DEEP LEARNING FOR DEVELOPING CLASSIFICATION PIPELINE TO DETECT METASTATIC BREAST CANCER FROM HISTOLOGICAL WHOLE SLIDE IMAGES (WSI)

by

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To my parents and my siblings.

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ABSTRACT

DEEP LEARNING FOR DEVELOPING CLASSIFICATION PIPELINE TO DETECT METASTATIC BREAST CANCER FROM HISTOLOGICAL WHOLE SLIDE IMAGES (WSI)

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Cancer, the second most deadliest diseases on the planet is a generalized term for the class of diseases caused by proliferation of abnormal cells in a human body. These abnormal cells are caused due to unwanted growth of new cells and improper recycling process of old or damaged cells. They also have tendency to damage cells in its surrounding areas as well as in the areas far away from them, by spreading (metastasize) through different parts of the body. Breast cancer starts developing in breast cells. Metastatic presence in lymph nodes is one of the most important prognostic variables of breast cancer. Methods available today in medical industry are very time consuming as pathologist has to manually analyze sentinel lymph nodes, which requires him to scan entire whole slide image for detecting metastasis region. Moreover, in some cases it's very difficult to detect these metastasis as sometimes they are only visible under high resolution and remains invisible from visual cortex. Developing computer aided methods for analyzing whole slide images has remained a great interest of computer scientist for decades, but historical approaches to histological image

analysis in digital pathology have focused primarily on low level image analysis tasks (e.g., color normalization, nuclear segmentation, and feature extraction). These classical methods have not been proven useful for practical use in clinical practice as they require several manual parameters to be set manually for accurate results thus proves burdensome for pathologists. Also these techniques can't be generalized for every whole slide image as whole slide images prepared by different clinical laboratories happen to contain variety of staining like Haemotoxylin, Eosin and others.

In this thesis, a deep learning-based classification pipeline for detection of cancer metastases from whole slide images of breast sentinel lymph nodes is proposed and analyzed. The classification pipeline consists of five different stages: 1. Image processing for background subtraction. 2. Tiling. 3. Deep ConvNet for tile based classification. 4. Building Tumor probability heat-maps. 5. Heat-map post-processing for slide based classification. GoogLeNet, a deep 27 layer ConvNet is used to distinguish tumor positive areas from negative ones into digital whole slide images. The main challenge is to discriminate between hard negative areas from positives ones as tiles from hard negative areas mimic tiles from positive areas which results in too many false positives. Ensemble learning method using two Deep ConvNet model is developed to eliminate these false positives. Proposed system achieves an area under the receiver operating curve (AUC) of 0.91 which is quite close to score obtained by human pathologist while reviewing same images. Results in this thesis indicate that proposed platform can automatically scan any WSI for detecting metastatic regions. Moreover, following Deep Learning based approach, it can also be generalized for different types of whole slide images with minimal efforts.

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CHAPTER 1

INTRODUCTION

1.1 Cancer

Cancer [1] can start any place in the body. It starts when cells grow out of control and crowd out normal cells. This makes it hard for the body to work the way it should. Cancer can be treated very well for many people. In fact, more people than ever before lead full lives after cancer treatment. There are many types of cancer. Its not just one disease. Cancer can start in the lungs, the breast, the colon, or even in the blood. Cancers are alike in some ways, but they are different in the ways they grow and spread. The cells in our bodies all have certain jobs to do. The key property of cells is their natural way of reproduction. Normal cells divide in an orderly way. They die when they are worn out or damaged, and new cells take their place. Cancer is when the cells start to grow out of control. The cancer cells keep on growing and making new cells. They crowd out normal cells. This causes problems in the part of the body where the cancer started. Cancer cells can also spread to other parts of the body. For instance, cancer cells in the lung can travel to the bones and grow there. When cancer cells spread, its called metastasis. When lung cancer spreads to the bones, its still called lung cancer. To doctors, the cancer cells in the bones look just like the ones from the lung. Its not called bone cancer unless it started in the bones. Some cancers grow and spread fast. Others grow more slowly. They also respond to treatment in different ways. Some types of cancer are best treated with surgery; others respond better to drugs called chemotherapy. Often 2 or more treatments are

[1] http://www.cancer.org/cancer/

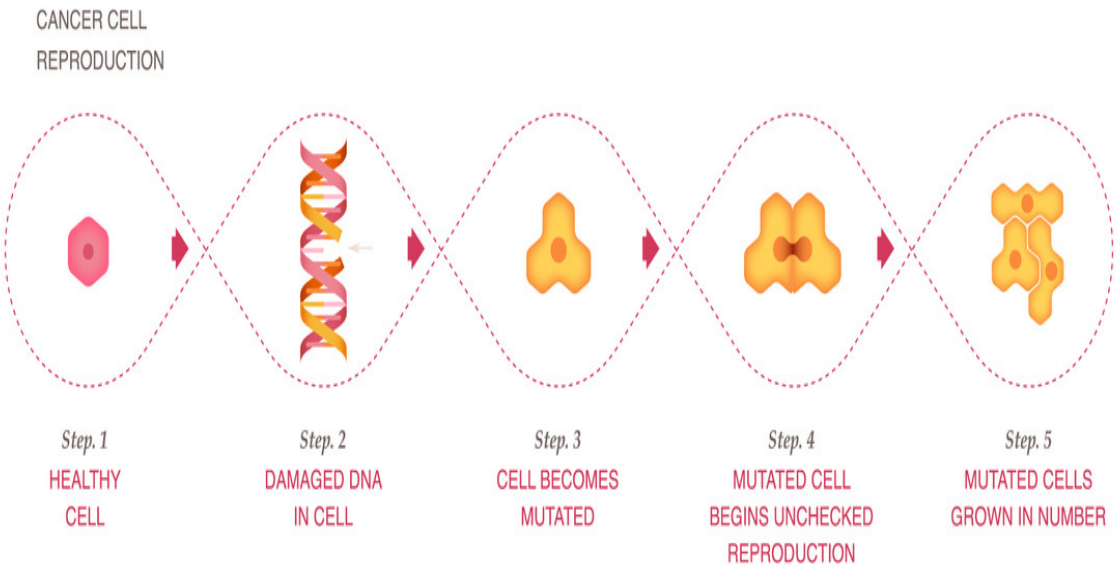

Figure 1.1. Cancer cells reproduction.

used to get the best results. When someone has cancer, the doctor will want to find out what kind of cancer it is. People with cancer need treatment that works for their type of cancer. Most cancers form a lump called a tumor or a growth. But not all lumps are cancer. Doctors take out a piece of the lump and look at it to find out if its cancer. Lumps that are not cancer are called benign (be-NINE). Lumps that are cancer are called malignant. There are some cancers, like leukemia (cancer of the blood), that dont form tumors. They grow in the blood cells or other cells of the body. The doctor also needs to know if and how far the cancer has spread from where it started. This is called the cancer stage. You may have heard other people say that their cancer was stage 1 or stage 2. Knowing the stage of the cancer helps the doctor decide what type of treatment is best. For each type of cancer there are tests that can be done to figure out the stage of the cancer. As a rule, a lower stage (such as a stage 1 or 2) means that the cancer has not spread very much. A higher number (such as a stage 3 or 4) means it has spread more. Stage 4 is the highest stage.

The most common treatments for cancer are surgery, chemotherapy, and radiation. Surgery can be used to take out the cancer. The doctor might also take out some or all of the body part the cancer affects. For breast cancer, part (or all) of the breast might be removed. For prostate cancer, the prostate gland might be taken out. Surgery is not used for all types of cancer. For example, blood cancers like leukemia are best treated with drugs.Chemo (short for chemotherapy) is the use of drugs to kill cancer cells or slow their growth. Some chemo can be given by IV (into a vein through a needle), and others are a pill you swallow. Because chemo drugs travel to nearly all parts of the body, they are useful for cancer that has spread. Radiation is also used to kill or slow the growth of cancer cells. It can be used alone or with surgery or chemo. Radiation treatment is like getting an x-ray. Sometimes its given by putting a seed inside the cancer to give off the radiation.

1.2 Breast cancer

Breast [2] cancer is the second leading cause of death among women. Breast cancer starts in the cells of the breast as a group of cancer cells that can then invade surrounding tissues or spread (metastasize) to other areas of the body. Breast cancer occurs when malignant tumors develop in the breast. These cells can spread by breaking away from the original tumor and entering blood vessels or lymph vessels, which branch into tissues throughout the body. When cancer cells travel to other parts of the body and begin damaging other tissues and organs, the process is called metastasis.

[2]http://www.nationalbreastcancer.org/about-breast-cancer

1.2.1 Types of Breast cancer

1. Ductal Carcinoma in situ: Ductal Carcinoma in Situ (DCIS) is a non-invasive breast cancer where abnormal cells have been contained in the lining of the breast milk duct.
2. Invasive Ductal Carcinoma: Invasive Ductal Carcinoma means that abnormal cells that originated in the lining of the breast milk duct have invaded surrounding tissue.
3. Triple Negative Breast Cancer: Triple negative breast cancer means that the cells in the tumor are negative for progesterone, estrogen, and HER2/neu receptors.
4. Inflammatory Breast Cancer: Inflammatory breast cancer is a less common form of breast cancer that may not develop a tumor and often affects the skin.
5. Metastatic Breast Cancer: Metastatic breast cancer is cancer that has spread beyond the breast, sometimes into the lungs, bones, or brain.

1.2.2 Diagnosis

1. Mammogram: A mammogram is an x-ray that allows a qualified specialist to examine the breast tissue for any suspicious areas. In a diagnostic mammogram, more x-rays are taken, providing views of the breast from multiple vantage points.
2. Ultrasound: A breast ultrasound is a scan that uses penetrating sound waves that do not affect or damage the tissue and cannot be heard by humans.
3. MRI: During a breast MRI, a magnet connected to a computer transmits magnetic energy and radio waves (not radiation) through the breast tissue. It scans the tissue, making detailed pictures of areas within the breast.

4. Biopsy: A breast biopsy is a test that removes tissue or sometimes fluid from the suspicious area. The removed cells are examined under a microscope and further tested to check for the presence of breast cancer.

1.2.3 Treatment

Working with a doctor to guide your breast cancer treatment decisions is key. Determine what you need to do to cultivate a positive partnership with your doctor and when it might be prudent to seek a second opinion. Also before selecting your breast cancer treatment plan, its a good idea to understand the difference between standard treatment and clinical trials so you can make an informed decision about what is right for you. Breast cancer standard treatments are methods that experts agree are appropriate, accepted, and widely used. These standard procedures have proven useful in fighting breast cancer in the past. A breast cancer clinical trial, on the other hand, is an approved research study that some doctors believe has a strong potential to improve standard treatments. When clinical trials demonstrate better results than the standard, that new treatment becomes the standard; hence all current standards were clinical trials at one time. Below are list of treatments that are in use for cancer treatment in clinical practices today.

1. Surgery: The most common form of treatment for breast cancer is surgery. This involves removing the tumor and nearby margins. Surgical options may include a lumpectomy, partial mastectomy, radical mastectomy, and reconstruction.
2. Chemotherapy: Chemotherapy is a breast cancer treatment method that uses a combination of drugs to either destroy cancer cells or slow down the growth of cancer cells.

3. Radiation Therapy: Radiation therapy (also called radiotherapy) uses high-energy rays to kill cancer cells. It affects the nearby skin or cells only in the part of the body that is treated with the radiation.
4. Hormone therapy: If the cancer cells have hormone receptors, you may be prescribed hormone therapy drugs, such as blockers or inhibitors. Both types of drugs help to destroy cancer cells by cutting off their supply of hormones.
5. Targeted therapy: Breast cancer targeted therapy uses drugs that block the growth of breast cancer cells in specific ways. For example, targeted therapy may block the action of an abnormal protein (such as HER2) that stimulates the growth of breast cancer cells. For example, Trastuzumab (Herceptin) or lapatinib (TYKERB) may be given to a woman whose lab tests show that her breast tumor has too much HER2. Currently, these targeted methods are commonly used in combination with traditional chemotherapy. However, targeted drugs often have less severe side effects than standard chemotherapy drugs.
6. Hormone therapy: If the cancer cells have hormone receptors, you may be prescribed hormone therapy drugs, such as blockers or inhibitors. Both types of drugs help to destroy cancer cells by cutting off their supply of hormones.

1.3 Problems & Challenges in diagnosis

The medical specialty of pathology is tasked with providing definitive disease diagnoses to guide patient treatment and management decisions. Standardized, accurate and reproducible pathological diagnoses are essential for advancing precision medicine. Since the mid-19th century, the primary tool used by pathologists to make diagnoses has been the microscope. Limitations of the qualitative visual analysis of microscopic images includes lack of standardization, diagnostic errors, and the significant cognitive load required to manually evaluate millions of cells across hundreds

of slides in a typical pathologists workday. The evaluation of breast sentinel lymph nodes is an important component of the American Joint Committee on Cancers TNM breast cancer staging system, in which patients with a sentinel lymph node positive for metastatic cancer will receive a higher pathological TNM stage than patients negative for sentinel lymph node metastasis, frequently resulting in more aggressive clinical management, including axillary lymph node dissection. The manual pathological review of sentinel lymph nodes is time-consuming and laborious, particularly in cases in which the lymph nodes are negative for cancer or contain only small foci of metastatic cancer. Many centers have implemented testing of sentinel lymph nodes with immunohistochemistry for pancytokeratins, which are proteins expressed on breast cancer cells and not normally present in lymph nodes, to improve the sensitivity of cancer metastasis detection. However, limitations of pancytokeratin immunohistochemistry testing of sentinel lymph nodes include: increased cost, increased time for slide preparation,and increased number of slides required for pathological review. Further, even with immunohistochemistry stained slides, the identification of small cancer metastases can be tedious and inaccurate.

1.3.1 Digital Pathology

Pathology is a 150-year-old medical specialty that has seen a paradigm shift over the past few years with the advent of digital pathology. Digital pathology is enabled in part by virtual microscopy, which is the practice of converting glass slides into digital slides that can be viewed, managed, and analyzed on a computer monitor. With the advent of Whole-Slide Imaging (WSI), the field of digital pathology has exploded and is currently regarded as one of the most promising avenues of diagnostic medicine in order to achieve even better, faster and cheaper diagnosis, prognosis and

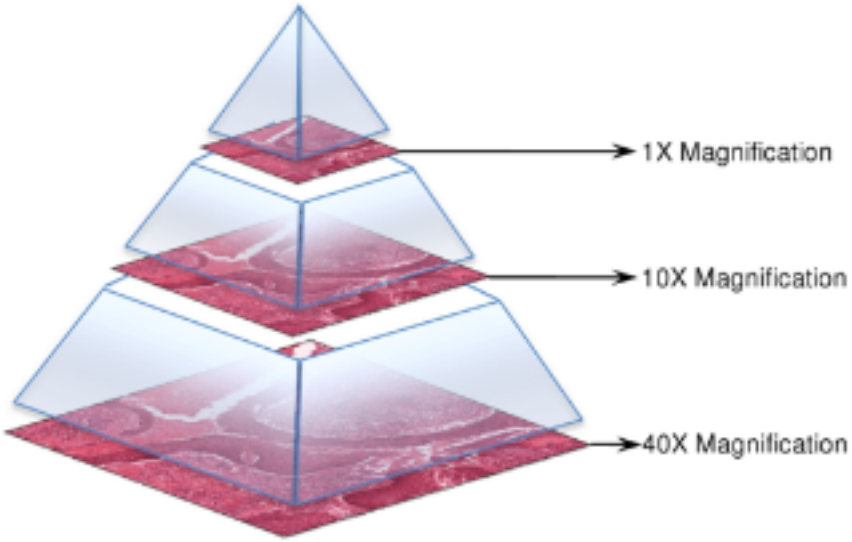

Figure 1.2. Multi-resolution Whole Slide Image.

prediction of cancer and other important diseases. Figure 1.3 [3] displays a layer model depicting steps involved in preparation and viewing of WSI. While proliferation of digital pathology is at an all time high, the industry has not crossed the rubicon into clinical diagnostics due to inherent problems. The discipline is plagued with human variability from tissue acquisition, improper staining techniques, and subjectivity in diagnosing under a microscope. Pathologist look for patterns in a tissue sample and use their medical training to interpret those patterns and make a diagnosis. As evidenced through many applications in myriad industries, computer-assisted pattern recognition software can match or even supersede a humans ability to recognize patterns. Though digital pathology is on the precipice of wide-spread adoption, the difficulties in hardware scanning variability and fear of black-box computational tools has lead to a longer adoption curve than seen in other medical specialties that

[3]http://www.hopkinsmedicine.org/mcp/PHENOCORE/CoursePDFs/2013/13 19 Cornish Digital Path.pdf

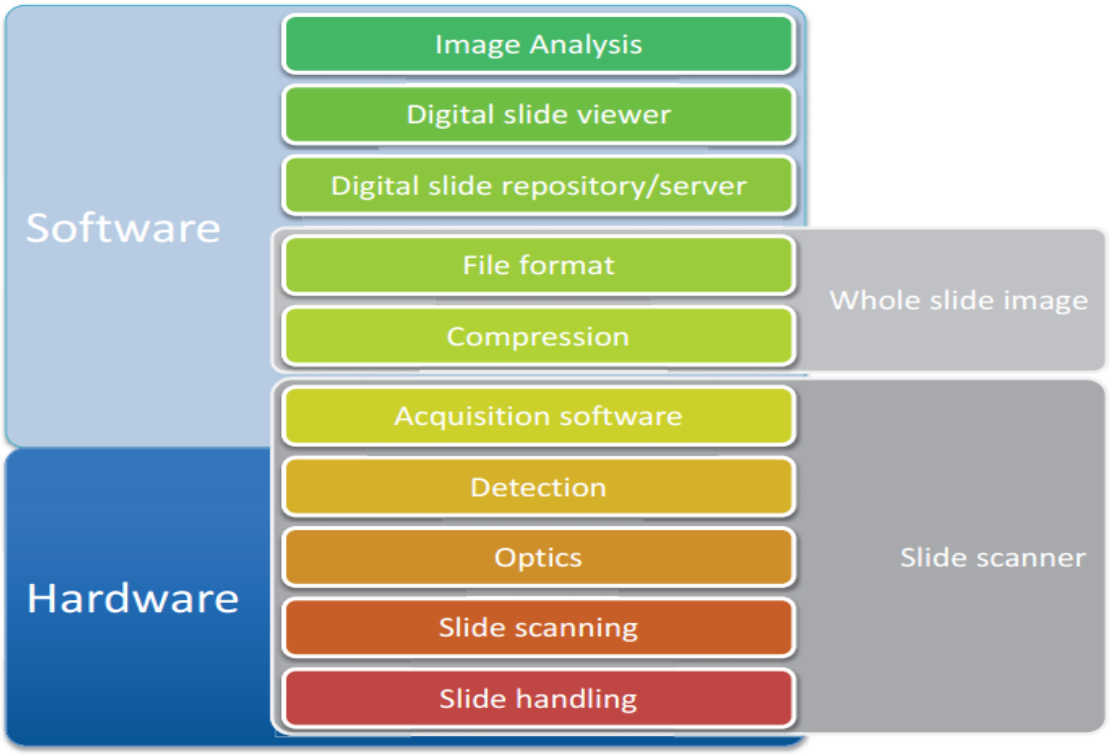

Figure 1.3. A layer model depicting steps involved in preparation of WSI.

have gone totally digital, e.g. radiology. Over the past several decades there has been increasing interest in developing computational methods to assist in the analysis of digital microscopic images in pathology. Consequently, computer-assisted image analysis systems have been developed to aid in the detection metastatic tissues from digital slides of sentinel lymph nodes; however, these systems are not used clinically due to lack of standardization of image formats, system noise, and lack of clinical and technical studies on digital pathology systems. Thus, the development of effective and cost efficient methods for sentinel lymph node evaluation remains an active area of research, as there would be value to a high-performing system that could increase accuracy and reduce cognitive load at low cost.

1.4 Deep Learning

Deep Learning is a new area of Machine Learning research, which has been introduced with the objective of moving Machine Learning closer to one of its original goals: Artificial Intelligence. Various deep learning architectures such as deep neural networks, convolution deep neural networks, deep belief networks and recurrent neural networks have been applied to fields like computer vision, automatic speech recognition, natural language processing, audio recognition and bio-informatics where they have been shown to produce state-of-the-art results on various tasks. Convolutional Networks fondly known as ConvNets is biologically inspired form of artificial neural network with local connections and shared weights. ConvNets are most important tool of machine learning in the current generation with a wide application to Image recognition tasks in the field of Computer Vision. Some of the popular and highly used ConvNet models are:

1. LeNet: The first successful applications of Convolutional Networks developed by Yann LeCun in 1990s. Of these, the best known is the LeNet architecture that was used to read zip codes, digits, etc.
2. AlexNet: The first work that popularized Convolutional Networks in Computer Vision, developed by Alex Krizhevsky, Ilya Sutskever and Geoff Hinton. The AlexNet was submitted to the ImageNet ILSVRC challenge in 2012 and significantly outperformed the second runner-up (top 5 error of 16% compared to runner-up with 26% error). The Network had a very similar architecture to LeNet, but was deeper, bigger, and featured Convolutional Layers stacked on top of each other (previously it was common to only have a single CONV layer always immediately followed by a POOL layer).
3. GoogLeNet: The winner of ILSVRC 2014, developed by Szegedy et al. from Google. Its main contribution was the development of an Inception Module that

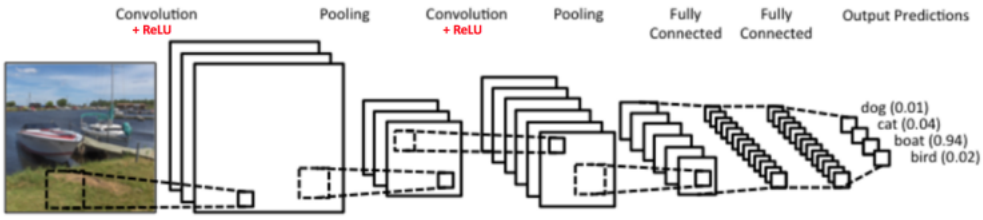

Figure 1.4. ConvNet Architecture.

dramatically reduced the number of parameters in the network (4M, compared to AlexNet with 60M). Additionally, this paper uses Average Pooling instead of Fully Connected layers at the top of the ConvNet, eliminating a large amount of parameters that do not seem to matter much. There are also several followup versions to the GoogLeNet, most recently Inception-v4.

4. VGGNet: The runner-up in ILSVRC 2014, from Karen Simonyan and Andrew Zisserman that became known as the VGGNet. Its main contribution was in showing that the depth of the network is a critical component for good performance. Their final best network contains 16 CONV/FC layers and, appealingly, features an extremely homogeneous architecture that only performs 3x3 convolutions and 2x2 pooling from the beginning to the end.
5. ResNet: Residual Network developed by Kaiming He et al. was the winner of ILSVRC 2015. It features special skip connections and a heavy use of batch normalization. The architecture is also missing fully connected layers at the end of the network. ResNets are currently by far state of the art Convolutional Neural Network models and are the default choice for using ConvNets in practice.

There are three main types of layers to build ConvNet: Convolutional Layer, Pooling Layer, and Fully-Connected Layer. We can list out different components in a convolution network as follows:

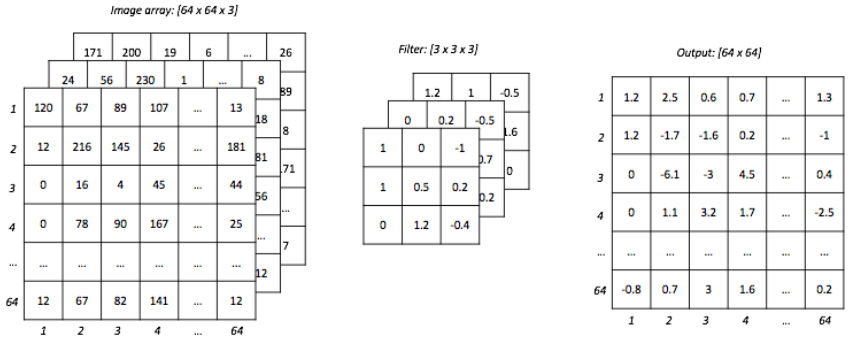

Figure 1.5. Convolution operation.

1. CONVOLUTION: computes the output of neurons that are connected to local receptive field of the input, computing a dot product between weights and local region of input volume. See Figure 1.5.
2. ACTIVATION: to apply element wise activation function such as ReLU.
3. POOLING: to perform down sampling operation along the spatial dimensions of the input. See Figure 1.6.
4. FULLY CONNECTED: This is similar to a neural network where each neuron is connected to all neurons in previous layers. This layer helps to estimate class scores.

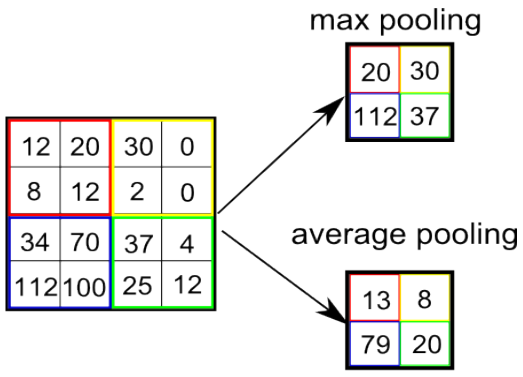

Figure 1.6. Pooling operation.

1.5 Goal of Thesis

CHAPTER 2

RELATED WORK

CHAPTER 3

DEEP LEARNING FOR DETECTING METASTATIC BREAST CANCER

3.1 WSI Classification pipeline

3.1.1 Image processing for background subtraction

3.1.2 Tiling

3.1.3 Deep ConvNet for tiles based classification

3.1.4 Building Tumor probability heat-maps

3.1.5 Heat-map post-processing for slide based classification

CHAPTER 4

EXPERIMENTAL RESULTS

4.1 Dataset

4.2 Experimental setup

4.3 Evaluation metrics

4.3.1 ROC curves

4.4 Model-1 results

4.5 Model-2 results

4.6 Ensemble method results

CHAPTER 5

CONCLUSION AND FUTURE WORK

The aim of this thesis was to evaluate the feasibility of applying Convolutional Networks for the purpose of Cell Segmentation from histopathology images. The importance of cell segmentation in digital pathology is realised by the fact that cancer being a disease proliferating by means of cells, accurate preliminary of localization of cells in digital images aid radiologists to accelerate preliminary diagnosis of patients [9]. Currently convolutional neural networks outrun all previous methods in many vision perception applications like classification by winning challenges over huge margin. The onset of ConvNets success influences researchers to apply its techniques for structured prediction tasks like pixel level classification. Off late numerous researchers experiment effectiveness of ConvNets in segmentation approaches with respect to different applications. This curiosity fuels the goal of our thesis to evaluate effectiveness of deep learning approaches in cancer diagnosis.Due to the fact that large annotated dataset is missing for cancer histopathological images and ConvNets can be highly exploited only in the presence of huge labelled datasets there are very few research tasks being performed in cell segmentation using deep learning. We took this as a challenge and successfully evaluated three deep learning approaches and its efficacy for effective cell segmentation by resorting to techniques like use of data augmentations and development of simple image labelling tool to generate gold standard annotation images.

From the experiments performed on two different datasets, we conclude that convolutional networks with appropriate loss functions and training methods can very

efficiently segment cancer cells from micro-slide images. We also prove that crowd-sourcing labeling process seems effective to train our models as convolution networks inherently have the ability to understand data in a coherent manner for the application it is being trained. Despite the results that shows CNN's have power to generalize between different type of cells tumor or non-tumor with little data there exists a huge arena to optimize the performance of convolution networks for cell segmentation. Based on our evaluations a future research direction could be to apply training on whole open source dataset of kidney cancer images and fine-tune it on TCGA's lung cancer data to deliver more detailed report on generalization capability of convolution networks. Also another suggestion for future research direction to boost accuracy of cell segmentation would be the use of Ensemble methods for cancer diagnosis using deep learning.

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BIOGRAPHICAL STATEMENT

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