ACCURACY AND RELIABILITY OF DOLPHIN 3D VOXEL BASED SUPERIMPOSITION IN GROWING PATIENTS.

By

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DEDICATION

To the soul of my father who dedicated his life to our family and made sacrifices for us, I know he is proud of me.

To my mother, you are my hero. Your unconditional love, endless support and prayers, are the reasons behind my success.

To my lovely wife, Hebba. You are my strength and courage. Anything good that has come to my life has been because of your guidance and love.

To the best thing that ever happened to me, my kids Alhusain, Taha, Fatima and Abdalla. I love you.

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Abstract

Background: Cephalometric Imaging has allowed serial radiographs to be taken leading to the development of superimposition techniques to quantify skeletal and dental changes resulting from treatment and growth. However, errors are involved in its landmark identification. In addition, cephalometric radiography has a limitation as being a 2D evaluating tool to 3D skeletal structure. Cone Beam Computed Tomography (CBCT) provides a three-dimensional undistorted and more accurate dental and skeletal imaging and analysis. Between the 3D superimposition methods that have been developed, voxel-based superimposition is the most accurate with its automated use of the whole image intensity instead of points or lines. Recently various software programs have been developed with the ability of 3D superimposition in a fast and easy manner. **Aim**: to evaluate the accuracy and reliability of Dolphin 3D voxel-based superimposition in growing patients.

Methods: Scans of thirty growing patients were used in this retrospective study. Fifteen females and fifteen males. The mean age at initial scan (T1) was 11.8 ±0.5 years and at second scan (T2) was 14.2 ±0.8 years. The two time-point volumes were superimposed using 3D voxel-based method from Dolphin Imaging System and compared to Cevidanes method (ITK-snap & 3D Slicer) as a gold standard. T2 was superimposed on T1 using the anterior cranial base. In the same coordinate system, fit of the acquired registered T2s from both methods for each patient was evaluated

using the absolute closest point color map. The absolute surfaces distance at seven selected regions (Nasion, A point, right and left Zygomatic, chin, and right and left Gonion) were calculated. There is enormous difference between the times needed to perform each of the two methods; Dolphin superimposition takes minutes while the other requires about 3 hours. **Results**: Intraclass correlation showed excellent reliability (0.92). The mean surfaces distance between the two methods was less than 0.3mm (scanner voxel size 0.38mm). The least difference was found in Nasion region with an average of 0.15mm ±0.11, and the largest in Chin with 0.31mm ±0.22. **Conclusions**: Dolphin 3D voxel based superimposition in growing patients is accurate, and reliable to be used clinically and in research.

LITERATURE REVIEW

It is important in orthodontics to understand the influence of growth, treatment, or both on dental and skeletal changes within the craniofacial structure. Superimposition of 2D lateral cephalograms has been the standard in quantification of growth and treatment outcomes. Superimposing serial cephalometric radiographs has increased our knowledge and understanding about normal craniofacial growth and development as well as the treatment effects produced by various orthodontic, orthopedic, and surgical procedures.

Craniometry was the first measurement approach for evaluating growth, used since the 15th century (Finally 2009). This technique is precise, but it provides measurement only on dry skulls, another limitation is that all the growth data are cross- sectional. Anthropometry, which is the scientific study of the measurements and proportions of the human body, was then used as the gold standard because it can follow growth directly on each subject. Despite its accuracy, however, obtaining growth measurements through direct measurements is difficult because it is time-

consuming and requires patient compliance to remain still for a long time (Bartzela et al. 2012).

Cephalometrics and Cranial Base Growth

Arne Björk is internationally known for his contributions to the understanding of craniofacial growth where the implant method was used and annual radiographs were obtained from childhood to adulthood of his human subjects' sample. The systematic superimposition of these serial radiographs with the help of implants form the basis of his studies. Björk's structural superimposition method became the standard for the evaluation of conventional 2-D cephalometric images to monitor growth and adaptation in the craniofacial region (Björk 1968).

The cranial base consists of three parts including anterior, middle, and posterior. The anterior cranial base is composed of frontal (which includes nasion), ethmoid, presphenoid, and sella turcica (which include sella) regions. The cranial base is initially formed in cartilage, with ossification centers appearing early in embryonic life and with time, progressively replacing the cartilage with bone. However, in a young child there are four sites of growth in the cranial base between nasion and basion: (1) spheno-occipital synchondrosis, (2) sheno-ethmoidal synchondrosis, (3) cartilage between ethmoid and frontal bones, and (4) in the frontal bone itself, which

becomes thicker during childhood in association with enlargement of the frontal sinuses (Ford 1958).

The anterior cranial base is considered to have completed its most significant growth before other facial skeletal structures. It has long been considered a stable craniofacial structure to be used for cephalometric superimpositions during the usual orthodontic treatment age range (Bastir et al. 2006).

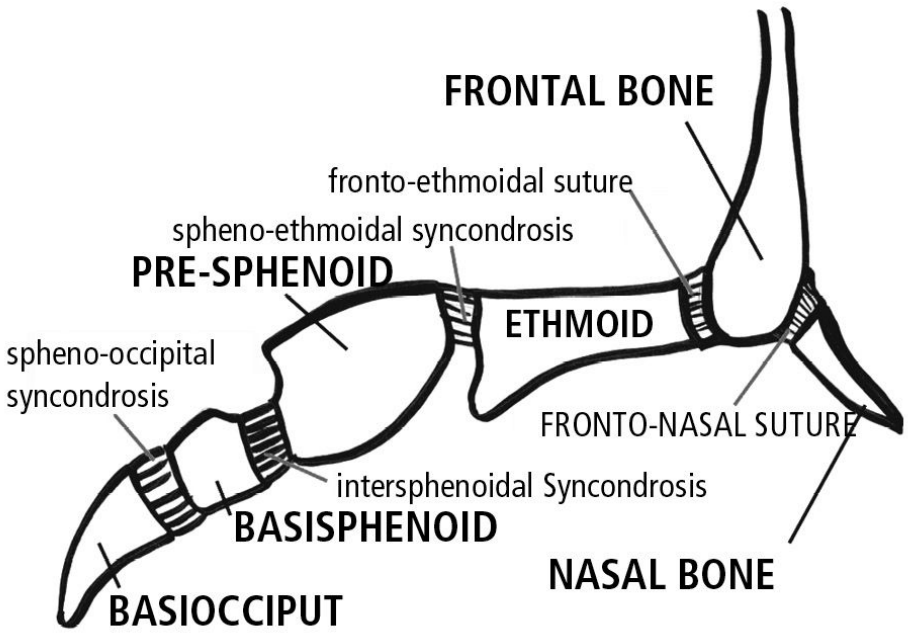


Figure 1 Syncondroses of cranial base https://pocketdentistry.com.

Cranial growth is largely dependent on the growth of the brain, and generally follows the neural pattern of growth (very rapid growth in the first two to three years, falling off rapidly and almost finished by the age of 7). Facial growth, however, is independent of brain growth and follows the general skeletal growth pattern. The cranial base located at the junction between cranium and the face might lead us to expect that the cranial base show a growth rate between neural and general rates. This is true for the cranial base as a whole, but parts have either the neural or the general skeletal growth rates, but not an intermediate one (Ford 1958).

Bastir et al discovered that midline cranial base matures in shape by 7.7 years of age and it reaches mature size at 13 years of age, which is roughly when the spheno-occipital synchondrosis ceases growing (Bastir et al. 2006). Different areas of the anterior cranial base complete their growth at different stages of life. The pre-sphenoid region's anteroposterior length was found stable after the age of 7 years as investigated by different methods (Ford 1958) (Melsen 1974) (Knott 1971).

Moss and Greenberg studied cross-sectionally the postnatal growth of human skull base from headfilms of 151 human crania from newborn to adult age. They stated

that the median structures of the anterior cerebral fossa are more stable than the lateral structures (Moss & Greenberg 1955).

DeCoster reported that the cribriform plane, which includes the cribriform plate and planum sphenoidale completes its growth by the age of 7, which was confirmed by Ford's work in 1958 on dried skulls. Ford found that the cribriform plate stops growing in length anterior-posteriorly after 2 years of age, and that the distance from pituitary point to foramen caecum stops growing in length after 6 to 7 years of age (DeCoster 1953) (Ford 1958).

Afrand et al. in their systematic review, concluded that the pre-sphenoid and ethmoid regions should be considered as fully developed by age 7 for the pre-sphenoid and age 4 for the ethmoid regions. They also added that identifying and using the cribriform plate, which is the most stable cranial base structure, as a reference for 2D growth studies requires high quality lateral radiograph and experienced eyes. The frontal and sella turcica regions continue remodeling until early adulthood. Nasion moves forward due to the increase in size of the frontal sinus

while sella is displaced downward and backward relative to the anterior wall of Sella (Afrand et al. 2014).

A study done by Knott et al. reported that nasion moves forward (upward or downward), with its forward movement due to frontal bone thickness increase, apposition in the glabella region, and frontal sinus enlargement. Knott also indicated that the distance between point W (sphenoid wing) and the pituitary point increased 0.1 mm between the ages of 6 and 9 years and remains completely stable from 9 to 15 years of age (Knott 1969). Similarly, Arat et al. have confirmed this observation by concluding that the landmarks T (tuberculum sella) and W points were the most stable points of the cranial base. Arat et al.'s result also indicated that Basion is the most variable landmark of the cranial base (0%), followed by Nasion with (16%) stability due to spheno-occipital synchondrosis and frontal sinus development respectively (Arat et al. 2001).

In Björk's early radiographic studies of the development of cranial base, he concluded that the Sella-Nasion plane was an adequate reference line during growth in adolescence (Björk 1955). By using implants in the maxilla and mandible as

reference markers in his later longitudinal studies, Björk identified other areas in the cranial base that were stable, whereas Sella-Nasion was not. With the guide of the histological investigations of Melsen and Scott, Björk's methods of cranial base superimposition were refined to identify areas in the cranial base that were stable at an early age (Melsen 1974) (Scott 1958).

Bjork noticed remodeling of the posterior wall of sella turcica during growth, resulting in downward and backward displacement of the sella. He also reported an elevation of the tuberculum sella in relation to other structures of the anterior cranial base (Björk 1955). In a cross-sectional study by Murata, it was found that sella displaces 2.3% from deciduous dentition to adulthood (Murata 2009).

Scott found that the mesethmoid unites with the facial parts of the ethmoid by the ossification of cribriform plate between the first and third year. He also found that the anterior cranial base reaches its adult dimension by age 7; thereafter making it stable (Scott 1958).

In Melsen's (Melsen 1974) comprehensive histological study on the cranial base, where she examined tissue removed at autopsy from 126 normal individuals aged 0

to 20 years, she found that the internal surface of the frontal bone and cribriform plate, are stable after the age of 6 to 7 years in both sagittal and vertical planes. She also found that the anterior part of sella turcica is by far the most stable after 5 years of age.

Steuer,(Steuer 1972) has done a five-year longitudinal study of the growth of the area from planum sphenoidale to dorsum sella by comparing a number of serial radiographs. He recorded deepening of the hypophyseal fossa when maximum congruence was obtained on the planum sphenoidale with as many other segments as possible. He also concluded that the anterior part of sella has good stability to be used for superimposition as a reference.

Two-dimensional Superimposition

Orientation and Registration

The process of cephalometric superimposition relies upon two main principles, orientation and registration. Registration is the process of aligning two traced images on a point or landmark, whereas orientation is the process determining the correct angular relationship. In order to superimpose properly, image registration sites must be stable. Our knowledge of bone biology is the basis of current 2-D and, to some extent, the ongoing advancing attempts at 3-D superimposition.

2D Superimposition methods

In 1931, Broadbent in the United States and Hofrath in Germany introduced the cephalometer (cephalostat) which inspired a large number of studies of the development of the dentition and growth of the craniofacial structures.

From 1951 to1985, Bjork studied facial growth longitudinally using small inert metallic implants as radiographic markers in the jaws of more than 200 humans (Björk & Skieller 1983). In Bjork's structural superimposition method, cranial and cranial base reference structures were used in the superimposition of the lateral cephalograms. These anatomical reference structures are (1) the contour of the anterior wall of sella turcica, (2) the anterior contour of the median cranial fossa, (3) the mean intersection point of the lower contours of the anterior clinoid processes and the contour of the anterior wall of the sella, (4) the inner surface of the frontal bone, (5) the contour of the cribriform plate, (6) the contours of the bilateral frontoethmoidal crests, and(7) the contour of the median border of the cerebral surfaces of the orbital roofs. Bjork used the changes in fronto-parietal suture,

occipital bone, point articulare and pterygomaxillare to control the superimposition. Bjork used SN line with sella as a registration point to assess changes in position of both jaws. However, as was mentioned earlier, he later questioned the use of SN line as a reference for estimating facial changes.

Bjork's structural superimposition was then considered as the gold standard since it had high validity and moderate to high reproducibility. However, it required high quality X rays, time, and effort.

Steiner used the SN line with registration point at sella to evaluate sagittal changes in mandibular positions and at nasion to evaluate the position of the maxilla (Steiner 1953).

Baumrind et al. compared cephalometric superimpositions using SN registered on S, anterior cranial base-best fit, palatal plane and mandibular border. He found that the usefulness of the data derived is, however limited by the fact that the physical act of superimposing tracings is performed with some error. He concluded that the rotational errors of the best fit superimposition method were unexpectedly somewhat smaller than those for the SN superimposition (Baumrind et al. 1976).

Ghafari et al. concluded that best fit method might be better than the others because it takes into account the detailed individual anatomy of the cranial base, rather than simplifying this anatomy into lines or planes that may be modified by growth (Ghafari et al. 1987). Pancherz and Hansen, on the other hand, found that no actual differences were found between the SN method and cranial structure based-best fit method. They concluded that there is higher risk for an increased registration error in the cranial base-best fit method as compared to the SN method (Pancherz & Hansen 1984).

Broadbent recommended the use of the bolton-nasion line with registration at R point which is the midpoint on the perpendicular to sella is erected from the Bolton-nasion plane. This was based on his cross sectional observations of 3 to 18 years' dry skulls where he compared the cranial base planes: bolton-nasion, porion-nasion, and sella- nasion (Broadbent 1935).

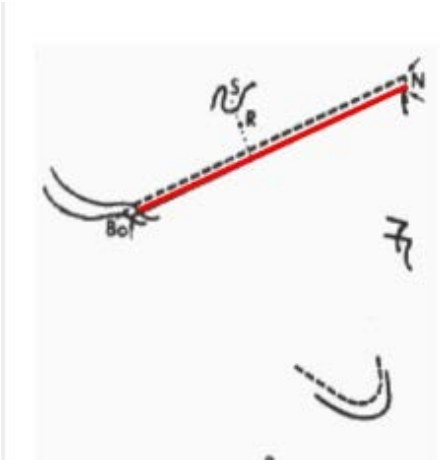


Figure 2: Bolton cranial base superimposition method (Broadbent 1935).

In 1979, Ricketts advocated the use of basion-nasion plane with a perpendicular line from pterygoid point (pt: on the lower rim of the foramen rotundum as the highest and the most posterior point of the pterygopalatine fossa) to cephalometric gnathion. CC point is the intersection of the two planes and is used as a reference center.

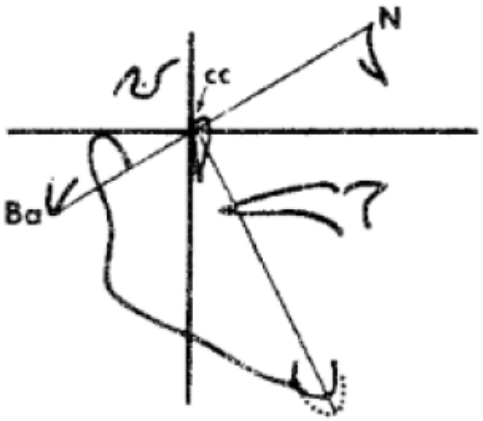


Figure 3: Rickets cranial base superimposition (Ricketts et al. 1960).

He suggested that the cranial base angle exhibits a change of 5 degrees in either direction over a 3-year period, so he recommended that the use of Ba instead of S helps take into account some of extremes in divergent growth conditions (Ricketts et al. 1960). There is some doubt about the reliability of this line because of the variability of the growth at nasion, also the remodeling at the anterior part of foramen

magnum and the growth in the spheno-occipital synchondrosis are making basion a variable landmark (Melsen 1974).

Rickets et al. had suggested that the use of Frankfort horizontal (FH) is an appreciably better reference than SN (Ricketts et al. 1976).

Glidden et al. compared 4 methods for cehalometric tracing superimposition. They are FH at porion, SN at sella, least-squared averaged 5 landmarks (LS-5), and manual geometric-best fit. They found that the error of both best fit and LS-5 methods was within 0.5 mm and the LS-5 method had its advantage because it could be automated by the computer (Gliddon et al. 2006).

In the Ghafari et al. study previously mentioned there was a comparison made between 4 different methods of superimposition evaluating spatial changes in growing jaws: Bjork's, Steiner's, Ricketts, and Broadbent's which showed little agreement at all anatomic landmarks assessed. The authors stated that conclusions about facial changes may be made only in reference to the superimposition method used (Ghafari et al. 1987). The same conclusion was found by Arat et al., where they evaluated the direction and degree of displacement of reference landmarks on the

cranial base and face using 3-superimposition methods of Björk, Steiner, and Ricketts. Their final statement indicated that differences in superimposition method should be considered when analyzing changes as a result of treatment (Arat et al. 2003) .

Two-dimensional (2D) radiography has been used for a very long time in diagnosis, treatment planning, evaluation of growth and development, and assessment of treatment progress and outcomes. It has its limitations being a 2D imaging tool to evaluate the orthodontics and dentofacial orthopedic problems, which involve the third dimension in space.

There is no doubt that 2D cephalometric analysis studies and their use helped in understanding craniofacial growth and development as well as treatment effect. However, these studies have some limitations with respect to accuracy and reliability. The FH (Frankfort) plane and SN (sella-nasion) plane are standard for most superimposition methods, but these planes are difficult to construct on 2D cephalometric images, and the error may be magnified depending on facial structure.

Several studies have evaluated the accuracies of different superimposition methods and have found that those using the SN and FH planes were not accurate and had poor reproducibility (Baumrind et al. 1976) (Ghafari et al. 1987) (Pancherz & Hansen 1984) (Gliddon et al. 2006) (Cooke & Wei 1991).

Landmark identification error is without a doubt the most important. For example landmarks that are placed on anatomically formed edges or creases are easy to identify, whereas those that are placed on curves with wide radii show proportionally greater errors of measurement (Baumrind & Frantz 1971). In another article by Houston et al, it was stated that the greatest contribution to the error variance is from the tracings (Houston 1983).

The use of accurate three- dimensional representations of craniofacial and dental structures could help eliminate those previously stated problems and might provide additional diagnostic information.

Cone beam computed tomography (CBCT)

Medical 3D imaging was introduced in the late 1990s adding another dimension for another century. Cone beam computed tomography (CBCT) was introduced to the dental profession in the United States between 2001 and 2004. Cone Beam CT CBCT uses a flat panel sensor and a projection beam to capture the 2D images that are then mathematically converted to a 3D image. CBCT imaging is uniquely suited to dentistry and orthodontics because it has high resolution (translating voxel sizes as small as 0.1 mm) and significantly lower radiation than does spiral CT. The higher radiation doses for spiral CT allow better separation of tissues of similar density (ie, nerve and muscle); however, the structures we want to see have relatively high differences in density (eg, air vs bone) (Hans et al. 2015).

During a CBCT scan, the scanner (x-ray source and a rigidly coupled sensor) rotates, usually 360 degrees, around the head to obtain multiple images (ranging from approximately 150 to 599). The scanning software collects the raw image data and reconstructs them into viewable formats. The scan time can range between five and forty seconds, depending on the unit and the setting. Some CBCT scanners can

collect complete volume data during a half rotation around the patient in only 9 seconds.

The x-ray source emits a low mill-ampere (mA), and a shaped or divergent beam. The beam size is constrained by a circular or rectangular collimator to match the sensor size, but in some cases, it can be constrained (collimated) further to match the anatomical region of interest. After the scan, the resultant image set or raw data are subjected to a reconstruction process that results in the production of a digital volume that is composed of elements called “voxels”. These are stacked in rows and columns of anatomical data that can be visualized with specialized software. Voxels are the smallest subunit of a digital volume and CBCT voxels are generally isotropic (that is, X, Y, and Z dimensions are equal) and range in size from approximately 0.07 to 0.40 millimeters per side. Each voxel is assigned a scale value up to 16,384 shades of gray that approximates the attention value of the represented tissue or space. The small isotropic voxel size along with the large number of gray levels have contributed to accuracy and precision when clinicians measure the dimensions on anatomical structures and visualized anatomical forms (Hatcher 2010) (Ludlow et al. 2009) (Chung et al. 2009).

CBCT technology has several beneficial applications in the clinical setting. Providing us with accurate 3D measurements of objects scanned. Ballrick et al. compared CBCT measurements to the direct digital caliper measurements and showed that even though it was statistically significant, the absolute difference was less than 0.1 mm and is probably not clinically significant for most applications (Ballrick et al. 2008). Gribel et al., in their comparison study found that CBCT craniometric measurements are accurate and potentially can be used as quantitative orthodontic diagnostic tools. They also stated that 2D cephalometric norms cannot be readily used for three-dimensional measurements because of differences in measurement accuracy between the two exams (Gribel et al. 2011). High intra- and inter-observer reliability of CBCT measurements were reported (Lagravère et al. 2009) (de Oliveira et al. 2009).

The analysis of CBCT images has been valuable in numerous applications such as: (1) diagnosis of impacted and supernumerary teeth, in which the 3D images were superior to the conventional 2D images, (2) treatment planning for placement of skeletal anchorage devices, in which CBCT scans allowed for the evaluation of bone thickness and density in different areas in the mandible and maxilla, (3) 3D

volumetric assessment of the upper airway, and (4) 3D analysis for diagnosis and treatment planning of orthodontic and orthognathic patients (Bayome et al. 2015).

Three-dimensional Superimposition

With the increased use of CBCT images for orthodontic diagnosis and treatment planning, ways to superimpose these images for evaluation of the craniofacial growth and/or treatment changes have been introduced and there are now three ways of super-imposing the 3D images.

Methods for 3D superimposition

Different techniques have been used for superimposition of 3D images, which include landmark-based superimposition, surface based superimposition, and voxel-based superimposition. The accuracy of the first two techniques depends on the landmark identification and the quality of the surface models respectively whereas the voxel-based superimposition was developed to avoid operator error.

The initial method describing 3D superimposition was landmark based. Locating landmarks in 2D radiographs is usually easily identified due to the overlap of multiple structures, but this is not the case in the curved surfaces 3D images. Analysis of 3D images is much more complex than the analysis of 2D cephalometric radiographs.

Surface based superimposition was developed later and it deals with the 3D rendered surface model requiring high quality surface models in order to get accurate results (Hajeer et al. 2004) (Baik & Kim Seoul 2010). Ong et al. used 3D surface models to quantify and visualize the immediate 3D changes of the mid-face following rapid maxillary expansion. They concluded that the use of 3D surface models allows quantification and visualization of the 3D changes in the mid-facial skeleton at anatomical sites distant from RME activation (Ong et al. 2015).

Gkantidis et al. evaluated five superimposition techniques using surface models (3P: three-point registration, AC: anterior cranial base, AC+F: anterior cranial base+ foramen magnum, BZ: both zygomatic arches, 1Z: one zygomatic arch). They found that the AC+F technique was the most accurate followed by AC and BZ

superimpositions whereas 3P and 1Z were the least accurate superimpositions. Importantly they found that BZ superimposition has the additional advantage of being applicable in smaller field of view (FOV) scans, which require less radiation dose and cost. They also concluded that superimposition of 3D images using surface models can provide accurate, precise, and reproducible results (Gkantidis et al. 2015).

Tai et al. used surface based superimposition technique by applying the interactive closest point (ICP) method in the cranial base (excluding the peripheral zone) and demonstrated its accuracy when used for a valid and reproducible assessment of treatment out-comes for growing subjects (Tai et al. 2010).

Lately, a new method of 3D superimposition has been introduced to the medical research field. Known as voxel based registration, It has been widely used for various medical applications and research purposes, including diagnoses, treatment planning and assessment of a variety of cases utilizing CT, CBCT, MRI, and 3D ultrasound. Cevidanes et al. introduced the new method of voxel-based superimposition to dental research in which the skull base is used as a stable reference structure for image superimposition (Cevidanes et al. 2005).

Voxel based registration utilizes the gray scale difference of the voxels to align the two DICOM images to the best superimposition achieving the least total gray scale density difference between the two images. Voxel based registration uses the intensities throughout the entire selected volume and therefore uses the image content as the basis of the registration. It is also useful where it is difficult to detect distinct surface topography features.

Voxel based registration deals with the raw information of the DICOM image by comparing the gray scale intensity of the voxels, whereas surface based registration requires an extra step involving 3D model rendering to generate a three-dimensional surface mesh model. This step may introduce a possible source of error since the algorithm used for segmenting the 3D model depends on the Hounsfield value of the DICOM images. This extra step also increases processing time and implies the need for multiple software packages for 3D model rendering which is unnecessary in the case of voxel based registration.

Surface based registration demonstrates a higher variability in superimposition, whereas voxel based registration has a low variation in the superimposition process.

Surface based registration for hard tissue is as accurate and consistent as the voxel based registration. Voxel based registration produces a more accurate representation of the soft tissue changes as compared to surface based registration (Almukhtar et al. 2014).

Cevidanes et al. evaluated the superimposition of CBCT images of growing patients. They reported that the range of inter-observer errors for each anatomic region was 0.4 mm for the zygomatic process of maxilla, chin, condyles, posterior border of the rami, and lower border of the mandible, and 0.5 mm for the anterior maxilla soft-tissue upper lip. The conclusion was that this method is a valid and reproducible assessment of treatment outcomes for growing subjects (Cevidanes et al. 2009).

Cevidanes et al demonstrated the use of voxel based registration in multiple orthodontic research(Claudia Toyama Hinoa et al. 2011) (Cevidanes et al. 2010) (de Assis Ribeiro Carvalho et al. 2010) (Cevidanes et al. 2007) (Franco et al. 2013) (Motta 2011) validating the method as accurate and valid. The drawbacks of this

voxel based method are that the superimposition process requires several different steps in various software programs and are time consuming.

Nada et al. in 2011 tested the reproducibility of the voxel-based method using a commercial software “Maxilim” for CBCT superimposition on the anterior cranial base and zygomatic arch using 16 surgical orthodontic patients. The authors concluded that the method is accurate and reproducible, and the superimposition on the zygomatic arches could be considered as an alternative to the cranial base in smaller field of view scans for non-growing patients (Nada et al. 2011).

Weissheimer et al. recently evaluated a fast method of 3D voxel based superimposition using OnDemand 3D software, which was first introduced by Choi and Mah. Weissheimer concluded that the mean superimposition error was less than 0.5 mm in growing and non-growing patients (Weissheimer et al. 2015) (Choi & Mah 2010).

The 3D voxel based technique by Cevidanes involves creation, registration, and superimposition of 3D surface models. Potential sources of variations between examiners are threefold. 1) Low gray-scale contrast in anatomic regions with thin cortical bone prevents automatic definition of these structures’ boundaries and manual editing can introduce slightly different outlining of surface boundaries by different examiners. 2) The user input to define the properties of 3D surface model creation could also lead to minor surface variations. 3) Variations in quantification

of treatment outcomes could stem from examiner choice of the isoline contours on the color map.

Cevidanes et al. studied the variability between observers that might arise from those potential sources during the process of quantification of treatment outcome. They used color-coded distance maps for different anatomic regions on 3D CBCT models registered on the anterior cranial base and they found an inter-examiner range of measurements across anatomic regions equal or less than 0.5 mm (Cevidanes et al. 2009). Since the distance maps are constructed on the 3D surface models, they could be dependent on the accuracy of the segmentation or the selection of the bone threshold values of these models. However, the potential source of variation due to segmentation is very small.

Cone beam computed tomography (CBCT) is a tool that is now part of contemporary diagnosis and treatment. It can be an effective tool to study growth and treatment results because it provides actual measurements without magnification, allowing image comparison with accuracy and precision. It also enable volumetric measurements of an object, and gives the ability to assess changes in contour and shape. 3D images can also be superimposed using thousands of points, shapes and volume rather than lines and curves.

3D superimposition studies have been conducted recently to validate the methods used in regional 2D superimpositions for maxilla and mandible. The studies evaluated their use as regional references in 3D superimposition where adding the

transverse dimension might affect their validity because of added transverse growth. It also might be due to the fact that the use of small regional references previously used in 2D superimposition could not provide control of the 3D translation and rotation of superimposed structure: e.g. maxilla or mandible (Ruellas et al. 2016) (De Oliveira Ruellas et al. 2016).

Bazina et al., using a sample of adult surgical patients at Case Western Reserve University, concluded that Dolphin 3D voxel based superimposition, as a fast and user-friendly method, is accurate and reliable. They compared 3D voxel based superimpos-ition method from Dolphin to the accepted method used by Cevidanes et al. Both used the anterior cranial base to superimpose on the parts of the cranium that stopped growing: anterior wall of sella, anterior clinoid process, lesser wing of sphenoid, planum sphenoidale, superior aspect of ethmoid and cribriform plate, cortical ridges on the medial and superior surfaces of orbital roof, and inner cortical layer of frontal bone (Mohamed Bazina et al., 2015).

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STATEMENT OF THESIS

The purpose of this study is to evaluate the accuracy and reliability of Dolphin 3D voxel-based superimposition in growing patients. Cevidanes' method of voxel base superimposition was used as a gold standard for a comparison, and it is hypothesized that there is no difference between the two software packages in the superimposition of CBCT images of growing patients. If rejected, there is a difference between the two software packages.

Manuscript

Accuracy and Reliability of Dolphin 3D Voxel Based Superimposition in growing patients.

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Keywords: Cone beam computed tomography, CBCT, superimposition.

Aim: to evaluate the accuracy and reliability of Dolphin 3D voxel-based superimposition in growing patients.

Methods: Scans of thirty growing patients were used in this retrospective study. Fifteen females and fifteen males. The mean age at initial scan (T1) was 11.8 ±0.5 years and at second scan (T2) was 14.2 ±0.8 years. The two time-point volumes were superimposed using 3D voxel-based method from Dolphin Imaging System and compared to Cevidanes method (ITK-snap & 3D Slicer) as a gold standard. T2 was superimposed on T1 using the anterior cranial base. In the same coordinate system, fit of the acquired registered T2s from both methods for each patient was evaluated using the absolute closest point color map. The absolute surfaces distance at seven selected regions (Nasion, A point, right and left Zygomatic, chin, and right and left Gonion) were calculated. There is enormous difference between the times needed to perform each of the two methods; Dolphin superimposition takes minutes while the other requires about 3 hours. **Results**: Intraclass correlation showed excellent reliability (0.92). The mean surfaces distance between the two methods

were less than 0.3mm (scanner voxel size 0.38mm). The least difference was found in Nasion region with an average of 0.15mm ±0.11, and the largest in Chin with 0.31mm ±0.22. **Conclusions**: Dolphin 3D voxel based superimposition in growing patients is accurate, and reliable to be used clinically and in research.

Introduction:

Since invention of Cephalometry by Broadbent in 1931, it became essential and important tool in understanding the influence of growth, treatment, or both on dental and skeletal changes within the craniofacial structure. Cephalometric Imaging allowed serial radiographs to be taken leading to the development of superimposition techniques to quantify skeletal and dental changes resulting from treatment and growth. It became the language of orthodontics, and a diagnostic tool to confirm the clinical finding using cephalometric measurements.[1] There is no doubt that 2D cephalometric analysis studies and their use helped in understanding craniofacial growth and development as well as treatment effect. However, these studies have some limitations with respect to accuracy and reliability. The error involved in landmark identification is without doubt the most important. In addition, cephalometric radiography has a limitation as being a 2D evaluating tool to 3D skeletal structure.[2 3 4 5]

Medical 3D imaging was introduced in the late 1990s adding another dimension for another century. Cone beam computed tomography (CBCT) was introduced to the dental profession in the United States between 2001 and 2004.[1]

The analysis of CBCT images has been valuable in numerous applications such as: (1) diagnosis of impacted and supernumerary teeth, in which the 3D images were superior to the conventional 2D images, (2) treatment planning for placement of skeletal anchorage devices, in which CBCT scans allowed for the evaluation of bone thickness and density in different areas in the mandible and maxilla, (3) 3D volumetric assessment of the upper airway, and (4) 3D analysis for diagnosis and treatment planning of orthodontic and orthognathic patients.[6 7 8]

As CBCT images use for orthodontic diagnosis and treatment planning increased, ways to superimpose these images for evaluation of the craniofacial growth and treatment changes have been introduced.

Currently, there are three ways of superimposing the 3D images. The initial method describing 3D superimposition was landmark based. Locating landmarks in 2D radiographs is usually easily identified due to the overlap of multiple structures, but this is not the case in the curved surfaces 3D images. Analysis of 3D images is much more complex than the analysis of 2D cephalometric radiographs.

Surface based superimposition was developed later[9 10] and it deals with the 3D rendered surface model requiring high quality surface models in order to get accurate results. Ong et al. used 3D surface models to quantify and visualize the

immediate 3D changes of the mid-face following rapid maxillary expansion. They concluded that the use of 3D surface models allows quantification and visualization of the 3D changes in the mid-facial skeleton at anatomical sites distant from RME activation.[11]

Gkantidis et al. in their comparative study of 3D superimposition techniques using surface models, concluded that superimposition of 3D images using surface models can provide accurate, precise, and reproducible results.[12]

Lately, a new method of 3D superimposition has been introduced to the medical research field known as voxel-based registration. It has been widely used for various medical applications and research purposes, including diagnoses, treatment planning and assessment of a variety of cases utilizing CT, CBCT, MRI, and 3D ultrasound.

Cevidanes et al.[13] introduced the new method of voxel-based superimposition to dental research in which the skull base is used as a stable reference structure for image superimposition. Voxel based superimposition uses the gray scale values of the voxels to align the two CBCT images to the best superimposition achieving the least total gray scale density difference between the two images. Voxel based superimposition is fully automated and uses the image content as the basis for the registration, which removes the chances of having operator's errors that was the main disadvantage of the previous methods.

Cevidanes et al demonstrated the use of voxel based registration in multiple orthodontic research validating the method as accurate and valid. The drawbacks of this voxel based method are that the superimposition process requires several different steps in various software programs and are time consuming.[14 15 16 17 18 19]

Bazina et al., using a sample of non-growing surgical patients at Case Western Reserve University, concluded that Dolphin 3D voxel based superimposition, as a fast and user friendly method, is accurate and reliable. Using the anterior cranial base to superimpose, they compared 3D voxel based superimposition method from Dolphin to the accepted method used by Cevidanes et al..[20] The aim of this study was to evaluate the accuracy and reliability of Dolphin 3D cranial base superimposition in growing patients.

Material and Methods

A sample of thirty growing patients were used in this retrospective study. Scans were selected from the database of the Craniofacial Imaging Center at Case Western Reserve University. The scans were acquisitioned by Hitachi CB MercuRay scanner, set at 120 KVp, 2 mA, large field of view, and a scan time of 10 Seconds. The images were reconstructed with 0.377-mm slice thickness and exported as Digital Imaging and Communications in Medicine (DICOM) files. Fifteen female and fifteen male growing patients were used (Table 1). The mean age at initial scan (T1) was 11.8 ±0.5 years and at second scan (T2) was 14.2 ±0.8

years (Table 2 & Figure 1). De-identified growing patients, who have two CBCTs taken two to three years apart were included and the scans were taken by the same machine with the same setting. Any scans of craniofacial anomalies & syndromes, missing targeted Field of View (FOV) or distorted images were excluded.

Cevidanes' method of voxel-based superimposition using 3D Slicer was used in this study as a gold standard to evaluate the accuracy of Dolphin 3D voxel-based superimposition. Flowchart of study methodology is shown in (Figure 2).

Dolphin 3D superimposition: (Figure 3).

The 3D images (T1&T2) for each patient were superimposed on the anterior cranial base using the voxel-based superimposition tool in Dolphin 3D (Chatsworth, CA -version 11.8.06.15 premium) (Figures 4-6). Dolphin does the voxel-based superimposition by moving T2 as a result of superimposing T2 to T1 on the cranial bases creating a new positioned T2 named Registered T2 (RegT2). This T2 was registered to the unaltered acquisitioned T1 position in a shared coordinate system. The precision of Dolphin 3D superimposition was then verified using the slice view (sagittal, axial, and coronal views) and the RegT2 from Dolphin was exported as DICOM file. Using ITK-snap (version 3.4.0) and 3D Slicer (version 4.4.0) tools: Intensity Segmenter and Model Maker, steps were taken then to create a surface model of RegT2 for each particular patient.

3D Slicer Superimposition: (Figure 7)

After changing DICOM format to an easy computing GIPL (Guy Image Processing Lab) format for each patient using ITK-snap (version 3.4.0), the anterior cranial base of T2 was manually approximated to the anterior cranial base of the unaltered T2. The newly positioned T2 was named Approximated T2 (AproxT2) and was done using 3D Slicer (version 4.4.0). Since slicer 3D superimposition uses segmented cranial bases to register the two time-point images, segmentation of the anterior cranial bases for (T1&T2) was then obtained using ITK-snap (Figures 8&9). The two images (T1 & AproxT2) and the two anterior cranial base segmentations (T1Seg & T2Seg) were imported next into 3D slicer for registration using CMF growing rigid auto registration (Figure 10). Once a registered T2 (RegT2) was obtained, the same steps as in Dolphin 3D superimposition were done using Intensity Segmenter and Model Maker 3D slicer tools to create a surface model of RegT2 for each patient.

Assessment of 3D Dolphin superimposition:

The key to assess and compare Dolphin 3D superimposition to the golden standard 3D slicer method is that T1in both methods is having unaltered acquisitioned position in the same coordinate system. Assuming that 3D Dolphin superimposition is as accurate as 3D slicer, the resultant RegT2s from both methods should perfectly fit over each other.

Visual quantification of the differences was done by measuring the distance between the two surface models using closest-point color maps (Figure 11).

Seven areas were selected using 3D slicer Pick' n Paint tool to measure the absolute differences between the two models (Figures: 12 & 13). The areas are Nasion, A point, right zygomatic arch, left zygomatic arch, right gonial angle, chin, and left gonial angle. After area selection, the absolute difference in distances between the two surfaces at those areas was calculated using Mesh stats tool. The mean absolute distance, standard deviation, maximum and minimum distances were obtained and the mean value for each one of the seven areas was then calculated.

Results

To test the reliability, protocol was repeated for ten patients after two weeks and Intra-class correlation coefficient was used to assess reliability. ICC was 0.92 (Table 3).

Results obtained from this study showed that the quantification of the superimposition difference by color mapped surface distances showed that the absolute mean difference was less than 0.3mm. The least difference was found in Nasion region with an average of 0.15mm ±0.11, and the largest in Chin with 0.31mm ±0.22. (Table 4).

Discussion

Cone beam computed tomography (CBCT) is a tool that is now part of contemporary diagnosis and treatment. It provides actual measurements without magnification, allowing image comparison with accuracy and precision. It also enables volumetric measurements of an object, and gives the ability to assess changes in contour and shape. 3D images can also be superimposed using thousands of points, shapes and volume rather than lines and curves. This study has validated the use of Dolphin software 3D superimposition method for CBCT images of growing patients' craniofacial structures. Cevidanes et al were the first to describe voxel-based superimposition in dentistry.

Among 3D superimposition methods, Voxel based superimposition became the most validated because it is operator independent and uses the entire selected volume like anterior cranial base for superimposition. Almukhtar et al. demonstrated in their study the fact that Surface based registration has a higher variability in superimposition, whereas voxel based registration has a low variation in the superimposition process. They also found that surface based registration for

hard tissue is as accurate and consistent as the voxel based registration while voxel based registration produces a more accurate representation of the soft tissue changes as compared to surface based registration.[21] Voxel based superimposition compares the image gray scale intensity of the voxels; whereas surface based superimposition requires an extra step of creating an image Hounsfield dependent three-dimensional surface model. The image Hounsfield dependent variability between image volumes could introduce an error factor in the superimposition process.

The 3D voxel based technique by Cevidanes involves multiple steps using 2 open source software programs which require segmentation, registration and surface model superimposition with potential sources of variations between examiners - 1) Low gray-scale contrast in anatomic thin cortical bone prevents their automatic definition that could introduce slightly different outlining of surface by different examiners. 2) Variabilities in the 3D surface model created since it is user dependent 3) Examiner variations in the isoline contours choice on the color map could affect quantification of treatment outcomes. Although those potential variations in Cevidanes method exist, they are very small making this method the gold standard in 3D superimposition.[14] However, this method requires extensive training, time and is not applicable for clinical chairside use.

As in the Bazina et al. study,[20] the same methodology was used in the current study where it was applied on adult patients and found that Dolphin 3D voxel based superimposition was accurate and reliable. The reason for the current investigation emerged from Bazina's study examining Dolphin 3D superimposition in growing patients where the cranial base is not as stable as in adults because of growth. Dolphin 3D Imaging as being a developed tool that requires few steps, is fast, and does not require extensive training is now tested valid for 3D superimposition in adults and growing patients and can now be used clinically as well as in research.

The absolute mean difference between T2's surfaces in this study was found to be more than Bazina et al.'s study by a tenth of a millimeter, 0.3mm and 0.2mm respectively, which is insignificant and small where both results were less than the scanner voxel size (same scanner used in both studies). Interestingly the least and largest differences in this study were found in Nasion and Chin areas respectively, indicating superimposition error occurring due to rotation around side-to-side axis i.e. "pitch". Whereas in Bazina et al.'s the least and largest differences were respectively found in left zygomatic and right Gonion areas which indicates the error was due to rotation around vertical axis i.e. "yaw". These differences even though they are very small and insignificant could be due to extension variation of cranial base area of superimposition between the two studies where the extension in growing patients was more limited than in the adult.

3D superimposing in growing patients compared to adult patients is more challenging due to the changes of the gray scale value of the growing cranial base. In addition, a challenge exist when comparing two CBCT images acquisitioned by different scanners due to different gray levels produced from the two scanners, which could have an effect on the superimposition outcome.

The scanner milliamperage setting-mA, and the capture time, control the number of the photons released from the X-ray tube and subsequently the number of photons that reach the detector voxels. When more photons are hitting the voxels, more information can be obtained from the grayscale.[22] Scanner mA setting in the current study was 2mA compared to 15mA in the Bazina et al study with subsequently lesser image quality than Bazina et al The current results show that Dolphin 3D superimposition is accurate and reliable using a sample of less image resolution and quality.

Potential variations in 3D superimposition results have been observed during this study especially in male patients who expressed a large amount of growth. Similar observation has been reported in Ghafari et al. study[4] comparing cephalometric superimposition methods. They reported that clinically and statistically significant differences were found for boys in the total sample. Further investigation is needed to look into 3D superimposition in male patients where large growth occurred between the two time points.

Nada et al.[23] and Weissheimer et al.[24] tested the accuracy and reliability of voxel-based superimposition using Maxilim software and OnDemand 3D software programs respectively. Nada et al. reported that superimposition using the anterior cranial base is accurate and reliable and the use of zygomatic arch in non-growing subjects is an alternative for cranial base superimposition in small Field of view scans. Whereas Wessheimer et al using a fast method of 3D superimposition found that the error was acceptable and clinically insignificant in growing and non-growing subjects.

Possible study limitation is a single operator, and unfeasibility of operator blinding due to the nature of the study. A known limitation of Dolphin 3D software is that it is commercially available.

Conclusion

Dolphin 3D voxel based superimposition in growing patients is accurate, and reliable to be used clinically and in research.

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Figures:

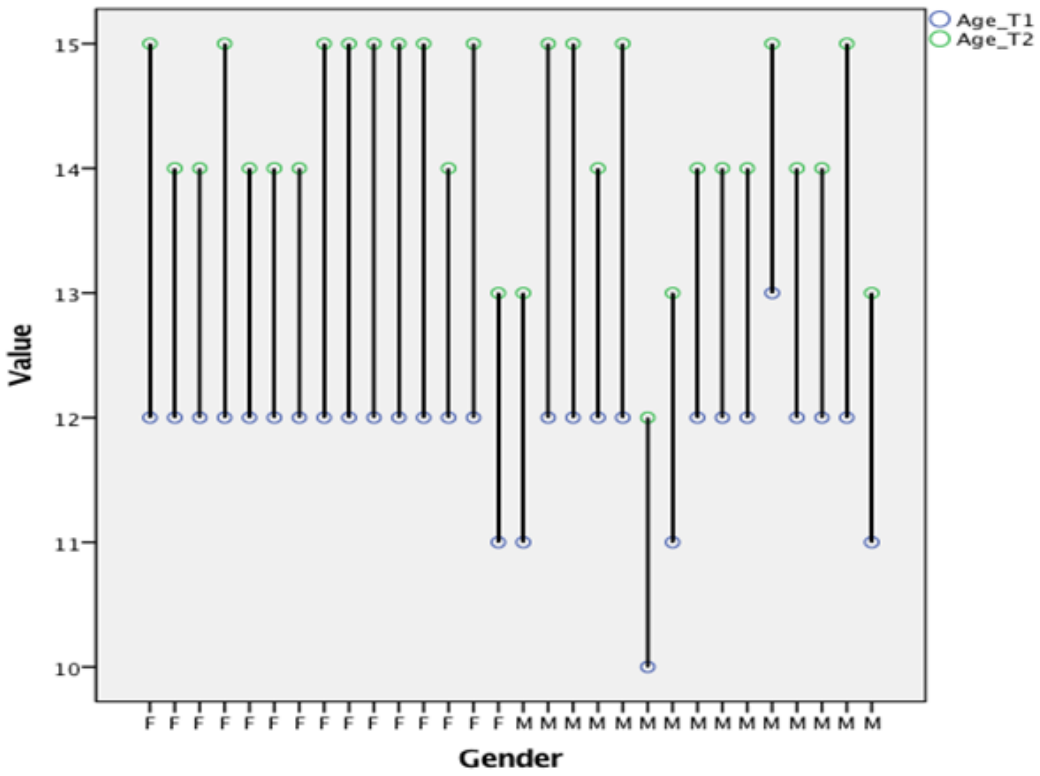


Figure 1 Showing sample age distribution at T1 and T2 for males (M) and females (F).

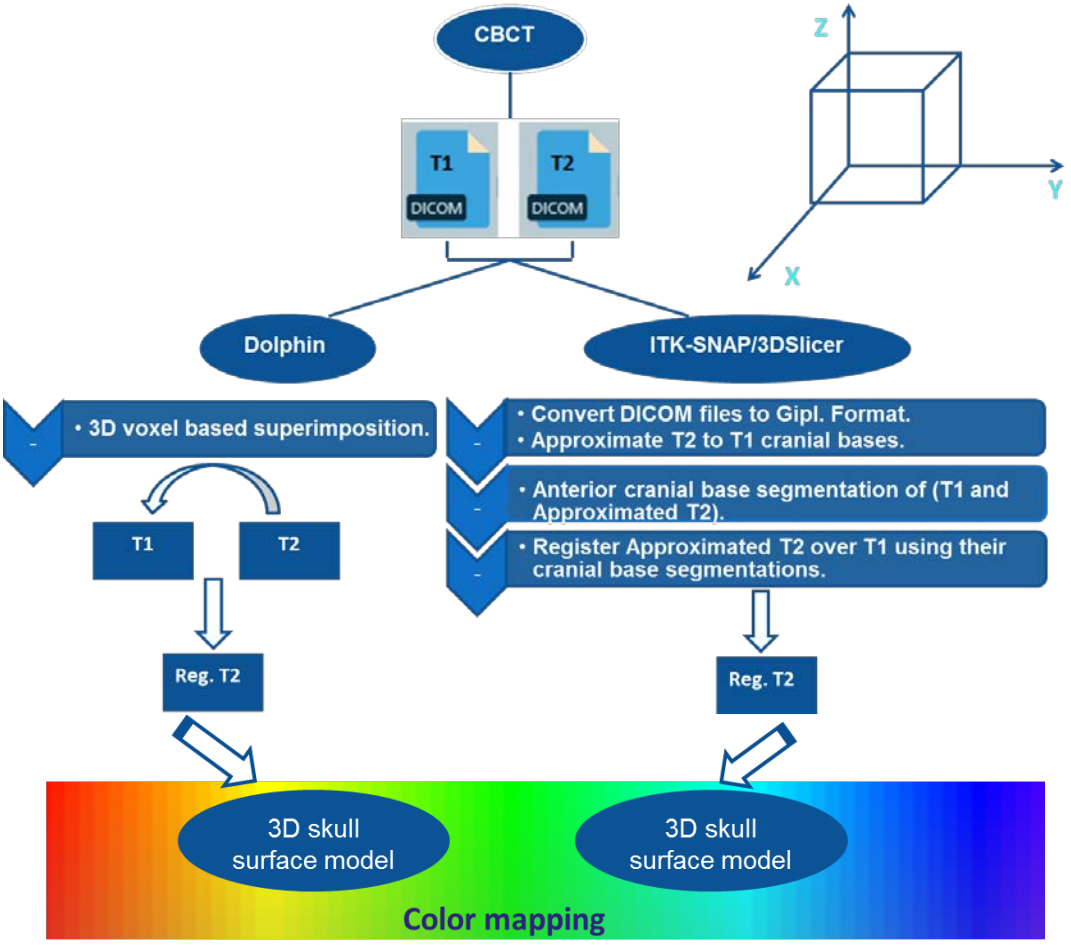


Figure 2 Flowchart showing study methodology.

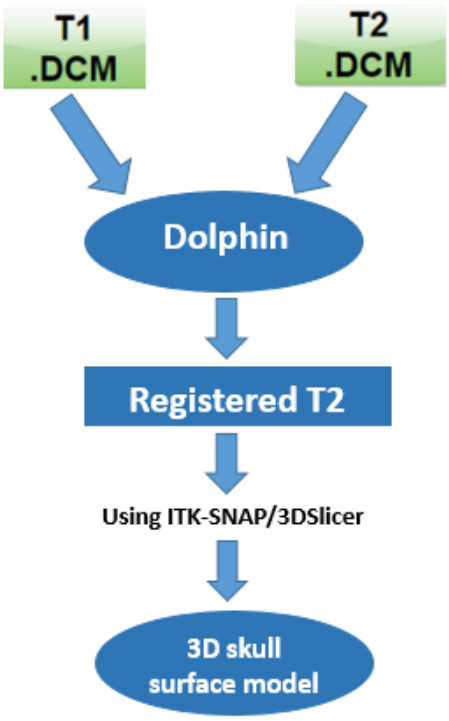


Figure 3 Dolphin 3D voxel-based superimposition and surface model creation for the comparison.

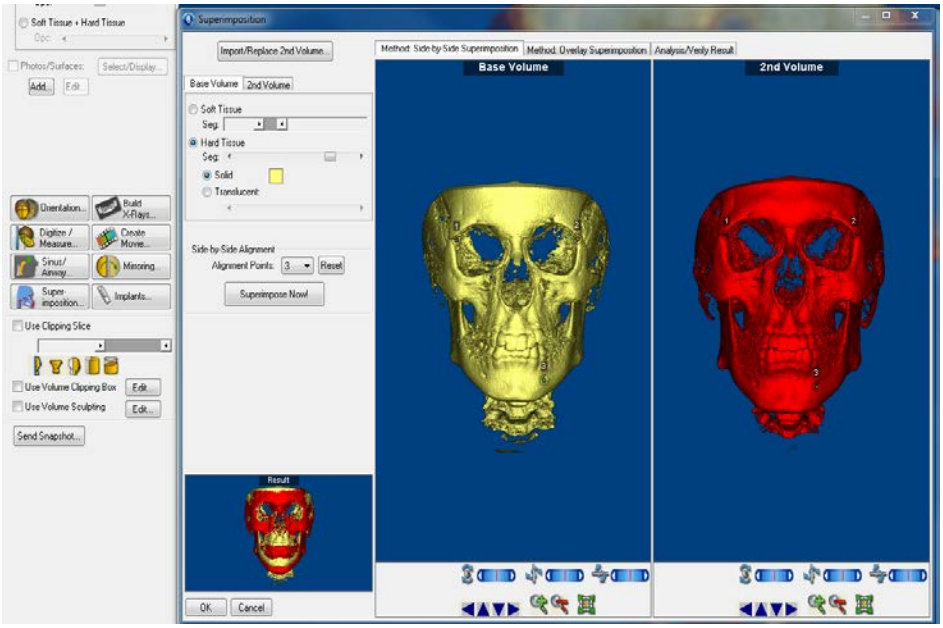


Figure 4 Dolphin 3D superimposition-Approximation of T1&T2 using landmark method.

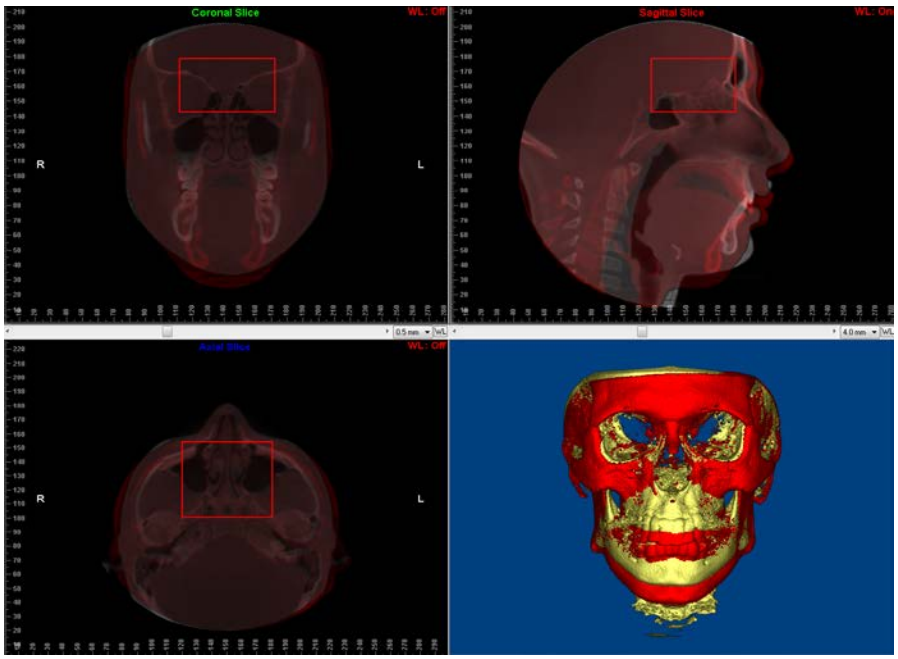


Figure 5 Dolphin 3D voxel-based superimposition on the anterior cranial base.

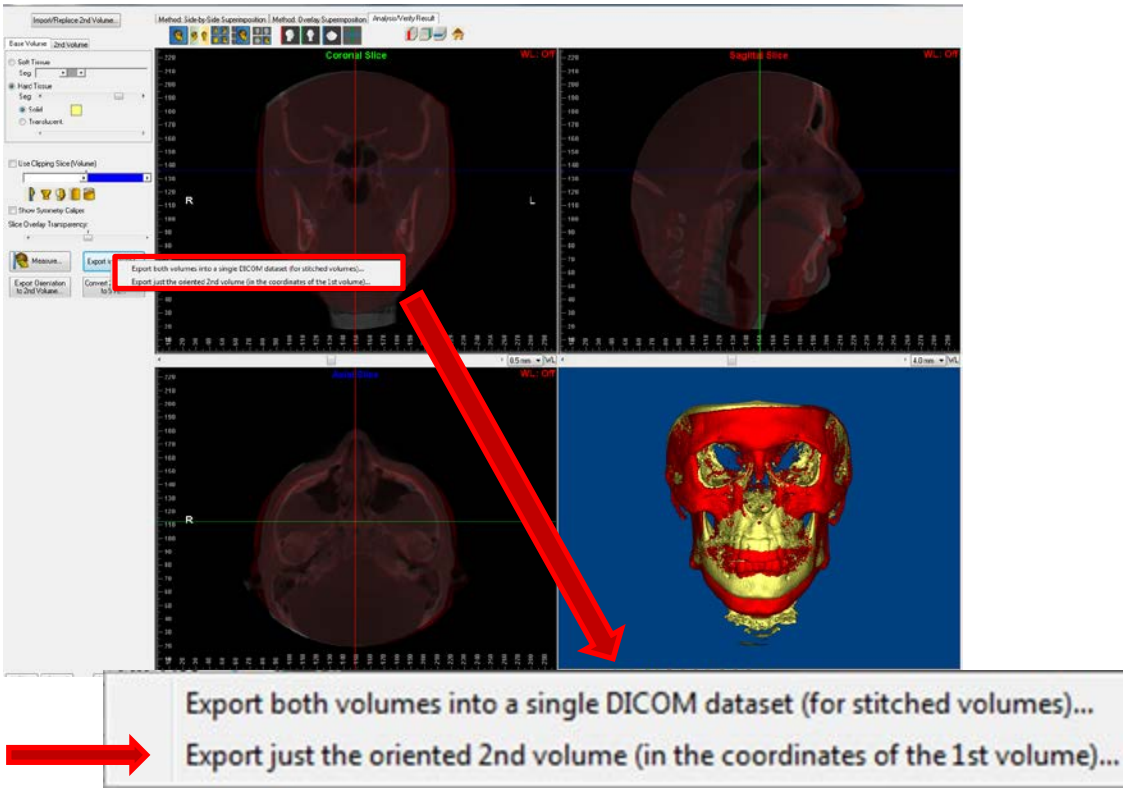


Figure 6 Dolphin 3D voxel-base superimposition- exporting registered T2.

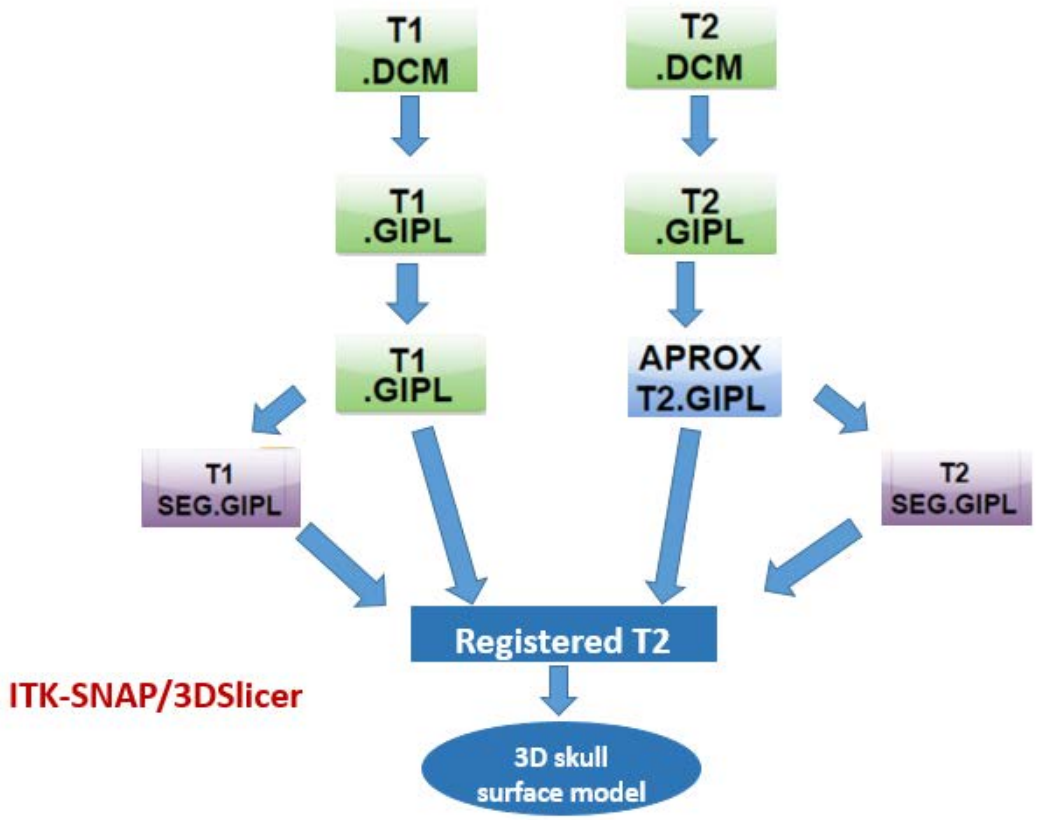


Figure 7 Cevidanes method steps of voxel based superimposition using ITK-SNAP and 3DSlicer.

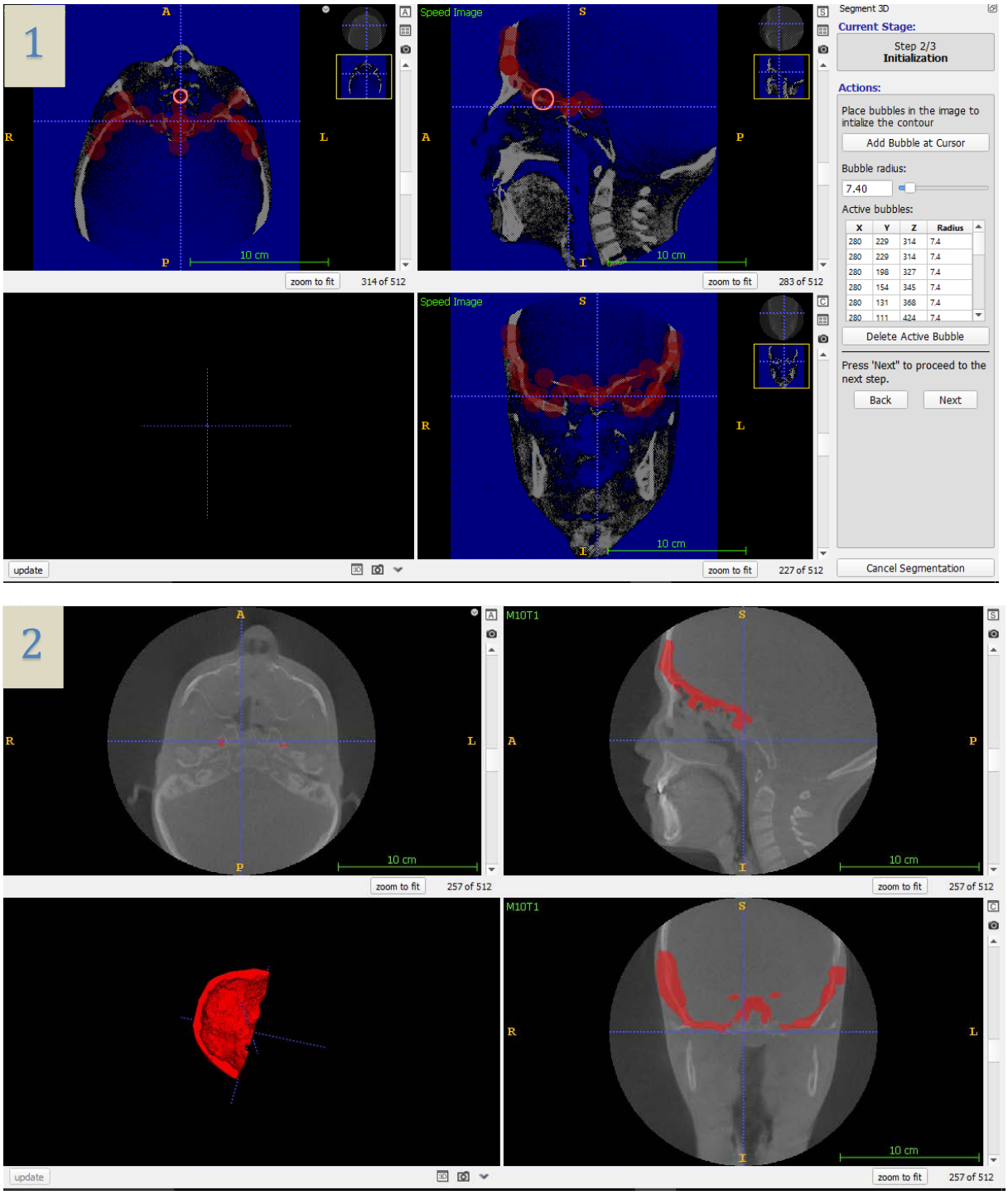


Figure 8 Anterior cranial base segmentation using ITK snap: 1) Adding bubbles to Region of interest. 2) Obtaining anterior cranial base segmentation.

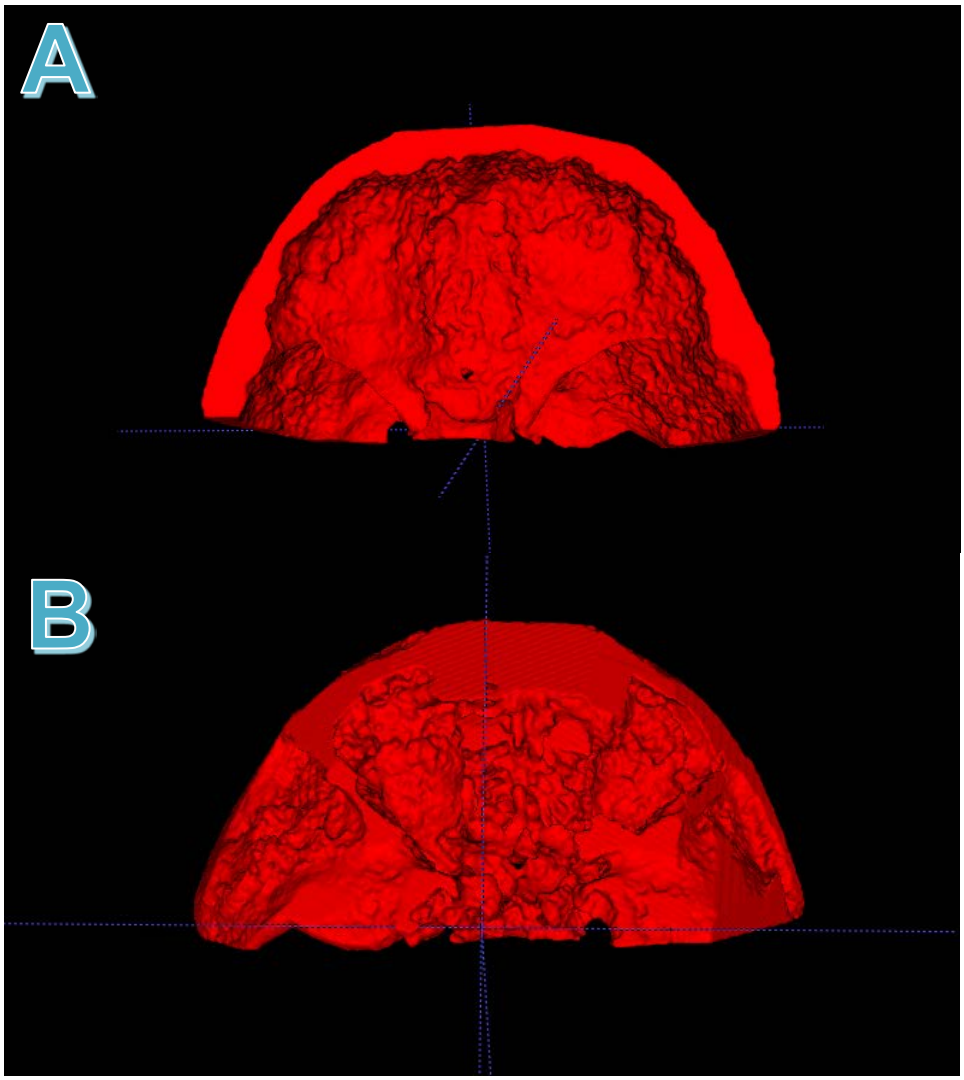


Figure 9 **Anterior cranial base segmentation using ITK-Snap. A) Superior view. B) Inferior view.**

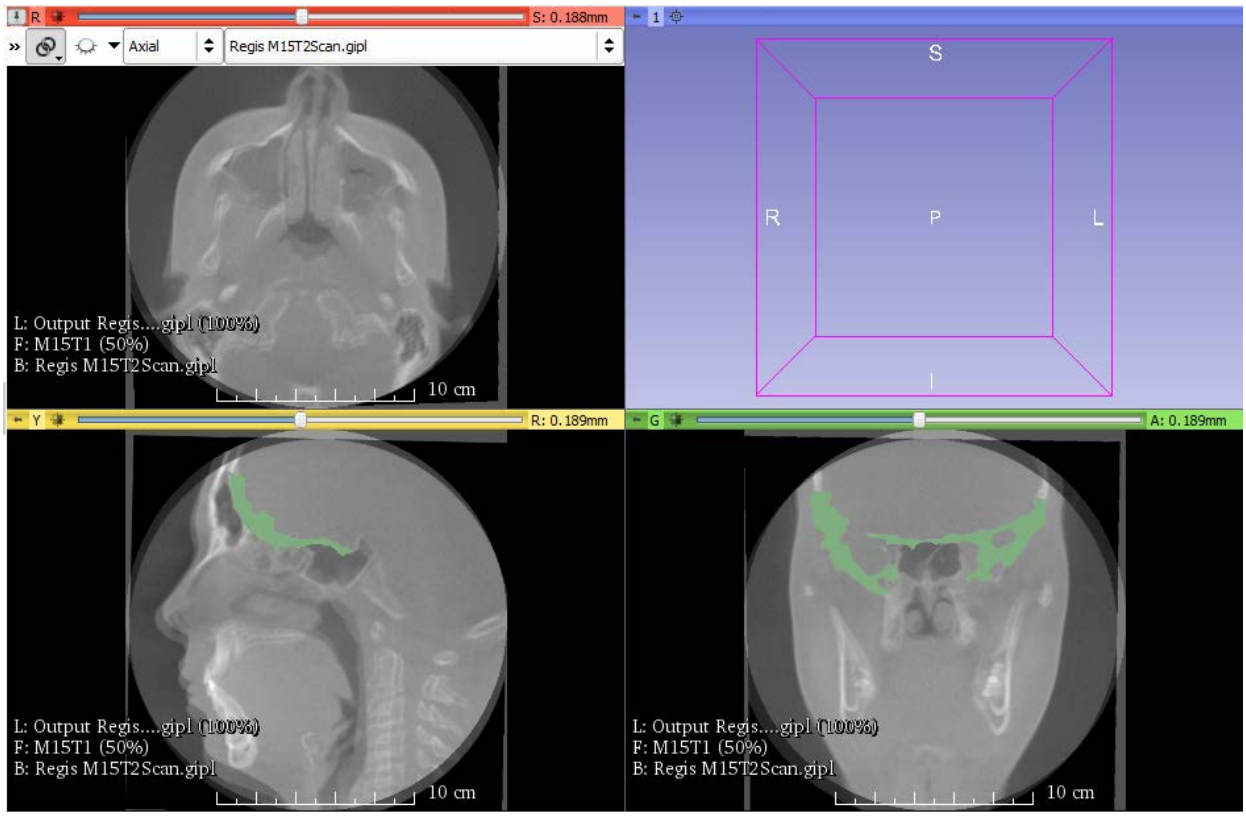


Figure 10 **Voxel-based Registration of T2 on the anterior cranial base using 3D Slicer.**

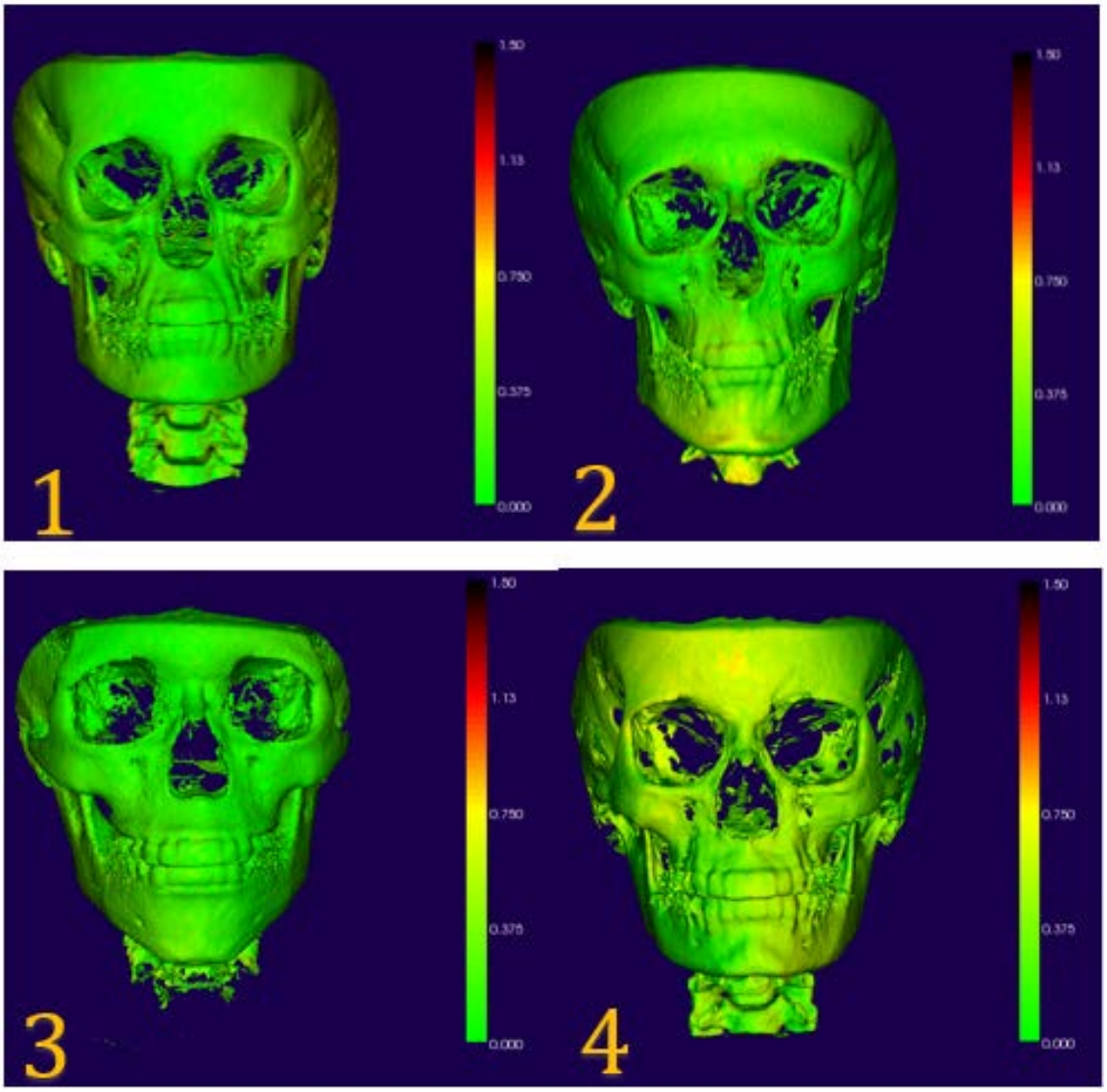


Figure 11 **3D Color map of the registered T2 models from both software programs. Four examples of sample studied.**

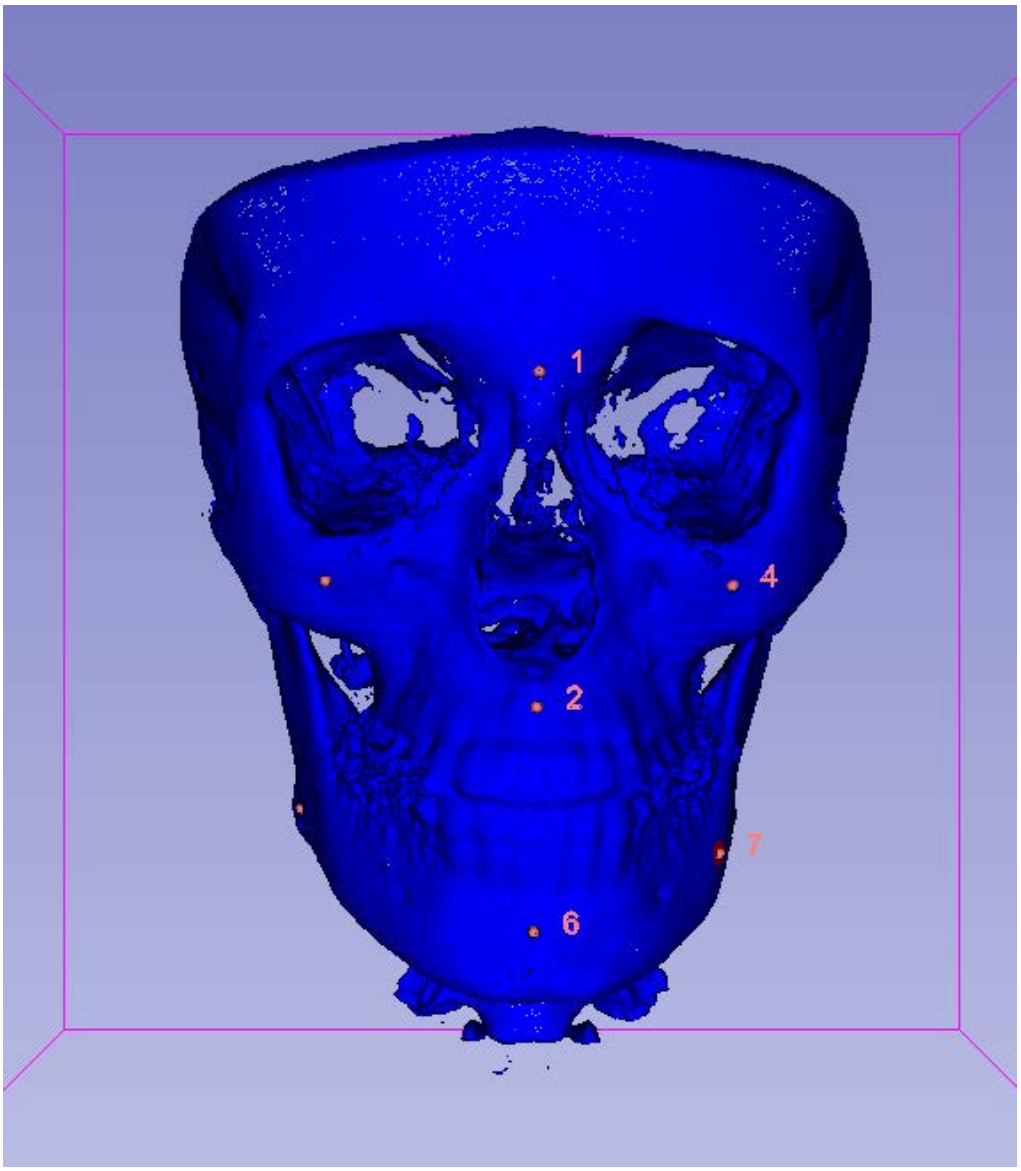


Figure 12 **Fiducial areas were selected using Pick ‘n Paint tool in 3D Slicer.**

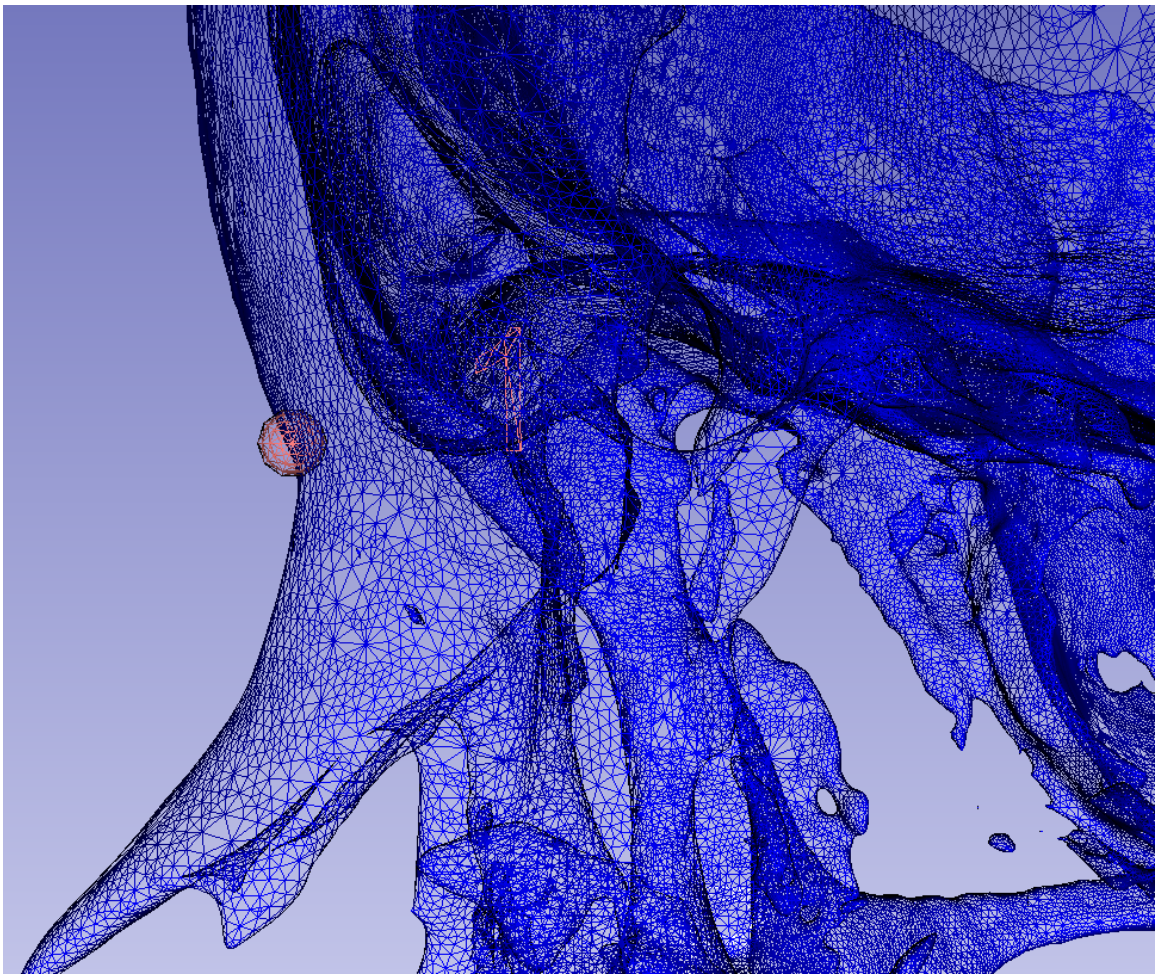


Figure 13 **Fiducial area number 1 in Pick ‘n Paint tool (close-up side view).**

	Frequency	Valid Percent
Valid	Female	50 %
	Male	50 %
	Total	100 %

Table 1 Gender distribution. N=30

	N	Range	Minimum	Maximum	Mean	Std. Deviation
Age at T1	30	3	10	13	11.83	.531
Age at T2	30	3	12	15	14.23	.817

Table 2 Descriptive statistics showing age distribution at time point one (T1) and time point two (T2).

Intraclass Correlation Coefficient							
		95% Confidence Interval		F Test with True Value 0			
	Intraclass Correlation[b]	Lower Bound	Upper Bound	Value	df1	df2	Sig
Single Measures	.860[a]	.535	.963	13.289	9	9	.000
Average Measures	.925	.697	.981	13.289	9	9	.000

Table 3 Intra-class correlation.

Two-way random effects model where both people effects and measures effects are random.

a. The estimator is the same, whether the interaction effect is present or not.
b. Type C intraclass correlation coefficients using a consistency definition. The between-measure variance is excluded from the denominator variance.

	N	Range	Minimum	Maximum	Mean	Std. Deviation
NasionA	30	.492	.016	.508	.14903	.113885
ApointA	30	.438	.032	.470	.21493	.131909
RtZygoA	30	.466	.019	.485	.16473	.112857
LtZygoA	30	.437	.028	.465	.15583	.097685
RtGonialA	30	.654	.057	.711	.24317	.166788
ChinA	30	.880	.038	.918	.30593	.224583
LtGonialA	30	.640	.065	.705	.25477	.169127

*All measurement are in mm

Table 4 Descriptive statistics showing absolute difference in the distances between the two surface models at the seven areas obtained using Pick 'n paint and Mesh Stats tools.

Appendix

Raw Data

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0	0.229	0.074	0.063	0.16	0.175
2	0.018	0.291	0.205	0.059	0.264	0.278
3	0.102	0.228	0.153	0.027	0.179	0.213
4	0.001	0.265	0.087	0.059	0.146	0.175
5	0.003	0.447	0.115	0.083	0.195	0.245
6	0.027	0.335	0.175	0.07	0.256	0.305
7	0	0.353	0.116	0.071	0.182	0.251

Case 1

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0.04	0.357	0.158	0.082	0.271	0.332
2	0.209	0.549	0.437	0.073	0.509	0.533
3	0.201	0.308	0.26	0.022	0.283	0.298
4	0.042	0.228	0.145	0.037	0.178	0.196
5	0.078	0.444	0.243	0.078	0.344	0.39
6	0.374	0.687	0.59	0.052	0.641	0.659
7	0.032	0.234	0.12	0.037	0.157	0.183

Case 2

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0	0.086	0.031	0.022	0.055	0.065
2	0.001	0.223	0.122	0.041	0.164	0.179
3	0.146	0.246	0.201	0.024	0.224	0.238
4	0.181	0.303	0.256	0.028	0.285	0.292
5	0.148	0.504	0.365	0.092	0.452	0.488
6	0.001	0.167	0.069	0.04	0.113	0.136
7	0.389	0.528	0.444	0.029	0.47	0.5

Case 3

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0	0.281	0.112	0.072	0.195	0.225
2	0.001	0.595	0.395	0.148	0.529	0.561
3	0.063	0.284	0.176	0.047	0.222	0.261
4	0.047	0.214	0.142	0.041	0.188	0.199
5	0.019	0.317	0.202	0.082	0.281	0.308
6	0.827	1	0.918	0.038	0.955	0.981
7	0	0.39	0.141	0.105	0.257	0.348

Case 4

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0.001	0.074	0.025	0.016	0.042	0.055
2	0.025	0.261	0.173	0.055	0.223	0.243
3	0.214	0.34	0.261	0.026	0.29	0.316
4	0	0.073	0.028	0.021	0.052	0.065
5	0.001	0.268	0.128	0.058	0.192	0.226
6	0.034	0.457	0.291	0.054	0.341	0.379
7	0.001	0.29	0.099	0.049	0.147	0.184

Case 5

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0.077	0.307	0.197	0.042	0.245	0.267
2	0	0.141	0.067	0.037	0.107	0.132
3	0.104	0.18	0.145	0.018	0.164	0.175
4	0.097	0.268	0.178	0.039	0.218	0.259
5	0.255	0.479	0.395	0.043	0.441	0.453
6	0.086	0.423	0.218	0.071	0.289	0.367
7	0.032	0.486	0.334	0.079	0.404	0.421

Case 6

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0.002	0.123	0.054	0.03	0.088	0.104
2	0.073	0.183	0.124	0.022	0.145	0.163
3	0.09	0.178	0.148	0.02	0.169	0.174
4	0.029	0.144	0.085	0.026	0.116	0.13
5	0.002	0.374	0.235	0.085	0.309	0.342
6	0.13	0.357	0.254	0.045	0.302	0.319
7	0.078	0.339	0.23	0.045	0.274	0.303

Case 7

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0	0.123	0.059	0.026	0.087	0.099
2	0.284	0.41	0.354	0.023	0.377	0.397
3	0.005	0.104	0.046	0.022	0.069	0.086
4	0.184	0.3	0.239	0.026	0.27	0.286
5	0.004	0.207	0.121	0.052	0.173	0.186
6	0.345	0.617	0.488	0.048	0.531	0.549
7	0.045	0.363	0.244	0.057	0.3	0.322

Case 8

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0	0.281	0.113	0.058	0.173	0.221
2	0.148	0.357	0.266	0.042	0.305	0.333
3	0.082	0.249	0.157	0.043	0.212	0.23
4	0.043	0.182	0.107	0.027	0.128	0.158
5	0	0.262	0.102	0.055	0.166	0.19
6	0.224	0.448	0.328	0.047	0.37	0.403
7	0.002	0.376	0.162	0.073	0.229	0.276

Case 9

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0	0.216	0.059	0.042	0.095	0.135
2	0.024	0.422	0.259	0.097	0.371	0.387
3	0.108	0.215	0.178	0.019	0.193	0.198
4	0	0.092	0.029	0.022	0.055	0.074
5	0.043	0.545	0.373	0.097	0.461	0.482
6	0.226	0.572	0.462	0.071	0.536	0.548
7	0.308	0.723	0.495	0.07	0.567	0.612

Case 10

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0.041	0.326	0.205	0.069	0.272	0.286
2	0.095	0.398	0.293	0.076	0.37	0.379
3	0.149	0.295	0.229	0.033	0.26	0.276
4	0	0.142	0.067	0.03	0.096	0.108
5	0.001	0.264	0.085	0.05	0.135	0.171
6	0.258	0.492	0.376	0.051	0.438	0.458
7	0	0.233	0.068	0.051	0.125	0.161

Case 11

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0	0.132	0.036	0.032	0.072	0.102
2	0.283	0.445	0.384	0.029	0.413	0.427
3	0.039	0.232	0.128	0.037	0.168	0.204
4	0.165	0.325	0.269	0.032	0.3	0.31
5	0	0.29	0.077	0.055	0.146	0.176
6	0.45	0.622	0.531	0.028	0.559	0.574
7	0.002	0.369	0.157	0.078	0.234	0.284

Case 12

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0.09	0.355	0.194	0.046	0.237	0.285
2	0	0.234	0.032	0.034	0.062	0.089
3	0.213	0.358	0.292	0.022	0.316	0.328
4	0.26	0.431	0.355	0.042	0.406	0.421
5	0.137	0.891	0.711	0.133	0.82	0.846
6	0	0.384	0.114	0.082	0.188	0.284
7	0.42	0.842	0.705	0.088	0.792	0.824

Case 13

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0	0.061	0.016	0.012	0.029	0.04
2	0.001	0.244	0.071	0.04	0.102	0.131
3	0.002	0.183	0.074	0.041	0.121	0.148
4	0.058	0.198	0.122	0.028	0.154	0.168
5	0.006	0.274	0.159	0.058	0.219	0.254
6	0.016	0.187	0.135	0.032	0.165	0.173
7	0.043	0.377	0.201	0.065	0.275	0.327

Case 14

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0.292	0.682	0.508	0.064	0.57	0.615
2	0.142	0.551	0.413	0.09	0.505	0.528
3	0.388	0.582	0.485	0.053	0.545	0.563
4	0.379	0.531	0.465	0.035	0.496	0.511
5	0.103	0.3	0.199	0.045	0.256	0.285
6	0.157	0.546	0.397	0.087	0.495	0.521
7	0.054	0.395	0.252	0.085	0.337	0.375

Case 15

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0.227	0.382	0.291	0.031	0.32	0.349
2	0.018	0.19	0.084	0.034	0.118	0.147
3	0.116	0.179	0.142	0.014	0.159	0.165
4	0.099	0.253	0.192	0.031	0.229	0.243
5	0	0.23	0.057	0.042	0.108	0.138
6	0	0.282	0.038	0.037	0.078	0.118
7	0.001	0.193	0.082	0.048	0.141	0.157

Case 16

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0.001	0.184	0.053	0.042	0.1	0.137
2	0.003	0.587	0.234	0.144	0.407	0.472
3	0.001	0.226	0.094	0.054	0.155	0.179
4	0	0.281	0.086	0.069	0.155	0.219
5	0.226	0.649	0.49	0.068	0.561	0.593
6	0.009	0.63	0.342	0.172	0.54	0.587
7	0.258	0.805	0.55	0.118	0.682	0.744

Case 17

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0.098	0.246	0.174	0.026	0.202	0.214
2	0.029	0.229	0.133	0.052	0.186	0.212
3	0	0.054	0.02	0.015	0.037	0.048
4	0.178	0.315	0.237	0.031	0.269	0.297
5	0.046	0.626	0.461	0.102	0.538	0.558
6	0.001	0.265	0.123	0.077	0.217	0.24
7	0.13	0.714	0.498	0.099	0.596	0.624

Case 18

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0	0.317	0.088	0.088	0.196	0.296
2	0.225	0.626	0.47	0.099	0.561	0.587
3	0.002	0.125	0.054	0.029	0.08	0.113
4	0.079	0.276	0.172	0.042	0.217	0.245
5	0	0.324	0.064	0.054	0.108	0.18
6	0.501	0.942	0.758	0.095	0.855	0.887
7	0	0.23	0.065	0.051	0.131	0.156

Case 19

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0.001	0.133	0.076	0.031	0.111	0.121
2	0	0.166	0.045	0.03	0.078	0.095
3	0.017	0.115	0.072	0.021	0.092	0.107
4	0.037	0.139	0.082	0.022	0.108	0.119
5	0.007	0.409	0.221	0.077	0.293	0.348
6	0	0.327	0.131	0.058	0.188	0.223
7	0.097	0.328	0.223	0.052	0.274	0.289

Case 20

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0.021	0.248	0.144	0.045	0.192	0.219
2	0.096	0.238	0.173	0.031	0.206	0.22
3	0	0.121	0.025	0.025	0.049	0.072
4	0.055	0.206	0.119	0.034	0.155	0.176
5	0.004	0.338	0.211	0.053	0.264	0.295
6	0.218	0.448	0.343	0.053	0.406	0.426
7	0.146	0.396	0.278	0.065	0.339	0.367

Case 21

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0	0.172	0.081	0.046	0.13	0.153
2	0.001	0.21	0.099	0.042	0.144	0.156
3	0	0.07	0.019	0.018	0.041	0.058
4	0	0.143	0.033	0.033	0.068	0.106
5	0.015	0.39	0.207	0.065	0.266	0.325
6	0.032	0.333	0.148	0.058	0.209	0.241
7	0.002	0.402	0.223	0.083	0.303	0.325

Case 22

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0.002	0.743	0.364	0.177	0.554	0.627
2	0.001	0.691	0.282	0.19	0.52	0.642
3	0.081	0.277	0.192	0.038	0.24	0.255
4	0.003	0.359	0.229	0.087	0.3	0.325
5	0	0.582	0.346	0.134	0.47	0.517
6	0.001	0.413	0.147	0.106	0.27	0.357
7	0.275	0.851	0.549	0.148	0.725	0.798

Case 23

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0.006	0.349	0.234	0.075	0.302	0.32
2	0.003	0.658	0.443	0.175	0.595	0.634
3	0.15	0.438	0.278	0.053	0.326	0.372
4	0.126	0.344	0.215	0.046	0.264	0.301
5	0.002	0.57	0.416	0.153	0.543	0.556
6	0.676	0.823	0.753	0.042	0.806	0.818
7	0.001	0.397	0.192	0.075	0.268	0.332

Case 24

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0.048	0.313	0.185	0.062	0.252	0.274
2	0.131	0.329	0.211	0.04	0.242	0.297
3	0.377	0.536	0.456	0.033	0.497	0.515
4	0.052	0.183	0.11	0.029	0.14	0.153
5	0.002	0.789	0.588	0.177	0.709	0.75
6	0.016	0.355	0.243	0.05	0.286	0.311
7	0.201	0.628	0.423	0.083	0.504	0.522

Case 25

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0.069	0.33	0.237	0.064	0.294	0.311
2	0.07	0.22	0.159	0.033	0.193	0.201
3	0.044	0.161	0.109	0.027	0.144	0.153
4	0.02	0.127	0.071	0.026	0.101	0.112
5	0.001	0.248	0.109	0.05	0.166	0.206
6	0.118	0.314	0.206	0.036	0.249	0.27
7	0	0.275	0.11	0.05	0.157	0.193

Case 26

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0	0.166	0.064	0.041	0.112	0.144
2	0.082	0.313	0.196	0.057	0.254	0.293
3	0.048	0.189	0.111	0.033	0.148	0.173
4	0.028	0.173	0.1	0.031	0.131	0.141
5	0.007	0.276	0.14	0.058	0.2	0.235
6	0.12	0.329	0.25	0.039	0.286	0.296
7	0.049	0.378	0.222	0.078	0.304	0.342

Case 27

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0.111	0.348	0.262	0.053	0.322	0.334
2	0.017	0.173	0.097	0.038	0.141	0.157
3	0.003	0.163	0.071	0.034	0.105	0.133
4	0.1	0.223	0.165	0.027	0.192	0.201
5	0.006	0.226	0.121	0.049	0.167	0.181
6	0.025	0.322	0.226	0.057	0.27	0.292
7	0.019	0.29	0.154	0.048	0.203	0.247

Case 28

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0.149	0.408	0.281	0.059	0.343	0.384
2	0	0.354	0.148	0.103	0.274	0.32
3	0.115	0.265	0.185	0.028	0.219	0.235
4	0.008	0.18	0.125	0.027	0.15	0.164
5	0.002	0.338	0.089	0.069	0.163	0.224
6	0	0.19	0.069	0.049	0.125	0.161
7	0.001	0.202	0.085	0.048	0.141	0.175

Case 29

POINT	Min	Max	Ave	STD	PER 85	PER 95
1	0	0.281	0.096	0.082	0.209	0.242
2	0.002	0.233	0.079	0.041	0.113	0.14
3	0.055	0.312	0.181	0.066	0.257	0.283
4	0.06	0.262	0.165	0.041	0.211	0.231
5	0.149	0.35	0.265	0.045	0.312	0.331
6	0	0.143	0.055	0.036	0.101	0.118
7	0.014	0.421	0.221	0.093	0.317	0.347

Case 30