POLITECNICO DI TORINO

Master's Degree Course in Mechanical Engineering

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Fetal face normotype from the analysis of 3D ultrasounds

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To my mother Marcela and my siblings Nicolás, Soad, Nayib and Williams.

To my boyfriend Nicolás.

Dedicated to the memory of my father Nicolás Jadue Kuncar.

Abstract

Three-dimensional technology has been revolutionizing the world since its creation. Its applications are countless as well as its benefits in actual daily life. An example of this is the medical field which through this technology has seen improved the quality of their medical analyses improving in turn the quality life of people. Inside this field, obstetrics have taken in advantage this advance but there are a lot of investigation areas still uncovered with big expectations about their results. Three-dimensional fetal face analysis could be considered as one of this area due to the low amount of actual literature with this topic.

This work intends to be a starting point in constructing a fetal normotype through measuring distances or relations between soft-tissue landmarks settled on 3D fetal face models and through the comparison of this measurements with respect to a reference values obtained from investigations about three different and common diseases: Down syndrome, fetal alcohol syndrome and micrognathia. All of this abnormalities involve facial dysmorphologies. In this thesis, 15 healthy fetuses with a gestational age around 21 weeks from 15 patients have been used for their analyses. Their data and the methodology followed are detailed in the first section.

Second section is a state of art related with the effects of three-dimensional technologies in the medical field in general and, particularly, in obstetrics. Their benefits, achievements, scopes and prospective are treated in this part. Also, it is discussed about biometry in human face in its importance and advantages -like assertive medical diagnoses and facial recognition- and the biometric analyses of fetal faces.

Next sections explain in details the phases for: 1) obtaining 3D models from a medical software (4D View) where 3D ultrasounds have volumetric format and must be converted in CAD files, 2) modelling of CAD files through a 3D design software (Geomagic Studio) in order to have a define and clear fetal shell, 3) files exportations as point clouds and their remeshing in Matlab into a squad-mesh and 4) the localization of each one of landmarks (landmarking) through a Matlab algorithm or manually in case of the code doesn't work correctly.

Subsequent section is related to description of the medical conditions taken as reference and the facial features that present alterations in case of a positive diagnostic from one of them. In addition, for each one of abnormalities is defined the measurement(s) to be evaluated and compared.

Final part presents the results obtained as well as reference values. It is defined by simple comparison whether each measurement is candidate for a fetal face normotype or not and the reasons. Error source analyses and a self-criticism take place in Discussion subsection to conclude the work.

Acknowledgements

I dedicate this achievement to my father who passed away some years ago and who I miss so much. I know he would be proud of me but I wish he were here.

I would like to thanks all of that persons who have supported me during my life and along this -sometimes loneliness- adventure of living abroad. In first place I thanks to my mother who has been always beside me and my siblings with comprehension, love, patience, wisdom and bravery. I am very lucky to have her as mother. I would also like to thanks to my sister Soad for being a real partner in all these years, for being sweet, brave and beautiful both in the inside and the outside as well. I really hope that her adventurous soul do never change. I can't leave out my brothers Nicolás, Nayib and Williams: three exasperating and funny men with souls of child.

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Introduction

Technology development is going everyday faster and further in all fields of human life. Things that can be made normally today were seemed impossible at the end of past century and the best example is the internet with all its facilities which, surely, will become larger in the future. But not just the technology changes and moves on, also human mentality and human needs changes with it: for every technological advance, human beings have new needs and, in consequence, they try to go steps forward. Medicine is an excellent example of this, also because it encloses the hope of a long and better quality life. In this line, what could be more hopeful than a new life?. The aims of this research looks for being a help in medical area of obstetrics, dedicated to the healthcare of those who have not seen the light yet.

In particular, this research work had as objective the creation of a normotype of typical fetal face characteristics in base of three relatively common conditions of abnormalities: Down syndrome, fetal alcohol syndrome and micrognathia. All three of them involves well-known facial dysmorphologies studied for years by experts, but principally through two-dimensional images. In fact, the innovative point of these thesis lies on that analysis are made over facial soft-tissue (facial skin) of fetuses obtained from three-dimensional ultrasounds (3D US). This does not mean that present investigation is first in his type, but certainly there is a few number of them with the same line, even when 3D US have demonstrate to be stronger in diagnoses accuracy and allows a larger number of analysis about conditions impossible to diagnostic before.

First of all, a normotype is a database of biometric measurements which define normality standards of some individuals. In simple words, a normotype allows to know with a certain level of accuracy if the anthropometric features of an individual or a group of them are normal or abnormal and, in case of abnormality, how much is the level of the same. Tools like these are very useful in medical fields because physical dysmorphologies are often related with deeper problems that could involve tumors, organ or system dysfunctions, mental retardation and others. The referential syndromes used here could involve mental retardation, growth deficits, behavioral problems and dangerous functional disorders.

With the sophisticated technology reached by 3D US is possible to obtain detailed 3D images (volumes) of fetuses, but especially the fetal face have became clearer and its analysis had entered to form part of prenatal diagnoses as a strong tool. Along this project, are described the processes made in order to take six different measures of fetal face and to constitute with them a normotype.

First part presents the information about models that correspond to health fetuses and work methodology followed with them. Afterward, the section about the state of art deals with how the three-dimensional technologies such as 3D ultrasounds and 3D printing have contributed positively into medical field. With the 3D visualization of human body and their processes had been reached good medical results improving accuracy of diagnoses, reducing false-positive rates and obtaining earlier diagnostics of anomalies. On the other hand, 3D printing techniques have revolutionized medicine with their multiple uses such as educational tool and training methods, their huge potential about prostheses and, of course, the challenge of create functional organs through 3D printers.

It is also presented a review of the benefits of 3D technologies in obstetric where prenatal diagnoses have improved notoriously, providing tranquility to parents and preparedness capacity and response in case of need it if, for example, fetus has some abnormality. How was mentioned before, 3D exams are directly related with earlier and accuracy medical diagnoses and in obstetric this factors give to parents the option to interrupt pregnancy with low risk for mothers.

Subsequently, state of art section talks about biometric face analysis in humans in general through the use of landmarks (i.e. specific points on face) that can be compared with the same face for authentication or security, or with a database for identification as is used in criminal and forensic fields. Also, fetal face analysis is reviewed as a new science with high future prospects in medicine.

Next sections describes in detail the procedures made in models, from their extraction from a medical software, passing for a 3D design software for cleaning fetal face masks, until the analysis in a mathematical software for measuring searched distances based in three medical conditions of abnormality.

Finally, results are exhibits as well as reference values from literature in order to define a coherent normotype. The discussion is made according with the level of satisfaction provided by results in comparison with referential values, possible error sources are described and, also, together with conclusions, some recommendations are given for future studies.

1 Models data and methodology

How it was explained before, the objective of this research work is to establish a normotype of facial morphology of a fetuses around 21th week. In order to reach it, is proposed a methodology based in treatment of gynecological 3D ultrasounds as three-dimensional file through an engineering software used for designing processes. So, this is a working together between medical and engineering fields, and this complementarity doesn't rest only in information or document transfer, but also in the knowledge of how to be obtained ultrasounds to be treat them in the best way after. Unfortunately in this case, there wasn't a direct communication with the doctor or person responsible of taking exams to have a mutual feedback. A clear demonstration of this is the fact that there were received at least 40 volumetric files (ultrasounds) to work on them but only 15 were selected to be used, even many of them were rejected after all of the processes because they didn't accomplish minimum requirements.

Creation of a normotype is a labor which should be based on a hundred -or better thousands- of files analysis, but in this thesis have been worked 15 3D models, therefore, this work pretends to be a start point for future complementations and, of course, a point of reference for medical analysis. About this last intention, is important to keep in mind that even medical analysis are intermediate stages in a path which looks for people's welfare and their families. An appropriate diagnosis, when involves not optimal circumstances, leads to a better preparation of the couple, in other words, it gives the possibility to terminate the pregnancy without any danger for the mother or, alternatively, gives time for the best preparation (medical, psychological, equipment, etc) for the moment of birth according to baby's needs.

Now, about studied models, they were obtained with the collaboration of professor Domenico Speranza and the Hospital St. Scholastica (Cassino, Italy). They consist in 15 healthy fetuses with the attributes showed in Table 1. Written informed consent was obtained from the parents for publication of clinical details, clinical images, and videos. Principles outlined in the Declaration of Helsinki have been followed.

Then, about followed methodology, ultrasound exams have been taken with *GE Healthcare* equipments, which guarantee the highest quality in medical technology. Consequently, 3D images have been processed with software 4D View, a work station of the same company, that allows a wide range of visualization types including by slices (most common way), 3D view

Name	Sex	Gestational week
A	F	22
B	M	23
C	M	22
D	F	20
E	M	22
F	M	21
G	F	21
H	F	21
I	M	20
J	M	22
K	M	20
L	F	21
M	M	21
N	F	21
O	M	21

Table 1: Analyzed models and their basic information

through rendering techniques and 4D view which consist on displaying the 3D ecography in time, as a video. From this computer program, is obtained a 3D model, made directly by 4D View, in format STL which is a standard format for triangulated meshes.

After this point, the three-dimensional model is imported into Geomagic, a software dedicated to 3D design in the world of engineering and created by the company *3DSystems*. Once the file is open, the strategy is to clean the model from all of these things that cause disturbance in fetal face mask, keeping it as realistic as possible. This task can take several hours depending of initial state of the model, quantity and type of disturbances and the expertise of the operator. In this case, which involves the treatment of free form bodies is necessary be careful with the process due to there are functions that once used, it is not possible turn back and the operator should start again from zero. However, when the design job is finished, i.e. the face mask is complete and their characteristics are recognizable, an option is to put a flat cover in the backside and, in that way, the model is ready for a 3D printer, the other option -chosen in this case- is leave it open. To conclude this stage, the file must be saved in PLY format which properties will be discuss latter.

A PLY file is a dataset with the information of every vertex and every face (triangle) of a polygon presented as a list of their coordinates. This information is taken from a text editor and imported as tables into Matlab to be re-organized into a squared mesh in order to process it better. As a consequence of this changing mesh there is a error quantity that would represent a error in quantified measurements at the end which, however, is neglected in posterior analysis.

Continuing with Matlab program, models are submitted into an algorithm to determinate landmarks localization, constructed in based of studies about the behavior of surface of fetal face. Nevertheless, for models here presented the algorithm presents a low rate of effectiveness and, for this reason, is required manual selection of bad-localized landmarks. When all of the 13 landmarks are properly situated in all of the models, they pass into another Matlab code, created for this project, in order to extract measurements considered interesting in base of relatively common medical conditions.

As final phase, obtained results are compared with previous studies and proposed as a normotype, with the objective to be a contribution to early medical diagnoses.

2 State of Art

The high technological level surrounding daily life sometimes leads people to forget that, a couple of decades before, a considerable amount of actual facilities were only ideas. This technological explosion have been transversal to all fields where humans have some grade of influence: from hi-tech cooking tools until improvement in space travels. The medical field is not the exception. Beginning of three-dimensional techniques applied in medicine, in the decade of 90s, marked maybe a break point between old medicine and the actual one. This sections is a review of the impact of 3D technology in medical field and, in particular, in obstetrics. Then, preparing the entry to the specific argue of this thesis, there is a section about biometry in face analysis for facial recognition and in fetal face analysis as a potential tools for prenatal diagnoses.

2.1 3D technology in medical world

Since some decades three-dimensional technologies have been an important support in the medical field. An accurate visualization of the entire human body and its processes through 3D ultrasounds had permitted a better understanding of patients situations, which implies precise medical diagnoses and, in consequence, a better response from experts to them, improving people's quality of life and life expectancy which represents the main objective of medicine. This is why 3D advances in medicine is a continuously growing area and every year hundreds of new related studies, more and more specifics and advanced, are published.

In order to help people, almost all engineering branches joint together to create advanced machines, algorithms, proceedings, materials, among others and, nowadays, all areas of medicine count on three-dimensional approaches for viewing, parameters measurement and printing their respective object of interest. This is feasible since three-dimensional modelling consists in creating a virtual 3D reconstruction of a physical surface or object from imaging data and this can be converted, in turn, in a physical 3D model through 3D printers.

Due to 3D printing was a technique principally industrial, at the beginning in medicine, it has been used for plastic surgery, orthopaedics and dentistry fields, but today there are important approximations in the world of 3D organic models, i.e., creation of functional organs, veins, arteries, soft tissues and others completely compatible with the patient. This means a great advance in cases of transplantation, which always had been a critical point saving humans life because, first, there are a global low rate of organs donation, second, when there exist an available organ for a specific patient, if it is not compatible with his/her body there is nothing to do except to wait for another opportunity. In addition, even after an operation of this kind, there exists possibilities of complications for the patients which could be seen highly reduced with an organ printed specially for the case.

In this direction, the aim seems to be do not depend on donors when a patient needs a transplantation, but just in a 3D printer. Still is necessary some time to arrive at that point, but anyway, every day there are new succeed cases of bioprinted structures transplanted. As examples, in 2013 the University of Princeton printed the first bionic ear able to hear radio frequencies, another is the Wake Forest Institute for Regenerative Medicine where is possible to print skin directly over damage tissue thanks to an advanced device that can measure the extension and depth of an injury [22].

Another extension of the three dimensional simulation and printing is the possibility of to print complex simulations of human structures that can be used for educational approaches and as practices for doctors who have to face complex surgeries. In both of cases, they are not functional but their size, consistence, even a simulated pumping blood make them highly sophisticated and excellent preparation tools. Some examples are the Jikei University Hospital of Tokyo which uses this technique to make hyper-realistic kidneys for their students. [22]

In 2014 The Polytechnic University of Catalonia together with Fundación CIM created an exact copy of a tumor and its surrounding areas of a little boy for practicing a dangerous surgery and at the end, they were able to remove the tumor and save the boy's life. In the same year, the Hospital of Kosair (Washington) made a bioprinted heart copy of a 14 months baby to diagnose him better and to decide the treatment.

A more extended practice is that of prostheses. The simplest ones are crutches and castings, and about that 3D modelling had allowed the design of more appropriate structures for each specific case with better materials that bring comfort and security to patients. Orthopeadic braces, castings, cervical collars and more in the same line can be printed following the specific-patient needs and according to his/her body shape, which could result in a faster and better recovering.

More interesting are intern prostheses and complex robotic members and exoskeletons made with the help of 3D tools in order to improve the adaptation of them to the patient.

A symbolic case occurred in 2014 when a 22-years-old holand woman became the first person in the world to receive a cranium prostheses made entirely by a 3D printer. Cause a rear disease, her cranium increased around 5 cm pressing the brain, but after a long and risk surgery in the University Medical Centre of Ultrecht (Holand) the implant was settled and months after, the surgery was declared successful. In the same year, in the Hospital of Beijing, the first implant of a vertebra, made by a 3D printer was achieved in a 12-years-old boy with bone cancer.

Another representative case was a north american woman paralytic due a skiing accident who thanks to an exoskeleton and a crutch constructed by Ekso Bionics and 3D System - companies specialists in 3D modelling and printing- could walk again. She gave her first steeps after 12 years in a conference in Budapest (Hungary) arranged by the academic organization Singularity University.

Fortunately, examples like these increase everyday, but still there is a long way to go before they become more routine than novelty.

2.2 3D modelling in obstetrics

Before the 3D visualization, structures were observed in two planes, just through a mental process and a long training from who practiced this kind of studies they could be appreciate as a volume, but thanks incorporation of a third orthogonal plane (Figure 1) now is possible to have a three dimensional shape in screens.

The reason why a third plane had mean such development is because through this third orientation view was possible to take "photos" of the object of interest -in this case a fetus- in its depth each few millimeters. Once a proper number of pictures have been taken (around 200-300 two-dimensional images), they are put one over the other and, then, a 3D view is created.

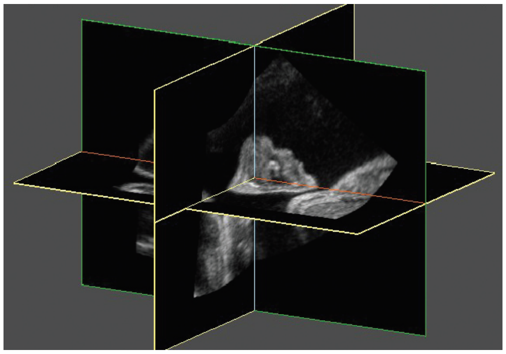


Figure 1: Three orthogonal planes

Figure 2: Rendered 3D ultrasound

Firsts 3D ultrasonography (3D US) equipments came to the light in 1991 but until 1998 they needed 25 seconds to storage one image and minutes or hours to make a entirely 3D reconstruction. However, the never ending development in technology had permitted to make the same process in seconds which means an almost real time appreciate of the studied object and their movements, bringing a new modality: 4D or volume plus time [20].

One of the advances is the creation of DICOM (digital imaging and communications in medicine) file format in which the volume obtained is storage as well as the information of patient and this allows doctors to review exams as many times as he/she needs and make, for example, consultations to other doctors [19].

When 3D technologies started in medicine, gynecology and obstetrics were one of the first medical field studied with this new application. Some researches were published with normal fetal descriptions and, little after, studies about fetal structures and fetal organs characterization were added. As could be expected, comparisons between 2D and 3D approaches appeared and, of course, they showed how second one was more precisely with a significant reduction of errors. Obviously, this means better diagnosis of fetal behavior and some quantitative analysis talk about an improvement in certainty in more than 70%, specially in some specific areas of fetuses like head, neck, column, abdominal wall and extremities[20].

Effectively, there are very few things resting in shadows with respect to fetal status using this so advanced technology and, in front of this clearness, parents are in a better position to take decisions such as abortion in case of fetal anomalies. This is one of the biggest bioethics issues but while legal and medical conditions are favorable for the mother, she can decide to terminate pregnancy if she considers it as the best option. However, during literature collecting it was not found a direct correlation between technological development and abortion rates. It has sense due to a disrupt pregnancy is a multifactorial consequence difficult to be classified or measure even for experts.

A different and interesting point in this area is the psychological aspect with respect to future parents, who have the possibility of to see their baby before birth. Before 3D ultrasound, it was difficult for parents to see their child with a 2D exams which seemed to be made for doctor's understanding and, anyway, this approximation to the baby generated solid affective links. Nowadays, mothers and fathers have the opportunity of see a clear and realistic representation of the baby and many related studies conclude that through baby's 3D viewing and printing, parenthood bounds are reinforced [22].

Once 3D visualization had been reached, is normal to think that the next steep is the 3D printing of fetuses. Medical advantages of fetal 3D printing are numerous and they are described in former section considering it like another medical object. However, there exist some companies like "Baby 3D Print" (Spain), "Baby:Boo" (England), "Wolfprint 3D" (Estonia), "IN UTERO3D" (Polonia), among others, which print 3D model of fetuses as keepsake for future parents. Two strong points to be mentioned related to babies 3D print are: first, what this represents for blind parents who, until now, haven't had the possibility of "see" their child before birth; second, in case of abortion, parents can keep a positive memory of the baby [22].

2.3 Biometric face analysis

Biometry (from greek *bios* = life, y *metron* = measure) is the study of standard measurements of living being and their biological processes. In the present work, the meaning to take is first one, neglecting thus about processes.

Ancient cultures like Greeks, Egyptian, Romans and Chinese gave important attention at human body shape and almost independently one to the others they did measurement studies of it. Well-known are efforts made by greeks in the study of human body proportions as artistic tool, achieving the creation of detailed and harmonious sculptures. After, with the annexation from Romans, they took greek knowledge and used it for their pleasure without giving good continuing to investigations.

With the empowerment of sciences and arts in century XVI, human body analysis returned and little by little biometry took importance in scientific-medical field. However, the human body studies were considered as a dark science for a long time, so is not a surprise that serious studies and applications were published many years after. Taking into account that facial analysis was not an “urgent” topic in that moment, only around of century XIX it became an argue of interest, specially in criminal and forensic areas. For example, Alphone Bertillon, as a part of parisian police, developed an anthropometric system that consisted in some head measurements for criminals identification [7].

From that point, facial measurements have been related to head size, facial length and width, distance between eyes, eyes colors, eye socket, scars, moles and birthmarks. This kind of analysis were principally developed with police interests but also in medicine, in order to study facial deformities and particular diseases. However, there is a big obstacle in defining biometrics because general morphology, and specially facial morphology, may vary according to characteristics like: sex, age, race and even environment can affect. Then, when a biometry is define must be with determined conditions from studied individuals [3].

When technological explosion of lasts decades started, it opened the door to facial recognition in automatic way. It became a very desired tool due to the several advantages that can contribute in fields like entertainment, medical diagnosis and surgery, authentication, security, historical research and more.

Then, for facial recognition had been established a series of critical points in all facial surface, in fact, can be determine more than 80 landmarks for a completely recognition but softwares actually do not use all of them due to data overload [7].

It has to be differentiate two kind of landmarks: hard-tissue landmarks which lie on the skeleton and the soft-tissue ones which lie on the skin. First one are identified through lateral cephalometric radiographs and the second type through 3D point clouds obtained by scanning or directly in images [24]. The present work deals only with soft-tissue landmarks. In Figure 3 [24] is possible to see the most famous points, but, anyway, they can vary depending on the kind of studies or applications they are used for.

Figure 3: The most famous landmarks in adult face

The idea of an automatic facial recognition lies on the objective of extract automatically all or part of these landmarks and compare them with a model that can be a previous extraction of the same facial mask which can be used as a authentication or security method or, in the other hand, compare with a data base where there is a registry of faces like is often used in forensic, criminal and medical fields. About medical field, it had demonstrated to be a powerful tool at the moment of diagnosing syndromes, sickness, deformity seriousness and as support in corrective and plastic surgeries.

This thesis focuses in prenatal face and, in that way, things chance a little due to the object of study is changing rapidly and is not completely formed morphologically. Cause of that, the number of landmarks are reduce in fetal face and the application of software for an automatic extraction of landmarks have not the same positive results. A deeper description of this is made in the next section.

2.3.1 Fetal face analysis

Pregnancy is considered one of the most beautiful period in people's life, but together all hormonal and physical changes in mother must be added the anxiety of waiting and about baby's wellness. Until 60 years ago, there was no method to know about baby's health but through mother's condition. Then, the ultrasound technology appeared and prenatal diagnosis were more accurate about baby's wellness and bringing the capability of parents to see their child.

However, the limited view of the fetus turned represented a challenge for practitioners at time of a complete prenatal evaluation. In this scene and during a lot of years, there were analyzed relationships between abnormalities and the measurable parameters into a bidimensional ultrasounds. Examples of that could be the established relation between the nasal bone length and prenasal thickness with down syndrome, or long bones length with growing abnormalities.

Through the entry of 3D ultrasounds at beginnings of 90s, start a new level of prenatal analysis and diagnoses. There are many more syndromes or dysmorphisms that can be evaluated prenatally and even those before evaluable have seen increased the accuracy of their diagnostic and, maybe more important, can be discovered earlier. This last factor is especially critical because an earlier knowledge of the baby's condition could give the possibility of an effective treatment or the adequate medical preparation for childbirth.

Actually, there are many syndromes involving physical dysmorphisms that may affect the functioning of internal organs or of the whole organism, bring cognitive and behavioural deficits or growth retardation [16]. Particularly, in this research will be seen three relatively common scene: Down syndrome, fetal alcohol syndrome and retrognathia and micrognathia. However, it's needed to have in mind that there are many more syndromes and conditions and a clear example is cleft lip and palate, which have been strong points of fetal face studies through 3D ultrasounds.

Then, in order to conduct an analysis over the fetal face, it had been identified some landmarks which can vary depending on gestational age and/or the aims of analysis are looking for. Forehead, eyebrows, eyes, nasal region, lips, and chin are the most common soft-tissue landmarks. In the present research work have been considered 13 facial landmarks which will be described forward in section 5.

3 Obtaining 3D models

A good starting point for this section should be a little description of actual biotechnology in medical field, specifically in area of gynecology and obstetrics. Nowadays, equipments for ultrasound are very advanced and every year become more and more developed. As a consequence, companies dedicated to their fabrication are in constant competition, resulting this in closed systems of ultrasound machines and their correspond software. It means that each company of biotechnology has their own machines and data extracted from them can be analyzed only through the software created by itself. Some companies dedicated ultrasound machine creation are GE Healthcare, Siemens Healthineers and Philips. However, all these machines and softwares work with similar algorithm and standards, then there shouldn't be big differences in results obtained regardless which equipment was used.

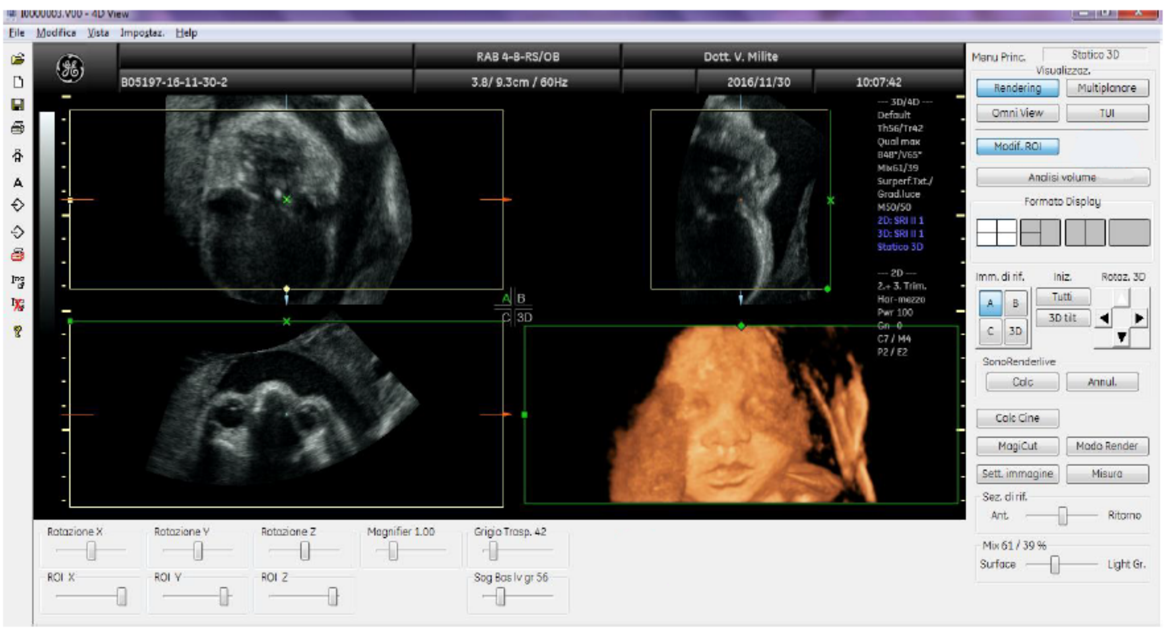


Figure 4: Principal screen of 4D View software with three orthogonal planes and render view

Ultrasound softwares create a work station in which fetal volumes are constructed by two-dimensional slices separated by a little distance, commonly 2-4 mm, then putting in order one beside the other is feasible a 3D visualization. How was seen in section 2.2 they use three orthogonal planes (Figure 1) called: sagittal, axial or transverse and coronal. In addition, softwares create a renderization of the volumetric image to produce a realistic interpretation of the baby and, even more, they include the time variable to generate a four-dimensional representation which is basically a short video of the fetus, see Figure 4.

Together with the volumetric file, is important to save the patient's data in order to keep the information attached to images for future analysis of doctors (Figure 5). Once the specialist have finished the evaluation, images and data can be put in a DICOM file (described before) that allows the transference of information among different equipments with standard parameters. This is a very useful tools in medicine cause it permits medical interconsultations when is needed and give patients the flexibility of change doctor if they desire without information looses, both of them nowadays regular practices.

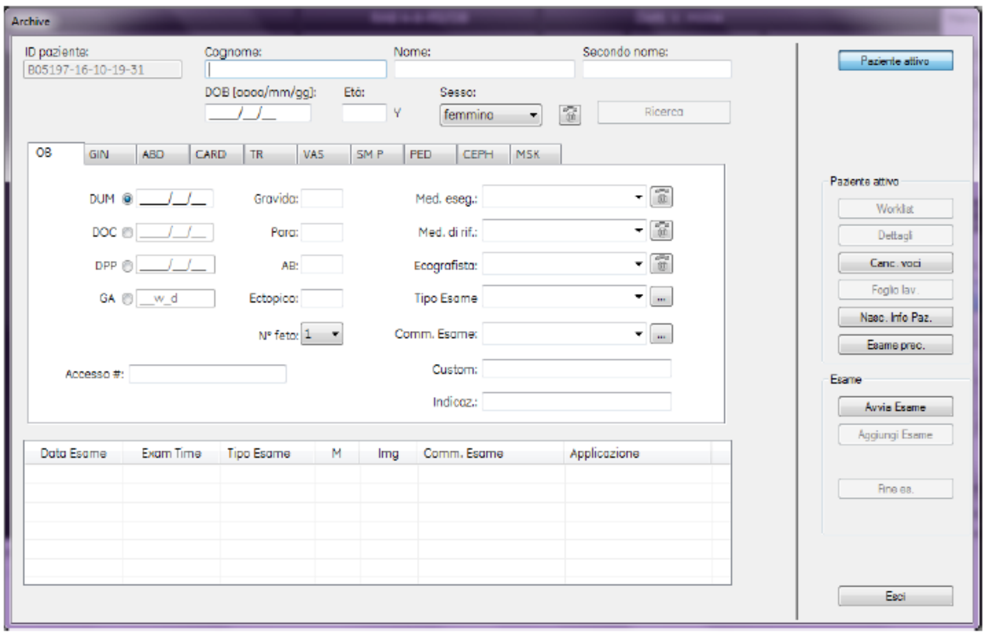


Figure 5: Patients information form to be fill in by practitioners

In this particular case, all of 3D models have been obtained trough the software *4D View*. This program was developed by *GE Healthcare* which is a branch of the *General Electric Company*. It offers hundred of tools for measure, visualization, data storage, exporting and others. About importing files, 4D view receives volumetric file format with extension *.voo*, which, of course, is a kind of file just for this software and extracted by a GE Healthcare ultrasound equipment.

As a example of how is a volumetric file is presented the Figure 6[1] where the ultrasound is about a fetal heart. Then, it is easy to see the method in which is created a volumetric

[1]image obtained from https://obgynkey.com/three-and-four-dimensional-ultrasound-of-the-fetal-heart/

file through slices. In the acquisition of the file there are involved some parameter like the acquisition angle, the frequency of the ultrasound and other parameters that are not important to know for this research.

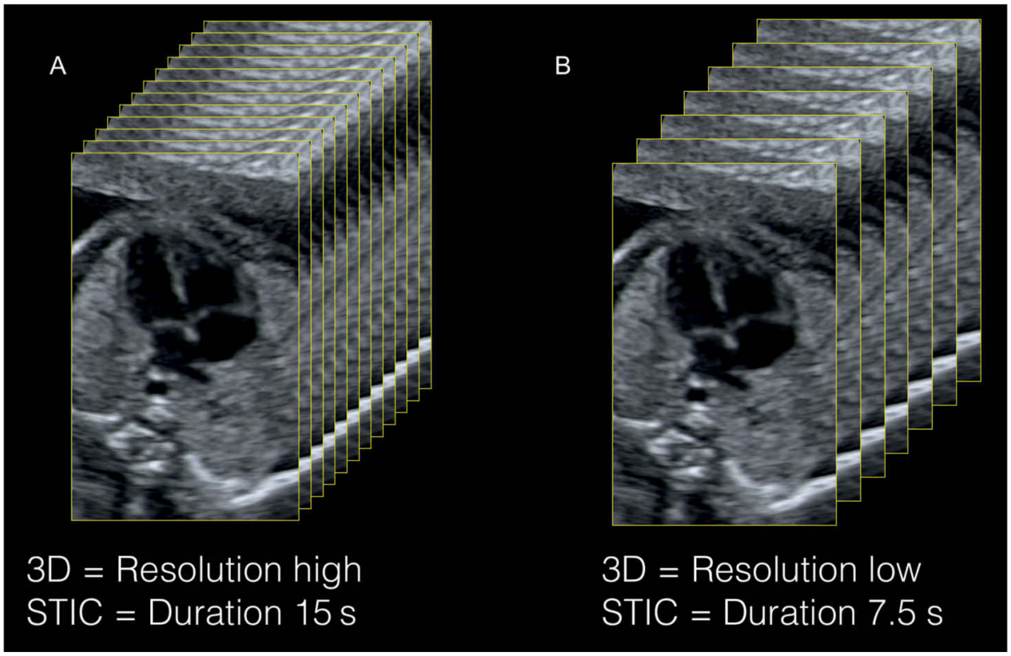


Figure 6: Working method of a 3D ultrasound. STIC = Spatiotemporal image correlation

Continuing with the obtaining process of 3D volumes, even when 4D View software has capability of export ultrasounds as 3D objects through format STL, the initial idea was to extract them slice by slice, i.e., saving each two-dimensional image of the sagittal plane and then made a reconstruction through another software like *Simpleware ScanIP* which can import, analyze and export as 3D object segmented images. This was based in the uncertainty in how the program does the file exportation. However, each ultrasound is composed by approximate 250 slices and is not so easy to sail through them one by one due to the program has any kind of slice counter, then the process require attention and rigor. But this was not a reason for why the extraction was not made with that method. The mean reason was that at the moment of saving the images as such, they are resized without a defined proportion and subject to particular parameters of the computer in which is made the extraction. Considering that the present project is about measuremnts, is unacceptable this level of inaccuracy, overall in an initial steep.

In consequence, 3D models have been obtaining by simple exportation of volumetric images as STL files which are ready to be modify for a CAD modelling software.

4 Working with 3D CAD models

This section is about CAD model treatment of fetal face. At this point, they were subject to processes as if they are simple engineering products. The aim of this steep is cleaning surfaces for a better landmarks recognition, taking off all of disturbances drown from ultrasounds that could be generated due to placenta, proper material of mother womb or by baby's hands over the face. In order to reach the objective, it was used the engineering 3D software called Geomagic Studio, specialized in data scanning and point clouds.

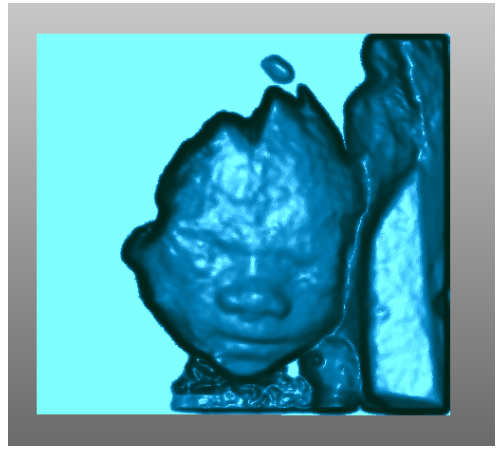
Geomagic Studio (actual version called Geomagic Design X) is a software of the company *3D Systems* created in order to convert 3D scan data into high-quality CAD models. The software counts on with a wide range of tools that allow to virtually design all type of bodies, from engineering to organic (free form) field, through its advanced mesh editing and point cloud processing tools.

4.1 Importing CAD files

How it was explained before, from software 4D View is possible to obtain surface-mode and full-mode 3D CAD models of the same file (Figure 8). In the former case, the face is often deformed by materials surrounding the fetus like placenta, umbilical cord and others, which regardless they see separated from baby face in volumetric file, are superposed and jointed into one main empty surface (nothing behind face mask) how is desired. In the other hand, a full-mode CAD model file considers all of the structures present in the ultrasound, i.e organs and other internal bodies of the fetus not important in this study (noise). However, at moment of importing in Geomagic all of these noises are disposed such as is showed in its original position, allowing to see fetal face more complete in its form but with rougher superficial definition.

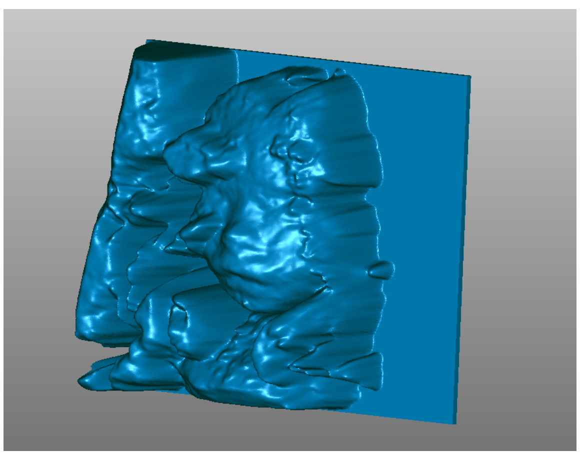
In some of models have been taken advantage of this duality to reproduce the fetal face in one model as accurate as possible with respect to reality. However, this technique was used in the few of cases and, instead, it was preferred work only over surface-mode CAD model in order to avoid problems which could distort the mask and, in consequence, distort future measurements.

(a) Model with software 4D View

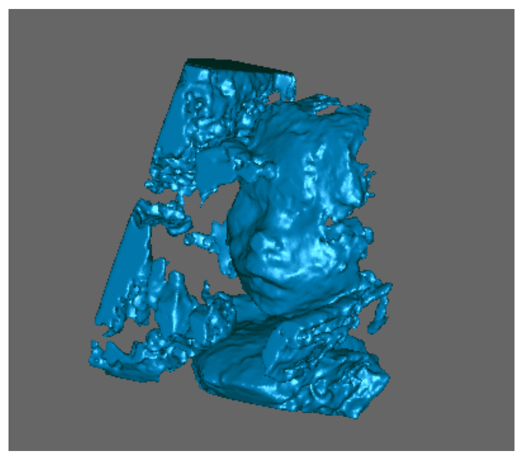


(b) Model with software Geomagic

Figure 7: 3D model in both of 4D View and Geomagic softwares



(a) Surface-mode CAD



(b) Full-mode CAD

Figure 8: Same CAD file obtained with surface-mode and full-mode

4.2 Fetal faces processing

In this section, it will see how was worked one of the fetal-face CAD model in Geomagic in order to show the procedures done over it. It is important to note that each model had its own modification requirements as a result that each ultrasound was different from the others and, consequently, models have been submitted to different procedures for to arrive to the desired end, it means, a clear fetal mask.

Another important point is the fact that work was done over fetus around week 21 which means that the level of physical development characteristics on baby faces was still incomplete and this, together with proper ultrasound noises and the spatial disposition of faces, represented a notorious challenge in achieving the purposes. In fact, many of works were rejected cause it was impossible to reach a complete face -at least what was needed- without fall in personal designs and interpretations which could create a not completely real fetal mask.

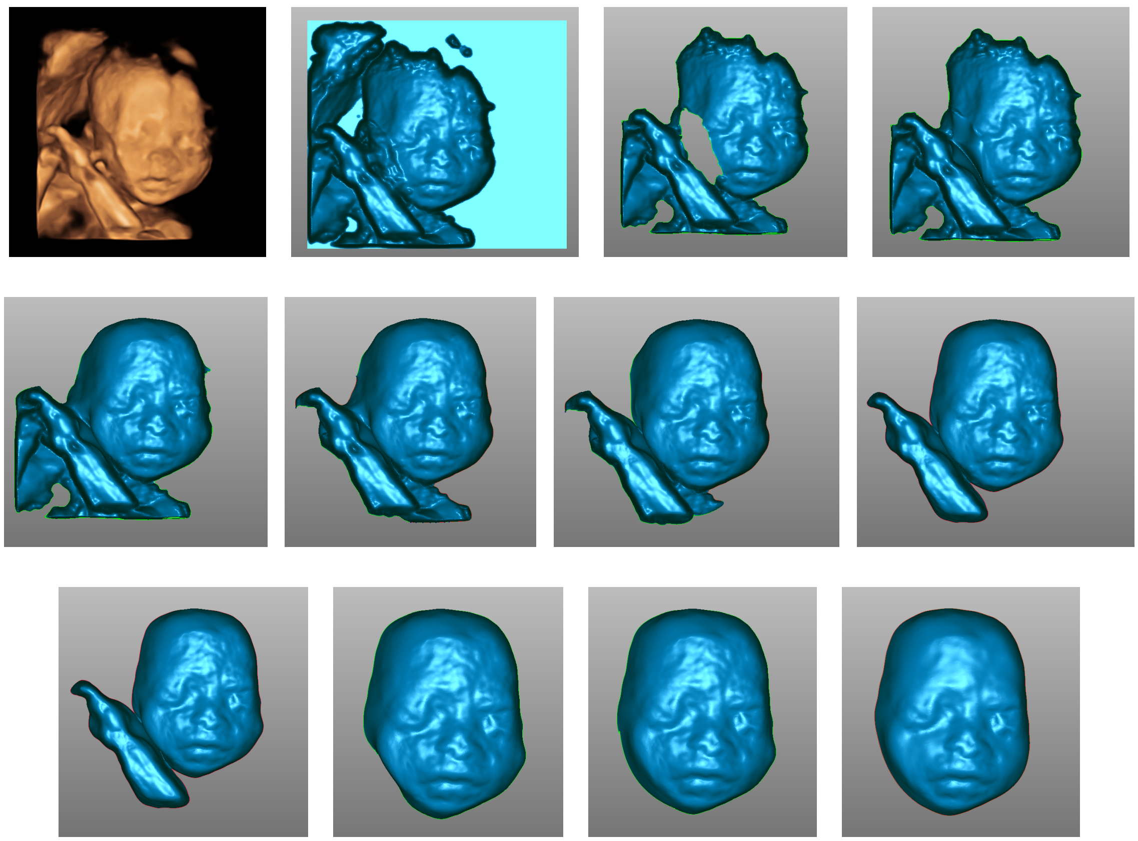


Figure 9: Geomagic processing of a model

As a summary of the work at this stage, Table 2 presents a little overview of the processes done in each one of fetuses. Also, there are some quantities representative of processes made by through the software where is possible to appreciate how much were altered fetal shell from the initial state until the moment of exporting them for next steeps like the number of initial and final triangles ("Ti" and "Tf " respectively) and the standard deviation (SD) in millimeters. About the substantial difference between number of triangles, is necessary take into account the great amount of disturbances in the CAD model as well as the unnecessary structures like fetal neck, arm, hands, placenta material and others. On the other hand, SD adds an estimation of changes and could be considered as a error factor in final results and analysis.

4.3 Exporting 3D models

Once all of procedures over fetal face in Geomagic have finished, the model is saved with ".wrp" extension. This file is ready for a 3D printer and can be used -for example- as a keepsakes for parents. However, this is not what this research is looking for because next steep is a face-recognition analysis through Matlab. So, it is necessary to take off the backside cover and save the not close fetal-face mask with format PLY.

PLY is file format known as **Polygon File Format** or **Stanford Triangle Format** that contains the information of a triangle-based 3D polygon as a list of the coordinates of each node and branch of a 3D model. It will see later that through this two matrices: one of the vertexes and the other of faces, is possible to reconstruct the model in Matlab. But, for a not known reason, the ply file from Geomagic doesn't work as should be and, hence, it is necessary open it with a software like *Blender* and export it again with the same extension (.ply). Only then the ply file can be open as a text in a notepad (even the simplest) for to obtain the matrices.

File	Ti	Tf	SD [mm]	Works done
A	82.788	40.370	0,6945	Modelling of superior part of forehead. General smoothing over the face
B	319.116	336.852	0,7134	Modelling of superior right contour. Little details in general surface
C	237.636	180.430	0,891	Reconstruction in right side of superior forehead and left cheek
D	279.008	144.368	0,671	Modelling of left side of face, especially in forehead and cheek. Reduction of cranium height
E	312.968	212.146	0,6967	Adjustment of superior contour of the model. General smoothing
F	282.290	135.341	0,5425	Reconstruction of right contour from the middle of forehead to almost the chin
G	305.282	152.460	0,454	Little tasks around contours and few superficial details
H	292.272	166.180	0,4838	Reconstruction tasks in superior contour and around chin
I	244.942	132.042	0,6752	Principal works over left cheek and mouth. Zone below nose have been reconstructed from combining full and surface modes
J	360.730	263.334	0,722	Modelling of superior front and inferior right parts, right contour and chin
K	268.352	161.170	1,0856	Modelling from combining full and surface modes. Little tasks over left contour. General smoothing
L	324.462	306.641	1,2606	Reconstruction of left superior and inferior contours, nasal tip. Surface details.
M	318.600	170.116	0,6748	Reconstruction of left superior part from the eye.
N	338.254	151.418	0,9466	Joining of full and surface mode. Smoothing around joint and little surface details
O	245.328	119.156	0,7754	Modelling of whole superior part and left cheek. Important smoothing jobs due to lot of surface roughness

Table 2: Summary of processes made over 3D CAD models

5 Extraction of Landmarks

In 2014 professor Vezzetti *et al* presented a research work to propose a geometrically-based landmark extraction algorithm for fetuses which was summarized in charper State of Art. The ideal way to extract landmarks should be through this algorithm, but it was thought for to be applied over fetuses around week 31, it means, babies completely developed in their facial characteristics. Another point is that the method was made to be ran over front-oriented face masks. Last is important due that most of the models doesn't satisfy this require and, consequently, was necessary to localize almost all or all of landmarks manually.

Over the face of fetuses have been recognized thirteen landmarks: nasion (N), pronasal (PN), subnasal(SN), labrum superior (LS), labrum inferior (LI), left/right inner eyebrow (IEsx/IEdx), left/right endocathion (ENsx, ENdx), left/right chelion (CHsx, CHdx) and left/right alae (ALAsx, ALAdx). Their localizations are described below[2] and showed in Figure 10

- Nasion: point at the top of the nose, nearly between the eyes. In the horizontal direction, it lies on the high part of the nose bone; in the vertical direction it is in the hollow under the forehead.
- Pronasal: point on the nose tip.
- Subnasal: point which lies exactly below the nose, in that little dimple above the mouth.
- Labrum superior: point which lies on the upper lip of the mouth approximately in the middle, on that little bump under the subnasal.
- Labrum inferior: point which lies on the lower lip of the mouth, approximately in the middle, closer the hollow located above the chin.
- Inner eyebrows: points which lie at the connection between the nose bone and the eye-brows themselves.
- Endocathions: two points at which the inner ends of the upper and lower eyelid meet.
- Chelions: two points on the outer corners of the mouth, where the outer ends of the upper and lower lips meet.
- Alae: the two points which lie on the left and the right of the widest part of the nose.

[2] Descriptions have been taken literally from [25]

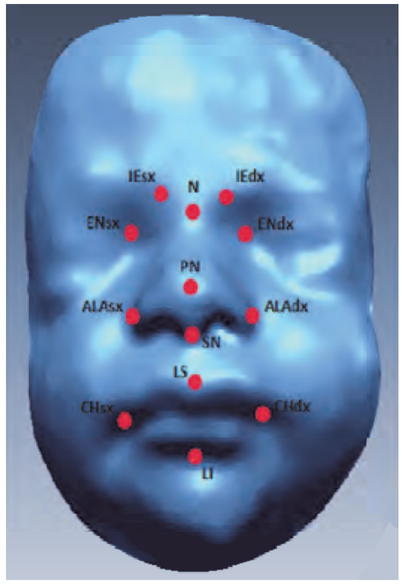


Figure 10: Fetal face landmarks

To extract them, is required to do an initial or previous work starting from the PLY file (obtained from *Blender* software) in order to generate a suitable mesh for the algorithm.

5.1 Previous work

Starting steep consists in open PLY file in a notepad. It shows a set of data structured as follow:

1. Information of the file: here is possible to see the principal model's data as source (where is model came from), number of vertexes and faces and type and disposition of present data. (Figure 11)
2. Vertexes coordinates: each row of float-type values represents one vertex and column's order is coherent with the order showed in the first part, i.e. x,y,z,nx,ny,nz. (Figure 12)
3. Faces coordinates: this information is different from the previous one because data are integer values and each row represents a face. In this case, first value is always 3 which means that face is a triangle, others three data are x, y and z coordinates respectively. (Figure 13)

File Modifica Cerca Visualizza Formato Linguaggio Configurazione Strumenti Macro Esegui Plugin

Aceto Teresa.ply

```
ply
format ascii 1.0
comment Created by Blender 2.79 (sub 0) - www.blender.org, source file: ''
element vertex 71625
property float x
property float y
property float z
property float nx
property float ny
property float nz
element face 23887
property list uchar uint vertex_indices
end_header
```

Figure 11: Information of the PLY file

```
end_header
-5.042279 18.645081 44.873837 -0.164102 0.387723 0.907051
-5.187966 19.131750 44.639450 -0.164102 0.387723 0.907051
-5.626221 18.704611 44.742744 -0.164102 0.387723 0.907051
-5.187966 19.131750 44.639450 -0.168336 0.386362 0.906856
-5.042279 18.645081 44.873837 -0.168336 0.386362 0.906856
-4.485554 19.079584 44.792061 -0.168336 0.386362 0.906856
-4.522350 18.137877 45.160252 -0.169552 0.347061 0.922389
-5.042279 18.645081 44.873837 -0.169552 0.347061 0.922389
-5.384040 18.154633 44.995552 -0.169552 0.347061 0.922389
-5.042279 18.645081 44.873837 -0.149984 0.365098 0.918808
-4.522350 18.137877 45.160252 -0.149984 0.365098 0.918808
-4.485554 19.079584 44.792061 -0.149984 0.365098 0.918808
-5.384040 18.154633 44.995552 -0.171407 0.348165 0.921629
-5.042279 18.645081 44.873837 -0.171407 0.348165 0.921629
-5.626221 18.704611 44.742744 -0.171407 0.348165 0.921629
```

Figure 12: Vertexes coordinates, float numbers

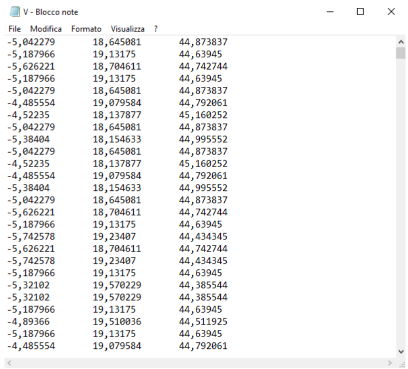
File Modifica Cerca Visualizza Formato Linguaggio Configurazione Strumenti Macro Esegui Plugin

Aceto Teresa.ply

```
-21.387373 -18.444674 24.015051 -0.867660 -0.494964 0.046650
-21.829481 -17.617348 24.570189 -0.867660 -0.494964 0.046650
-21.229372 -18.698868 23.979326 -0.845544 -0.531964 0.045496
-21.354218 -18.444313 24.635462 -0.845544 -0.531964 0.045496
-21.387373 -18.444674 24.015051 -0.845544 -0.531964 0.045496
-21.009180 -19.018749 24.331316 -0.845129 -0.532701 0.044573
-21.229372 -18.698868 23.979326 -0.845129 -0.532701 0.044573
-20.969790 -19.115595 23.920759 -0.845129 -0.532701 0.044573
-21.009180 -19.018749 24.331316 -0.835771 -0.546903 0.048821
-21.387373 -18.444674 24.015051 -0.867658 -0.494967 0.046656
-21.354218 -18.444313 24.635462 -0.867658 -0.494967 0.046656
-21.829481 -17.617348 24.570189 -0.867658 -0.494967 0.046656
3 0 1 2
3 3 4 5
3 6 7 8
3 9 10 11
3 12 13 14
3 15 16 17
3 18 19 20
3 21 22 23
3 24 25 26
3 27 28 29
3 30 31 32
3 33 34 35
3 36 37 38
3 39 40 41
```

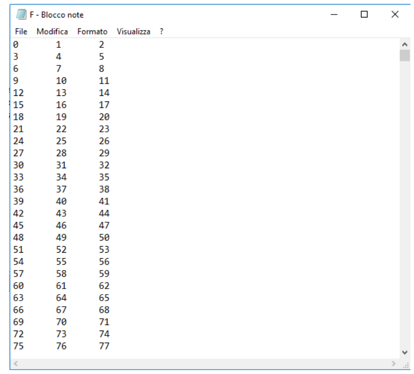
Figure 13: Faces coordinates, integer quantities

Once it had been identified the parts, vertex and face coordinates data are copied separately into two different excel documents. For vertex data, only must be considered first three columns neglecting the others. This file is the vertex matrix and had to be saved as a text (.txt) with the name “V”. Then, for face data, the first column -which contains only value 3- is canceled. This becomes the face matrix and had to be saved as a text -as before- with the name “F”.


V - Blocco note
File Modifica Formato Visualizza ?

-5,042279	18,645081	44,873837
-5,187966	19,13175	44,63945
-5,626221	18,704611	44,742744
-5,187966	19,13175	44,63945
-5,042279	18,645081	44,873837
-4,485554	19,079584	44,792061
-4,52235	18,137877	45,160252
-5,042279	18,645081	44,873837
-5,38404	18,154633	44,995552
-5,042279	18,645081	44,873837
-4,52235	18,137877	45,160252
-4,485554	19,079584	44,792061
-5,38404	18,154633	44,995552
-5,042279	18,645081	44,873837
-5,626221	18,704611	44,742744
-5,187966	19,13175	44,63945
-5,742578	19,23407	44,434345
-5,626221	18,704611	44,742744
-5,742578	19,23407	44,434345
-5,187966	19,13175	44,63945
-5,32102	19,570229	44,385544
-5,32102	19,570229	44,385544
-5,187966	19,13175	44,63945
-4,89366	19,510036	44,511925
-5,187966	19,13175	44,63945
-4,485554	19,079584	44,792061

Figure 14: Resulting vertex matrix as a text file


F - Blocco note
File Modifica Formato Visualizza ?

0	1	2
3	4	5
6	7	8
9	10	11
12	13	14
15	16	17
18	19	20
21	22	23
24	25	26
27	28	29
30	31	32
33	34	35
36	37	38
39	40	41
42	43	44
45	46	47
48	49	50
51	52	53
54	55	56
57	58	59
60	61	62
63	64	65
66	67	68
69	70	71
72	73	74
75	76	77

Figure 15: Resulting face matrix as a text file

Finally, through a Matlab code into which are introduced matrices V and F, the triangular configuration of 3D model is converted into a square mesh grid where separating distance among new nodes is regular for both of x and y direction. As outputs, the code gives matrices X,Y and Z which latter one is the heights' matrix of each node of the grid. This process is relevant because it permits open the model and does easier future analysis over the mesh. Like all of transformations of this kind, there exist an accuracy error which is also measured with an auxiliary code. The outputs of the previous work for each model are matrices X,Y,Z and its error value.

5.2 Landmarks' positioning

Continuing with Matlab, professor Federica Marcolin and colleagues created a Matlab code which can localize these points of interest. How it was explained before, this code was made for face mask of fetus near of the birth and front oriented. Of course, also there exist a big issue that affect the search and it is the deficiencies because previous steeps like the Geomagic manipulation that can be translate in roughness of face mask. Cause all of these, majority of landmarks weren't found optimally, and this can be see in figures bellow where had been put some of models studied here, processed with the mentioned code.

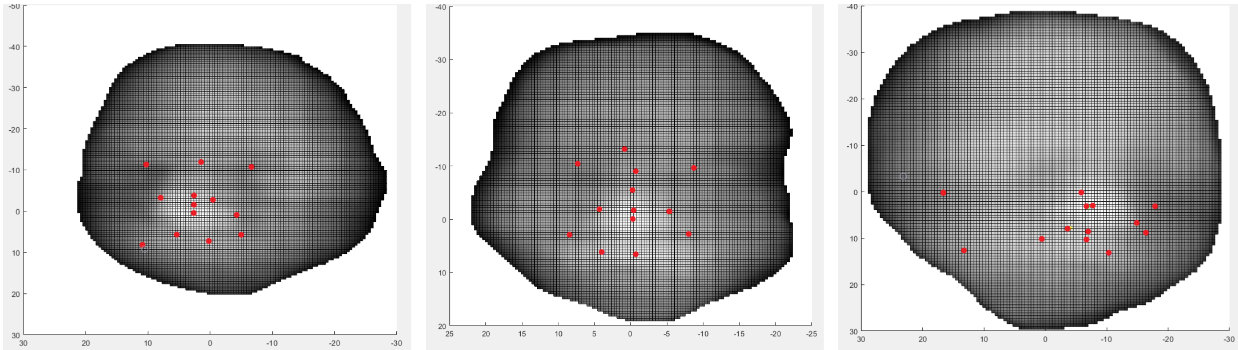


Figure 16: Three examples of landmarks' extraction with Matlab algorithm

Landmarks best positioned were both of alae (points at both of side of the nose) and pronasal (nose tip) which is expected due to the nose, being the most prominent part of a face, is easily identifiable in a recognize process. About the rest of landmarks, they were nowhere near of the ideal position taking apart the nasion that, in some of cases, was really close to correct place.

Now, therefore, missing landmarks have to be localize manually. This consists in the simple work of selecting points over the 3D figure on Matlab and saving them with a defined name which permit the code -now modified (see Appendix)- to take them as landmarks. So, for example, if there is a variable called *pronasal* which corresponds to the manually taken data, it will be the first option for the code instead of variable PN (as is defined this point originally) for pronasal landmark. Similar way for all the other landmarks.

However the simplicity of the work, it will represent a new errors source in the posterior processes, i.e. distances measurements between landmarks, taking into account that is a procedure done by a human operator instead of the algorithm. In addition, this breaks the automatic flow of measurement-taking which involves to apply time in each particular case, reducing the possibility of analyze a large number of fetus face in a short time. Figures bellow show one of models with landmarks localized by the algorithm (Figure 17) and manually (Figure 18). It is possible to see that alae landmarks have been found correctly while not the others.

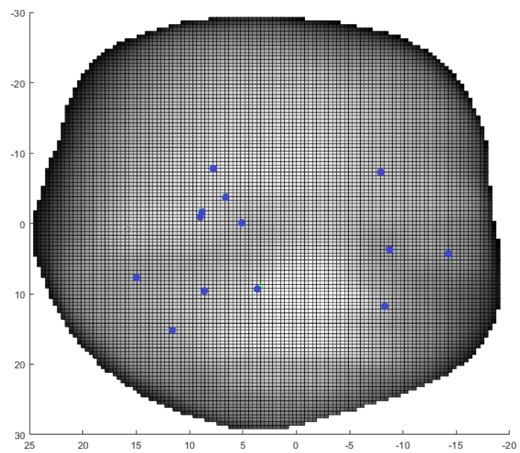


Figure 17: Landmarks obtained with the algorithm in one of the models

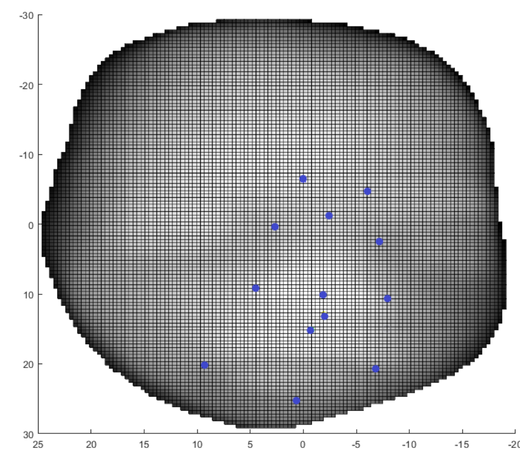


Figure 18: Landmarks obtained manually in the same model as before

Finally, the collecting process is finished and models are prepared for to take characteristic distances on it.

6 Definition of measures to take

The aim of this research project is to propose a normotype of fetus face around 21th week, but with thirteen landmarks on a face there are a lot of possibilities of measurements: euclidean distance, geodesic distances, angles and others. About euclidean and geodesic distances, the first one is the classical distance from one point to another in straight line, in other words, the norm of a vector that joins together two of landmarks; the other one (geodesic) is the shortest path between points over a surface. It is very used in the geography field: its denomination, indeed, comes from this area. In figures below[3] is possible to see graphically the difference mentioned.

Figure 19: Euclidean distance example

Figure 20: Geodesic distance example

Turning back to measures selection, with a simple calculus of combination is easy to know how many subgroups of two landmarks can exist. So, considering $n = 13$ as the total of elements and $p = 2$ as the number of elements in each subgroup, is obtained:

$$C_n^p = \binom{n}{p} = \frac{n!}{p!\,(n-p)!} = \frac{13!}{2!\,11!} = 78$$

Then, there are 78 combinations of two landmarks, which in turn can be compared in different ways like -said before- euclidean distance, geodesic distance and the distance between their respective coordinates in x,y and z. If also angles among three distinct landmarks are considered, there is a considerable quantity to add to previous value. So, with $n = 13$ and

[3]Figures recovered from [24]

$m = 3$:

$$C_n^m = \binom{n}{m} = \frac{n!}{m!\,(n-m)!} = \frac{13!}{3!\,10!} = 286$$

In sum, neglecting other kind of measures, there are $78+286 = 364$ options to consider for analysis. In view of this scenario, is logical to establish a selection criteria based on typical situations of interest like frequent deformities which could present baby faces. But again there are hundreds of sickness or situation which could lead a deformation on a baby face as tumors, cleft lip and others.

In this case, it had been selected three relatively-common syndromes in order to study their physical effect in the fetal face. They are Down syndrome, Fetal alcohol syndrome and Micrognathia and Retrognathia. Hence, a short review of every scenario will be considered in next subsections and then will be presented how will be faced each one of them in the present investigation: what measures will be taken and whether are comparison and/or proposes with respect to literature.

6.1 Down syndrome

Down syndrome (DS) is the most common chromosomal disorder in the world, principally caused by the presence of an extra chromosome 21. In the United States alone, there are about 6,000 babies born with Down syndrome, which is about 1 in every 700 babies born. [13]. It involves mental retardation, congenital heart disease, anomalies of the gastrointestinal tract and several other dysfunctions. In addition, this syndrome yields well-known physical characteristics on the face of patient like flattened face -especially the bridge of the nose-, almond-shaped eyes that slant up, separated eyes, a tongue that tends to stick out of the mouth, among many others [16]. These are the principal features of an affected person with respect to face morphology, but there are may other related to the size of head, hands, legs, feet, etc.

Comas *et al.* presented a work about prenatal diagnosis of chromosome abnormalities (CA). It says that they focus on the selection of high-risk pregnancies, to perform invasive diagnostic procedures. Advanced maternal age is the main risk factor for DS and prenatal invasive procedure is routinely performed in women over 35 years. However, this strategy only detects about half of DS cases, with many women undergoing an invasive procedure for each CA detected. Second trimester prenatal screening includes maternal age, maternal serum levels of proteins and hormones. Biochemical parameters together with maternal age increased the detection rate for DS to 60% for a 5% false-positive rate (FPR). During the first decade of 2000, first trimester prenatal screening were developed; this includes maternal age, maternal serum studies and pregnancy-associated plasma protein, combined with one ultrasound measurement, the nuchal translucency (NT) which consists in the sonographic appearance of fluids under the skin behind the fetal neck (Figure 22 [4]). Implementation of early combined screening should enable to identify up to 90% of DS cases for a 5% FPR. Currently, DS screening is the most common and costly prenatal detection policy.

The present fetal face analysis looks for either increase percentage of diagnosis or reduce false-positive rates. Unfortunately, regardless several characteristics mentioned former of a Down syndrome patient, few of actual baby face landmarks are appropriate for study them. However, following measures are proposed and showed in Figure **??**:

- Euclidean distance between endocathions (ENEN) in order to have a control about eyes separation.
- Depth between endocathions (average of both of Z-coordinate) and nasion (ENN) as a measurement of flatness of nasal bridge.

Figure 21: Ilustration of a baby with Down syndrome

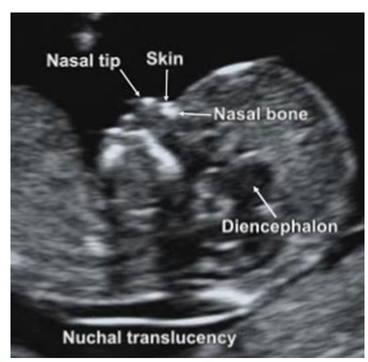


Figure 22: Nuchal translucency in an ultrasound

[4]Figure recovered from http://www.newkidscenter.com/Nuchal-Translucency-Screening.html

6.2 Fetal alcohol syndrome

FAS, as its name says, is a common and often not recognized medical condition related to mother's consumption of alcohol during pregnancy. FAS is a branch of fetal alcohol spectrum disorders (FASD) which includes, in addition, partial fetal alcohol syndrome (pFAS), alcohol related neurodevelopmental disorders (ARND) and alcohol related birth defects (ARBD). According to the German Guideline (version 2013) about FAS, it affects 0.02-0.8% of all annual births with an elevated number of undiagnosed cases. Fetal alcohol syndrome has a big number of physical characteristics in affected persons and, in fact, they are a strong point for its diagnosis, even without knowledge of prenatal alcohol exposure. But more serious than physical effects are consequences like major birth defects, mental retardation, significant growth deficiencies, cognitive impairment and behavioral manifestations including secondary disabilities. All of these brings important issues in personal life of patients and their families. [11].

Even if this condition is suspected during pregnancy due to an evidence of baby had been submitted to alcohol exposure, the diagnosis is confirmed -or not- only once the baby is born. However, this not occur intermediately considering FAS diagnosis needs the positive presence of 4 factors from different fields to be validated as such and they are: (1) growth deficits, (2) facial characteristics, (3) abnormalities of the central nervous system (CNS) and (4) confirmed or unconfirmed intrauterine alcohol exposure [17]. Then, the intention of study this syndrome in a fetal analysis research is, precisely, improve the rate of early discovery of this disease and preparation of all type for parents and doctors in the assistance of the new born kid.

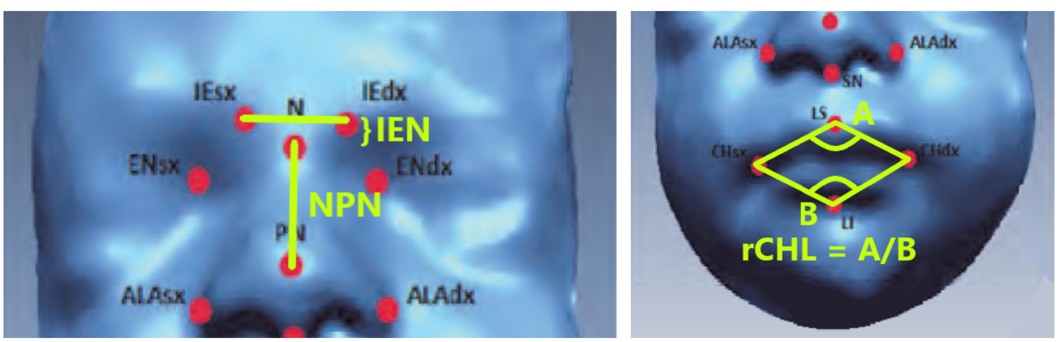
A list of physical features presented by people affected with FAS is presented below from where have been chosen points 5,6 and 8 to be studied according to landmarks position.

1. Growth deficits
2. Small head circumference
3. Short palpebral fissures
4. Smooth philtrum
5. Thin upper lip
6. Short nose

7. Epicanthal folds
8. Low/flat nasal bridge
9. Railroad track ears
10. Micrognathia
11. Abnormal palmar creases
12. Others

Following measurements have been taken from models in order to evaluate the presence of FAS signs. They are summarized in Figure 24.

- Ratio between angles formed by chelions points and superior labrum and angle formed by chelions points and inferior labrum (rCHL), related to thin upper lip feature.
- Euclidean distance between nasion and pronasal (NPN), related to short nose feature.
- Euclidean distance between inner eyebrows line and nasion (IEN), related to low nasal bridge feature.



(a) IEN and NPN measurements (b) rCHL measurements

Figure 24: Measures to take related to FAS

Nowadays, thin upper lip condition is measure through a pictorial lip-philtrum guide that consists in a five-point Likert scale shown in Figure 25. The ABC scale included is used to rank upper lip thinness and philtrum smoothness. When a patient reach a B or C score, then exist the possibility of a diagnostic of fetal alcohol syndrome. The columm called "Upper Lip Circularity" is a parameter calculated as $perimeter^2/area$ where the perimeter corresponds to the outline of the upper vermillion border and denominator is the mouth area. This parameter can be used to facilitate the ranking of upper lip thinnes [2].

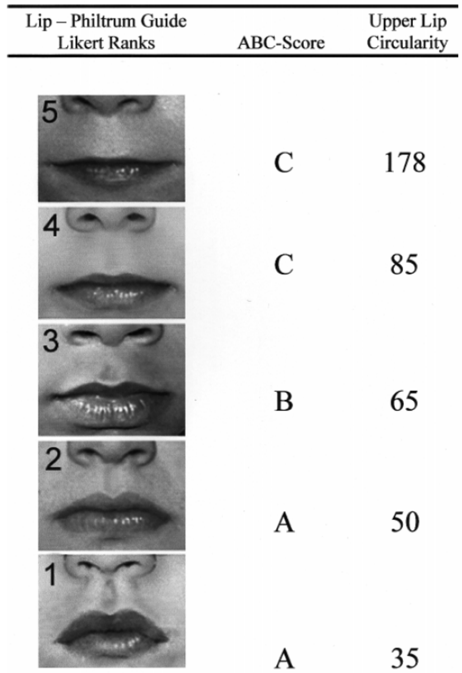


Figure 25: Lip-philtrum guide

6.3 Micrognathia

Micrognathia is a facial malformation characterized by an underdeveloped mandible and receding chin. It is related to several syndromes like Pierre Robin sequence, hemifacial microsomia and -how it was seen- fetal alcohol syndrome. It is also associated with various chromosomal anomalies such as trisomies 18 and 13, triploidy and those involving gene deletions or translocations. This condition can induce very risk situations, specially on babies, since the tongue may obstruct the upper airway generating suffocation [21]. Taking account of this, is easily see the importance of its early detection in order to have proper resources during birth.

Craniofacial malformations like this have a high rate of detection (close to 90%) through sonography [6]. However, being a notorious physical feature, there is not established protocol tests more than the naked eye and can be diagnostic from around a gestational age of 18 weeks although the common is in the mid of 20s, in addition, it is not a condition studied for itself but through the search of another anomalies [21].

Then, the next propose looks for an objective measurements of micrognathia and its early detection. It consists in:

- Difference in depth (z-coordinate) between labrum superior and inferior (zLSLI) as Figure 26 shows.

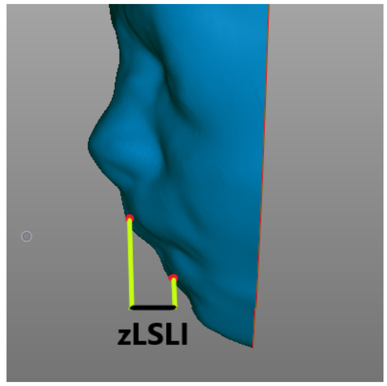


Figure 26: zLSLI measurement related to micrognathia

This measure is a proposal of this research and has no equivalent in present literature, hence, theoretically there isn't a reference value to compare and analyze at the end of calculations which would be useless for objectives pursued. For that reason, it is also proposed a reference value inspired in the investigation done by Rotten *et al.* (2002) titled "The fetal mandible: a 2D and 3D sonographic approach to the diagnosis of retrognathia and micrognathia". Analyses conducted by them have been redirected in such a way that may provide a referential measurement. This adaptation is explained in detail following and had as aim to estimate how much the labrum inferior landmark is retracted with respect to labrum superior one.

In the mentioned work, authors evaluate micrognathia through 2D ultrasounds using what they define the inferior facial angle (IFA) (Figure 27) obtained from "*(...)a line orthogonal to the vertical part of the forehead, drawn at the level of the synostosis of the nasal bones (reference line) and a line joining the tip of the mentum and the anterior border of the more protrusive lip (profile line)*" over a sample of 371 normal and 12 affected fetuses between 18 and 28 weeks of pregnancy.

After measurements processing, they conclude first that IFA angle does not change during the studied GA (18 to 28 weeks of pregnancy) and the second conclusion was that in normal fetuses the mean value of IFA is 65,5 (SD 8,13)° while for those affected by micrognathia the referential value is 49,2° but can be cut off in 50° without detriment of results.

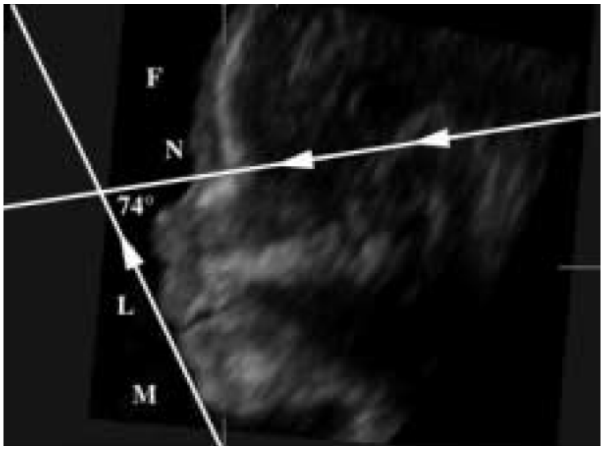


Figure 27: Inferior facial angle by Rotten *et al.* in a normal fetus

Figure 28: Inferior facial angle by Rotten *et al.* in an affected fetus

From their methodology, an own analysis has been conducted in order to transfer their results into useful ones for this project. This analysis consists principally in a geometrical study about IFA. The Figure 29 shows the IFA parameter in a normal fetus through while lines, blue line represents the variation of the profile line in case of micrognathia. Green line passes through labrum inferior landmark and is parallel to the reference line.

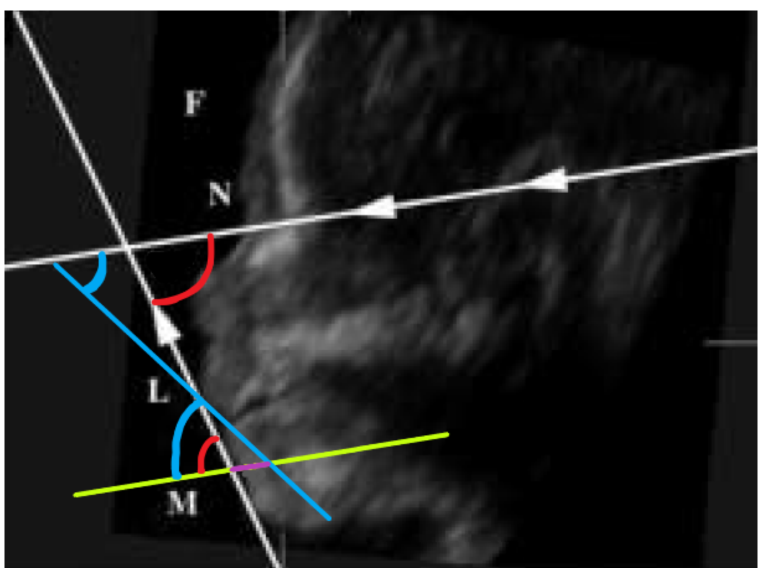


Figure 29: Geometric analysis of IFA

The objective is to estimate the length of purple line considering two assumptions: 1) labrum inferior landmark moves along the green line and 2) the difference in length between blue and white lines is negligible in comparison with the length of purple line, hence, it is possible to consider that the length of profile line remains constant.

Then, simple geometry leads to know that red angles and blue angles are equal respectively. It is important to take in mind that the common point between white and blue lines is essentially labrum superior landmark and from that point is drawn a straight line orthogonal to green line building two rectangle triangles. Then, calling α the red angle, β the blue one, "h" the portion of the profile line which forms the hypotenuse of rectangle triangles, "x" the length of purple line and $d_{initial}$ and d_{final} the length of adjacent legs to red and white angles, following is obtained:

$$\cos(\alpha) = \frac{d_{initial}}{h} \qquad \& \qquad \cos(\beta) = \frac{d_{final}}{h}$$

$$x = d_{final} - d_{initial}$$

$$x = (\cos(\beta) - \cos(\alpha)) * h$$

Applying the results derived by Rotten *et al.* $\alpha = 65,5°$ and $\beta = 50°$, hence $x = 0,2281 * h$. The hypotenuse value, how was described here, is the distance between labrum superior and labrum inferior and models shows a mean value for this distance equal to 9,49 mm (SD 2,29 mm) thus, x is 2,16 mm

Finally, it is concluded that labrum inferior should be at least 2,16 mm more retracted than normal with respect to labrum superior to consider that a fetus is affected by micrognathia.

7 Results and discussion

The present section shows the numerical results obtained after all procedures described previously. Next section includes a table with significant values and a detailed explanation of it for a better data reading. After that, in section 7.2 the discussion about results and their implications is taken place. Also, in the same section, it is present a general review of the project for analyzing error sources and, particularly, as a method of self-criticism about the performance.

7.1 Results

Results obtained from 3D models are presented in Table 3 with the following legend:

- ENEN = euclidean distance between endocathions
- ENN = depth difference between endocathions and nasion
- NPN = euclidean distance between nasion and pronasal
- IEN = euclidean distance between inner eyebrows line and nasion
- rCHL = ratio between angle formed by both of chelions and labrum superior and angle formed by both of chelions and labrum inferior
- zLSLI = depth difference between labrum superior and labrum inferior

Then, acquired results can be represented by the mean value of each dataset and its standard deviation (SD). In addition, Table 3 shows the minimum and maximum value of each column. The final row of the table shows the values at which measurements should be considered abnormal according to the syndrome from which was taken the measure. In that line, firsts two values are related to Down syndrome; next three value about fetal alcohol syndrome and the last value correspond to a reference value at which fetus could be considered affected by micrognathia.

Reference values for Down syndrome have been taken from a research conducted by Guihard *et al.* titled "Biometry of Face and Brain in Fetuses with Trisomy 21" published

Model	ENEN [mm]	ENN [mm]	NPN [mm]	IEN [mm]	rCHL	zLSLI [mm]
A	11,5101	2,1016	9,8190	7,2115	1,1922	6,2722
B	13,59	1,8865	12,3901	5,5682	0,9383	6,0730
C	10,0375	1,9402	11,7620	4,433	0,9350	7,2221
D	9,0968	1,194	11,6327	1,6186	0,9932	6,4578
E	13,8722	3,344	11,3857	4,6788	0,7751	5,2250
F	11,0402	0,497	10,2115	3,1131	1,0000	-0,0045
G	12,8029	4,0208	10,7326	2,5489	1,1463	4,5014
H	11,8644	2,2973	9,3608	4,9562	0,8891	4,6695
I	9,8823	2,2814	11,8905	5,644	1,2459	4,8542
J	12,4973	2,6022	12,3536	3,1796	1,0285	5,7333
K	9,8195	1,8028	12,1046	5,5475	0,9245	6,0097
L	13,132	2,1888	11,0220	5,9096	0,8765	5,3629
M	11,473	1,5393	11,4957	2,9035	1,1542	5,1122
N	10,5285	2,6687	12,4819	4,8085	0,7932	5,0958
O	12,3059	2,5958	11,6033	4,5627	1,1287	4,9340
Min	9,0968	0,497	9,3608	1,6186	0,7751	-0,0045
Max	13,8722	4,0208	12,4819	7,2115	1,2459	7,2221
Mean	11,5995	2,1872	11,4422	4,3529	1,0014	5,1679
SD	1,4352	0,8118	0,9901	1,4960	0,1411	1,6169
Condition	DS	DS	FAS	FAS	FAS	Microg.
Ref. values in case of disease	> 14,04 SD 2,44	< 1,94 SD 0,7	< 10,30	> 5,58	> 1,38	> 7,33
Literature reference	[15]	[23]	[17]	[17]	based on [2]	own elab. based on [21]

Table 3: Results of measures

in 2006 and from the work done by Tournemire *et al.* titled "Prenasal thickness to nasal bone length ratio: effectiveness as a second or third trimester marker for Down syndrome" published in 2015.

The result for the distance between endocathions can be rounded in a mean of 11,6 mm (SD 1,44 mm) while Down syndrome diagnostic criteria is for distances higher than 14,04 mm, hence, there is a separation of 2,44 mm between them but only a 0,05 mm from the maximum found (13,87). It is worth to consider that the second maximum calculated is 12,8 mm (1,24 mm from reference value).

A different scene is presented with distance between endocations and nasion: mean value is 2,19 mm, very close to the referential value equal to 1,94 mm. In addition, minimum value (0,5 mm) complies widely with the diagnostic criteria which has no sense since fetuses studied are all of them healthy.

About fetal alcohol syndrome, reference values have been taken from "Diagnosis of fetal alcohol syndrome (FAS). German version 2013" (Landgraf *et al.*) and from "Measuring the facial phenotype of individuals with prenatal alcohol exposure: correlations with brain dysfunction" (Astley and Clarren, 2001).

According with calculations, length of nose measurements (distance between nasion and pronasal landmarks) are very similar among then which is reflected in a mean value of 11,44 mm (SD 0,99 mm) with a minimum of 9,36 mm and a maximum of 12,48. Nevertheless, the reference value (10,3 mm) -which is an upper limit from where there is a risk of abnormality- is close to results obtained and, more important, is within the values obtained from the models.

Similar situation present measurements of distance between inner eyebrows and nasion with the difference that particular values of models vary notoriusly with each other having a variation around 5,6 mm between maximum and minimum values.

With respect to rCHL parameter is important to highlight that it has not equivalence in literature like is presented in this thesis, instead, is a constructed parameter that works as alternative of the upper lip circularity (see Figure 25) which is measure on a computer by tracing the contour of upper lip and mouth. In order to be coherent with Likert scale, rCHL parameter must be introduced into the equation: $Circularity = 44,5 * (rCHL)^2$ derived during this work. Through this, minimum, maximum, mean and reference values are respectively: 26,7 - 69,1 - 44,6 and 84,7 (around 85 is the limit at which someone could be considered in risk of FAS).

Regarding last reference value, linked to micrognathia, is a suggested value and does not correspond a measurement obtained in previous investigations. How was explained before, it was based in the research work done by Rotten *et al.* in 2002 (see section 6.3). It demonstrates a good behavior comparing with models measurements even when maximum distance from models (7,22 mm) is close to reference proposed (7,33 mm) because the second highest measurement is 6,46 mm which has a notorious difference with first maximum, then is reasonable to suppose that it was a particular case and doesn't represent a good parameter of comparison. In addition, models showed similar values among them validating the measures taken.

7.2 Discussion

From the six measurements obtained, half of them have showed results in conformity with initial expectations: the distance between endocathions (ENEN), the ratio between angles on the mouth (rCHL) and the depth difference between both of labrums (zLSLI). In consequence, they are acceptable candidates for to construct a fetal face normotype. However, this is a preliminary work that can be definitely complemented and improved in the future, hence, it can be considered satisfactory in base of results reached and emerging opportunities.

The discrepancies in the other outcomes between themselves and in relation with referential values may be derived from multiple factors. A general review of the work done and the methodology followed could clarify those sources of error with the purpose of having a feedback of the work conducted and offering support to future investigations related with this argument.

As a first approximation, the number of times that models were manipulated from the medical software until the landmarks were extracted is high: fetus models suffered changes at least four time before they were able to be measured and all of these modifications bring with them some level of uncertainty or error. About the first change, i.e., from medical program to a CAD model, there is no manner to quantify an error because there is no a real clarity about how the software transform the volumetric data into a CAD one and, in addition, possible calculus to do for comparisons between them are few and they lack precision. Also, intermediate steps like file format transfers and especially Matlab remeshing may carry significant variations in final measurements.

Another important factor of errors is the manual intervention. This investigation had required high level of it in most critical parts, namely, modifications of the CAD models as free forms through a design software and the landmarks localization due to the low performance of the extraction code. Regarding design 3D modelling, the outputs quality lies largely on operator expertise, then, the particularity of every model is a strong point to consider in errors analysis. About localizing landmarks, only 9 of a total of 195 landmarks were placed mathematically (through the code) while from 150 landmarks really used, 5 were calculated by the algorithm.

Continuing with landmarking, the reasons why extraction code didn't work correctly during this project are assumed to be due two factors principally: 1) code was intended for using over adult who have physical features completely developed and more marked than fetuses, 2) fetal face models were "bad oriented" according with code parameters, i.e., they were "rotated" with respect a frontal view of fetal face and this affected negatively to landmarking process. Furthermore, this "rotation" of faces is presumably the principal reason why IEN measurements in models registered such level of discrepancies among them.

Conclusion

Since 3D ultrasound technology entered in the medical field, it has proved to be a great advance in the accuracy of diagnosis and the reduction of false-positive rates as well as the amount of analysis of a patient had been increased. However, three-dimensional fetal face analyses are still an innovative work since there are not many studies in this area.

This thesis consisted in studying of fetal face morphology through measuring of six facial characteristics in healthy fetuses around 21 gestational weeks. It was looked for to be a contribution to a fetal normotype with the aim of to be, in a future, a concrete help in prenatal diagnoses.

Measurements analyzed had been chosen considering as reference three common diseases that affect fetuses and produce them recognizable facial deformities. These diseases and the number of measures taken for them are Down syndrome (2), fetal alcohol syndrome (3) and micrognathia (1). With the objective of to calculate measurements of normality to compare with reference conditions, along this inform had been described in details the processes conducted for each model in order to arrive to a fetal face mask, where was possible to localize the landmarks among which measures were performed.

Measurements obtained showed coherence with initial expectations in three of cases, one for each reference condition. In the section 7.2 had been reviewed error sources and factors that could led all discrepancies. However, taking into account this is a preliminary work and may be improved and complemented in future, results are considered satisfactory.

Regarding future works, in order to achieve better results in future, they could be intended in reaching a point clouds data transfer more efficient between 3D design software and Matlab. Also, a more mathematical and/or programming proposal could be the modification of landmarks extraction code to adapt it such a way that even for “rotated” fetal faces it works properly. On the other hand, studies in the same line of this research could verify, correct and complement the results obtained here with others abnormalities, other measures or with fetuses at similar gestational age but from difference geographical location.

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