CHAPTER 1

INTRODUCTION

The chronological situations of humans are described by certain indices such as height, dental age, and bone maturity. Of these, bone age measurement plays a significant role because of its reliability and practicability in diagnosing hereditary diseases and growth irregularities. Bone Age Assessment (BAA) using a hand radiograph is an important clinical tool in the area of pediatrics, especially in relation to endocrinological problems and growth disorders. Based on the skeletal development of the left-hand wrist, bone age is assessed and compared with the chronological age. A remarkable difference between the skeletal age and the actual chronological age of a child is an indication of growth abnormalities. This practice is used in the management and diagnosis of endocrine disorders and it also serves as an indication of the therapeutic effect of the treatment. It indicates whether the growth of a patient is accelerating or decreasing, based on which the patient can be treated with growth hormones. BAA is universally used due to its simplicity, low level of radiation exposure, and the availability of many ossification centers (growth indication spots of bones) for evaluation of maturity.

1.1 DEFINITION OF SKELETAL AGE

There are three types of ages for a child, the chronological age, the dental age and the skeletal age. The chronological age is the actual age in years, determined from the child’s birth date. The dental age is the age estimate of the maturity of the child’s teeth. The skeletal age, also termed as skeletal maturity describes the degree of maturation of the child’s bones. Skeletal age is the age at which an average child reaches a particular stage of bone maturation. Of the above three ages, skeletal age or bone age plays a vital role in diagnosing growth disorders in humans. The bone age of children is apparently influenced by factors such as gender, race, nutrition
status, living environments and social resources. In most children, growth, puberty and related endocrine changes follow a well orchestrated pattern, but the pace of maturation varies widely so that these events should be related to physical maturity rather than chronological age. For this reason, bone age, which reflects physical maturity, may be considered as “biological age”. Bone age is particularly useful in the clinical evaluation of children with growth and/or puberty disorders.

1.2 SIGNIFICANCE OF SKELETAL AGE ASSESSMENT

The development of the skeleton is of great importance to the health and maturation of a growing child. Bone development is influenced by a number of factors, including nutrition, hormonal secretions and genetics. Abnormality of skeletal development is usually one aspect of the manifestation of some pediatric endocrine diseases. For this reason, skeletal age assessment is critical for the analysis of growth disorder and plays an important role in pediatrics. This procedure is frequently performed in the management and diagnosis of endocrine disorders as well as the monitoring of growth hormone therapy. Bone age determination is also commonly used to predict individual’s final height or adult height (Gilsanz 2005). At each stage, bones have specific characteristics. Therefore, comparing with chronological age, skeletal age assessment is a more accurate way to reflect the level of individual growth development and the degree of maturation. Thus, the skeletal age is significant in determining the biological age, as well as to understand the potential for growth and development in children.

1.3 FUNDAMENTAL PRINCIPLES OF SKELETAL AGE ASSESSMENT

The methods for assessing skeletal bone age from radiographs are based on the recognition of maturity indicators (Zeva Hochberg 2002). Maturity indicators are radiographic features of bones that reflect the three-dimensional shapes of the external surface of bones. These surfaces change shape during maturation as the bone develops. Skeletal age is assessed by analyzing ossification centers in the various wrist bones such as the carpal bones, the epiphyses in the tubular bones,
which include distal, middle, and proximal phalanges, metacarpals, as well as the radius and ulna bones. Among these, the stage of epiphyseal development is the most relevant bony structure considered in assessment of skeletal maturity. In the examination, the patient’s left hand wrist radiograph is examined to assess a given bone age (Alan Oestreich 2010, Gaskin and Kalm 2011).

1.4 APPLICATIONS OF BAA

Bone age is necessary:

- to confirm the diagnosis of the normal variants of growth, such as Familial Short Stature (FSS) and Constitutional Growth Delay (CGD), associated with the bone age
- to interpret hormone blood levels in children at the pubertal age
- to diagnose precocious puberty or conditions of hyperandrogenism characterized by advanced bone age and delayed puberty or conditions of hypoandrogenism characterized by delayed bone age
- to decide whether to treat or not children with the above mentioned conditions, and to monitor the response of skeletal maturation to the treatment
- to predict adult height in normal children.

To summarize, bone age is useful in diagnosing growth disorders (Tanner and Whitehouse 1982) and in predicting adult height (Tanner et al 1966).

1.5 CLINICAL METHODS FOR BAA

The main clinical methods for skeletal bone age estimation are the Greulich and Pyle (GP) method and the Tanner and Whitehouse (TW) method. GP is an atlas matching method while TW is a score assigning method (Spampinato 1995). GP method is faster and easier to use than the TW method. In GP method, a left-hand wrist radiograph is compared with the series of radiographs grouped in the atlas according to age and sex (Greulich and Pyle 1971). The atlas pattern which appears
to be the closest match to the clinical image is selected. Since each atlas pattern is assigned to a certain year of age, the selection assesses the bone age. The disadvantage of this method is the subjective nature of the analysis performed by various observers with different levels of training. This kind of a general comparison of the radiograph with the atlas pattern is the reason for high discrepancies in this method. By a more detailed comparison of individual bones, ambiguous results can be obtained.

On the other hand, TW method uses a detailed analysis of each individual bone (shown in Figure 1.1). It relies on the systematic evaluation of the maturity of all the bones in the hand and wrist. It assigns each individual bone to one of eight classes reflecting its developmental stage. This leads to the description of each bone in terms of scores. The sum of all scores assesses the bone age. This method yields the most reliable results. In spite of the high complexity of the TW method, its reliability makes its automation worthwhile.

Figure 1.1 Bones of hand and wrist considered for bone age assessment

(Tanner et al 2001)
The original Tanner-Whitehouse method (Tanner 1962) was presented by Tanner, Whitehouse and Healy. Based on stages of the bones, scores were assigned and later on added to obtain the final skeletal age. TW2 was a revision of TW1, especially in relation to the scores associated to each stage and also to differentiate between both sexes (Tanner et al 1983). The TW2 method does not use a scale based on the age, rather it is based on a set of bone’s standard maturity for each age population. In detail, in the TW2 method, twenty Regions Of Interest (ROIs) located in the main bones are considered for the bone age evaluation (Tanner et al 1994). Each ROI is divided into three parts, Metaphysis, Epiphysis and Diaphysis, as shown in Figure 1.2.

![Figure 1.2 Division of a ROI into metaphysis, epiphysis and diaphysis](image)

The development of each ROI is divided into discrete stages, as shown in Figure 1.3 and each stage is given a letter (A,B,C,D,.. I), reflecting the development stage as:

- Stage A – absent
- Stage B – single deposit of calcium
- Stage C – center is distinct in appearance
- Stage D – maximum diameter is half or more the width of metaphysis
- Stage E – border of the epiphysis is concave
- Stage F – epiphysis is as wide as metaphysis
- Stage G – epiphysis caps the metaphysis
- Stage H – fusion of epiphysis and metaphysis has begun
- Stage I – epiphyseal fusion completed.

By adding the scores of all ROIs, an overall maturity score is obtained. This score is correlated with the bone age differently for males and females.

![TW stages for phalanx bone](image)

**Figure 1.3 TW stages for phalanx bone**

For TW2 method, three score systems have been developed, as follows:
- TW2 20 bones - characterized by 20 bones including the bones of the first, third and fifth finger and the carpal bones.
- RUS - considers the same bones of the TW2 method except the carpal bones.
- CARPAL - considers only the carpal bones.

TW3 method is an evolved version of TW2, which calibrates the bone age scoring method on the North American children (Tanner et al 2001). Bull et al (1999) performed a large scale comparison of the GP and TW method and concluded that TW method is more accurate of the two. The comparison confirmed that the bone age assessed with TW method were slightly greater than those measured with GP method. The measured intra-observer variation was greater for the GP method than for the TW method (Milner et al 1986). This accounts for much of the discrepancy between the two methods. In GP method, the greatest potential source of error comes from the comparison of the overall appearance of the radiographs with the standard reference radiographs to obtain the best match. They concluded that the GP and TW methods produced different values for bone age, which were significant in clinical practice. They also showed that the TW method was more reproducible than the GP method. They finally suggested TW method to be preferably used as the only BAA method when performing serial measurements of a patient.
Gilsanz and Ratib (2005) divided skeletal development into six categories and highlighted the specific ossification centers that are the best predictors of skeletal maturity for each group, as follows:

i) Infancy - the carpal bones and radial epiphyses  
ii) Toddlers - the number of epiphyses visible in the long bones of the hand  
iii) Pre-puberty - the size of the phalangeal epiphyses  
iv) Early and Mid-puberty - the size of the phalangeal epiphyses  
v) Late Puberty - the degree of epiphyseal fusion of the phalanges and  
vi) Post-puberty - the degree of epiphyseal fusion of the radius and ulna.

1.6 NEED FOR COMPUTERIZING BAA

It is technically feasible to automate the assessing of bone age, deriving skeletal maturity information from radiographs of the hand and wrist. However, this task is not trivial. The hand-wrist radiographs contain a complex collection of bones that change shape and size over time, with some bones overlapping, and others not even being present at various stages of development. Analyzing the bones and deriving a bone age is a complex task, when done manually. The manual methods suffer from severe inter and intra-rater variability. The limitations of these manual methods and the importance of skeletal maturity estimation in the management and diagnosis of growth and endocrine disorders make its automation desirable. Researchers have recognized the importance of automating the assessment of bone age. Some research has resulted in computerized bone age assessment systems that have been used in clinical research. Hence, there comes a certain necessity to computerize BAA. This research has focused on four such computerized approaches for estimating the bone age from radiographs.

1.7 CHALLENGES IN AUTOMATING BAA

Building a system as described above requires processing the radiographic image, in a similar way to radiologists. The challenges can broadly be divided into three. Those that are related to the structure of the radiographic image (like orientation of the hand, the variation in the placement of the finger), those that arise
from the nature and the quality of the image and finally those that relate to estimating ages without much rater variability. The bones of the hand and the wrist in a radiograph cannot be seen clearly without special lighting to read the radiographs, as usually done in clinical practice. Computerized techniques have to cope with images with differing clarity. The lower part of the radiograph image has higher gray levels than the upper part. The gray level differences are due to the focusing of the X-ray beam. For skeletal maturity estimation purposes, it is often focused around the wrist. Furthermore, the quality of these images is also affected by the different ways by which the tissue and the bones of the hand absorb the X-rays. In clinical radiology, annotation is done, which is the process of placing marks around the borders of objects of interest in an image. When trying to delineate the borders of the bones of the hand and the wrist, it is difficult to be consistent. This is because there are insufficient anatomical points to describe the bones consistently. This presents a great challenge to computer vision methods. There is also a lack of uniformity in the bones appearing in each image. The same bones are not found in all the radiographic images. A number of bones in very young children are still in the form of cartilage and are not visible on the radiographs. Most model building methods require similar objects to exist in the images for which a model is intended to be built. Getting around this problem is a challenge. The image processing task required to analyze the radiograph is equally as complex. Image noise and the poor contrast of some bone edges further add to the challenge of automated assessment. In young children, there is a lack of an established sequence of appearance of some of the carpal bones as a child grows. In young adults, bones are beginning to merge. The various stages of merger are manifested in different appearances (texture changes). Differentiating the different levels of merger is a huge challenge. Furthermore, at the stage of adulthood some bones actually overlap. Extracting image features in such images is often a difficult task. The variability in the structure of the hand makes alignment of the hands difficult. The variation in the positioning of the fingers is very large. Similarly the variation of the orientation of the hand could equally be large. Finding a way to train the computerized BAA system without
depending on the radiologist's reading is difficult. Most previous systems used the so called expert reading to train the models that predict age. But such systems inherit the inter and/or intra rater variability. Also, designing a skeletal age system covering the entire growth period from infancy to puberty (0-15 years) is a challenge. Most methods fail at the extremes.

1.8 NEED AND OBJECTIVES OF THE RESEARCH IN BAA

BAA is of great significance in pediatrics to diagnose growth abnormalities in children and to predict their adult height. A computerized method for BAA is mandatory to overcome the limitations in the manual procedure. Current research in BAA shows evidence of the necessity for improved accuracy and precision in the estimation of bone age, at the same time by deploying simplified classification methods. The existing methods lack either in achieving better accuracy and precision of classification or in providing a straight forward bone age estimation mechanism. This research is undertaken to develop new promising techniques for computerized BAA with improved accuracy, specificity, precision, and recall. The objectives of the research are:

i) To study the existing techniques available for BAA.

ii) To develop new convex hull based approach for bone age estimation by using features from the carpal bones.

iii) To propose new feature ratio approach for bone age estimation by combining features from the carpal and radius bones.

iv) To develop new decision tree approach for bone age estimation from the radius and ulna bones.

v) To propose new Hausdorff distance approach for bone age estimation from the Epiphysis/ Metaphysis Region of Interest (EMROI) of the phalangeal bones.

vi) To analyze and compare the performance of the proposed four BAA methods using Partitioning technique.

vii) To optimize the performance of BAA by the proposed four BAA approaches.
1.9 CONTRIBUTIONS OF THE THESIS

The contribution of the thesis is given as follows. The thesis presents four new computerized approaches for BAA listed below, based on the features from various wrist bones considered.

i) Convex Hull approach using Carpal bone features
ii) Feature Ratio approach using Carpal and Radius bone features
iii) Decision Tree approach using Radius and Ulna features
iv) Hausdorff distance approach using Epiphysis/ Metaphysis features

Medical studies reveal that the carpal bones were proven to be very reliable for bone age assessment in children during their early stages of life from 0 – 7 years (Johnston and Jahina 1965). In fact, the very first ossification center to appear in hand and wrist radiographs is the Capitate, the first carpal bone. Hence, BAA from the carpals has been widely followed and there are good research methods available in the literature for BAA from the carpals. But the existing systems are deficient in not exploiting all the carpal bones for BAA. They concentrate only on the first appearing dominant carpal bones, the Capitate and the Hamate. In this research, two BAA methods (new convex hull approach and new feature ratio approach) have been proposed using features extracted from the carpal bones, which are the vital contributors to BAA during the earlier stages of life. Few earlier studies have estimated bone age from the radius and ulna wrist bones. But, they suffered from problems of ignoring the extreme classes (initial and final classes). In this research, a new decision tree approach is proposed, which exploits the radius and ulna bones in estimating the bone age for the entire range of age classes, Class A – Class J. Although there has been a significant amount of research on the computerized assessment of bone age, especially with respect to the phalanges, there remain gaps in knowledge and opportunities for improving the assessment. The existing BAA using phalanges do not consider the fusion of epiphysis and metaphysis. This research has investigated the Epiphysis/ Metaphysis development of
phalangeal bones for BAA using the Hausdorff distance approach, including the features that explain the extent of fusion of the epiphysis and metaphysis. Four new approaches for BAA which overcome the limitations of the earlier methods and which exhibit improved performance in terms of accuracy, specificity, precision, and recall have been developed and reported in this thesis.

1.10 FRAMEWORK OF A BAA SYSTEM

The framework of a BAA system is explained as follows. The input to the BAA system is the hand radiograph image, which is initially preprocessed to remove noise and enhance the image. From the preprocessed image, the specific bones of interest (ROI) are cropped and extracted. Features that describe the size, shape and structure of the bones are extracted from the cropped bones, which are used in training the system and to classify the input image into its corresponding bone age class (Class A – Class J). The bone age class is in turn mapped on to the final bone age in years. The bone age obtained as output may be used clinically in the diagnosis of growth disorders and to predict the adult height of children.

1.11 ORGANIZATION OF THE THESIS

The thesis is organized as follows.

In Chapter 2, a detailed survey of literature is presented on the computerized methods in determining the skeletal bone age.

In Chapter 3, the proposed convex hull approach for skeletal bone age assessment is explained. The extraction of geometrical features from the convex hull of the carpal wrist bones and the bone age estimation process from the extracted carpal features are discussed.

In Chapter 4, the proposed feature ratio approach that uses a combination of carpal bones and the Radius bone for BAA is described. The extraction of geometrical CROI feature ratio and RROI feature ratio from the above bones and
the classification of the input radiograph image into any of the ten age classes based on the mean value of the CROI and RROI feature ratios are discussed.

In Chapter 5, the proposed decision tree approach for bone age assessment based on the radius and ulna wrist bones is presented. The formation of the decision tree classifier based on the Boolean representation of the features and bone age estimation using the classifier are explained.

In Chapter 6, the EMROI based skeletal BAA method proposed by Giordano et al (2010) and the extension done in the system to estimate the bone age using the Hausdorff distance approach are briefed. The results of the proposed Hausdorff distance approach are compared with that of the existing system.

Chapter 7 presents the summary of the research and a detailed discussion on the results obtained by the proposed convex hull approach, feature ratio approach, decision tree approach and Hausdorff distance approach. It elaborates the partitioning technique employed in investigating the performance of the four proposed approaches by altering the partition of data sets used in training and testing.

Chapter 8 states the concluding remarks from the work done in this thesis and outlines areas requiring further development.