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HYBRID DEEP LEARNING AND SVM FOR BIOMARKER OF COLORECTAL CANCER TISSUE DECOMPOSITION

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ABSTRACT

Colorectal Cancer (CRC) is the third most common form of cancer and the second deadliest disease. The development of targeted therapy for cancer treatment increased demand for identification of molecular targets, such as driver mutations in cancer cells. However, some molecular tests, including next-generation sequencing, are not available to all cancer patients because of high cost and technical barriers. Standard biomarkers often pertain to costly and slow genetic tests. In recent development, Hematoxylin and eosin-stained biopsy slides are regularly available for colorectal cancer patients. Fortunately, rapid development has shown that objective biomarkers can be extracted from these images using Deep Learning (DL) approaches especially convolutional neural networks. This report proposes the hybrid method based on Deep Learning with CNN architecture as feature extractor and SVM as classifier to decompose nine classes of colorectal carcinoma slides images. This research has two main contributions, first, this research can provide insight to medical expert and computer scientist related to the current state of development deep learning based approaches for histopathological images classification especially in colorectal carcinoma (CRC). The second contribution of this research proposes alternative method in framework development of biomarker decomposition of CRC feature extraction, feature selection and classification of slides images. The results show that the proposed method has accuracy between 95%-99.5% in training data set and 94%-98.5 in the external data set. The biomarker of CRC classes LYM, STR and TUM successfully had been decomposed with high percentage of decomposition

Keywords: *Deep Learning, Convolutional Neural Networks, Support Vector Machine, Colorectal Carcinoma, Cancer Biomarker*

1. INTRODUCTION

As widely known that Colorectal Cancer (CRC) is the third most common form of cancer and the second deadliest disease (1). Furthermore, according to the American Institute of Cancer Research the cases for colorectal cancer world-wide are expected to rise by 60 percent over the next fifteen years, therefore, the required steps for diagnosis will also increase rapidly which would prove disastrous if pathologists only relied on manual examinations (2). The introduction of targeted therapy for cancer treatment increased demand for identification of molecular targets, such as driver mutations in cancer cells (7,11). However, many molecular tests, including next-generation sequencing, are not available to all cancer patients because of high cost and technical barriers.

In recent development, Hematoxylin and eosin-stained biopsy slides are regularly available for colorectal cancer patients (6,29,30). However, the slides are often not used to define target biomarkers for patient stratification and treatment selection. Standard biomarkers often pertain to costly and slow genetic tests (7,11). Fortunately, rapid development has shown that objective biomarkers can be extracted from these images using Deep Learning (DL) approaches especially convolutional neural networks (CNNs) (3,4).

The Deep Learning based biomarkers could predict colorectal cancer patient outcomes comparably to gold standards. Extracting CNN-biomarkers is fast, automatic, and of minimal cost. CNN-based biomarkers rely on the ability of CNNs to recognize distinct tissue types from microscope whole slide images. The quality of these biomarkers (coined 'Deep Stroma') depends on the accuracy of CNNs in decomposing all relevant tissue classes. Improving tissue decomposition accuracy is essential for improving the prognostic potential of CNN-biomarkers.

With the advancement in the field of Artificial Intelligence, including several Deep Learning approaches as part of AI, it has been applied to identify biomarker colorectal carcinoma cancer (5,6,12). Deep Learning as the latest method in the field of AI has been widely used in fields including the biomarker identification using slides images with high accuracy and speed that exceeds several methods in traditional Machine Learning [2]. More recent development, CNN based approach with ensemble learning using SVM introduced in (5) with promising results. However, this approach requires lots of computation with could prevents large scale images data applications.

In order to identify biomarker of colorectal carcinoma using slides images of patients based on a hybrid Deep Learning and a well-defined classifier technique, a novel training strategy to a hybrid model CNN and SVM will be introduced. These methods were used to be more efficient in term of computational complexity and low-cost hardware requirements.

The advantages of Deep Learning based approaches can be viewed as the powerful 'feature extractor' of slides of cancer composition. Then, those extracted features will be selected using a well-defined feature selection technique. Finally, a classifier will decompose slides images into their expected category of colorectal carcinoma (CRC).

The ultimate goal of the proposed model is expected to reduce the losses function due to misclassification of the images and in the same time will increase the accuracy of the model prediction to external data set (8,9,10,11). The objective of this paper is two-fold. First, the current Deep Learning based approaches for classifying slides images CRC patients will be reviewed. Second, the proposed hybrid of Deep Learning and with various feature selection and classifier will be experimentally explored. The paper mainly focuses on supervised learning approaches especially Convolutional Neural Networks (CNN) based model with Support Vector Machine framework. Thus, the method related to the unsupervised learning and Recurrent Neural Network are beyond scope of paper.

This study has two contributions: first, this research can provide insight to medical expert and computer scientist related to the current state of development deep learning based approaches for histopathological images classification especially in colorectal carcinoma (CRC). The second contribution of this research proposes alternative method in framework development of biomarker decomposition of CRC feature extraction, feature selection and classification of slides images.

This paper will be organized as follows. First, Deep Learning Architecture mainly in Deep Convolutional Neural Networks (CNN) will be reviewed. Next, the CNN based approaches and transfer learning for biomarker decomposition of CRC will be explored. Then the experimental settings will be introduced. The results and discussions will show some findings from the experiments. The paper will be concluded by some recommendations the use of proposed frameworks for handling biomarker decomposition of colorectal carcinoma.

2. CONVOLUTIONAL NEURAL NETWORKS (CNN)

Convolutional Neural Network (CNN) is part of Deep Learning and the general form of artificial neural networks (ANN) which is mainly used to extract the image feature from the grid-like matrix dataset. CNNs have been extensively deployed in a range of different applications, including computer vision [14], speech processing [15], Face Recognition [16], etc. The structure of CNNs was inspired by neurons in human and animal brains, similar to a conventional neural network. The structure of CNN will be explored as follows.

2.1 CNN Architecture

Convolutional Neural Network consists of multiple layers which consist of the input layer, Convolutional layer, Pooling layer, and fully connected (fc) layers. The Convolutional layer uses filters to the input image to extract features of image. While the Pooling layer down samples the image to reduce computation, and the fully connected layer will do the final prediction. The network learns the optimal filters through backpropagation and gradient descent [13,17].

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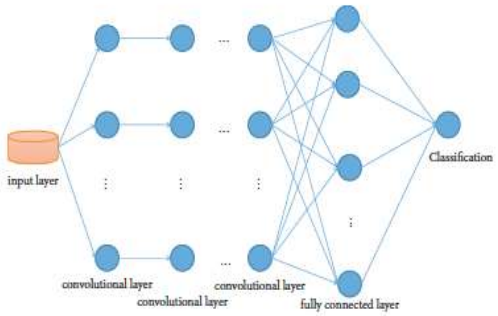

Figure 1. CNN Architecture (17)

2.2 Transfer Learning

Transfer learning (**TL**) is a technique in Deep Learning in which knowledge learned from a task is re-used in order to boost performance on a related task. Transfer learning methods on deep learning aim to reduce the cost and training time, and the necessity of extensive training datasets which can be hard to harvest in some areas such as Colorectal carcinoma slides images. In this work, the Densenet121 with ImageNet weight is used as based model in the transfer learning approach.

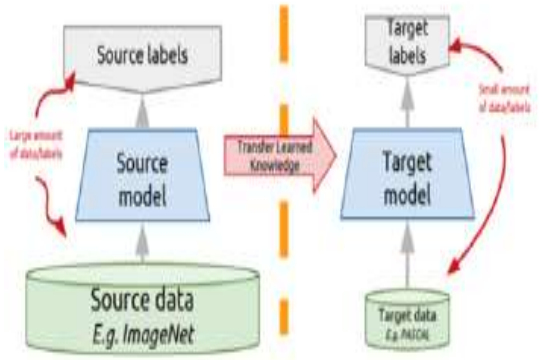

Figure 2. Transfer Learning In Deep Learning (19)

3. SUPPORT VECTOR MACHINE (SVM)

The SVM is as a new type of universal learning machine that implements the strategy of keeping the value of the empirical risk fixed minimizing the confidence interval (21). The separating hyperplane is the intermediate hyperplane of two parallel hyperplanes, one letting above the vectors of the first class and the other letting below the vectors of the second class.

Selecting relevant features is a challenge task, and feature selection approaches are used to detect such features. Indeed, the primary objective of feature selection is to determine the optimal set of relevant features without losing the salient characteristics of the data (19,20).

In the proposed model, the original of SVM as shown in Figure 7, is represented in the form *cost function* of CNN training model which is usually called as *L2-SVM* (16):

Cost function = Loss Function + L2-Regularized (1)

Where:

Loss Function is defined as

$$\ell(y) = \sum_{y \neq t} \max(0, 1 + \mathbf{w}_y \mathbf{x} - \mathbf{w}_t \mathbf{x}) \quad (2)$$

In *Keras of Tensorflow*, this loss function is called *Hinge Categorical loss* (22).

and

L2-Regularized is defined as follows:

$$\frac{1}{p}\|\mathbf{w}\|_2^2 \quad (3)$$

x,y ***w,*** and $\frac{1}{p}$ denote input, output, weight and regularized parameter, respectively.

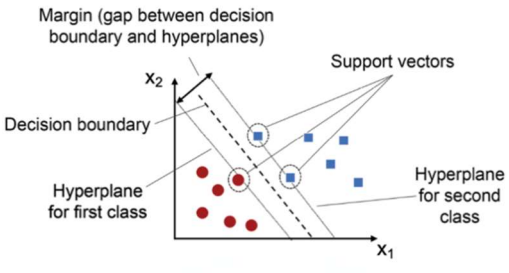

Figure 3. Support Vector Machi

4. EXPERIMENAL SETTINGS

4.1 Slides Images of Colorectal Carcinoma Data

The slides image data collected from (5) in the following public website:

https://zenodo.org/records/1214456#.XpWJbm46--w

4.2 Data Description

This downloaded colorectal carcinoma data is a set of 100,000 non-overlapping image patches from hematoxylin & eosin (H&E) stained histological images of human colorectal cancer (CRC) and normal tissue. There 8 tissue classes are: Adipose (ADI), background (BACK), debris (DEB), lymphocytes (LYM), mucus (MUC), smooth muscle (MUS), normal colon mucosa (NORM), cancer-associated stroma (STR), colorectal adenocarcinoma epithelium (TUM). LYM, STR and TUM classes have important role in colorectal carcinoma cancer. Those classes will be our primary analysis. This data set will be used as training data. For the validation dataset we used external data set which has 7180 images slides of colorectal carcinoma.

4.3 Transfer Learning with DenseNet-121

In the experiments, the base model DenseNet-121 (28) with weight from ImageNet. The architecture of DenseNet-121 is shown in Figure 4.

Layers	Output Size	DenseNet-121	DenseNet-169	DenseNet-201	DenseNet-264
Convolution	112 × 112	7 × 7 conv, stride 2			
Pooling	56 × 56	3 × 3 max pool, stride 2			
Dense Block (1)	56 × 56	[1 × 1 conv, 3 × 3 conv] × 6	[1 × 1 conv, 3 × 3 conv] × 6	[1 × 1 conv, 3 × 3 conv] × 6	[1 × 1 conv, 3 × 3 conv] × 6
Transition Layer (1)	56 × 56	1 × 1 conv			
	28 × 28	2 × 2 average pool, stride 2			
Dense Block (2)	28 × 28	[1 × 1 conv, 3 × 3 conv] × 12	[1 × 1 conv, 3 × 3 conv] × 12	[1 × 1 conv, 3 × 3 conv] × 12	[1 × 1 conv, 3 × 3 conv] × 12
Transition Layer (2)	28 × 28	1 × 1 conv			
	14 × 14	2 × 2 average pool, stride 2			
Dense Block (3)	14 × 14	[1 × 1 conv, 3 × 3 conv] × 24	[1 × 1 conv, 3 × 3 conv] × 32	[1 × 1 conv, 3 × 3 conv] × 48	[1 × 1 conv, 3 × 3 conv] × 64
Transition Layer (3)	14 × 14	1 × 1 conv			
	7 × 7	2 × 2 average pool, stride 2			
Dense Block (4)	7 × 7	[1 × 1 conv, 3 × 3 conv] × 16	[1 × 1 conv, 3 × 3 conv] × 32	[1 × 1 conv, 3 × 3 conv] × 32	[1 × 1 conv, 3 × 3 conv] × 48
Classification Layer	1 × 1	7 × 7 global average pool			
		1000D fully-connected, softmax			

Figure 4. Densenet-121 Architecture (23)

Having frozen the top layer of the DenseNet-121 then the last classifier is replaced by SVM which is represented by the L2- Regularized term and Categorical-Hinge Loss function as described in Section 3.

4.4 Evaluation of Performances

The accuracy and loss functions will used to determine the goodness of the proposed model. The pipeline of the experiments is shown in Figure 5. In order to determine the proportion of decomposition of biomarker of colorectal then the matrix of confusion will be performed.

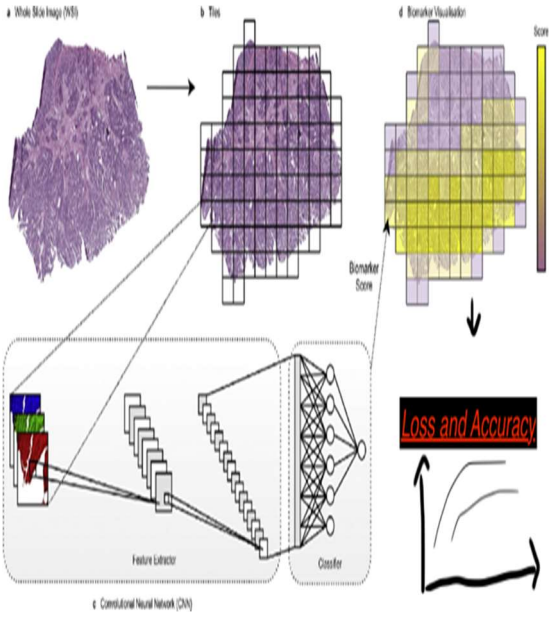

Figure 5 The Flow Of Experiments (5)

5. RESULTS AND DISCUSSIONS

The sample of each class in Colorectal Carcinoma which taken from (5) are shown in Figure 6. For all classes, the target to determine the proportion of Colorectal biomarker will be LYM, STR and TUM. The hardest part for biomarker decomposition will be STR and TUM as they almost have similar structure of image.

From the distribution of classes as shown in Figure 7. The TUM class has the largest number of slides of images, on contrary the MUC has the smallest number of images. However, the different number of images for each class would not lead to the imbalanced problem.

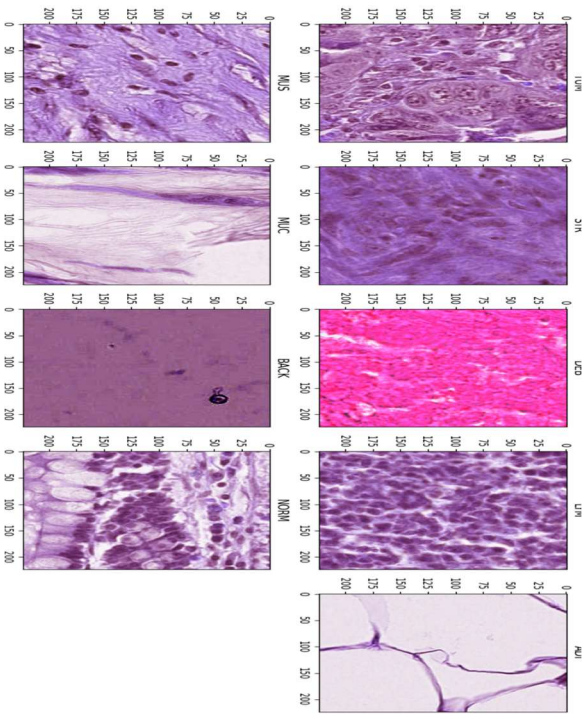

Figure 6. Sample Of Each Class Of Slide Images Which Consists Of Adipose (ADI), Background (BACK), Debris (DEB), Lymphocytes (LYM), Mucus (MUC), Smooth Muscle (MUS), Normal Colon Mucosa (NORM), Cancer-Associated Stroma (STR), Colorectal Adenocarcinoma Epithelium (TUM)

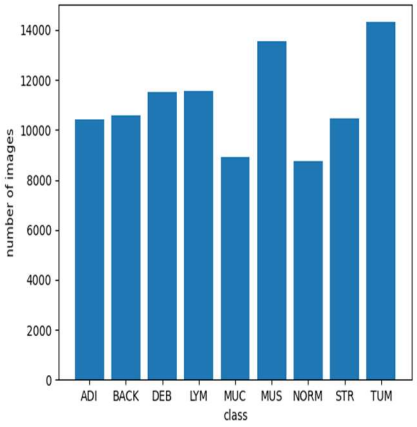

Figure 7. The Distribution Classes In Slides Of Colorectal Carcinoma

Having determined the distribution of classes, the CNN architecture will be used as feature extractor and the output of the extraction will be send to the SVM layer as classifier as described the previous section. The results of the training are shown in the Figure 7.

From Figure (8) and (9) show promising results the hybrid method CNN and L2_SVM with Hinge-Categorical loss function for classifying 9 classes of CRC slides data sets. Figure 8 shows the of the proposed method in the internal training data sets has accuracy about 99% with test accuracy also 99%. Furthermore, according Figure 9 the loss has relative small values.

To validate the model, the external data which consist of 7180 images are applied to the proposed model. The As shown Table 1. The proposed method has accuracy between 97.0% and 99.5%. Furthermore, the proposed hybrid model has very low loss values which has between 2% and 10%.

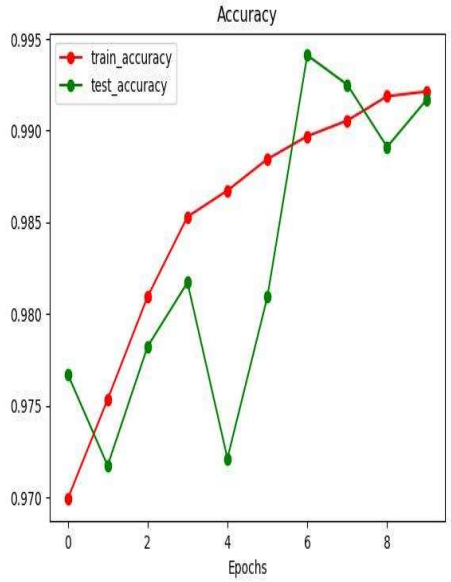

Figure 8. The Accuracy Of Hybrid CNN And SVM Classifier On Training Colorectal Carcinoma Slides Images.

In order to understand the structure of the image classes, then, the t-Stochastic Neighbor Embedding (t-SNE) (26) is used as shown in Figure 10. The figure shows that the images those to be classified by proposed model can be clustered in the well-defined structure by t-SNE.

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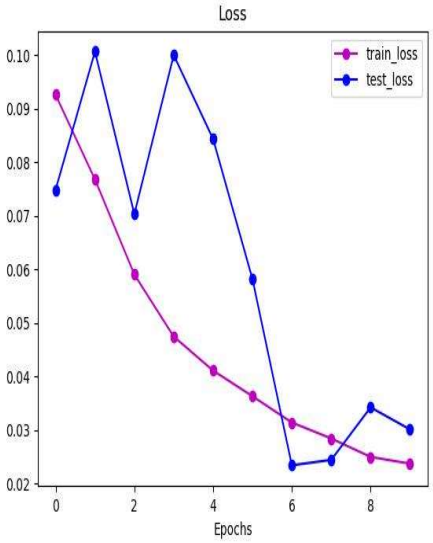

Figure 9. The loss of hybrid CNN and SVM classifier on Training Colorectal Carcinoma slides images.

Tabel1. The accuracy and Loss values of Hybrid CNN and SVM in training data CRC slides images

epoch	train_loss	train_acc	test_loss	test_acc
1	0.09257515	0.969925	0.07485959	0.97673722
2	0.07676483	0.9753625	0.1006462	0.97174521
3	0.05901923	0.98095	0.07028459	0.97823482
4	0.04742701	0.9853125	0.0999906	0.98172923
5	0.04106038	0.9867375	0.08432004	0.97214457
6	0.03627586	0.98845	0.05814945	0.98093051
7	0.03136803	0.9897	0.02337406	0.99410942
8	0.02839168	0.99055	0.02438853	0.99251198
9	0.02493676	0.991875	0.03419523	0.98911741
10	0.02368317	0.9921375	0.03007526	0.99171326

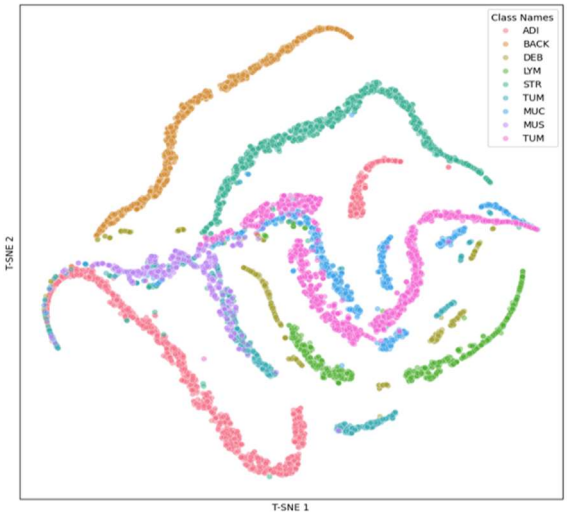

Figure 10. The Structure Of The Classes Of Slides Images

Having determined the structure of classes of slides images CRC patients. Then, the model those to be developed in the training step, will be validated using external slide images CRC dataset. The result is shown in Figure 11 and 12.

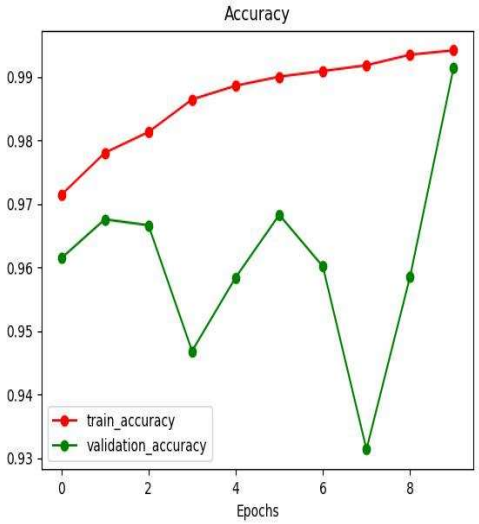

Figure 11. The Accuracy Of Hybrid CNN And SVM On Validation External Colorectal Carcinoma Slides Images

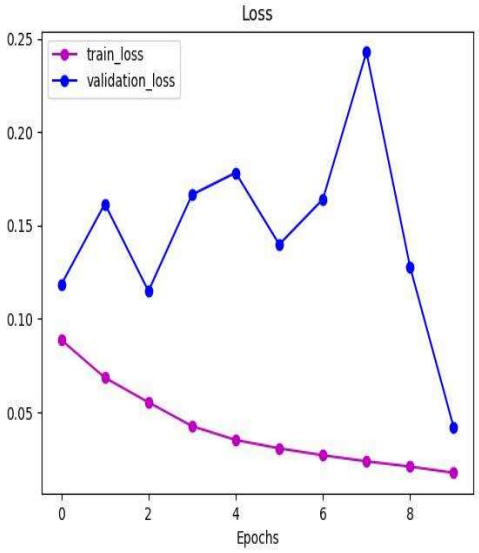

Figure 12. The Loss Of Hybrid CNN And SVM Classifier On Training Colorectal Carcinoma Slides Images.

Figure 11 and Figure 12 show that the accuracy of the proposed hybrid CNN and L2-SVM provide accuracy between 94% - 98.5% and loss values between 5% and 25%. As expected, the results show that the accuracy of validation model using external images data produces lower accuracy

as well as the loss values higher than the training model using internal data.

Finally, the confusion matrix will be used to determine the proportion of biomarker colorectal carcinoma which consist of the classes: LYM, STR and TUM as shown in Figure 13. For those three biomarkers, the rate of decomposition of biomarker can be determined based on the diagonal values of the predicted label compared to the wrong predicted label. Overall, result shows that the biomarker STROMA, LYM and TUM have average successful rate decomposition more than 95% (the number in diagonal relative to the rows and columns values). For instance, there 2134 images are correctly classified among total 2167 images, it means there is about 98% proportion of the TUM class successfully decomposed. Overall, from the figure 13 shows that the proposed method successfully decomposed the structure of biomarker in colorectal carcinoma slides images with higher proportion to be correct predicted classes.

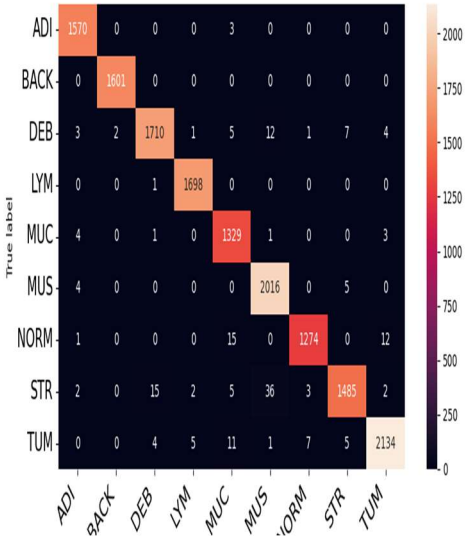

Figure 13. The prediction of Biomarker of Colorectal Carcinoma in the external slide images

6. CONCLUSIONS

This report proposes the hybrid method based on Deep Learning with CNN architecture as feature extractor and SVM as classifier to decompose nine classes of colorectal carcinoma slides images.

This study has two contributions: first, this research can provide insight to medical expert and computer scientist related to the current state of development deep learning based approaches for histopathological images classification especially in colorectal carcinoma (CRC). The second contribution of this research proposes alternative method in framework development of biomarker decomposition of CRC feature extraction, feature selection and classification of slides images.

In this report, the hybrid method which consist of CNN as feature extractor and L2_SVM as classifier has been implemented. The proposed method successfully classifies nine classes of colorectal carcinoma in training data and then validated using external data

In the training data, the proposed hybrid method has accuracy between 97.0% and 99.5% with relative low loss values. To convince ourselves, then we validate the feature extractor and classifier on external data set. The results show that the accuracy remain high between 94% and 98.5% with relative higher loss values. Overall, the results show that the hybrid method CNN and SVM has good performance.

Finally, we deployed the feature extractor using transfer learning and classifier to determine biomarker of colorectal carcinoma which consist of LYM, STR and TUM. From confusion matrix show that the biomarker STR, LYM and TUM could be successfully decomposed by hybrid method CNN and L2_SVM.

Overall, the proposed hybrid deep learning CNN and L2_SVM provide quite low loss values with high accuracy in the biomarker of colorectal carcinoma decomposition. This hybrid model has advantage compare to the other approach in term of the use of L2_SVM as classifier. Since the L2_SVM has more interpretable approach compare to the traditional approach such softmax classifier.

7. ACKNOWLEDGEMENT

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