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Research paper

Multi-Instance Image Classification for Cancer Diagnosis using Statistical Mapping Support Vector Machine

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Abstract

This paper presents multi-instance (MI) image classification for cancer diagnosis using statistical mapping Support Vector Machine (SVM). The existing MI image classification is limited to focusing on standard multi-instance classification (MIC) assumption, but do not generalize to the whole range of MI data and do not fully utilize the power of conventional SVM. The standard MIC assumption labelled a bag of image as positive if there is at least one instance in it which is positive. Unfortunately, this assumption is not applicable if there is less information about abnormal instances provided in a bag. Therefore, the paper aims to propose conventional SVM that utilized the basic statistical mapping to form a bag vector of instances in order to classify MI images and give the benefit of the automated image diagnostic procedure. Numerical tests examine the benefit of instances' features transformation to be a vector of bag representation using mean and covariance mapping to Linear-SVM, Square-SVM and Cube-SVM. The experiments used a secondary dataset. The numerical dataset extracted breast histopathology image of 58 patients, which contains 708 features and 2002 instances. The result obtained shows that the proposed SVM can achieve 100% sensitivity after utilizing the covariance mapping with Square-SVM. It means the classification task able to detect the malignant class. In conclusion, the conventional SVM has great potential to improve medical diagnostic procedure using MI image, particularly for cancer diagnostic after adapting statistical features transformation.

Keywords: *multi-instance classification; bag-level decision; statistical mapping; medical images; disease diagnostic*

1. Introduction

Medical images become an evidence-based guideline and provide an objective information to support clinical decision-making for diagnostics as well as the treatment planning. Conventional classification techniques concentrate on learning a single medical image. The medical image can only capture one brightness range of the view [1] represent at one position and it may give different interpretation if it is captured from another view. It may also not be sufficient to capture the subtle differences of all pairs of objects [2], ineffective [3], may lose their accuracy performance [4] and also unable to universally differentiate normal from abnormal cells or region due to small changes from normal. Furthermore, the conventional classification using a single image carries the risk of inter-observer inconsistence ,[6] and results in misclassification problem. For example [7] found that even though majority of the images look normal, however, a small retinal landmark is enough to alter the label of the image from normal to abnormal. Thus, medical diagnostic which use using multiple images give greater potential as suggested by [8] since the use of a multi-modal view of the tissue for clinical assessment or multi-view from mono-modal image will prevent the bias labeling toward majority information.

In the medical field, MI classification is referred to classify multiple images either patches from a single image (mono-modal image) or images from multi-modal of images. Recent studies have shown that different types of features may provide complementary information and more insights of the disease pathology and potentially lead to more accurate diagnosis compare with single-view features [9]. Findings by [10] also points the combination of different image facilitates much greater understanding of the underlying condition, resulting in improved patient care. MI of patches from a single image is implemented by MIC approach. It requires only image-level label, which can be generated much more efficiently.

In MIC, images are regarded as bags, and image regions as instances. The bag is labelled as normal if all instances are normal. While, the bag is labelled as abnormal if even one instance classified as abnormal. Each image is a bag, and each patch within an image is an instance. A bag with positive label denotes the existence of a cancer region within the core [11]. Although MIC has been extensively studied, it was only recently applied to histopathology image analysis [12]. This idea attracts a great interest in the computational histopathology where patches could correspond to cells that are believed to indicate malignant changes [13].

Studies are limited in solving an issue less information of abnormal instances in a bag. Non-bag mapping approach tend to face the challenge of information loss and a deterioration in classification performance [14]. While, recent studies show that through bag representation which transformation from instances' features in MIC can be cast to the conventional supervised learning [15].

Thus, this paper aims to presents image classification approach for cancer diagnosis using statistical mapping SVM to solve the disease diagnose issue when conventional SVM classifies the MI Medical Image. Lesser accuracy is diagnosed when conventional technique applied which cannot classify the MI medical image as a whole due to less information and biased toward majority class. Thus, this study uses instances' features transform into a vector of bag representation using mean and covariance matrix mapped to Linear-SVM, Square-SVM and Cube-SVM. In specific, this study aims to examine which parameter of statistical mapping under bag representation will show better performance of MIC in term of the sensitivity, specificity and accuracy when applied to conventional SVM. This paper present supervised SVM technique in handling disease diagnostic problems that acquire MI images for binary classification (benign or malignant label). This study contributes in demonstrate the great potential of conventional SVM classify MI data which literature ignored.

2. Experiments

SVM-based are powerful classifiers [17] which frequently applied in medical image classification at instance-level decision especially in breast cancer diagnosis [18] and ~~en~~able to achieve high accurate diagnostic result [19].

In MIC, SVM train the medical image using pre-labeled information [20]. The training algorithm builds a model that predicts whether a new medical image data diagnosed as cancer or non-cancer class [19]. The SVM model create a clear gap as wide as possible to separate normal and abnormal class from the representation of the numerical values of image attributes as points in space [19]. The clear gap called a best hyperplane which separates two classes with maximum margin. Feature vectors from each medical image lies on one side of the hyperplane belongs to class positive (cancer) while the others belong to negative class (non-cancer)[21]. The data points that are close to the hyperplane is called support vectors. SVM builds the hyperplane based on a kernel function [21]. Basically, SVM can be implemented using linear and non-linear kernel functions.

This experiment aims to analyze the classification performance of conventional SVM when transformation procedure implemented using mean per bag and covariance matrix mapped. Then, the results are compared between the conventional SVM in term of sensitivity, specificity and accuracy. From the result, the optimal statistical mapping and optimal kernel of SVM was identified. The three-kernel setting implemented in this experiment includes Linear-SVM, Square-SVM and Cube-SVM to performance of MIC when applied conventional SVM. The performance comparison of conventional supervised learning be as a preliminary stage to explore these techniques for future enhancement in improvise the diagnostic result involved multi-view medical image.

2.1 Labelling Medical Image Stages

The general labeling process follow the five fundamental steps whereas images acquisition, image pre-processing, features selection, classification task and performance evaluation. However, as for this study which focusing on classification task, the first and second steps will not be repeated and discussed in detail. Since the steps have been completed by other researcher, the derived MI dataset was obtained and used as benchmark input for upcoming steps which discuss in the following section.

2.2 Input Multi-instance Image Dataset

In MIC for cancer diagnosis, an image of a patient is represented by bag, B_i (refer Figure 1). Each bag consists of n grouped instances $\{x_{i1}, x_{i2}, ..., x_{iN}\}$ and each instance $x_{ij} \in R_d$ is a d-dimensional feature vector. Let $D = \{(B_1, y_1), (B_2, y_2), ..., (B_n, y_n)\}$ denotes a training dataset consist of n bags, where $y_i \in \{-1, +1\}$ is the label of bag B_i, with $y_i = +1$ indicates that B_i is a positive bag which indicates the patient is diagnosed has a cancer (positive) while $y_i = -1$ indicates that the patient is diagnosed is non-cancer (negative).

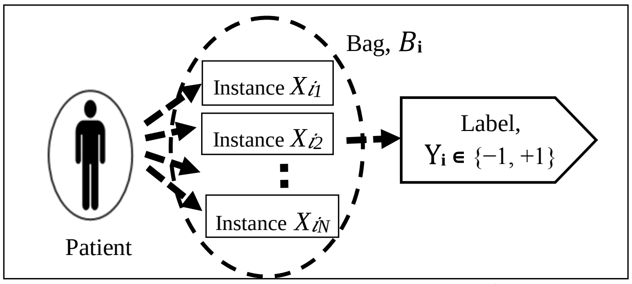
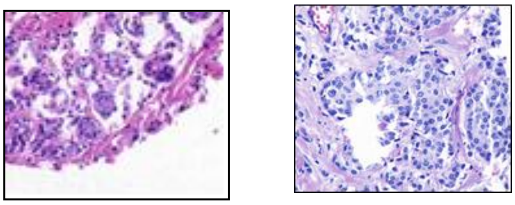


Fig. 1: Multi-Instance Medical Image Classification

As input for this experiment, secondary breast cancer dataset was adopted which obtained from [11]. The breast histopathology image dataset originally presented by Center for Bio-Image Informatics in University of California, Santa Barbara (UCSB). Histopathology deals with microscopic examination of anatomy of cells and tissues and hence deals with disease diagnosis at the tissue level [22]. The descriptions of the dataset are shown in Table 1. These image has been used by [23], [24], [25], [26] and [27] for perform research in medical images classification. The sample of the histopathology image from the datasets are shown in Figure 2.

Table 1: Description of UCSB breast dataset [28]

Total Images	Malignant bags	Benign bags	Min-max number of instances per bag	Total instances	Features attribute
58	26	32	21 - 40	2002	708



(a) (b)

Fig. 2: (a) Single-view of benign image, (b) Single-view of malignant image

Each image in the dataset is regarded as a bag. A bag is divided into multi-instance of images called patches. Each patch in the image is referred to as an instance. Malignant bag of images give the bag-level decision as cancer. While the benign bags gives none cancer of the diagnosis result.

2.3 Multi-Instance Classification Approaches

There are two Multi-Instance Classification (MIC) approaches adopted in the existing conventional SVM technique. The approaches are combination rules of single-instance prediction and bag representation [28].

2.3.1 Combination rules of single-instance prediction

In combination rules of single-instance prediction, an image is labelled individually by conventional classifier. Then labels of its instances are combined using specific rule to get a bag label. There are two common rules used included majority–based and presence-based. The bag level can be derived from the individual labels using the common rule as illustrated in Fig.3.

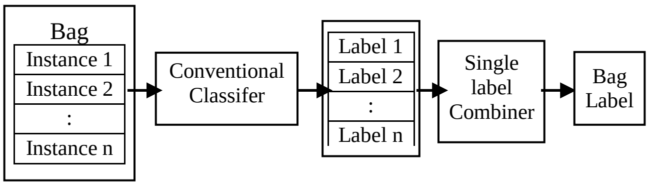


Fig. 3: Combination rules of single-instance prediction

2.3.2 Bag Representation

Recent study has drawn significant attention to apply bag mapping which transforms feature vectors from a bag into a single instance in a new bag vector [14]. In the bag representation, all instances from the same bag are considered to be of equal importance [15]. In straightforward way, to extract a new feature vector from a bag of instances, basic statistic of instances in a bag are computed, as the mean vector per bag and the covariance matrix per bag. Another alternative way of representing a bag by a single vector, is to rescale the data using mean and variance before compute the statistic measure used to standardize the range of features value of data. After the mapping completed, the conventional classifier will train and classify the new bag vector and get the bag label. Refer Fig.4.

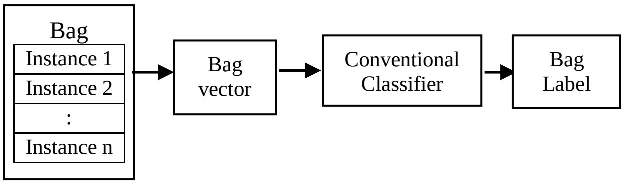


Fig. 4: Extend conventional classifier for MIC using bag representation

Since MIC system is a weakly supervised learning framework[29][30] and both approaches can be applied. However, the instance label information did not provide in the chosen dataset. Thus, this experiment implement the second approach with adaptation feature transformation which particularly relevant [15].

2.4 Classification Task

This experiment used stratified sampling strategy [31] with 60% for training dataset while 40% for testing dataset. In order to demonstrate our statistical mapping approach to the conventional SVM, the following generic steps was proposed:

Step 1: Split the dataset into train data and test data using percentage split (60% train)
Step 2: For each train data, map the instances' features into a bag vector using statistical bag mapping function, f(M_{ij})
Step 3: Use a Linear-SVM classifier to train the bag vector
Step 4: Train the classifier to training data and build a model
Step 5: Apply the model to the test data
Step 6: Evaluate the classification performance using confusion matrix

Above steps are applied to each experiment for Square-SVM and Cube-SVM with different M_{ij} method as listed in Table 2. As for this study, PRTools and MILTools of MATLAB were used to implement the classification task. To carry out the transformation procedure using MATLAB, milvector() and scalem() function were used (Refer Table 2). The milvector() function have been used to obtain a new bag vector with parameter 'm' for mean to compute the value of mean per bag. Meanwhile parameter 'c' used to compute covariance matrix for each bag instances. While scalem() function is used to rescale each features to the value of the parameter of a 'variance' and 'mean'. The rescaled parameter are applied to the mean per bag and the covariance matrix. Finally, the results for each method are compared in term of sensitivity (Sn), specificity (Sp) and accuracy (Acc) as recorded in Table 5 and Table 6.

Table 2: Matlab function with specific parameter setting to bag representation

Mapping Method, M_{ij}		The Function used and its parameter
M_1: Bag vector (Mean per bag)	M_{11} : Without scale	milvector([],'m')
	M_{12} : Variance Scale	scalem([],'variance')* milvector([],'m')
	M_{13} : Mean Scale	scalem([],'mean')* milvector([],'m')
M_2: Bag vector (Co-variance Matrix)	M_{21} : Without scale	milvector([],'c')
	M_{22} : Variance scale	scalem([],'variance')* milvector([],'c')
	M_{23} : Mean scale	scalem([],'mean')* milvector([],'c')

To apply SVM technique in labeling the images, svc() function used with kernel parameters are set to 'p' = 1 (Linear SVM), 'p' = 2 (Square SVM) and 'p' = 3 (Cube SVM). Next session will be discussing on the result obtained with the applied technique.

2.4 Evaluation

When addressing a two-class problem, the result of correct and incorrect classified examples of each class can be stored in a confusion matrix [32]. By using the confusion matrix, the efficiency of the classifiers can be measured based on classification accuracy. The confusion matrix in Table 3 show four situations in the binary classification whereas true positive (TP), False Positive (FP), False Negative (FN) and True Negative (TN). A confusion matrix has been calculated for bag-level decision.

From confusion matrix, four performance measurement can be derived and defined as in Table 4 which are accuracy (Acc), sensitivity (Sn), specificity (Sp) and precision (Prec). However, as for this paper, focus is only on the accuracy, specificity and sensitivity in order to examine the classification effectiveness.

Table 3: Confusion Matrix

		Predicted Label		Total bags
		Malignant (Positive)	Benign (Negative)	
Actual Label	Malignant (Positive)	TP	FN	TP+FN
	Benign (Negative)	FP	TN	FP+TN
Total bags		TP+FP	FN+TN	TP+TN+FP+FN

Table 4: Performance Measurement Derived from Confusion Matrix

Performance Measurement	Indication of Image Diagnostic Result
Acc = (TP+TN) / (TP+TN+FP+FN)	Probability that diagnostic test is correctly performed [33] from the total number of samples
Sn = TP / (TP+FN)	True positive classified is completeness of positive diagnostic which identifies that the image shows the disease
Sp = TN / FP+TN	True negative classified is effectiveness of negative diagnostic which identifies that the image does not show the disease
Prec = TP / (TP+FP)	Exactness of diagnostic makes the correct prediction

3 Result and Discussion

Medical image diagnostic involves a task which classify into two**;** cancer (positive) or non-cancer (negative). Hence, the main performance measurement focuses on the sensitivity and specificity. The sensitivity indicates a percentag**e** of classification detecting the true positive result diagnosed from the image. While, the specificity value is truly negative result. However, in cancer diagnosis, sensitivity was more important than specificity, because it show**s** the strong ability of classification technique in detecting positive class [34]. Table 5 shows the sensitivity and specificity performance of the classification using conventional SVM with linear, second and third order polynomial setting for statistical mapping of mean per bag and covariance.

The findings after rescaling features to variance show that the covariance mapping having significant value of the sensitivity consistently for all kernel setting (83.33% by Linear-SVM, 100% by Square-SVM and 91.67% by Cube-SVM). This shows that, for sensitivity, the variance scale suite with the covariance mapping method compare to without scaling and mean scale. This also shows tha**t** covariance matrix give promising generalizable bag representation [35]. As for specificity which identify the percentage those patients without cancer under covariance mapping, significant value is absence for all setting except Linear-SVM with mean scale and without scale (72.73%).

While, for mean per bag mapping, the highest sensitivity is recorded as 83.33% for Linear-SVM for variance scale with 66.67% for Square-SVM and Cube-SVM. While, under mean per bag mapping, Cube-SVM did not show any significant performance of specificity.

Table 5: Sensitivity and specificity performance of statistical mapping SVM vs conventional SVM

Method \ Kernel		Sn	Sp	Sn	Sp	Sn	Sp
		Linear-SVM		Square-SVM		Cube-SVM	
Conventional (Instance Label)		72.66	58.19	68.85	48.87	60.43	43.50
Bag vector (Mean per bag)	Without scale	66.67	45.46	83.33	45.46	50.00	72.73
	Variance Scale	83.33	45.46	66.67	18.18	66.67	54.55
	Mean Scale	66.67	45.46	83.33	45.46	50.00	72.73
Bag vector (Covariance Matrix)	Without scale	66.67	**81.82**	66.67	63.64	66.67	63.64
	Variance scale	**83.33**	54.56	**100**	45.46	**91.67**	54.56
	mean scale	66.67	**81.82**	66.67	63.64	66.67	63.64

Table 5 shows that the accuracy did not perform significantly for diagnosis even though there was 100% sensitivity performance under covariance mapping with variance scale. While Table 6 shows that, 73.91% of accuracy obtained from covariance mapping with or without scaling which better than conventional SVM and mean per bag mapped. The poor accuracy is 43.5% under conventional Cube-SVM. As a conclusion, bag vector using covariance mapping shows the best suite to implement conventional SVM for classifying MI data.

Table 6: Accuracy performance of statistical mapping SVM vs conventional SVM

Method \ Kernel		Linear SVM	Square SVM	Cube SVM
Conventional (Instance Label)		66.02	59.66	52.66
Bag vector (Mean per bag)	Without scale	56.52	65.22	60.87
	Variance scale	65.22	43.48	60.87
	Mean scale	56.52	65.22	60.87
Bag vector (Covariance Matrix)	Without scale	**73.91**	65.22	65.22
	Variance scale	69.57	**73.91**	**73.91**
	Mean scale	**73.91**	65.22	65.22

4 Conclusion

Cancer diagnostic avoid the risk of missing a patient could potentially the person is untreated decrease. A confusion matrix used to evaluate the successful of cancer diagnosed from a medical image. From the matrix, percentage of accuracy, sensitivity and specificity of diagnosed result can be derived. This study shows the statistical mapping SVM gives higher percentage that this diagnostic test is correctly performed accuracy compare with conventional SVM. The conventional SVM classify at instance-level. When an instance is less information in the conventional technique, it could not distinguish an image's label accurately. Thus, there is a need for collective information from all instances in a bag to get accurate diagnosis that represents the image as a whole. For the case of cancer diagnosis using UCSB data, covariance mapping shows a better performance compared with mean mapping in term of accuracy, specificity and most significant on sensitivity. Moreover, the statistical bag mapping of Square-SVM shows slightly good accuracy. Therefore, the transformation procedure in MIC will give beneficial for nonlinear in disease diagnostic procedure in general. For future research, utilizing the statistical mapping for features bag transformation have great potential for future enhancement of the conventional supervised classification in improvising the performance of cancer diagnosis.

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