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Detection and Semantic Segmentation of Nucleus Cells in Histological Images with Deep Neural Networks

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Abstract: *In this paper we presented a method to nuclei image segmentation and detection on public nuclei cancer images which we used from Kaggle 2018 Data Science Bowl data sets. For segmentation the deep neural network with semantic approaches are used. For accuracy evaluation we used the confusion matrix that calculate the sensitivity, specificity and accuracy. Also, for more details of the analyzing of the performance the JI, Dice, Precision, Recall, and F1 Score are used. We compared the output result with the ground truth images. For each pixel we calculated these criteria. The average result for sensitivity, specificity and accuracy was 96.67, 95.97 and 97.78 respectively.*

Keywords: *Image segmentation, Nuclei Cells Detection, Deep Neural Network.*

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I. Introduction

The cell nucleus, is a membrane-covered organelle found in most eukaryotic cells. Most of the cell's genetic information is found in chromosomes formed by the combination of long linear DNA molecules, such as histones , and many proteins inside the cell nucleus[1]. The genes inside these chromosomes make up the cell's nuclear genome. The function of the cell nucleus is to maintain the integrity of these genes and to increase gene expressionand controlling cell functions. Every cell whose core is removed dies after a while.

Nuclei image segmentation helpsclinicians focus on a particular area of the disease and extractdetailed information for a more accurate diagnosis.

Cancer detection is one of the most challenging problems of the computer-based systems. In literature, there are several methods used for cancer nuclei detection, segmentation and classification in histological images[2-7]. In this paper, a semantic deep learning, is used to segmentation and detection.

Semantic image segmentation is the task of classifying each pixel in an image from a predefined set of classes.The algorithm should figure out the objects present and also the pixels which correspond to the object. Semantic segmentation is one of the essential tasks for complete scene understanding.

Semantic segmentation is one of the core jobs of imageprocessing and analysis. During the segmentation process,original images or videos are separated into different regionsbased on plenty of semantic features and recover to pixel-wisedprobability maps at the end of the model[8].

Convolutional Neural Networks (CNNs) have shown stateoftheart performance for automated medical image segmentation[9]. For semantic segmentation tasks, one of theearlier Deep Learning (DL) architecture trained end-to-endfor pixel-wise prediction is a Fully Convolutional Network.

Also, multi-threshold algorithm and morphological techniques were applied to eliminate firstly the presence of noise signal on images.

In general, image semantic segmentation by deep learning can be defined as detecting pixel-wise region categories by CNN-based network's parameter training. Among plenty of semantic segmentation jobs, medical image segmentation is one of the most challenging tasks due to its lack of samples and labels. In clinical research and application, medical image segmentation is a significant procedure for clinical evaluation and diagnosis. Detecting cancer at an early stage has been the focus of health domain. The purpose of this study is segmentation and detection of the nuclei cells from cancer image. for this the semantic segmentation with deep learning methods is used.

In this work, a convolutional neural networks (CNN), is used to segmentation and detection. Also, multi-threshold algorithm and morphological techniques were applied to eliminate firstly the presence of noise signal on images.

The aim of this paper is detecting and segmenting the nuclei cells in histology images. For detecting and segmentation of these cells we used the semantic deep learning. Also calculating the criteria like the confusion matrix and get high accuracy than other studies.One of the main functions in the proposed work is detect the centers of nuclei, then extract the regions of interest (ROI). To achieve the purpose of this step, Semantic Segmentation with CNN is applied to histological images. At the end of each step the ground truth being compared with the extracted ROI.

II. Literature Review

In this section we present a comprehensive overview of the studies related to the subject of our proposed work.

In recent literatures [10-12] the authors worked on the deep learning method to detection and classification of the nuclei cells. The convolutional neural networks are used to their implementation.

In [10], the computational approach based on Deep Convolution Neural Networks (Deep CNN) for breast cancer histology image classification is developed. In their method they used Hematoxylin and eosin stained breast histology microscopy image dataset. They used several deep neural network architectures. They used the Area Under Curve (AUC) criteria and the 97.3% they got it. For the sensitivity and specificity, the 96.5% and 88.0% get respectively.

The multi-segmentation method for automatic breast cancer detection and histopathological images classification presented by Singh et al has an overall accuracy of 96.34% for training classification, 95.54% for validation and 95.80% for testing mode[13]. Singh's method shows a color thresholding-based cell level segmentation for automatic breast cancer determination and histopathological image classification[14].

The multi-resolution approach by [15] proposed segmentation which reproduced slide examination done by a pathologist. The analysis of each resolution level focuses on coarser resolution level. At these various resolution levels, a spatial refinement with label regularization to obtain accurate segmentation around boundaries. The proposed methodology requires no supervision due to the specific information available.

The marked point processes (MPP) model for the extraction of multiple objects from images is used in [16]. The advantage of the MPP model is the ability to recognize the geometry of objects, their spatial information and repartition in images.

Similarly to [13] and [14], George et al. [15] propose a diagnosis system for Bee Colony based on the nuclei segmentation of cytological images using different machine learning models, such as neural networks and support vector machines (SVMs). This methodology had an accuracy rates ranging from 76% to 94% on a dataset of 92 images.

There was a new approach based on the analysis of cytological images of FNB, which used the circular Hough transform together with subsequent removal of incorrect or less reliable detections using SVM-based procedure was suggested by George et. al.[17]. The effectiveness obtained by this approach was 98.5%.

Although there are many researches on nuclei detection and segmentation, there have been restricted researches on it using CNN. In this part of the study, some of important researches focusing on nuclei detection and segmentation using CNN have been mentioned.

After a deep study of the state of art in automatic detection of breast cancer nuclei and segmentation we found that Deep Neural Network (DNN) has been recently introduced for biomedical image analysis. Specifically, a combination of CNN is proposed for breast cancer nuclei detection. By comparing the proposed method with the existing ones, we suppose a higher rate of the accuracy in breast cancer nuclei detection and segmentation, as well as we will pay attention to have a less processing time.

III. The Proposed Method

At the first the input Nuclei Image is read. Then the image convert to Gray scaled image. After converting to gray scaled image the Triangle Segmentation Network is loading. the Semantic image segmentation using deep learning is applied to the image. At this step the overlay label matrix regions on 2-D image is used to the result of this image.

The threshold value is used to segmentation scores for each categorical label. In this method we used semantic segmentation for extraction of the nuclei from image.

For post processing the morphological structuring element with "Square" operator is created and then apply close morphological function to image.

3.1 Detection Methods

One of the main functions in the proposed work is detect the nuclei, then extract the regions of interest (ROI). To achieve the purpose of this step, CNN was applied to 105 histological imagesfrom Kaggle 2018 Data Science Bowl (https://bbbc.broadinstitute.org/BBBC038), then a combination of these methods was applied.
At the end of each step the ground truth being compared with the extracted (ROI).

3.1.1 Convolutional Neural Network (CNN)

Figure shows the general topology of a CNN.

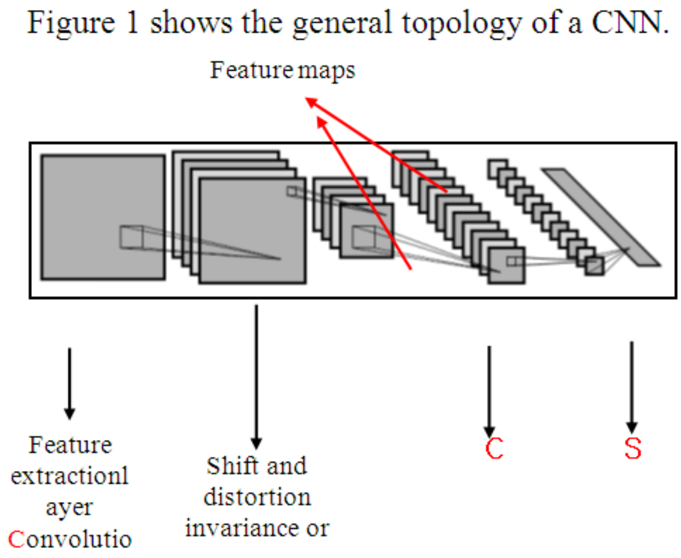


Figure1. CNN's Topology

CNN is a modified variety of deep neural net which depends upon the correlation of neighboring pixels. It uses randomly defined patches for input at the start, and modifies them in the training process. Once training is done, the network uses these modified patches to predict and validate the result in the testing and validation process.

The CNN architecture has two main types of transformation. The first is convolution, in which pixels are convolved with a filter or kernel. This step provides the dot product between image patch and kernel. The width and height of filters can be set according to the network, and the depth of the filter is the same as the depth of the input. A second important transformation is subsampling, which can be of many types (max_pooling, min_pooling and average_pooling) and used as per requirement.

The size of the pooling filter can be set by the user and is generally taken in odd numbers. The pooling layer is responsible to lower the dimensionality of the data, and is quite useful to reduce overfitting. After using a combination of convolution and pooling layers, the output can be fed to a fully connected layer for efficient classification. For detection and semantic segmentation, we use fully convolutional layer The visualization of the entire process is presented in this figure 2.

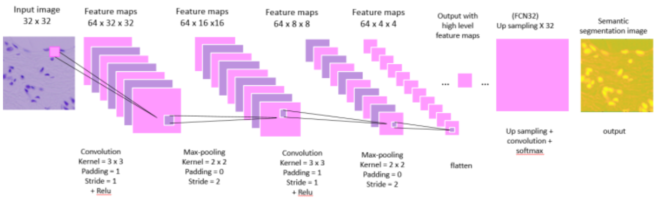


Figure.2 graphic of CNN architecture

For proposed method 5 steps are implemented:

i. Initialization

In this step the breast cancer nuclei image is import to the matrix. After recalling the image we convert to the gray scale image.

ii. Implement the CNN on the Image

Here we load the triangle segmentation network for using in the semantic image segmentation based on deep learning method. Then we overlay label matrix regions on 2-D image.

iii. Morphological operations

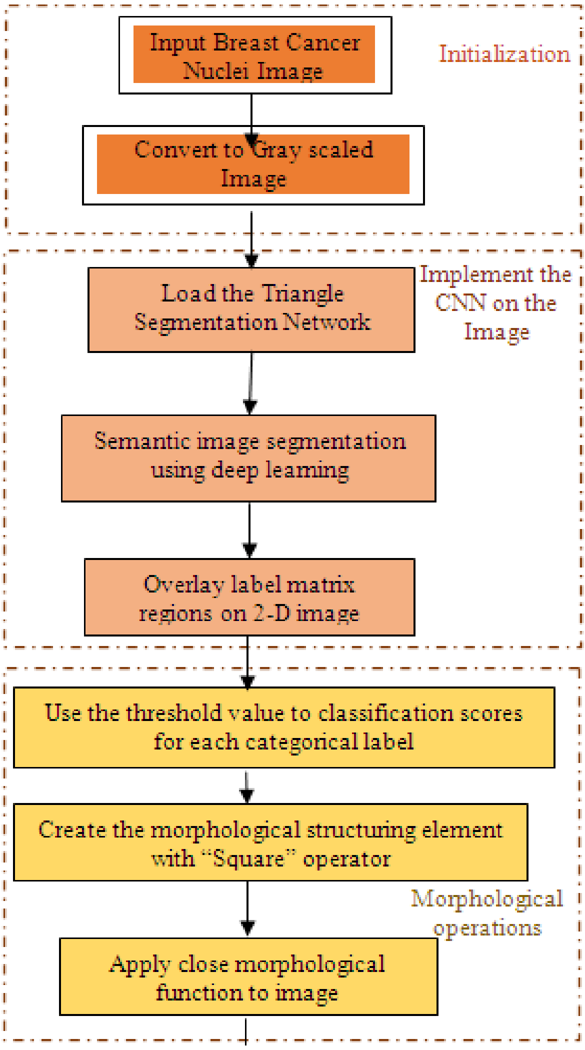
In this step we use the threshold value to segmentation scores for each categorical label. Then we create the morphological structuring element with "Square" operator. Finally we apply close morphological function to image.

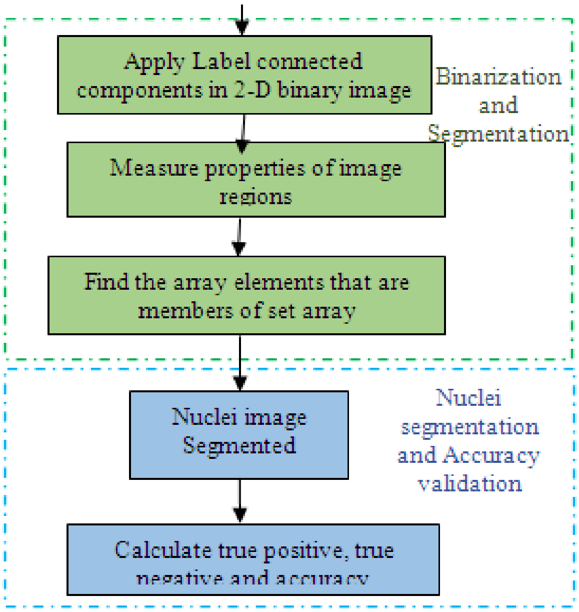
iv. Binarization and Segmentation

In this step we apply label connected components in 2-D binary image. Then we measure properties of image regions and find the array elements that are members of set array.

v. Nuclei segmentation and Accuracy validation

This step is last step and here the nuclei image is segmented. Finally, we calculate true positive, true negative and accuracy.





3.1.2 Multi-threshold algorithm OTSU

This method is used for dividing the image into several classes. Thus, the work of this technique depends on the nature of the lesion contrast. So, applying this method to segment the abnormality requires careful choosing of the number of the classes.

Otsu's method is used to perform automatic thresholding from the shape of the histogram of Image. The algorithm then assumes that the image to be binarized contains only two classes of pixels, (that is to say the foreground and the background) then calculates the optimal threshold which separates these two classes so that their within-class variance is minimal. The extension of the original method to do multi-level thresholding is called Multi Otsu method. The name of this method comes from the name of its initiator [18-20].

In Otsu's method, the threshold that minimizes the intra-class variance is sought from all possible thresholds:

$\sigma_w^2(t) = \omega_0(t)\sigma_0^2(t) + \omega_1(t)\sigma_1^2(t)$ (1)

ω_i represent the probability of being in the σ_i^2ith class, each separated by a threshold t. Finally, the σ_i^2 are the variances of these classes.

Otsu shows that minimizing the intra-class variance amounts to maximizing the inter-class variance:

$\sigma_b^2(t) = \sigma^2 - \sigma_w^2(t) = \omega_1(t)\omega_2(t)[\mu_1(t) - \mu_2(t)]^2$(2)

which is expressed in terms of the class probabilities $\omega_i$and class averages $\mu_i$which in turn can be updated iteratively. This idea leads to an efficient algorithm.

Algorithm

1. Calculate the histogram and the probabilities of each level of intensity.
2. Define the $\omega_i(0)$ and $\mu_i(0)$ initials.
3. Browse all possible thresholds $t = 1$ ... max intensity.

Update ω_i and μ_i

Calculate $\sigma_b^2(t)$

4. The desired threshold corresponds to the $\sigma_b^2(t)$maximum.

3.2 Database

This study supposed to be carried out on a raw database provided from Kaggle 2018 Data Science Bowl,this image data set contains a large number of segmented nuclei images and was created for the Kaggle 2018 Data Science Bowl sponsored by Booz Allen Hamilton with cash prizes. The image set was a testing ground for the application of novel and cutting edge approaches in computer vision and machine learning to the segmentation of the nuclei belonging to cells from a breadth of biological contexts. In the current work 105 microscopic slides of H & E stained samples of histological biopsy have been used. the samples of these dataset are shown in figure 3.

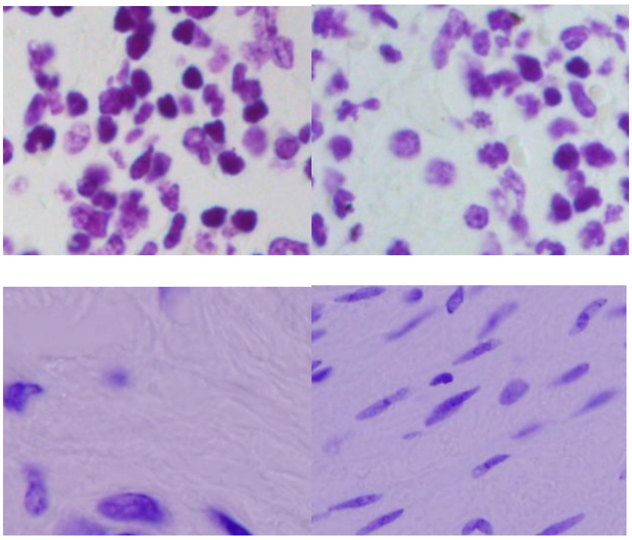


Figure 3. Sample images taken from whole slide images of histological tissue, Hematoxylin and eosin (H&E) stained breast specimen containing invasive ductal carcinoma.

3.3 Performance analysis

Consider a binary class prediction problem, in which the results are labeled positive (p) or negative (n). There are four possible results from a binary classifier like the one proposed. If the result of a scan is p and the given value is also p, then it is known as a True Positive (VP); however, if the real value is n then it is known as a False Positive (FP). Similarly, we have a True Negative (VN) when both the scan and the given value are n, and a False Negative (FN) when the result of the prediction is n but the real value is p. An approximate example of a real problem is the following: consider a diagnostic test that seeks to determine if a person has a certain disease. A false positive in this case occurs when the test predicts that the result is positive, when the person does not actually have the disease. A false negative, on the other hand, occurs when the test result is negative, suggesting that you do not have the disease when you really do.

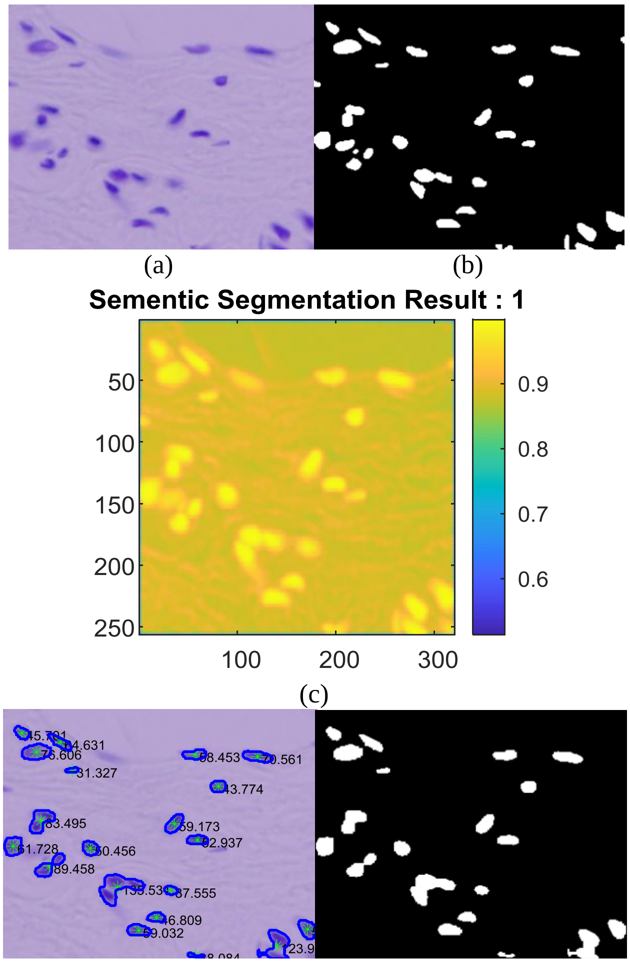
Let's define an experiment from P positive and N negative instances. The four possible outcomes can be formulated in a 2x2 Contingency Table as figure 4:

		Value in reality		
		p	***n***	**total**
Outcome prediction	***p '***	True positives	False positives	P '
	n '	False negatives	True negatives	N '
total		P	N	

Figure 4. true positive, false positive, false negative and true negative illustration

IV. Experimental Results

This section shows the results that obtained after applying detection methods from the simulation using MATLAB 2019a.The original image, ground truth image, result of semantic segmentation, segmentation result and binary result are shown in figure 5.



(a) (b)

(c)

(d) (e)

Figure 5. a) original image, b) ground truth image, c) result of semantic segmentation, d) segmentation result, e) binary result.

The all experimental results that are obtained by implement semantic segmentation with CNN are shown in figure 5.

Also we used the convolutional neural network for semantic segmentation, by Matlab 2019a version. The computer that we use is the Core i7, Ram 8GB, with CPU 12 GB. For post processing we used the structure elements with disc shape, because in the post processing the best shape was disk. To quantitatively evaluate the segmentationmethods, five pixel-based performance metrics, namely, precision, recall, F-measure, Jaccard Index (JI), and Dice similarity coefficient (DSC), were computed for each algorithm. The examined methods are evaluated by comparing with ground truth images. Each connectedregion in the segmented results is considered as one nucleus while ignoring the number of nucleus inside the region.

$$\text{precision}(\text{Pre}) = \frac{\text{true positive}}{\text{true positive} + \text{false positive}}$$

$$\text{recall}(\text{Re}) = \frac{\text{true positive}}{\text{true positive} + \text{false negative}}$$

$$\text{Fmeasure}(\text{Fm}) = \frac{2 * \text{precision} * \text{recall}}{\text{precision} + \text{recall}}$$

$$\text{JI} = \frac{\text{true positive}}{\text{true positive} + \text{false positive} + \text{false negative}}$$

$$\text{DSC} = \frac{2 * \text{true positive}}{2 * \text{true positive} + \text{false positive} + \text{false negative}}$$

This table show the result that we get by applying proposed method on Kaggle 2018 Data Science Bowl data sets.

Image No.	Sensitivity	Specificity	Accuracy	JI	Dice	Precision	Recall	F1 Score
1	83.29	99.79	98.80	80.62	89.27	96.17	83.29	89.27
2	95.54	96.12	96.00	82.54	90.43	85.84	95.54	90.43
3	81.85	99.86	98.78	80.08	88.94	97.38	81.85	88.94
4	89.42	97.18	96.14	75.63	86.12	83.06	89.42	86.12
5	82.49	99.49	97.24	79.79	88.76	96.06	82.49	88.76
6	87.45	98.14	97.23	72.83	84.28	81.33	87.45	84.28
7	71.77	99.96	98.50	71.28	83.23	99.06	71.77	83.23
8	93.58	97.59	96.80	85.22	92.02	90.51	93.58	92.02
9	83.99	99.71	98.20	81.75	89.96	96.83	83.99	89.96
10	82.87	99.32	97.32	79.03	88.29	94.46	82.87	88.29
11	91.23	98.81	97.32	87.02	93.06	94.96	91.23	93.06
12	90.72	99.82	99.45	86.92	93.00	95.40	90.72	93.00
13	89.89	98.59	97.18	83.81	91.19	92.53	89.89	91.19
14	80.77	99.73	97.39	79.26	88.43	97.69	80.77	88.43
15	79.80	99.91	97.70	79.20	88.39	99.06	79.80	88.39
16	97.16	99.74	99.71	79.11	88.34	80.98	97.16	88.34
17	86.05	99.09	98.70	66.68	80.01	74.75	86.05	80.01
18	73.87	99.97	97.29	73.69	84.85	99.66	73.87	84.85
19	93.77	98.53	97.69	87.77	93.49	93.21	93.77	93.49
20	78.74	99.94	99.06	77.60	87.39	98.16	78.74	87.39
21	88.18	98.26	96.44	81.76	89.96	91.82	88.18	89.96
22	100.00	96.85	96.87	14.07	24.67	14.07	100.00	24.67
23	94.73	97.57	97.27	78.72	88.09	82.32	94.73	88.09
24	95.18	96.89	96.70	76.62	86.76	79.71	95.18	86.76
25	87.22	99.04	98.21	77.25	87.16	87.11	87.22	87.16
26	75.90	99.79	97.04	74.69	85.51	97.91	75.90	85.51
27	95.47	99.36	99.23	80.00	88.89	83.16	95.47	88.89
28	91.45	97.30	96.62	75.88	86.29	81.67	91.45	86.29
29	87.10	98.37	96.37	80.99	89.50	92.04	87.10	89.50
30	87.34	99.79	99.01	84.74	91.74	96.60	87.34	91.74
31	84.13	99.76	98.56	81.77	89.97	96.68	84.13	89.97
32	89.09	97.74	96.96	72.58	84.11	79.67	89.09	84.11
Average	**87.19**	**98.81**	**97.68**	**77.15**	**86.32**	**88.43**	**87.19**	**86.32**

For the task of semantic segmentation, we need to retain the spatial information, hence no fully connected layers are used. That’s why they are called fully convolutional networks. The convolutional layers coupled with down sampling layers produce a low-resolution tensor containing the high-level information.

Taking the low-resolution spatial tensor, which contains high-level information, we have to produce high-resolution segmentation outputs. To do that we add more convolution layers coupled with upsampling layers which increase the size of the spatial tensor. As we increase the resolution, we decrease the number of channels as we are getting back to the low-level information.

This is called an encoder-decoder structure. Where the layers which downsample the input are the part of the encoder and the layers which upsample are part of the decoder.

When the model is trained for the task of semantic segmentation, the encoder outputs a tensor containing information about the objects, and its shape and size. The decoder takes this information and produces the segmentation maps.

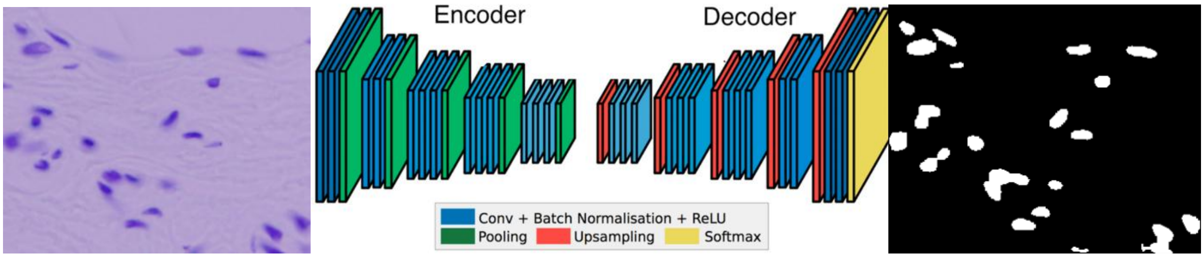


Figure 5. Encoder-Decoder architecture

V. Conclusion

In this paper, nuclei image segmentation and detection on public breast cancer images is done. For segmentation of the nuclei images the convolutional neural network is used. For the post processing the morphological operations are used. For the convolutional neural network, the semantic segmentation is applied. The results show that the proposed method has high accuracy than the other methods. As the results demonstrated that using a Convolutional Neural Network (CNN), was an effective way for cancer nuclei cellsdetection. Wherefore, a convolutional neural network (CNN) has been used to segmenting of the cells cancer nuclei, then the extracted centers were compared with the ground truth samples. Three famous criteria used to evaluating the performance of the method that were sensitivity, specificity and accuracy and the obtained result was 96.67, 95.97 and 97.78 respectively.

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