Dimensions of histopathology and automated computer aided tool to unravel bone cancer

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Abstract

Any research need foreground information for analysing to proceed further. To design and develop CAD one has to study the manual procedures and subject specific areas. This research is revolved around primary bone cancer. But it is acknowledged that minimal research is carried out in bone cancer domain. Reason is limited availability of data sources and digital technology initiative. Moreover, it is hard to discover plenty of features present in bone cancer. But today, bone cancer is very common and enforced to embrace research in this area. Hence, it is significant and this proposed research work is an attempt for the burning health issue. There are different methods, techniques and processes involved to discover suitable remedies. As a consequence of this study, the best accurate result was obtained when compared to all other previous work carried out.

Keywords: Bone cancer, computer aided diagnosis, histopathology, radiology

1. Introduction

1.1 Motivation & Scope of the Work

Countries with healthy people significantly contribute for overall growth of national GDP. Liability of one country is its sick people. Today, rapid technology advancement is also standstill in tackling health issues. Diseases outnumbered and difficult to categorize due to its complexity. Decades ago, cancer had its limited fragrance. Today, scenario changed drastically and majority of people suffer from cancer. Instantly, research studies took its dimension to combat life threatening disease. Automation tools are developed and ray of hope infused among scientists in the medical field. Presently, bone cancer also becoming very common among people including children. Its diagnosis is complicated because of bone architecture complexity. The growth in digital histopathology motivated engineers and doctors to develop a computer aided diagnosis solution. Today, digital histopathology data sets are readily available to conduct the research work in this field. Doctors in Pathology,

Radiology and Oncology specialists along with Engineers had the urge to discover automated solutions. Medical workshops, case studies are motivated people to intervene in this research area.

Cancer made people lose their feeding family members. The mental agony and loss of life support are the outcome of this disease. Development of research in digital histopathology can save millions of people through quick and accurate automated diagnosis process. This is the major contribution to the society at large. Doctor's manual diagnosis work is tedious and it will be made easier with the digital histopathology automation. Through simple and quick diagnosis procedure thousands of patient's screening can be done with the automation tool. However, this automation procedure will save the time of doctors.

The main component of this research area is bone cancer. Bone cancer has complex features and difficult to diagnose within short time in the manual method. Multiple feature study is difficult to study and to declare the malignancy status. Therefore, this study has wider scope for multiple feature exposure.

1.2 Objectives of the work

The framework of this research work has clear cut objectives which are unique and challenging one due to variation in bone cancer, complex tissue structure and its relationship. Features are incomparable from one another. There is a need to create different features sets according to the nature of bone cancer such as osteosarcoma, chondrosarcoma and Ewing sarcoma.

2. Bone cancer

Health is wealth for any human being. Otherwise those will imbalance the entire system. Technical advancement is the boon to improve life expectancy. Rapid automation development in all fields reduced physical exercise of human beings. Accordingly, organizations demand people with multiple skills in this competitive era. Business growth strategies increase the stress level of workforce. Lack of exercise, family and work life related stress, living style and food habits are the common factors for unhealthy society. Today, diseases are very common in every family. Moreover, cancer is spreading like any other epidemic disease.

Bone cancer also increased and more commonly present in Asian Continent. Diagnosis is a challenge and timely treatment is nightmare because non availability of doctors as per the proportion of population. Due to this feeding and supporting family members lost their life due to cancer.

From the WHO report it is understood that cancer is the reason for death of 9.2 million people in the year 2018. There was 0.4% of primary bone cancer is reported as per [WHO, 2023] [1]. The American cancer society (2023) stated that 3,300 people with bone cancer and 1,490 people are predicted to die [2]. Asian continent is leading and it can be overtaken by America within short span of time. From these entire observations one can understand that bone disease is rampant across the world like any other epidemic. Therefore, research in bone cancer is indispensable to save millions of people.

2.1 Overview of bone formation

Bone and cartilage are connective tissue [3] made up of cells and extra cellular matrix. The main categories of bone are osteoblasts, osteocytes and osteoclasts. Osteoblasts are a bone-synthesis cell develops into osteoid gradually turn into harder bone. At the time of bone formation Osteoblasts are buried in the bone matrix and which turns into osteocytes. These osteocytes can be seen more commonly in matured bone. Osteoclasts plays very crucial role in repairing bone and remodelling. Osteoclasts are large, multinucleated cells found on bone surfaces. The feature of cartilage is a strong, flexible and semi-rigid supporting tissue consists of chondroblasts and chondrocytes.

2.2 Diagnostic bone pathology

The cytology of bone cancer [4] is rely on bone forming cells such as osteocytes, osteoblasts, osteoclasts chondrocytes and chondroblasts, its morphology. In bone cancer the abnormality pattern outgrowth by the sarcomas can be seen. The cancer category is usually based on cells pleomorphism, mitosis and its proliferation. Pathologist who describe, evaluate and grade the malignancy stage of cancer.

The distinction can be made between benign cartilage lesions and chondrosarcoma is based on state and quality of tissue, degree of structural abnormality and cancerous growth as compared with normal bone. Differentiating benign cartilage lesions from chondrosarcoma by visual and subjective observation is tedious task for pathologists.

Thus, this issue is to be addressed with utmost priority through integrating radiological and pathological findings in all diagnoses of cartilage lesions. Huge variants of osteosarcoma and complicate cell morphology make diagnosis process more complex. The small cell form of osteosarcoma and Ewing's sarcoma may exhibit same features. Likewise, overall structural features of bone giant cell tumor [5] and its consistency genuinely produce clear result in the diagnosis in many cases. Apart from this, other common features present are deposition of osteoid, fibroblast foci, group of foamy cells or cystic degeneration. The stromal cells and the osteoclasts cells are viewed as reactive.

Pathologist unable to differentiate some variants of osteosarcoma and fibrosarcoma [6]. In fibrosarcoma, malignant clustered pattern of spindle cells and inadequate bone osteoid generation is common. It is very difficult to demarcate high-grade fibrosarcoma from fibroblastic osteosarcoma due to less bone matrix production and accuracy depends upon appropriate biopsy sampling.

Sometimes malignant fibrous histiocytoma classified as spindle cell and pleomorphic bone sarcomas. From this classification presence of bone matrix production is unable to see. Same feature also be seen in osteosarcoma with minimal osteoid production like features in fibrosarcoma.

2.3 Classification of bone tumor

One can classify tumors either benign or malignant. From benign tumor no harm and parts of body may not be affected. Primary bone cancers begin in the bone spread all over in the body is called malignant tumors. Generally, this malignant tumor will be found in bone, muscle, cartilage etc. Accordingly, there are various types of primary

bone cancers and its diagnosis can be made through considering affected area of bone and the type of cell forming the tumor, age.

Bone tumor classification depends on features like histological and cytological such as cell structure and its rapid growth which provides useful information about the tumor. In many cases the tumor grows from the type of cell it produces. In Ewing sarcoma there is abnormal growth of tissue those are significantly undifferentiated without exhibiting any kind of tissue creation. This will be classified into benign and malignant primary bone tumor. Following table describes the general classification of bone tumor [7]. Table 2.3 depicts Classification of bone tumor (WHO).

Table 2.1: Classification of bone tumor (WHO)

Bone Tumor Classification (WHO)		
General type	**Benign**	**Malignant**
Bone-forming Tumors [8]	Osteoid osteoma	Osteosarcoma
Cartilage tumors [9]	Chondroma	Chondrosarcoma
Fibrohistiocytic Tumors [10]	Fibroma	Fibrous histiocytoma
Giant cell tumor of bone [11]	Aneurysmal Bone	Malignant Giant Cell Tumor
Ewing Sarcoma [12]	Eosinophilic Granuloma	Myeloma

Primary bone sarcoma includes the osteosarcoma, chondrosarcoma, Ewing sarcoma [13].

More than 70% of bone cancers are osteosarcoma, chondrosarcoma and Ewing's sarcoma. Statistics of bone cancer in Table 2.2.

Table 2.2: Bone cancer statistics (statistics as per American Cancer Society 2023)

Primary Bone Cancer	**Adults**	**children**
Osteosarcoma	28%	56%
Chondrosarcoma	40 %	6%
Ewing's Sarcoma	8%	34 %

Osteosarcoma, Chondrosarcoma and Ewing sarcoma are considered as primary bone cancer. This emanates to other region as well. If automated feature extraction tool succeed for all these primary cancer it can be applied to all other forms of cancer. Pathologist diagnoses the disease based on their subjective knowledge of bone such as age, common site, distributions of both benign and malignant tumor [14]. Common site of bone cancer in Table 2.3.

Table 2.3: Common Sites of Bone Cancer

Primary bone tumors	**Common sites**
Osteosarcoma	The humerus, femur and tibia, jaw and the pelvis.
Chondrosarcoma	Pelvis, femur and humerus.
Ewing's Sarcoma	Pelvis, skeleton, ribs.

3. Histopathology and Radiology

Pathology and radiology are inter related and findings from the both are crucial for cancer diagnosis. Pathology focuses on distinct cytological aspects of tissues whereas radiology focuses on tumor location and suggests physical exams, laboratory tests and biopsies. There is need of correct and accurate pathology description for complete diagnosis of the patient for best treatment [15].

The findings in the radio diagnosis process helps in detecting affected area which is used for histopathological confirmation as shown in figure 2.1. Pathologists in Histopathology examines biopsy sample with using microscope to understand the tissue pattern and its related diseases. Biopsy is the process of extracting tissue sample from the affected area and pathologist who investigates for confirmation of cancer. Pathologists use this method to identify the type and grade of the cancer. Two methods for biopsy procedure [16].

- **Needle biopsy:** This is performed after giving small dose of usual anesthesia. A thin needle is injected into the bone and a sample of tissue is extracted.
- **An open biopsy:** Surgery is needed to expel large tissue sample from the affected bone for further analysis.

Radiologists use the image technique in the system to obtain best visuals of the tissue area. Pathologist will study and analyze the pattern sample tissue structure through microscope. There are standard techniques such as Hematoxylin and Eosin for staining slides which clearly exhibits cell morphology and its architecture. These techniques are widely used in diagnosis of cancer and its application in histopathology phenomenal often termed as golden standard. Application of combined solution of Hematoxylin and Eosin will produce the cell colors such as blue, red, violet and pink in color. The staining method includes utilization of hemalum, where in the nuclei o blue in color can seen. When you apply alcoholic solution of eosin eosinophilic structures in various color shades such as pink, red and orange can be seen.

The biopsy report includes the following information [17]:

- Details of abnormal pattern of cells and its grading level. Classification of malignancy level is called grading high or low. Low level cell is like healthy cell grow slowly whereas high level cell growth is fast and spread quickly.
- Mitotic activity of cell which is the deciding factor in determining the type of cancer and the stages of cancer.
- It also documents the overall status of cancer whether which has spread to nearby tissues.

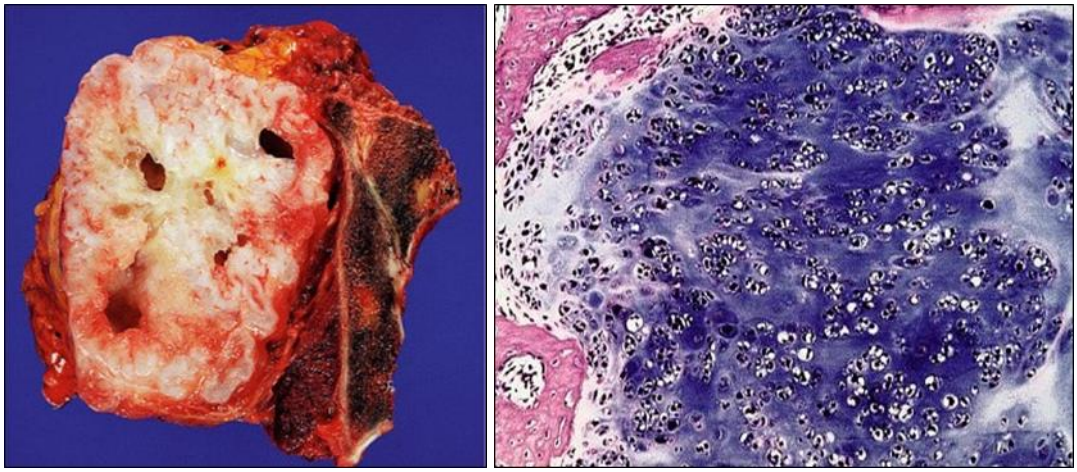


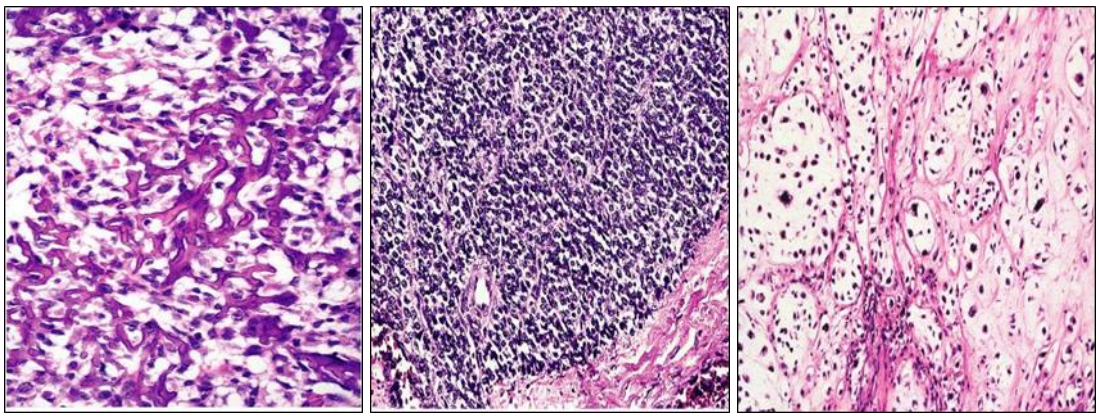
Fig 2.1: Comparison of Radiological Image and Pathological Image

3.1 Histopathology

Detailed microscopic diagnostic features in common bone tumor as mentioned below [18].

3.1.1 Osteosarcoma

- In High grade cancer different cell texture can be found in terms of losing actual size, shape when compare to normal cells-hyper cellularity.
- Higher side presence of abnormal cells and spindle shaped cells shows different sizes and shapes-pleomorphism.
- Large nuclei and thin scanty layer of cytoplasm, 2:1 nuclei-cytoplasm ratio.
- Increased abnormal pattern of mitotic activity.
- Peculiar hyper chromatic nuclei.
- More Osteoid production and produce lace-like pattern between the cancer cells and produce pink in color with H&E stains.
- No uniformity of cells on the surface of trabecular of osteoid.
- Not mineralize osteoid commonly seen in microscopic bone image.



(a) **(b)** **(c)**

Fig 3: a) Osteosarcoma with Malignant Osteoid, 3b) Chondrosarcoma Shows Huge Pleomorphism 3c) Small Cell Ewing Sarcoma

3.1.2 Chondrosarcoma

This is the malignant tumor containing cartilage substance and chondrocytes. Osteoid development is not the part of this tumor. Chondrosarcoma tumor can be determined with the presence of site of lesion, cell differentiation or histological variant.

During observation of chondrosarcoma digital slide small, round, oval or spindle shaped neoplastic cells are found. There is poor formation of Lacunae and have round or ovoid nuclei. Image may contain islands of collagen resembling osteoid.

- Cells are pleomorphic and hyper cellular.
- Cells are bi-nucleated variation in size and shape.
- Mitotic figures not occurring very often.
- Higher grade chondrosarcoma exhibits unusual and clumsy myxoid tissue.
- Cartilage to be seen on both sides of the bone trabecle.
- In Chondrosarcoma the presence of spindle shaped cell is seen very often.

3.1.3 Ewing sarcoma

- Ewing sarcoma is composed of undifferentiated, small round, polygonal mesenchymal cells rich in glycogen. Sheets of uniform cells with scanty light cytoplasm and without clear cell boarders are more common.
- Small cell Ewing Sarcoma signifies varying degree of neural tube epithelium separation. Generally, these cancers will be found in soft organs or bone.
- In some cases, Ewing sarcoma shows more pleomorphic cells.
- Biopsy doesn't show matrix production.
- Rosettes type formation can be seen occasionally and it is related to neuroectodermal differentiation and this tumor is highly malignant.

3.2 Cancer grading

Completed diagnosis process enables the pathologist to derive the possible grade of bone cancer. Grading imparts the information about proliferation of cancer cells and its spreading status across the organ [19, 20].

Generally pathologist defines 3 stages:

- **Grade 1:** Low-grade and cannot be seen in other organs.
- **Grade 2:** Rapid growth of cancer cells and its growth cannot be found in other organs and still it is diagnosed as high-grade one.
- **Grade 3:** Rapid growth of tumor cells and status showing the picture of cancer spread to other part of the bone, such as the lungs, breast etc.

4. Digital histopathology

Living style of people, food habits, nature of job and environment made human life disastrous. This led to lot of health-related issues. As a solution quick, speedy, efficient and precise diagnosis system is very essential to adopt.

Manual diagnosis process is time consuming limit the speed and accuracy of result. Therefore, automation revolution in this field is crucial to overcome all the obstacles in manual diagnosis process.

Digital image automation in Pathology is the most prominent techniques that might develop novel ideas in integration of digital images technology. In future there will be huge scope of research for digital imaging in the medical field. One can use Digital images for accurate diagnosis through sending many experts across the globe for second opinion. Digital image technology helps in Preservation, tracking, research in pathology, analysis of images, marketing and business purposes, applying artificial intelligence and deep learning.

The main research area is digital histopathology where glass slide images are converted into digital slides. These slides exhibit the site of disease and its growth on tissues for easy diagnosis. This research area is challenging and interesting for passionate professionals to develop, design efficient automated tool for extracting diagnostic features.

The digital pathology investigation process is effective with the usage of appropriate imaging instrument called microtomy. To prepare consistent, high quality digital slide pathology uses the device microtomy for the preparation of thin uniform slice of tissues. This tissue is laid on the surface of microscope for further investigation. Consistent staining is performed for image standardization for obtaining its thickness, orientation, and quality. Inappropriate staining process may make the process complicated for device to identify the tissue structure, and may introduce extra hand work.

4.1 Trend in Digital Histopathology

Growth of cancer is our own contribution by leading unhealthy life style. This rapid growth of cancer made huge number of people to undergo manual screening. It is hectic job for pathologists. Lack of automation in this area would be the reason for delay in manual screening for cancer detection. Hence, research work in computer assisted tools in radiology and pathology needs to be concentrated for quick diagnosis and finally domain expert doctor will certify this abnormality. This is the reason why digital pathology field gained importance for research.

Minute research work in bone cancer is needed greater attention for complete development of automation. Here research work is limited because of complexity in structure of bone cancer. Abnormalities present in bone cancer digital slide is problematic because of variation exists in bone tissue. Magnitude features in cancerous bone cells are to be derived through the automation process for clarity. This process helps to understand different techniques to construct automation in bone cancer.

Early screening of cancer can prolong one’s life. Transition from manual microscopy to digitization technology has brought change in histopathology. This digitization process laid the foundation for research in pathology related automated tool. Automation in Radio Diagnosis gives confirmation reports to pathologist and clinicians for final cancer diagnosis. Computer assisted tools in pathology will help and support in the radiological diagnosis. The automation research work was initiated few years ago in histopathology but lack of dataset and domain knowledge made the

research work slow [21, 22, 23]. The development in digital histopathology influenced to obtain maximum images for the study of tissue pattern.

This automation process would minimize the manual microscopic work. Expertise of pathologist will be crucial one in the automation tool development process. Histopathology is the study of biopsy sample to examine the tissue morphology and related abnormalities by the pathologist. A biopsy is the procedure in which the tissue is extracted from a part of the body and analysed under the magnifying lens to examine the cell morphology. The slides examined exhibit the tissue structures through standard procedures in histopathology preparation for example, haematoxylin and eosin to show the tissue structure and cell components [24]. In advanced histopathology, glass slides are converted into digital slides. These slides expose comprehensive site of pathology and its effect [25].

Work load of pathologist increased because of a greater number of cancer cases. Manual screening is difficult for pathologist to confirm the cancer in a quick manner. There are chances for wrong diagnosis under heavy workload pressure. So, this diagnosis interpretation may mislead under stress condition of pathologist. Only automated bone cancer tool will develop the confidence of pathologist in their analysis. Cancer is life threatening disease people may not trust the first diagnosis report and they approach other doctor for the second opinion. This is time consuming and expensive process. Therefore, automated diagnosis is more accurate, less time consuming and it is trust worthy. Today, almost all the doctors depend upon automated tool for diagnosis. By doing so, they can screen maximum number of patients. Doctors can be relieved of physical strain such as microscopic examination, calculation of abnormal tissue cells and categorization of normal and abnormal cells. Study of Bone cancer pathology is more complex with varied features when compare to breast and prostate cancer. The complex tissue morphology and abnormality detection are challenging in the automation. Hence, this is the main focus area of proposed research study. Currently, there is high demand for Computer Assisted Diagnosis in the field of pathology. Several automated cancer diagnosis tools are developed. Tools developed are rely on various types of organs. The design of automated system mainly depends on the tissue structure of the organ and cancer type. Some of the approaches developed focus on finding difference between benign tumours with malignant tumour cell; while others are aim at classifying them into different grades.

5. Research Gaps

Research works with significant number of articles have been published since two decades in the field of pathology. Nuclei segmentation and classification in different images of Pathology are the one prime area had the focus of research. Apart from this, some areas left out unattended which are attained challenging gravity. Major concern and emphasis must be made to study and develop an automated diagnostic tool for bone cancer detection and classification. This unique research challenge ahead to study for the mankind. Research people had used their own mode of study and data set which failed to derive and construct further study due to without proper narration

of ground truth. So, people wishes to carry out research work enforced to continue with limited disseminated knowledge from previous work. Truth or fact cannot be obtained until and unless large evidence and dataset collected from various sources for ground truth of result. Whoever interested in research should have standard and common statistical analysis technique for feature detection. Moreover, clear attention to be made related to training and testing dataset and need to coherent explanation of evaluation method for good understanding. Up course technology in medical field reached its peak, still effort should be made to strengthen and develop the research findings. Time and Space are important factors for development of any algorithm. Accuracy and speed must go hand in hand in any field. Most of research studies failed to emphasis on time and space efficiency of developed algorithms. In medical area, images are too complex for analysis because these images contain too many features. Parallel processing technique can overcome the time constraint. Medical images contain variety of features but all the features not necessary to derive result. By the method of dimensionality reduction statistical co variance method can be used to reduce the redundant features in the image dataset. Pathologist detects cancer through manual process. In automated diagnosis, image analysis plays pivotal role but impact of other parameters neglected. Physical condition and quality of microscope, scanners, light distribution, biopsy sample of various parts of body differ in nature, type and proportion of staining elements usage might affect the overall result. It is very essential to develop an algorithm for color normalization and noise removal. In precise, overall contribution of various research studies on standardizing image is remarkable and outstanding. Limitation of study is whatever technique proposed here unable to apply for bone biopsy slide. The biopsy of bone slide contains different tissue cells such as osteoblasts, osteoclasts, chondrocytes all these are morphologically different. The tissue components in sample bone biopsy of various parts of bone differ in structure, shape and size. Due to this complexity the existing pre-processing algorithm fails to extract desired features in bone digital slide. Commendable work has been done on segmentation and classification of nuclei to detect abnormalities. In cancer, due to mitotic Figure accurate result cannot be anticipated. With this discussion, constructive framework and system of automation can be developed for the mankind. Literature survey carried out so far shows development of automation in the area of cancer. Today, cancer is very common. All the research conducted covering only general cancer which failed to discover more of bone cancer research. Reason is variety of bones with different tissue cells as the obstacle in this research work. The result of Research study conducted on general cancer are given in the table 5.1. Classification accuracy measures are explained in the table 5.2.

Table 5.1: Methods used in Computer assisted diagnosis for different cancer histopathology images

Method	Year	Cancer Type/data set
Artificial Intelligence [26]	2019	Lung cancer

Color deconvolution [27]	2022	breast cancer
Binarization and watershed transform [28]	2017	Microscopic Images of breast cancer
Delaunay triangulation [29]	2008	Colon tissue
Cluster segmentation [30]	2020	Breast cancer
Digital stain separation for histological images [31]	2010	H&E
Graph segmentation [32]	2020	H&E
Multilevel graph [33]	2011	Colon tissue images
Deep graph based [34]	2020	H&E Images
Watershed segmentation [35]	2020	Breast cancer
Ensemble classifier [36]	2021	Breast cancer
Image-Specific Color Deconvolution [37]	2017	Public mitosis
Genetic Algorithm [38]	2022	Breast cancer
Expectation-Maximization (EM) algorithm [39]	2018	Liver cancer

Table 5.2: Description of the performance metric used in various Methods

Performance Metric	Definition
Recall/Sensitivity	Sensitivity/recall measures the proportion of true positives that are correctly determine as it is. Sensitivity = $\frac{\text{total true positive}}{number\ of\ true\ positive + number\ of\ false\ negatives}$
Specificity	Specificity measures the proportion of true negatives that are correctly determine as it is. Specificity = $\frac{\text{total true negative}}{number\ of\ true\ negatives + number\ of\ false\ positives}$
Precision	Precision is the measure where algorithm determine correct result was actually correct. Precision = $\frac{true\ positive}{true\ positive + false\ positive}$
F-Measure	It is measure of accuracy uses both recall and precision $FMeasure = 2 \times \frac{recall \times precision}{recall + precision}$
Accuracy	Accuracy = Sensitivity $\times \left(\frac{positive}{positive + negative}\right) + specificity \times \left(\frac{negative}{positive + negative}\right)$
Error rate	Error rate = 1-accuracy
Cross validation	Randomly divide the dataset into k distinct subset DD_k of equal size. At each iteration i, D_i is selected as test set and remaining are training set. The accuracy measure is the overall number of correct classifications from k-iteration, divided by the total number of records in the original dataset.

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