.*, 2013; Gu *et al.*, 2014). With cases of existing methods performed pathway selection using t-test and Fisher-test, such as redundancy removable pathway-based feature selection method and the network and node selection approach.



Pathway Activities (in Matrix Form)

Samples	KEGG Pathway IDs			
	00565	04020	04512	04080
Normal	-0.61387	-0.53494	-1.27299	-1.36665
	-0.36942	-1.17521	-2.10884	-0.73796
Tumour	1.19931	0.33466	-2.38167	1.07191
	-0.01128	0.09501	-0.33811	0.89074
t-scores	11.50769	9.69802	8.13174	7.48264

Pathway Activities (in Matrix Form)

Samples	KEGG Pathway IDs		
	00565	04020	04512
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	-0.01128	0.09501	-0.33811
t-scores	11.50769	9.69802	8.13174

Pathway Data

KEGG Pathway IDs	Gene Entrez IDs			
00565	8611	8540	5048	8681
04020	1131	5901	7514	8665
04512	6696	3371	3908	3913
04080	1131	1511	2147	2900

Pathway Data

KEGG Pathway IDs	Gene Entrez IDs			
00565			5048	
04020	1131	5901		
04512	6696			
04080	1131		2147	

Figure 1.2 The presence of non-informative genes in a pathway.

In literature, random walk used the theory of Markov chain to rank genes from high to low probabilities, but it extracted local information from a large graph without knowledge of the whole graph data (Liu *et al.*, 2013a, 2017b; Liu *et al.*, 2015b; Zhang *et al.*, 2016; Dimitrakopoulos and Beerenwinkel, 2017; Wang and Liu, 2018; Peng *et al.*, 2019). Hence, a large directed graph can include non-informative genes, which can result in low accuracy of the methods (Evangeline *et al.*, 2013; Peng *et al.*, 2019). Besides, DRW used the theory of random walk to identify the genes having similar structural properties of networks (Re and Valentini, 2012; Petrochilos *et al.*, 2013). However, most methods (including DRW) ignored the interaction between multiple genes in a directed graph and the genes with missing edges (Madhukar *et al.*, 2015; Liu *et al.*, 2017a). Figure 1.3 illustrated the common neighbour and non-informative genes in a directed graph. A gene was important (e.g., gene Entrez ID 5901) if it interacted with many other genes (Zhu *et al.*, 2018).

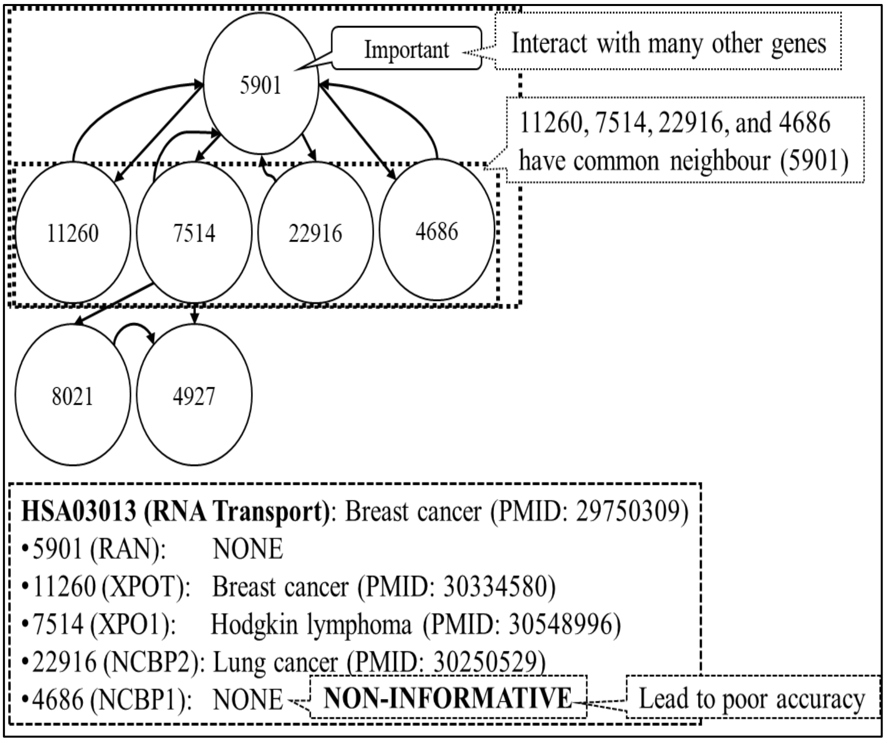
5901
Important
Interact with many other genes
11260, 7514, 22916, and 4686 have common neighbour (5901)
11260
7514
22916
4686
8021
4927
HSA03013 (RNA Transport): Breast cancer (PMID: 29750309)
•5901 (RAN): NONE
•11260 (XPOT): Breast cancer (PMID: 30334580)
•7514 (XPO1): Hodgkin lymphoma (PMID: 30548996)
•22916 (NCBP2): Lung cancer (PMID: 30250529)
•4686 (NCBP1): NONE
NON-INFORMATIVE
Lead to poor accuracy

Figure 1.3 The presence of common neighbour and non-informative genes in a directed graph.

Several previous studies have noted the importance of clustering to identify co-expressed genes in a cluster and inactive genes in another cluster (Mehmood *et al.*, 2018; Chandra and Tripathi, 2019). Clustering can also discover the fundamental hidden structure of biomedical data and identify cancer subtypes that used for diagnosis and treatments. DRW is also one of the density-based clustering techniques, but it has a high runtime analysis to detect clusters (Deng *et al.*, 2018b). Detection of clusters using partitioning clustering has low time complexity and high computing efficiency, which can solve the issue above (Xu and Tian, 2015). Researchers focused on partitioning clustering techniques (e.g., k-means clustering) by assuming the number of clusters beforehand, which can lead to the poor quality of clusters (Bajo *et al.*, 2010; Wang *et al.*, 2018a; Majhi and Biswal, 2019).

1.3 Problem Statements

Pathway topology-based microarray analysis used pathway data, directed graph, and gene expression data to identify pathway and gene markers in cancer classification. However, most existing techniques analyse the datasets by grouping different cancer subtypes into disease sample only. All the pathways consisted of the specified gene were selected and considered these pathways equally. Several current methods ignore the genes with missing edges and the interaction between multiple genes. All the issues can lead to low accuracy and large-scale variation in weight vectors. Partitioning clustering techniques are useful to detect clusters, but it can lead to poor quality of clustering by assuming to initialize the number of potential clusters beforehand.

The main research question of this research is:

How to identify pathway and gene markers for multiclass cancer expression data in order to improve the use of weight strategy in pathway topology-based microarray analysis?

Thus, the following issues will be considered to solve the problem:

- *How to identify pathway markers between multiple classes of samples in order to improve the weight of genes?*

- *How to identify pathway markers from all the pathways and increase the accuracy of the method for multiclass cancer expression data?*

- *How to identify the number of potential clusters needed to initialize for k-means clustering technique in order to improve the quality of clustering?*

- *How to integrate k-means clustering and average silhouette method into the method in the directed graph for identifying gene markers for multiclass cancer expression data?*

1.4 Research Goal

The goal of the research is to propose enhanced directed random walk with improved use of weight strategy in topology-based microarray analysis and consideration of the interaction between genes for identification of pathway and gene markers from multiclass cancer expression data.

1.5 Research Objectives

The objectives of the research are:

- To propose an enhanced directed random walk method (eDRW+) for identification of pathway markers from multiclass cancer expression data to improve the use of weight strategy and pathway selection based on the greatest reproducibility power.
- To propose skeDRW+ based on the integration of k-means clustering and average silhouette method into eDRW+ for identification of gene markers from multiclass cancer expression data in order to improve the quality of clustering.
- To biologically validate pathway and gene markers using PubMed text data mining and functional enrichment analysis in pathway data, directed graph, and gene expression data.

1.6 Research Scopes

This research focuses on the identification of cancer markers and emphasizes the issues of pathway topology-based microarray analysis. This research also aims to improve the weight of genes and improve the quality of clustering for identifying similar biological functions of genes. Figure 1.4 illustrated the flow of the research from bioinformatics to the discovery of cancer markers.

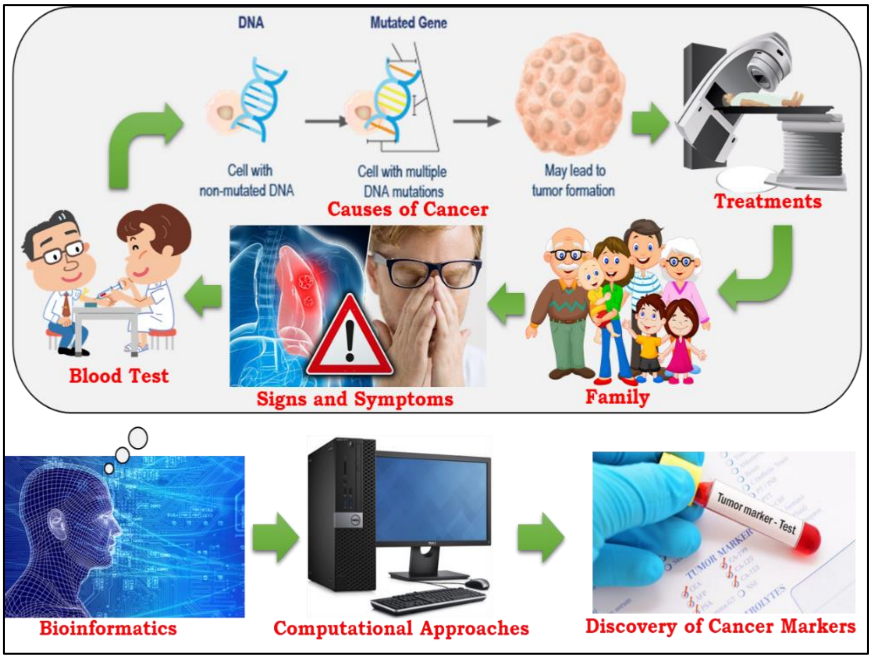

Figure 1.4 The flow of the research from bioinformatics to the discovery of cancer markers.

The following points are the research scopes:

- According to the research focus, three components constitute the scopes of the research. The research investigates *directed random walk method (DRW)* [WHAT] as pathway topology-based method in identifying pathway and gene markers for *multiclass cancer expression data* [WHERE] in order to improve *survival and quality of life* [WHY]. The cancer markers can identify drug targets and look for cancer subtypes with clinically distinct outcomes.

- This research uses gene expression data (lung, breast, and skin cancers), pathway data (metabolic and non-metabolic pathways), and directed graph.

- The development of the proposed methods is implemented in the R platform with version 3.3.3.

- The performance of this research is measured in a stratified ten-fold cross-validation, which was mostly used in previous works. The experimental results are compared in terms of area under the receiver operating characteristics curve (AUC) and accuracy (%) to justify the performance improvement.

- The identified pathways and genes are biologically validated using PubMed text data mining and functional enrichment analysis to show the relationship between pathways, genes, and cancers.

1.7 Research Significances

This research is considered significant as it tends to identify pathway and gene markers for multiclass cancer expression data using pathway topology-based microarray analysis. This method used multiple data types to infer a greater reproducibility power of pathway activity with higher classification accuracy. There is a need to classify the datasets into multiple classes of samples, which can deal with grouping different cancer subtypes into disease sample only. The use of pathway data can help to study molecular mechanisms based on cancer subtypes. Pathway selection can identify more pathway markers, although the non-informative genes included in the pathways. To increase the efficiency of identifying gene markers and improve the weight of genes in the directed graph, partitioning clustering and optimization techniques integrated into pathway topology-based microarray analysis can reduce the variation in weight vectors and improve its quality during initialization of the intended cluster number. Furthermore, the identified pathway and gene markers can be further used in new drug development and clinical implications for cancers. It can also help patients having early detection and diagnosis.

1.8 Thesis Organization

This thesis is organized into six chapters. The flow of the following chapters is presented as follows. Chapter 2 aims to describe some basic knowledge related to this research. This chapter also includes reviewing some preliminary collections of present works done in previous studies related to this research area. Chapter 3 aims to discuss the details of the research methodology employed in this research. The research framework is explained in this chapter to achieve the goal and objectives of the research. This chapter also includes input data, a summary of the proposed methods, software and hardware requirements used in this research. Performance measurements are also explained in this chapter to evaluate and compare among the methods. Chapter 4 aims to present the proposed methods, eDRW+ and skeDRW+, in identifying pathway and gene markers for multiclass cancer expression data. Chapter 5 aims to present and discuss the experimental results generated by eDRW+ and skeDRW+. Chapter 6 aims to conclude the findings, contribution, and suggestions for future works in this research.

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LIST OF PUBLICATIONS

Journal with Impact Factor

1. **Nies, H. W.,** Zakaria, Z., Mohamad, M. S., Chan, W. H., Zaki, N., Sinnott, R. O., Napis, S., Chamoso, P., Omatu, S. and Corchado, J. M. (2019). A Review of Computational Methods for Clustering Genes with Similar Biological Functions. *Processes*, *7*(9), 550. **(Q2, IF:1.963)**
2. **Nies, H. W.**, Zakaria, Z., Mohamad, M. S., Chan, W. H., Zaki, N., and Ibrahim, Z. **(under review).** An Enhanced Directed Random Walk Method to Identify Pathway and Gene Markers for Multiclass Breast Cancer Expression Data. *Computer Methods and Programs in Biomedicine*. **(Q1, IF: 3.424)**

Indexed Conference Proceedings

1. **Nies, H. W.**, Mohd Daud, K., Remli, M. A., Mohamad, M. S., Deris, S., Omatu, S., Kasim, S. and Sulong, G. (2017). Classification of Colorectal Cancer Using Clustering and Feature Selection Approaches. In *International Conference on Practical Applications of Computational Biology and Bioinformatics* (pp. 58-65). Springer, Cham. **(Indexed by SCOPUS)**
2. Remli, M. A., Daud, K. M., **Nies, H. W.**, Mohamad, M. S., Deris, S., Omatu, S., Kasim, S. and Sulong, G. (2017, June). K-means clustering with infinite feature selection for classification tasks in gene expression data. In *International Conference on Practical Applications of Computational Biology and Bioinformatic* (pp. 50-57). Springer, Cham. **(Indexed by SCOPUS)**

Non-Indexed Conference Proceedings

1. **Nies, H.W.**, Zakaria, Z., Mohamad, M.S., A. Samah, A., Chan, W. H., and Deris, S. (2018). Review on Pathway Topology-Based Microarray Analysis. In *7th International Graduate Conference on Engineering Science and Humanity 2018*.

3. **Nies, H.W.**, Zakaria, Z., Mohamad, M.S., A. Samah, A., Chan, W. H., and Deris, S., (2018). Review on Weighting Category of Pathway Topology-Based Microarray Analysis in Multiclass Classification. *UTM Computing Proceedings.*

Copyrights

1. **Nies, H. W.**, Zakaria, Z., Chan, W. H (2020). *Automation of PubMed Text Data Mining for Biological Validation of Genes and Pathways*. Universiti Teknologi Malaysia.

2. **Nies, H. W.**, Zakaria, Z., Chan, W. H (2020). *Integration of K-Means Clustering and Average Silhouette Method into Directed Random Walk to Increase the Efficiency of Identifying Informative Genes in the Directed Graph*. Universiti Teknologi Malaysia.

3. **Nies, H. W.**, Zakaria, Z., Chan, W. H (2020). *An Enhanced Directed Random Walk Method to Identify Informative Genes and Pathways from Multiclass Cancer Expression Data*. Universiti Teknologi Malaysia.