Toward Integrated Clinical and Gene- Expression Profiles For Breast Cancer Prognosis: A Review Paper

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Abstract

Breast cancer patients with the same diagnostic and clinical prognostics profile can have markedly different clinical outcomes. This difference is possibly caused by the limitation of current breast cancer prognostic indices, which group molecularly distinct patients into similar clinical classes based mainly on the morphology of diseases. Traditional clinical-based prognosis models were discovered to contain some restrictions to address the heterogeneity of breast cancer. The invention of microarray technology and its ability to simultaneously interrogate thousands of genes has changed the paradigm of molecular classification of human cancers as well as shifting clinical prognosis models to a broader prospect. Numerous studies have revealed the potential value of gene-expression signatures in examining the risk of disease recurrence. However, most of these studies attempted to implement genetic-marker based prognostic models to replace the traditional clinical markers, yet neglecting the rich information contained in clinical information. Therefore, this research took the effort to integrate both clinical and microarray data in order to obtain accurate breast cancer prognosis, by taking into account that these data complement each other. This article presents a review of the development of breast cancer prognosis models, concentrating precisely on clinical and gene-expression profiles. The literature is reviewed in an explicit machine-learning framework, which includes the elements of feature selection and classification techniques.

Keywords: Breast cancer, Prognosis, Gene-Expression Profiles, Feature selection, Classification.

1. INTRODUCTION

Cancer is a class of disease or disorder characterized by the uncontrolled division of cells to spread, either by direct growth into adjacent tissues through invasion or by implantation into distant sites by metastasis. Breast cancer, on the other hand, has become a major cause of cancer-related morbidity and mortality among female worldwide and remains a major health burden. Although in previous years most of the researches were concerned about diagnosing breast cancer, it is only recently that cancer researchers have attempted to look at cancer prognosis. This idea actually is a part of a growing trend towards personalized and predictive medicine. Prognosis can be defined as (pro: before; gnoscere: to know) foreknowledge of an event before its possible occurrence [1]. There are three prognosis foci, which are cancer susceptibility, cancer recurrence and cancer survivability [2].

Cancer recurrence has been attracting a lot of attention from patients and physicians. The major clinical problem of breast cancer recurrence is by the time primary tumor was diagnosed, microscopic or clinically evident metastases have already occurred. Although breast cancer patients are prescribed various types of treatments such as chemotherapy, endocrine and radiation therapy or even go through surgery there is no assurance that metastases will never occur. Despite significant advances in cancer treatment, the ability to predict the metastases behavior of tumors still remains one of the greatest clinical challenges in the oncology field. Various studies have been conducted to predict breast cancer recurrence. Traditional cancer prognosis relies on a complex and inexact combination of clinical and histopathological data. Age, tumor size, estrogen and progesterone receptors, and lymph-node involvement are some of the clinical and histopathological factors used in the conversional prognosis method. These classic approaches, however, may fail when dealing with atypical tumors or morphologically-indistinguishable tumor subtypes. The cause of these incidents is breast cancer is an extensively heterogeneous disease, which is not only based on clinical information but also involves genes-cellular proliferations.

Advances in the area of microarray-based expression have led to the promise of cancer prognosis using new molecular-based approaches. It has become a standard tool in many genomic research laboratories. The reason for this popularity is that microarrays have revolutionized the approach of biology research. Instead of working on a single gene basis, scientists can now study thousand of genes at once. Unfortunately, microarray data are often overwhelmed, over-fitting and confused by the complexity of data analysis. Although many studies are trying to solve these issues, most results reported are data dependent. Moreover, it is noticed that clinical data are often underused and a lot more focus is given to microarray data. This paper attempts to review the classification techniques employed in clinical and microarray data as well as explore feature-selection techniques that have been applied in extracting significant gene signatures. In addition, related works that integrate both clinical and microarray data were reported, even though only a few studies had been conducted in this area. The aim of this review is to develop a breast cancer prognosis model that incorporates both clinical and gene-expression profiles data, which could enhance and accurately predict the outcome. Furthermore, it would assist physicians make informed decisions regarding the potential necessity of adjuvant treatment and consequently this could ultimately contribute to the decrease in overall breast cancer mortality.

The remainder of this paper is organized as follows. Section 2 briefly explains the breast cancer domain, differentiates between benign and malignant tumors and identifies current prognostic indices that are applied in classifying breast cancer patients. The discussion is followed by revealing the most dominant classification techniques in cancer prognosis using clinical data in section 3. DNA microarray technology and its complexities which are associated with microarray data analysis are discussed explicitly in section 4. Section 5, meanwhile, addresses the works that have been done in feature selection using microarray data, which can be divided into three main groups; univariate, wrapper and embedded approach. The discussions of classification techniques in microarray data analysis are compared and related works in integrating clinical and

gene-expression data are conveyed in section 6 and section 7 respectively. Subsequently, validation methods in estimating prediction errors for microarray data analysis are explained in section 8. Section 9 then reveals the trends and directions in prognosis models. Lastly, section 10 offers concluding remarks.

2. BREAST CANCER

Breast cancer is a neoplastic disease, where normal body cells can be transformed into malignant (cancerous) ones. It is the most common cancer in women worldwide and the second leading cause of morbidity after lung cancer among Malaysian women [3]. Breast cancer can be grouped into two different tumor types, benign and malignant tumors. These tumors are different from one another in such a way that benign tumors do not spread, but malignant tumors, as in breast cancer, are made up of cells that can spread to and damage other parts of the body through the lymphatic systems or invade adjacent tissues. The cancer spreading mechanism can happen in three stages; local, where the cancer is confined to the breast or certain parts, which means the lymph nodes, primarily those in the armpits are involved. It is also possible cancers are found in other parts of the body, known as distant spreading.

The guidelines for early detection of breast cancer include breast self–exams (BSE), clinical breast examination (CBE) and screening mammogram [4]. BSE is a visual and manual examination of the breast that can be easily carried out by women, while CBE is the physical examination of the breast conducted by a trained medical or health professional. On the other hand, screening mammography is the most common imaging procedure for diagnosing breast cancer usually among women who are asymptomatic (have no complaints or symptoms of breast cancer). The goal of screening mammogram is to detect cancer when it is still too small to be felt by a woman or her physician. In order to determine whether an area of concern in a breast (found by BSE, CBE, or screening mammogram) is malignant (cancerous) or benign (not cancerous), a physician may perform a biopsy test. A breast biopsy is the removal of a sample of breast tissue for laboratory examination by a pathologist and is the only definitive way to determine if an abnormality is cancerous or not. Moreover, the biopsy result also indicates the cancerous stage as well as the appropriate treatments to be prescribed.

Despite the advance in diagnosis, breast cancer prediction remains a challenging task to physicians and patients. Currently, four prognostic indices are used to predict breast cancer patients, which include TNM Classification of Malignant Tumors (TNM), the National Institute of Health (NIH), the St. Gallen criteria and the Nottingham Prognostic Index (NPI) [5]. However, these cancer classifications have been based primarily on the morphological appearance of the tumor and have serious limitations. Tumors with similar histopathological appearances can follow significantly different clinical courses and show different responses to therapy. It is estimated that 70% of patients receiving chemotherapy or hormone therapy would have survived without them [6]. Nevertheless, many patients do not respond to specific treatments such as tamoxifen, which is a standard adjuvant treatment for patients with primary estrogen receptor-positive breast cancer [7]. This phenomenon proves that physicians have difficulties in deciding the appropriate treatments, which may lead to unnecessary adjuvant treatments, associated risks and expensive medical costs, whereas patients are more aware and demand for treatment that could improve the quality of life.

3. CLASSIFICATION TECHNIQUES IN CANCER PROGNOSIS USING CLINICAL DATA

Prognosis plays an important role in patient management tasks like treatment planning as well as evaluating the quality of health and the consequences of disease progression. Approaches to develop prognosis models vary from using traditional probabilistic techniques, obtained from the field of statistics, to more qualitative and model-based techniques, originating from artificial intelligence (AI). In the last decade, most of the prognosis models were based on regression

analysis such as the proportional hazard model and the Kaplan-Meier Curve [8, 9]. The Kaplan-Meier Curve is a nonparametric analysis and usually has some problems due to confidence bounds, which is wider than those calculated via parametric analysis. As a result, predictions outside the range of observations are not possible. In 1994, Burke *et al*.[10], compared the performance of Artificial Neural Networks (ANN), Logistic Regression and Principal Component Analysis (PCA) with traditional staging system termed TNM staging system (primary tumor, regional lymph nodes and distant metastases) and the results showed that ANN was superior than other statistical methods. The results were later confirmed by Laurentiis *et al*.[11], Jerez-Aragones *et al*.[12] and Kates *et al*.[13]. The idea behind this finding was the ANN ability in adding a large number of parameters that could enhance the accuracy of the prognosis model.

ANN is an information processing paradigm that is inspired by the nervous system, such as the brain. The key element of this paradigm is the interconnected processing elements called neurons working in unison to solve specific problems. The learning mechanism in the ANN system involves adjustments to the synaptic connections that exist between the neurons. Moreover, the ANN methodology represents a useful alternative to classical modeling techniques when applied to variable data sets presenting non-linear relationships. Therefore, ANN has broadly used in implementing various cancer prognosis models [14-18] to address the problems of highly correlated prognostic factors and censored data handling. Although the ANN technique has dominated many cancer prognosis models, it suffers mainly from two problems; first the selection of architecture and the value of the parameter involved and second, understanding the underlying rules is impossible since it is a black box processing system.

In contrast to ANN, Decision Tree (DT) represents outputs as a set of symbolic rules. Formally a DT is structured in a graph or a flow chart of nodes which will be used to determine the ultimate goal. In the case of cancer prognosis, the aims of most researchers usually can be categorized into two distinct classes; i) decision support system [16, 19] (for example, the probability of survival, recurrence within 5 year interval time) or ii) identifying prognostic factors in cancers [20-22]. Although DT is easy to interpret and can handle various types of data including numeric, nominal, and categorical data, missing values for an attribute can lead to ambiguity in choosing the right branch. Moreover, it may generate too many rules, which make it hard to be understood. Concerned with the importance to provide rules clarification for determining cancer prognosis and addressing the limitation of DT, another type of technique called XCS was introduced in [23]. XCS is a type of learning classifier system that consists of a set of rules and procedures for performing and discovering patterns. Later, a new rule-driven compaction approach was employed to obtain a new piece of knowledge and the results exemplified that XCS outperformed DT.

Support Vector Machine (SVM) is another type of classification technique. The underlying concept in SVM algorithm is to create a hyperplane that separates the data into two classes within the maximum margin. Like ANN, SVM can be used to perform non-linear classification using non-linear kernel. Lee *et al*.[24] has applied SVM to extract prognostic factors and to classify breast cancer patients into 3 different classes; i) good prognosis\node-negative patients (patients with no metastasized lymph nodes), ii) intermediate prognosis\node-positive patients (patients with 1 to 4 metastasis lymph nodes) iii) poor prognosis\node-positive patients (patients with more than 4 metastasis lymph nodes). However, from the literature review, we found out that SVM is almost unfamiliar compared to ANN and DT in the field of cancer prognosis. The same conclusion was mentioned in [2]. Other technique such as k-nearest neighbor is also rarely applied in this domain.

In addition, several common clinical prognostic factors that frequently had been employed to predict breast cancer recurrence were noted. The common ones were; age, lymph-node involvement, tumor size, histological grade. The next section will describe the problems associated with DNA microarray data analysis in examining cancer prognosis.

4. DNA MICROARRAY AND COMPLEXITIES

Microarray offers an efficient method of gathering data that can be used to determine the expression pattern of thousands of genes. The mRNA expression pattern from different tissues in normal and diseases states could reveal which genes and environmental conditions can lead to disease.

The experimental steps of typical microarray began with extraction of mRNA from a tissues sample or probe. The mRNA is then labeled with fluorescent nucleotides, eventually yielding fluorescent (typically red) cDNA. The sample later is incubated with similarly processed cDNA reference (typically green). The labeled probe and reference are then mixed and applied to the surface of DNA microarrays, allowing fluorescent sequences in the probe-reference mix to attach to the cDNA adherent to the glass slide. The attraction of labeled cDNA from the probe and reference for a particular spot on microarray depends on the extent to which the sequences in the mix (probe-reference) complement the DNA affixed to the slide. A perfect compliment, in which a nucleotide sequence on a strand of cDNA exactly matches a DNA sequence affixed to the slide, is known as hybridization. Hybridization is the key element in microarray technology.

The populated microarray is then excited by a laser and the consequential fluorescent at each spot in the microarray is measured. If neither the probe nor the reference samples hybridize with the gene spotted on the slide, the spot will appear in the black color. However, if hybridization is predominantly with the probe, the spot will be in red (Cy5). Conversely, if hybridization is primarily between the reference and DNA affixed to the slide, the spot will fluoresce green (Cy3). The spot can also incandescent yellow, when cDNA from probe and reference samples hybridize equally at a given spot, indicating that they share the same number of complementary nucleotides in particular spot. The process of microarray experiment is illustrated in Figure 1.

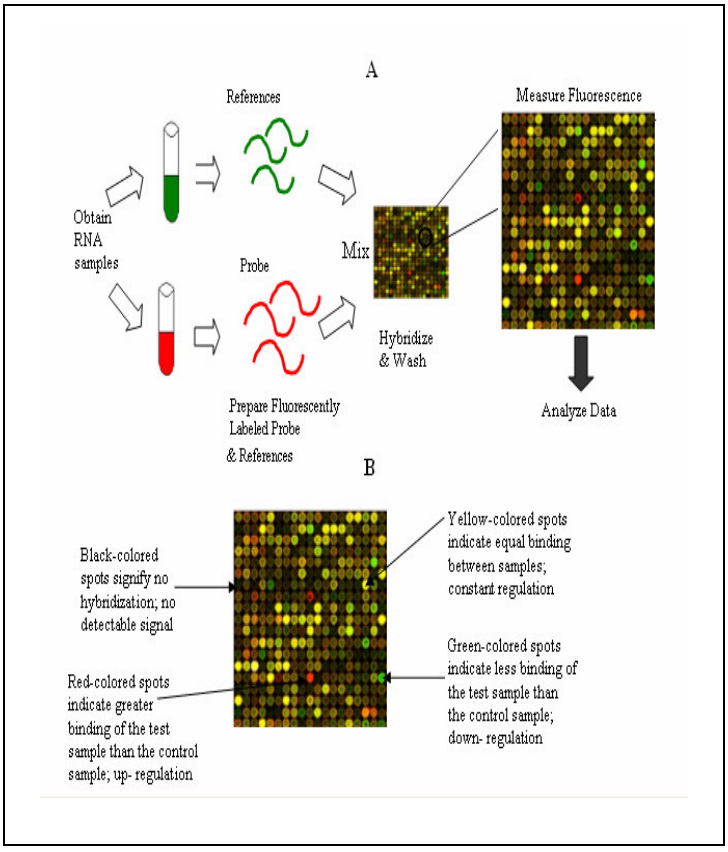

FIGURE 1: Microarray Experiment

Using image processing software, the red-to-green fluorescence will be digitized and providing the ratio values output indicating the expression of genes. Finally, the data of all samples are incorporated into one table constructing gene expression matrix G as shown in Figure 2. The rows of G correspond to single genes and the columns to single samples. Due to its high throughput nature, microarray data poses new challenges for data analysis. Computational approaches are generally necessary to divulge data structures. Although the type of analysis depends on the research questions posed, typical steps in the analysis of microarray data are; i) pre-processing and normalization, ii) detection of genes with significant fold changes, iii) classification and clustering of expression profiles. However, this paper will only focus on feature selection and classification techniques.

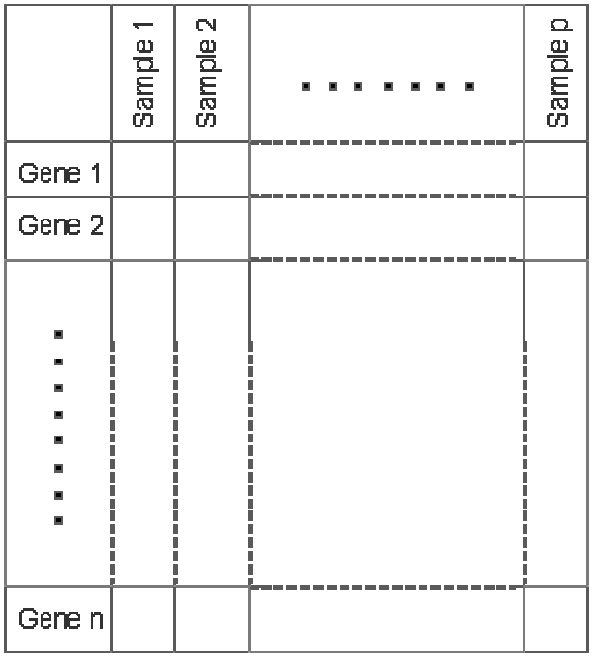

FIGURE 2: Gene Expression Matrix G

4.1 Microarray Data Analysis Problems

Although the invention of DNA microarray has opened a new opportunity to monitor thousands of genes simultaneously, there are many challenging problems in microarray data analysis that need to be addressed before new knowledge about gene expression can be revealed. Some of the problems are:

i. Bias and confounding problems, which occurred during the study-design phase of microarray which can lead to erroneous conclusion [25, 26]. Technical factors, such as differences in physical, batch of reagents used and various levels of skill in technicians could possibly cause bias. Confounding, on the other hand, takes place when another factor distorts the true relationship among the variables of interest.
ii. Cross-platform comparisons of gene-expression studies are difficult to conduct when microarrays are constructed using different standards. Thus, the results cannot be reproduced. To deal with this problem, Minimal Information About a Microarray Experiment (MIAME) [27] has been developed to improve reproducibility, sensitivity and robustness in gene-expression analysis.
iii. Microarray data is high dimensional data characterized by thousands of genes in a few sample sizes, which cause significant problems such as irrelevant and noise genes,

complexity in constructing classifiers, and multiple missing gene-expression values due to improper scanning. Moreover, most of the studies that applied microarray data suffered from data over-fitting, which required additional validation.

iv. Mislabeled data or questionable tissue results by experts are also other types of drawbacks that could decrease the accuracy of experimental results and lead to imprecise conclusions about gene-expression patterns [28].

v. Biological relevancy result is another integral criterion that should b taken into account in analyzing microarray data rather than only focusing on accuracy of cancer classification. Although there is no doubt in them gaining high accuracy, classification results are important in microarray data analysis. However, revealing biological information during the process of cancer classification is also essential. For instance, determination of genes that are under-expressed or over-expressed in cancerous cells could assist domain experts in designing and planning more appropriate treatments for cancer patients. Therefore, most of the domain experts are interested in classifiers that not only produce high classification accuracy but also reveal important biological information [29] .

5. FEATURE-SELECTION TECHNIQUES IN MICROARRAY DATA ANALYSIS

Feature-selection techniques, also known as gene-selection techniques have become a prerequisite in many large-scale gene-expression data analysis. The advance in genomic studies along with the exponential accumulation of microarray data has altered the feature-selection paradigm from being an optional to a compulsory need. It is because by cutting down the number of features to a sufficient minimum, classification performance can be improved. The taxonomy of dimensionality-reduction techniques can be divided into two categories; transformation or selection-based reduction. The key distinction made within the taxonomy is whether a dimensionality-reduction technique will transform or preserve the data set semantics in the process of reduction. Transformation-based reduction such as Principal Component Analysis (PCA) transforms the original features of a data set with a typically reduced number of uncorrelated ones, termed principal component. In contrast, selection-reduction techniques attempt to determine a minimal feature subset from a problem domain while retaining the meaning of the original feature sets. Thus, selection-based reduction techniques have become the main preference in many bioinformatics applications, especially microarray data analysis. This is due to its advantage of interpretability by a domain expert. The objectives of feature-selection techniques are various. The major ones are [30]:

i. To avoid over-fitting and improving model performance, for example, selecting highly informative genes could enhance the accuracy of the classification model.
ii. To provide faster and more cost-effective models, and
iii. To gain a deeper insight into the underlying processes that generated the data.

Although, feature-selection techniques have many benefits, it also introduces an extra complexity level, which requires a thoughtful experiment design to address the challenging tasks, yet provide fruitful results. Feature-selection methods can be structured into three factions; filter methods, wrapper methods and embedded methods. Filter methods rank each feature according to some univariate metric, and only the highest-ranking features are used while the remaining low-ranking features are eliminated. This method also relies on the general characteristics of the training data to select some features without involving any learning algorithm. Therefore, the results of the filter model will not affect any classification algorithm. Moreover, filter methods also provide very easy ways to calculate and can simplify large- scale microarray data sets since it only has a short running time.

Univariate filter methods such as Bayesian Network [31], Information Gain (IG), Signal-to-Ratio (SNR) [32-35] and Euclidean Distance [33, 34], have been extensively used in microarray data to identify informative genes. Information Gain has been reported to be the superior gene-selection technique by Cho et al. and Hu et al. [33, 36]. However, different types of univariate techniques

appear to be significant when they are trained over various data sets. Bayesian Networks, on the other hand appear to be the ideal platform for the integration of heterogeneous sources of information [37]. Besides the application of parametric techniques in determining informative genes from microarray data, Ben Dor *et al.*[38], Barash *et al.* [39] and Rogers *et al.* [40] had applied non-parametric techniques such as the threshold number of misclassification or TNoM score. This technique basically separates the informative gene by assigning a threshold value. However, it is hard to determine the most appropriate threshold. Other non-parametric techniques such as Pearson correlation coefficient [33, 34] and Significant Analysis of Microarray (SAM) [41] have been reported to be top feature-selection techniques.

Univariate filter methods have been widely utilized in microarray data analysis. This trend can be clarified by a number of reasons, for instance, the output or the result provided by univariate gene rankings are intuitive and easy to understand. These simplified versions of output could fulfill the aims and expectations of biology and molecular-domain experts who demand for validation of results using laboratory techniques. In addition, filter methods also offer less computational time to generate results which is an extra point to be preferred by domain experts. However, gene-ranking based on univariate methods has some drawbacks. The major one is the genes selected are most probably redundant. This means highly-ranked genes may carry similar discriminative information toward the defined class. Although we eliminate one high-ranked gene it may not cause any degradation of classification accuracy.

Since univariate filter methods do not count the relationship between genes, Koller and Sahami [42] developed an optimal gene-selection method called Markov Blanket Filtering, which can remove redundant genes to eliminate this problem. Based on this method, Yu and Liu [43] proposed the Redundancy Based Filter (RBF) method to deal with redundant problems and the results are quite promising. While the filter techniques handle the identification of genes independently, the wrapper method embeds a gene-selection method within a classification algorithm. In the wrapper methods [44] the search is conducted in the space of genes, evaluating the goodness of each found gene subset by the estimation of the percentage of accuracy of the specific classifier to be used, training the classifier only with the found genes. The wrapper approach, which is very popular in machine-learning applications, is not comprehensively used in DNA microarray tasks and only few works in the field make use of it [45, 46]. It is claimed by many authors [45, 47] that the wrapper approach obtains better predictive accuracy estimates than the filter approach. However, its computational cost must be taken into account. Wrapper methods can be divided into distinct groups; deterministic and randomized-search algorithm. Genetic Algorithm (GA) is a randomized-search algorithm and optimizes the mimicking of evolution and natural genetics. It has been employed for binary and multi-class cancer discrimination studies [48, 49]. A common drawback of wrapper methods, such as GA, is that they have a higher risk of over-fitting than filter techniques and are very computationally intensive. In contrast, wrapper methods incorporate the interaction between gene selection and classification model, which make them unique compared to filter techniques.

The third class of feature-selection approaches is embedded methods. The difference of embedded methods with other feature-selection methods is the search mechanism is built into the classifier model. Identical to wrapper methods, embedded methods are therefore, specific to a given learning algorithm. Embedded methods have the advantage in that they include the interaction with the classification model, while at the same time being far less computationally intensive than wrapper methods. Choosing an appropriate feature-selection technique is essential in obtaining accurate and precise results. The next section will describe, in detail, the classification techniques that have been applied in microarray data analysis.

6. CLASSIFICATION TECHNIQUES IN MICROARRAY DATA ANALYSIS

The development of microarray, based high throughout gene profiling, has led to the promising endeavor to classify tumors with an accurate and efficient means for predicting prognosis as well

as providing effective treatments. Many researchers have been studying problems associated with cancer classification using different gene-expression profiles data and attempting to propose the optimal classification technique to solve these problems. Several machine-learning techniques were previously used in classifying gene-expression data, including Fisher Linear Discriminant Analysis [51], k-Nearest Neighbor [49],[33],[41], Decision Tree, Multi-layer Perceptron [52, 53], Support Vector Machine [28],[54], Boosting [38], and Self-Organizing Map [35]. However, there is no single classifier that is superior over the rest, since the performances of classifiers also depend on gene-selection methods and the size of the data sets employed. Moreover, some of the methods only work well on binary-class problems and are not extensible to multi-class problems, while others are more general and flexible.

K-Nearest Neighbor is a non-parametric classifier that classifies the expression values of each gene based on the majority voting. It has been extensively used in microarray data analysis due to it robust characteristic to noisy and enormous training data and has been one of the first choices for a classification study when there is little or no prior knowledge about whether the distribution of the data is available [33, 41, 49, 55, 56]. Utilized as binary categorical classifiers, kNN has been noted to be a prominent technique in order to identify a subset of predictive genes from large noisy data [33, 49], which has been tested over the same three benchmark data sets; colon, leukemia and lymphoma data. However, these studies showed some diversity in results, which is basically due to different types of feature-selection methods and the choice of distance functions used in such as Euclidean Distance, Manhattan, and Pearson. Although kNN is reported as a known technique for classification, the main drawback of this technique is due to its non–scalability restriction, which is computationally intensive for large data sets. Therefore, this technique may be inappropriate to be used in cancer classification since the availability of gene-expression data sets probably increase and it requires too much computational time, unless prior efficient gene selection is done. In addition, the choice of the number of neighbors (k) is also another problem that needs to be taken into account [57].

Unlike kNN, Support Vector Machine (SVM) is scalable. SVM was introduced by Vapnik [58, 59] and successively extended by many other researchers. The fundamental idea behind this classifier can be viewed as a process of finding a max-margin hyperplane that separates the training tuples into different groups according to their corresponding classes. SVM's remarkable robust performance with respect to sparse and noisy data makes it preferable in a number of applications, especially in microarray data analysis, whether in binary or multi-class cancer classification [28, 33, 34, 38, 48, 54, 60]. Furey *et al.* [28] has applied SVM linear kernel with a signal-to-ratio feature-selection technique on colon, leukemia and ovarian data sets. Their results demonstrated that SVM not only can accurately classify new samples, but also assist in the identification of mislabeled samples by experts. However, this classification is fragile with respect to SVM parameter settings. Softness of margin and the number of genes selected as input could affect the correctness of the classifying sample.

Ben Dor *et al.* [38] on the other hand attempted to evaluate SVM linear kernel and SVM quadratic kernel performance using the same data sets. The results gained using colon data set were found aligned with the finding of Furey *et al.* [28], which stated that SVM linear kernel work well compared to complex kernel. However, it was noticed to be contradictory in the leukemia data set. This inconsistency may be due to the amount of gene-expression values in the leukemia data set, which is enormous, compared to the colon data set. Therefore, more complex kernel was required to be applied. Linear SVM also reported to be the most successful classifier in the studies of Symons et al. and Al-Shalalfa et al. [61, 62] and has been shown to consistently outperform other classification approaches including kNN[48, 63].

It is also noted that in past years, researchers relied on a single classifier and gene-selection method to analyze gene-expression data. However, the trends then shifted to investigating the performance of several classifiers over a few selected gene-selection techniques as were being done by Cho and Won [33] and Hu *et al.* [34] but it has become apparent that no particular classifier works well over different data sets. The main drawback of the SVM classification

technique is, similar to kNN, it is computationally expensive, thus the run-time is long and slow. Moreover, it originally suited binary class problems. As a result multi-class SVM lately is being studied [48, 64] and is still an on-going research problem.

Artificial Neural Networks (ANN) is another classification technique that was used in analyzing microarray data sets. It can model and reveal complex relationships among inputs (gene-expression patterns) and outputs (class-decisions) exemplified or embedded in the training data through different structures, linear or non-linear transfer functions and adjustment of weight-connection between nodes. Although there is still considerable skepticism about ANN among statisticians and bioinformaticians due to its black box approach, ANN has been applied in a broad category of class-prediction problems especially by domain experts. Examples of ANN in gene-expression profiles classification can be seen in studies of Khan *et al.* [52] Peterson *et al.* [65], Ringner *et al.* [66], Tusch *et al.* [67], Wei *et al.* [68], Bevilacqua *et al.* [69] and Eden *et al.* [70], which discussed the parallelism that exists among different ANN and concluded that ANN does offer several advantages such as unified approaches for feature extraction and classification and flexible procedures for finding good, moderately non-linear solutions.

The Bayesian Network proposed by Pearl [71], is a graphical model that encodes probabilistic relationships among variables of interest with mathematically-grounded framework. This graphical model has been used widely in analyzing gene-expression data [72, 73]. Meanwhile, Huang *et al.* [74] and West *et al.*[75] have applied the Bayesian technique to classify gene-expression values which are associated with the lymph node and estrogen-receptor status for breast cancer patients. These studies showed that the prognosis of the lymph node and the estrogen-receptor status are important elements and significant factors in accurate prediction of disease course. The preference toward this technique relies on the structure of the model, which encodes dependencies among all variables, thus it readily handles situations where some data entries are missing. Moreover, Bayesian Network can be used to learn causal relationships, and hence can be used to gain understanding about a problem domain and to predict the consequences of intervention. In addition, it is an ideal representation for combining prior knowledge (which often comes in causal form) and data. However, the main limitation of this technique is its assumption of a linear dependency of a child node on its parents, which is unrealistic since most regulatory relationships between genes are highly non-linear.

Despite the success of classification techniques reported in past years, none of them are superior to others. Hence, it is more desirable to make a decision by combining the results of various expert classifiers rather than by depending on the result of only one classifier. Ensemble approaches lately have become an on going research area [76-78]. Liu *et al.* [79] attempted to propose a combinational feature-selection method in conjunction with ensemble neural networks. Three feature-selection methods was adopted, which consisted of the Ranksum test, PCA, clustering and t test and each gene-selection result was then presented as input into three neural networks. In contrast, Kim *et al.* [80] had selected seven correlation analysis of feature selections in combination with multi-layer perceptron (MLP), k-nearest neighbor (KNN), the support vector machine (SVM) and the structure adaptive self-organizing map system (SASOM). Although these studies analyzed gene-expression data from different angles, they proved to enhance generalization capability compared to the single classifier.

7. RELATED WORKS IN INTEGRATING CLINICAL GENE-EXPRESSION DATA

In spite of enormous work being done in analyzing clinical and gene-expression data, only a few studies have focused on integrating clinical and gene-expression data, although many researchers agreed that clinical and genetic markers do complement each other and improve the prediction accuracy compared to those made by using clinical or gene expression alone [2, 74, 81-85]. To our knowledge, initial efforts to combine these two different data was done by Futschik *et al.* [81] by constructing separate classifiers for microarray and clinical data to predict the

outcome for diffuse large B-cell lymphoma (DLBCL). Evolving fuzzy neural network (EFuNN) has been used to construct a microarray predictor module. Meanwhile, the International Prediction Index (IPI) as Bayesian Network was applied to develop a clinical predictor module. The predictions of the two independent modules were merged into a single prediction, which led to higher accuracy compared to the previously most accurate prognostic model.

Furthermore, Bayesian Network was noted to be a preference technique in combining clinical and gene-expression data. It also has been used by Nevins *et al.* [82] to extend the invasion of axillary lymph nodes with meta-gene signatures, while in 2006 Gavaert *et al.* [31] employed Bayesian Network to evaluate three methods for integrating clinical and microarray data; decision integration, partial-integration and full-integration to perform breast cancer prognosis. These studies revealed that Bayesian Network can be used to combine clinical and gene-expression data and boost the performance of breast cancer prognosis. Given the complexity of breast cancer prognosis and the difficulties in extracting significant genes and clinical source, Sun *et al.* [83] developed I-RELIEF algorithm to identify hybrid factors from clinical and microarray data. This study has shown that a hybrid signature can provide significantly improved prognostic specificity over the existing gene signatures and current clinical systems.

On the other hand, Li *et al.* [84] applied SVM with linear kernel to combine clinical information and gene-expression profiles to accurately discriminate ovarian cancer patients who were likely to respond to therapy treatment. Features-selection using the T-test statistical analysis was used to extract significant gene expression and clinical data for developing prediction mode and the results showed an increase in average accuracy of the integrated model compared to the base SVM model. Even though some issues were addressed in these studies like heterogeneous factors involved in prognosis cancer and the challenging task in integrating both data, it was confirmed that gene-expression data add immense detail to traditional clinical source. Thus, the combination of clinical and gene-expression data could lead to customized health care strategies. However, a more practical and appropriate strategy needs to be developed to encounter heterogeneity in clinical and gene-expression data.

8. VALIDATION METHODS IN ESTIMATING PREDICTION ERRORS FOR MICROARRAY DATA ANALYSIS

The growing avalanche of microarray data has driven an explosion of high-throughput and discovery-based research during the past decade. Although a large number of researchers claimed to have successfully discovered the gene-expression markers for cancer prognosis, most of the researches cannot be reproduced, which consequently lead to disappointment and erroneous conclusions. These issues often arise when miniature or no validation is carried out during the research process. The sources of ambiguity in microarray studies are numerous and can occur from different stages, for example, experimental design, data quality (laboratory, platform, and batch effects), preprocessing (image analysis, normalization and filtering) and data analysis [25, 86, 87]. Each of these sources could generate uncertainty in gene-expression data, therefore requiring careful consideration and validation.

The predictive accuracy of a model can be validated using a cross-validation study, in which the analysis is repeatedly performed while removing a group of samples at reanalysis and predicting the outcome for the remaining group. Cross-validation can be used simply to estimate the generalization error of a given model, or it can be used for model selection by choosing one of several models that has the smallest estimated generalization error. Two types of cross-validation techniques have been widely used in microarray data analysis which includes leave-one-out cross-validation (LOOCV) [32, 38, 48, 88-90] and k-fold cross validation [91, 92]. LOOCV often works well for estimating the generalization error for continuous error functions such as the mean-squared error, but it may perform poorly for discontinuous error functions such as the number of misclassified cases. In the k-fold cross validation, the generalization error is preferred. However, if k gets too small, the error estimate is pessimistically biased because of the difference in

training-set size between the full-sample analysis and the cross-validation analyses. A value of 10 for k is popular for estimating generalization error[17, 19, 20, 23, 34].

Another validation method, which is extensively applied in the microarray data analysis, is receiver-operating characteristic, also known as ROC curves[31, 41, 66, 70, 83]. Most of the microarray studies are concerned about correctly classifying tumors by measuring the fraction of false positive (also known as false positive rate (FPR)) and true positive (also known as true positive rate (TPR)). A ROC curve plots the tradeoff between the sensitivity versus 1-specificity by contriving FPR and TPR in the x and y axes respectively. The best possible result would yield at coordinate (0, 1), where all positives cases are classified as positive and all negative are cases classified as negative, representing 100% sensitivity and 100% specificity. Although this is the best case, the procedure to get them can be very restricted with respect to gaining false-positive error with no false-negative price to pay.

9. TRENDS AND DIRECTIONS IN PROGNOSIS MODELS

Prognosis models have been evolved drastically during the past several decades. In ancient times, clinical data such as age, estrogen and progesterone receptors, lymph-node involvements and other prognostic factors have been extensively used to determine the recurrence of breast cancer among patients. Various approaches were applied to develop the prognosis model varying from the traditional probabilistic techniques, originating from statistical methods, for instance Kaplan Meier, and the proportional hazards-regression model to more qualitative and model-based techniques derived from the artificial intelligence domain. Although many artificial intelligence techniques have been applied, ANN was identified as the dominant technique in developing clinical prognosis models instead of other interpretable techniques due to its robust characteristics to noisy data and being capable of expressing complicated interactions. However, this technique is prone to over-fitting, which requires appropriate validation to be executed.

Numerous researches have been done to determine the recurrence of breast cancer using clinical data but this approach conveys drawbacks as it difficult to distinguish tumors with similar morphological subtypes. The invention of microarray technology, with the opportunity to examine thousands of genes simultaneously, has shifted the cancer-prognosis model to a new post-genomic era. Unlike, clinical prognosis models, gene-expression profiling offers a novel ways to understand the cancer-related cellular process, thus enhancing classification accuracy. However, overwhelming data generated from microarray technology requires proper data analysis to be done. Microarray data analysis mainly consists of two parts; feature selection and classification. Many studies have been conducted to address these problems. The classification trends have changed from using a single classifier to ensemble several classifiers into one to examining the difference in gene expression and recently to multi-class classification techniques. Moreover, it also noted heavy reliance toward univariate filter-feature selection techniques compared to wrapper and embedded methods. Currently, prognosis models show an imperative growing direction toward using integrated data such as microarray and clinical, or genomic and proteomic data instead of examining cancer recurrence in a separate manner.

10. CONCLUSIONS

This paper reviewed prognosis models for clinical and microarray data, precisely focusing on feature selection and classification techniques that have been employed in cancer prognosis. The main problems emerging from the breast cancer prognosis domain was explained in detail. Due to limitation in current practice clinical-prognostics has derived attention from researchers to develop the genetic marker-based prognosis model, particularly using microarray data. However, this approach also has its own dilemma in making sense of thousands of gene-expression values. Feature-selection techniques have become a prerequisite step in analysing gene-expression data. Currently, filter methods are more prominent techniques among the Bioinformatics

community compared to wrapper and embedded methods. On the other hand, various classification techniques have been used but none of them is superior than the others. Moreover, most classification techniques are found to be data dependent. In general, it was observed that most of the researchers have underrated the power of clinical factors, although it could add complementary information to gene-expression data. The proposal of integrating clinical and gene-expression profiles can be considered as one of the most promising future lines of the work, although but a lot of work needs to be addressed to minimize heterogeneity in clinical and gene-expression profiles for breast cancer prognosis.

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