Postgraduate Program on Biomedical Engineering

Master’s Thesis

“Simulation of Ultrasound Brain Cancer Imaging”

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This thesis is dedicated to my mother and my sister.
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**Introduction**

Ultrasound imaging is one of the most important ways of imaging the human body. The mainly application of ultrasound is for the soft parts of the body, due to the properties of tissues in the propagation of the ultrasounds. The brain with its normal shape is an appropriate organ for ultrasound imaging. But intraoperative ultrasound imaging may be effective in tumor localization and it can be used throughout surgery to monitor the extent of tumor resection. The ability to locate precisely a deeply situated intracranial lesion intraoperatively can reduce the risk of damage to normal tissue, assist in determining the extent of tumor resection and reduce the time surgery.

Intraoperative ultrasound holds great promise, but if it is to be used to its fullest extent, further modification of transducers must be developed. For this reason in this project we have done different simulations via the program Field II in order to evaluate the most appropriate transducers for the best depiction that can be achieved. We have to mention that those different experiments are based to the same code but with different specific parameters in every experiment.
Chapter 1

“Physics of Ultrasounds”

1.1 Introduction

The discovery of high frequency sound waves (ultrasound) was done by Lazzaro Spallanzani. The first mathematical description of sound waves was done in 1877 by Lord Rayleigh. The breakthrough came from Pierre Curie in 1880 with his discovery of piezoelectric effect. So, the reception of ultrasound waves was possible for first time. In 1914, underwater sonar navigation systems for submarines were developed to detect icebergs underwater from 2 miles away. In 1924 first radar (Radio Detection And Ranging system) was invented by Edward Appleton. In 1930s, Ultrasound Metal Flow detectors were constructed in order to check the integrity of the armor plates of battle tanks. In 1940, first claims on the effectiveness of ultrasound as curing modality were made.

The same year Gont and Wedkid presented the first paper that explored the possibility of using ultrasound as a diagnostic tool. So, the history of ultrasound imaging for medical diagnosis starts in the 1950s. Since then, the progress in the field has been enormous moving from the first single-line A-mode systems to real-time high resolution images of anatomy and blood-flow. Nowadays, diagnostic ultrasound is used in more than 25% of all medical imaging clinical procedures. It is used in virtually every medical specialty, with high popularity in obstetrics and cardiology. The great success of medical ultrasound lies primarily in low cost, mobility, safety, high processing speed and ability to integrate anatomical information with blood velocity monitoring in real-time.

1.2 Basic characteristics of ultrasounds

1.2.1 Ultrasound waves

Ultrasound is a mechanical vibration of matter that perturbs the particles of the medium around their mean positions. The frequency of the excitation is above the audible range, which is usually taken to be 20 kHz, but in practical systems the ultrasound frequencies used are between 2 and 20 MHz’s. If the medium is elastic, the oscillating particles produce adjacent regions of compression and rarefaction and in this way the vibration initiated at one location can propagate through the medium. The origin of an ultrasound wave is, therefore, the pressure change that occurs when an elastic medium is compressed or expanded. It is this pressure disturbance that propagates and no net displacement of the particles occurs [18], [19].
Figure 1.1: Propagation of sound waves. [20]

Figure 1.2: Propagation of sound waves. [20]
1.2.2 Parameters of sound waves

The main parameters and equations of sound waves are:

- The wavelength $\lambda$ (m): is the horizontal length of one cycle of the wave.
- The period $T$ (sec): is the time required for one wavelength to pass a certain point.
- The amplitude $A$ (m): is the maximum value of the wave function.
- The frequency $f$ (Hz): is related with the period.

$$f = \frac{1}{T}$$

- The speed of sound $c$ (m/s): is independent of the above parameters of the soundwave.

$$\lambda = \frac{c}{f}$$

The acoustic parameters of the medium are its density $\rho$ and adiabatic compressibility $\kappa$. It is the local changes in those two parameters that allow sound to propagate. The propagation speed of the disturbance is a property of the medium and is given by:

$$c = \sqrt{\frac{1}{\rho_0 \kappa}} = \sqrt{\frac{B}{\rho_0}}$$

Where $\rho_0$ is the mean density and $B$ is the adiabatic bulk modulus, assuming no net transfer of energy from the wave to the medium [20]. The speed of sound and the density of various tissues in the human body are given in table 1.1.

<table>
<thead>
<tr>
<th>Medium</th>
<th>Density [kg/m$^3$]</th>
<th>Speed of sound [m/s]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>1.2</td>
<td>333</td>
</tr>
<tr>
<td>Lung</td>
<td>$0.4\times10^3$</td>
<td>650</td>
</tr>
<tr>
<td>Distilled water</td>
<td>$1.0\times10^3$</td>
<td>1480</td>
</tr>
<tr>
<td>Blood</td>
<td>$1.06\times10^3$</td>
<td>1566</td>
</tr>
<tr>
<td>Fat</td>
<td>$0.92\times10^3$</td>
<td>1446</td>
</tr>
<tr>
<td>Kidney</td>
<td>$1.04\times10^3$</td>
<td>1567</td>
</tr>
<tr>
<td>Liver, spleen</td>
<td>$1.06\times10^3$</td>
<td>1566</td>
</tr>
<tr>
<td>Muscle</td>
<td>$1.07\times10^3$</td>
<td>1542-1626</td>
</tr>
<tr>
<td>Bone</td>
<td>$1.38 - 1.81\times10^3$</td>
<td>2070-5350</td>
</tr>
<tr>
<td>Brain</td>
<td>$1.03\times10^3$</td>
<td>1505-1612</td>
</tr>
</tbody>
</table>

Table 1.1: Approximate densities and sound speeds in human tissues [20].
The acoustic impedance $Z$ (kg/\([m^2 \cdot s]\)).

Using the electric analogue, where pressure corresponds to voltage and particle velocity to current, the acoustic impedance $Z$ is defined as the ratio of the pressure at a given point to the particle velocity at the same point and has units of kg/\([m^2 \cdot s]\), sometimes referred to as Rayl (1 Rayl = 1 kg/\([m^2 \cdot s]\)). The acoustic is a property of the medium and of the type of wave that is propagated. For a wave with equal pressure at any plane normal to the propagation direction (plane wave), the acoustic impedance is:

$$Z = \rho_0 c$$

The parameter of acoustic impedance has dramatic implications on the limitations of ultrasound imaging in human tissues. If an ultrasound wave encounters a tissue interface between two media with different acoustic impedances $Z_1$ and $Z_2$, only a percentage of the wave energy passes through. Using a transmission line theory, the reflection coefficient for an incident wave normal to the boundary can be defined as:

$$R_a = \frac{Z_2 - Z_1}{Z_2 + Z_1}$$

$$T_a = 1 - R_a$$

As we can see from the equation the reflection coefficient is a clear number without any measuring units. In figure 3, we can see two of the most important interfaces inside the human body which lead to the biggest limitations of the ultrasound. The first example is the fat/air interface where 99% of the sound wave is backscattered which makes very difficult to visualize the heart that is encased behind the ribs. Due to these limitations, the medical implications of ultrasound have been limited to soft tissue imaging, were the reflection coefficient is -10% to 10% [18], [19], [20].

![Figure 1.3: Reflection coefficients between two different mediums. Two of the most important examples are shown [18], [20].](image-url)
Also in table 1.2, we can see the values of density, propagation speed and acoustic impedance of some of the most important tissues of the human body.

<table>
<thead>
<tr>
<th>Medium</th>
<th>Density (kg/m³)</th>
<th>Speed of sound (m/s)</th>
<th>Acoustic Impedance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>1.200E+00</td>
<td>3.330E+02</td>
<td>3.996E+02</td>
</tr>
<tr>
<td>Lung</td>
<td>4.000E+02</td>
<td>6.500E+02</td>
<td>2.600E+05</td>
</tr>
<tr>
<td>Distilled water</td>
<td>1.000E+03</td>
<td>1.480E+03</td>
<td>1.480E+06</td>
</tr>
<tr>
<td>Blood</td>
<td>1.060E+03</td>
<td>1.566E+03</td>
<td>1.660E+06</td>
</tr>
<tr>
<td>Fat</td>
<td>9.200E+02</td>
<td>1.446E+03</td>
<td>1.330E+06</td>
</tr>
<tr>
<td>Kidney</td>
<td>1.040E+03</td>
<td>1.567E+03</td>
<td>1.630E+06</td>
</tr>
<tr>
<td>Liver</td>
<td>1.060E+03</td>
<td>1.566E+03</td>
<td>1.660E+06</td>
</tr>
<tr>
<td>Spleen</td>
<td>1.060E+03</td>
<td>1.566E+03</td>
<td>1.660E+06</td>
</tr>
<tr>
<td>Muscle</td>
<td>1.070E+03</td>
<td>1.630E+03</td>
<td>1.744E+06</td>
</tr>
<tr>
<td>Bone</td>
<td>1.600E+03</td>
<td>3.050E+03</td>
<td>4.880E+06</td>
</tr>
<tr>
<td>Brain</td>
<td>1.030E+03</td>
<td>1.550E+03</td>
<td>1.597E+06</td>
</tr>
</tbody>
</table>

Table 1.2: Approximate densities, sound speeds and acoustic impedances of human tissue [18], [20]

- The attenuation $A$ (dB/[MHz $\cdot$ cm]).

Another important property of the medium that strongly affects the medical implications of ultrasound is the attenuation. As a sound wave propagates inside a medium it loses part of its energy. This energy loss is called attenuation. Attenuation includes energy that is lost from both scattering of the sound wave and absorption. Absorption is the physical phenomenon where the energy of sound wave is absorbed by the tissue and turned into heat and it accounts for 75% of the total energy loss. The attenuation is depended both on the medium and the frequency of the propagating wave and as it is obvious it increases linearly as the depth increases.

The attenuation is equal to:

$$A(f, r) = e^{-2\pi f r \frac{dB}{MHz \cdot cm}}$$
Where \( f \) is the frequency of the wave, \( r \) is the distance that the wave has propagated in the medium. The units of attenuation is \( N_p/(MHz \cdot cm) \) or in \( dB/(MHz \cdot cm) \) where \( 1dB/(MHz \cdot cm) = 8, 685N_p/(MHz \cdot cm) \). In table 3, we can see approximate ultrasound attenuation values in human tissue [18], [19], [20].

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Attenuation (dB/(MHz cm))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>0.6 - 0.9</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.8 - 1.0</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.5 - 1.0</td>
</tr>
<tr>
<td>Fat</td>
<td>1.0 - 2.0</td>
</tr>
<tr>
<td>Blood</td>
<td>0.17 - 0.24</td>
</tr>
<tr>
<td>Plasma</td>
<td>0.01</td>
</tr>
<tr>
<td>Bone</td>
<td>16.0 - 23.0</td>
</tr>
</tbody>
</table>

Table 1.3: Approximate ultrasound attenuation values in human tissues [18].

**1.3 Description of basic system of ultrasound imaging**

**1.3.1 Generation of ultrasound**

Before analyzing these steps we have first to mention how the ultrasounds are created. In the figure below we can see the generation of an ultrasound with the use of piezoelectric effect.

![Generation of an ultrasound wave with the use of piezoelectric effect](image)

Figure 1.4: Generation of an ultrasound wave with the use of piezoelectric effect [18].

The way that an ultrasound wave is generated in almost all the available transducers is the use of piezoelectric crystal. Piezoelectric comes from the Greek words “Piezo” which means
“puss of exert pressure” and “electric” which means “electricity”. As it is obvious the terms piezoelectric refers to materials which when a voltage is applied on them then convert the signal into pressure oscillations in their surface via mechanical deformations. With the same way if a mechanical force is applied on the material this is then converting into electrical energy. This way by applying an electrical signal on one piezoelectric material we can monitor it, just by monitoring the voltage at the edges of the material [18], [19], [20].

### 1.3.2 Types of transducers

In this principle of piezoelectric effect the transducers are based in order to transmit and receive ultrasound waves. In figure 1.5, we can see a schematic of the parts of a typical ultrasound transducer.

![Schematic of typical transducer](image)

Figure 1.5: Schematic of typical transducer [20].

In order to avoid as possible the mismatch of the importance between the probe and the skin (in order to have low reflection coefficient and more acoustic energy to propagate in the body) a matching layer is used, which can also have a concave shape in order to achieve better focusing of the ultrasound beam. Behind the piezoelectric material is a sound absorbing backing layer is attached to it, in order to limit the mechanical ringing. The drawback with these backing layers is that they absorb a big portion of the backscattered energy and thus reducing the sensitivity of the transducer. This leads into an inevitable trade-off between the sensitivity and the bandwidth of the transducer.

The resonant frequency of the transducer is determined by the thickness of the slab. Ultrasound systems operate in frequency range of 1 to 30 MHz depending on the application.
Low range frequencies (1 to 5 MHz) are used in obstetrics, abdominal, liver scans and for cardiac imaging. Medium range frequencies (5 to 10 MHz) are used for breast scanning, vascular procedures and in pediatrics. Higher frequencies give better resolution, but the penetration depth is small, due to the frequency-dependent tissue attenuation. High frequencies are used in ophthalmology, as well as in intravascular imaging.

In order to reduce the acoustic impedance between the probe and the skin, a matching layer is present. Matching layers can be made flat or have a concave shape for better focusing. In order to limit the mechanical ringing and to provide a short acoustic pulse, sound-absorbing materials are attached to the back of the crystal. Such high impedance backing layers, however, absorb a big portion of the energy reducing sensitivity. Thus, the main trade-off in the design of transducers is that between sensitivity and bandwidth. Air backing yields excellent reflection and high output, but does not dampen the oscillations on the crystal, resulting in narrow-band long pulses. Thus, the design of the backing material depends on the application. For most applications, transducers are designed to have a 50 to 75% relative bandwidth, which is a good compromise between ringing and acoustic output.

The piezoelectric material commonly used in commercial transducers is barium titanate or lead zirconate titanate (PZT) which is piezoceramics. The recent advent of piezocomposites in the transducer technology has improved dramatically the performance. Piezocomposites are new piezoelectric materials resulted from mixing polymers with PZT. Piezocomposites have smaller acoustic impedance and tunable electromagnetical coupling constant, allowing bandwidth higher than 100% without sacrificing sensitivity. High bandwidth is a valuable resource in ultrasound imaging which improves resolution and can improve image quality through techniques such as coded excitation and harmonic imaging [18], [19],[20].

The beam shape that is generated by a transducer is determined by the design and construction of the probe. The two main categories are:

- **Flat crystals**, create a straight acoustic beam up to a distance slightly higher than half the wavelength, which then starts diverging.
- **Linear arrays**: acquire a rectangular image. The most widely used multi-element transducer. Typically, linear array consists of 64 to 256 elements, which are formed by slicing the ceramic into individual elements, each of them having its own electrical connection. The geometry of a linear array is shown in figure 1.6.
The center to center distance is called pitch and the gap between elements is the kerf of the array. The direction of the elements is called lateral (or azimuthal). The height of the elements corresponds to the elevation direction and the direction perpendicular to the transducer surface is the axial (or range direction).

In linear array imaging a focused beam can be transmitted into a region of investigation by selecting only the elements that are over the desired region, as shown in figure 7. In order to focus at a given depth, the applied delays on the active elements (sub-aperture) must have a concave profile, calculated from geometric optics. This implies that the elements act as omnidirectional point sources. The depth of the transmit focus can vary, by changing the curvature of the delay profile. The same or slightly larger sub-aperture can be used in reception and similar delay profiles can be applied on the received trades to focus in the same direction. If the received data are stored in memory, several receive focal zones can be applied, or continuous dynamic focusing for every sample. However, only one focal zone is possible in transmit. In modern scanners, more than one transmit focal zones can be placed at the cost of reducing the frame rate. This is done by transmitting with the same sub-aperture more than once using different focal depths and assembling the received data in depth [18], [19], [20].

Phased arrays: these transducers have the same geometry as the linear arrays, but they have a much smaller footprint and can scan an area much smaller than the size of the aperture. For typical frequencies of 2 to 10 MHz, phased arrays are about 1 to 3 cm long, while the linear arrays are about 10 cm long. They have a smaller number of elements compared to the linear array, typically 64 to 128 and their pitch is $\lambda/2$. It is possible to scan an area much larger than the size of the aperture in the azimuthal direction.
Phased array imaging essentially implements electronically the scanning process of a mechanically rotating single-element transducer. All elements are used both in transmit and in receive. As in linear array imaging, only a single transmit focus is possible for every emission, while several receive focal zones can be applied. The idealized beam pattern sketched in figure 1.8 corresponds to three different receive foci. Phased arrays are used in cardiology, where there is only a small “acoustic window” between the ribs and the labs [18], [19], [20].

![Figure 1.8: Phased array imaging [19].](image)

- **Concave crystals**, create a larger imaging region.

- **Convex arrays**: in order to scan a sufficiently large region, the array has to be large. An alternative way to obtain a larger imaging region is to use a rectilinear (or convex) array, in which the elements are placed on a convex surface as shown at the figure 1.9. The method for focusing and scanning is essentially the same as in linear array imaging. In this case, a sector scan is obtained, which is scan converted before display.

![Figure 1.9: Convex array imaging [20].](image)
1.3.3 Basic system description.

After analyzing the generation of ultrasounds and the types of transducers, we can know analyze briefly the basic system description of medical ultrasound imaging system. The main steps followed are below [18], [19], [20].

- **Transmission**: mainly based on piezoelectric effect with types such as:
  - Single frequency transducers: transmit in one central frequency lower amplitude in near frequencies.
  - Broadband transducers: transmit equal amplitudes in a range of frequencies.
  - Multi-frequency transducers: choice of central transmitting frequency.

- **Reception**: the backscattered echoes carry information about the structures along its propagation path. The echoes are converted to electrical signal based on the inverse piezoelectric effect.
  - Amplitude of echo: reflectivity and scattering strength of the tissue.
  - Time that the echo arrived: depth of the scatterer (average speed of 1540 m/s is used).

- **Time gain compensation**: is an amplification procedure of the echo, in order to compensate for the severe energy loss from attenuation of ultrasound waves when they propagate through the tissues.

- **Envelope detection**: after amplification the envelope of echoes is detected. The echoes in an RF signal band-limited to the transducer bandwidth.

- **Logarithmic compression**: all quantities are expressed in a logarithmic scale in order to decrease the range of echoes, which is very wide. The log-scale in terms of amplitude is calculated by:

\[
dB = 20 \cdot \log_{10} \frac{A}{A_0}
\]

- **Display modes (ways of depict)**:
  - A-mode: Amplitude Mode was the first mode ever used. Ultrasound pulse is sent to one direction. The backscattered echo was captured and was presented in x-y axis and the amplitude as a function of depth. It is used only to measure distance.
Figure 1.10: Diagram of an A-mode display [20].

- M-mode: Motion Mode is an evolution of A-mode. Provides information about the motion. In the M-mode several lines were emitted in the same direction and the backscattered echo was recorded (A-lines). By acquiring several A-lines and displaying each one side by side, information about the motion was seen. The acquired lines were presented in x-y axis, where x-axis corresponds to time and y-axis to the depth.

Figure 1.11: Diagram of an M-mode display [20].
B-mode: Brightness Mode is the breakthrough in the field of medical ultrasound. In the B-mode a series of focused fields, lines were transmitted in different direction, acquiring a series of A-lines that covered all the region of interest. The A-lines were then merged missing data were interpolated and a 2D image was created.
1.3.4 Properties of ultrasound images.

- **Beamforming:** is the manipulation of the elements of array transducers to enhance focusing and shape directivity of the beam. It is achieved electronically by changing the time delay and the amplitude of the voltage applied on each element. This is done by a beamformer that combines the echoes by delaying and summing those [20].

![Electronic focusing](image1)

Figure 1.14: Electronic focusing and steering using a phased array probe [20].

![Beamformer](image2)

Figure 1.15: Beamformer [20].

- **Focusing:** in all array transducers focusing is done by applying delays in the excitation pulses. The focus depth can vary, by changing the curvature of the delay profile. In transmit only one focal zone can be applied if only one line is transmitted by each element. Multiple transmit focal zone can be achieved if multiple lines are transmitted in the same direction with different focusing depth (cost of reducing the frame rate). In reception if the data are stored,
multiple focal zones can be applied or even continuous focus at all point along each line (dynamic focusing).

Figure 1.16: Focusing [20].

Figure 1.17: Focusing [20].

Figure 1.18: Focusing and axis [20].
\[ \tau_i = \frac{|r_c - r_f| - |r_i - r_f|}{c} \]

- \( \tau_i \): is the relative delay that it should be used from element \( i \).
- \( r_c = (x_c, z_c) \): is the reference point. Same reference point for the whole aperture, usually the geometric centre of the transducer.
- \( r_f = (x_f, z_f) \): is the point focus [20].

- **Image resolution**: is the ability of an imaging system to distinguish between closely-spaced scatterers. In system’s Point Spread Function (PSF) the resolution is evaluated by the acoustic pulse interrogation of a medium with a single point scatterers places at the focus point. It has mainly three components: axial, lateral, elevation [19], [20].

![Image of image resolution components](image)

Figure 1.19: Components of image resolution [20].

- **Axial resolution**: is determined by the duration of the acoustic signal generated on each element, which in turns is determined by the central frequency and the bandwidth of the transducer. Transducers with high bandwidth operating at high frequencies generate short acoustic pulses with good axial resolution [19], [20].
- **Lateral (azimuthal) resolution**: in general the lateral field of a focused beam consists of a main lobe and decreasing sidelobes around the main lobe. The width of main lobe defines the lateral resolution; a beam with a narrow main lobe corresponds to a better lateral resolution. The purpose of the beamformer is to achieve a lateral resolution for a large axial distance around the focal point (depth of focus). In qualitative terms, lateral resolution is inversely proportional to the aperture size (i.e. a large aperture can yield more focused fields. More precisely, it is proportional at a first order approximation to the f-number, the ratio between axial focal distance and aperture size. Thus, acoustic fields can be focused more strongly close to the transducer. In order to obtain an ultrasound image with desirable uniform focusing characteristics, a beamformer can, for instance, maintain a constant f-number, by updating constantly the delays and re-focus the beam for every depth with approximately constant lateral resolution and depth focus. Lateral resolution is also inversely proportional to the transmitted frequency. Therefore, migrating to higher frequencies improves lateral resolution, but reduces the penetration depth due to attenuation. The lateral sidelobes of the field degrade image quality by masking weaker scatterers present at the lateral extend of a strong reflector. They can be reduced by applying apodization across the aperture, which can also vary with depth (dynamic apodization) [19], [20].

- **Elevation resolution**: resolution in elevation is not directly visible in an ultrasound image, since it is the resolution on a plane orthogonal to the imaging plane. Similar to the lateral resolution, it is associated with the active acoustic aperture in that dimension. Linear arrays are often called one-dimensional arrays, since elements are positioned in one row along the azimuthal direction. Since there is only one element in the elevation direction, the beam characteristics outside the image plane cannot be controlled with the beamformer, and echoes coming outside the imaging plane degrade image quality. Commonly 1-D arrays built with concave-shaped elements in the elevation direction, in order to achieve a single focus. To address this problem, several transducer schemes have been proposed. In the so-called 1.25-D arrays, each array element is divided into sections along the elevation direction, allowing focusing over a limited range elevation direction are possible with these arrays, but steering is very limited due to the large element size. These designs attempt to alleviate the high cost of building truly 2-D probes. The construction challenge and the complexity in the electronics are
apparent, considering that for a 128x128 fully-populated 2-D array more than 16,000 elements and electrical connections are required. Different elements are also used in transmit and receiving, in order to optimize the pulse-echo effective aperture [19], [20].

- **Speckle:** looking an ultrasound image one can notice a characteristic grainy texture. Ultrasound images inherently have this granular appearance, which is referred to as a speckle. Homogeneous tissue does not have a constant gray level, as one would possibly expect. This is due to the fact that the structures that are imaged, such as fibrous and connective tissue and cells, are much smaller than the wavelength of an ultrasound wave and therefore, cannot be resolved. The backscattered ultrasound signal does not visualize microstructure, but it is rather a constructive and destructive interference of scattered waves by structures beyond the system resolution limit. Speckle is characterized in statistical terms, since it originates from a diffuse population of sub-resolution scatterers. Its mean value is zero and the amplitude distribution follows a Gaussian distribution, if the arrangement of the scatterers is spatially random (incoherent scattering). Speckle is not random as thermal noise (and therefore cannot be reducing by averaging) in the sense that the same signal will result from two measurements. The strength of the signal is determined by the composition of the tissue and can be an indication of pathology. The speckle size is directly to the system spatial resolution. Using autocovariance analysis on data from fully-developed speckle region in an ultrasound image can give a measure of the exact axial and lateral resolution of the system [20].

![Figure 1.20: Speckle on a B-mode ultrasound image of the fetus using a convex array](image_url)
Blood flow imaging: one of the big assets of ultrasound as an imaging modality is its ability to detect and monitor blood flow in real-time, making a valuable clinical diagnostic tool in the assessment of the cardiovascular system and the heart. In order to estimate blood flow, pulsed ultrasound is transmitted 4-8 times at the same direction. The acquired lines are segmented in depth zones and a blood velocity. Flow estimation is performed either using the Fourier transform or by estimating the phase shift for successive lines. This is one for a number of angles or scan directions, in order to obtain a two-dimensional velocity distribution. The estimated flow map is color-coded for display purposes and is super-imposed on the B-mode anatomic image.

Figure 1.21: Triplex mode: Color flow mapping of the carotid, superimposed on the B-mode image and spectral Doppler (sonogram), showing velocity information over time from a user-selected region at the center of the artery [19], [20].

In the figure 21 we can see an example of CFM (color flow mapping) for the carotid, the main artery supplying blood to the brain. The color coding is rather arbitrary, but a common convention is red for flow moving towards the transducer and blue for flow moving away from the transducer. Or red for flow in arteries and blue for flow in the veins. The brightness of the color shows the magnitude of velocity. The user can mark an area on the vessel lumen, where a sonogram can be displayed, showing the time evolution of flow. Such display mode is called triplex imaging [19], [20].
1.4 Ultrasound contrast agents (UCA).

1.4.1 Why they are used.

Using special agents in order to increase contrasts and therefore sensitivity and specificity of the produced image, is a technique broadly used in many medical modalities such as computed tomography (CT), magnetic resonance imaging (MRI) etc. In all these modalities though, the contrast agent doesn’t undergo changes after its interaction with the imaging technique, on the other hand the ultrasound contrast agent changes after its interaction with the ultrasound and it is because of this unique interaction that the UCA offer both improved diagnostic abilities and therapeutic techniques for gene and drug delivery.

The mechanism on which the UCAs are based, is to increase locally the amount of back scattered waves, due to there is high echogenicity. This way the contrast between the surrounding tissue and the blood is greatly increased and gives the ability to visualize micro and macro vasculature, to outline cavities, to measure the efficiency of the heart, to specify normal from abnormal tissue etc [18].

1.4.2 Physics of the UCAs.

As said before the UCAs improve the contrast between the tissue/blood interfaces due to high amount of the signal they backscatter. The intensity of this signal is calculated by the equation:

\[ I_s = \frac{I_i \sigma}{4\pi R^2} \]

Where: \( I_s \) is the backscattered intensity, \( I_i \) is the intensity of the incident pulse, \( \sigma \) is the scattering cross section of the scatterer. It is assumed that the \( R \gg r \) (\( r \)=the radius of the microbubble), which is true in all cases The scattering cross section in the case of microbubbles where the geometrical cross section and the scattering cross section are nonlinearly related, is calculated by:

\[ \sigma = \frac{4\pi}{9} k^4 r^6 \left[ \left( \frac{k_s-k}{k} \right)^2 + \frac{1}{3} \left( \frac{\rho_s-\rho}{2\rho_s+\rho} \right)^2 \right] \]

Where \( \kappa \) is the adiabatic compressibility, \( \rho \) the density of the medium, the subscript \( s \) denotes the properties of the scatterer; \( k \) is the frequency of the incident pulse.
As far as the resonating response of the bubbles is concerned, according to Goldberg (B. B. Goldberg 1994) resonating free air bubbles can produce 3 times bigger cross sections than the non resonating ones. The resonance frequency of an encapsulated bubble is equal to:

$$f_0 = \frac{1}{2\pi r} \sqrt{\frac{3\gamma}{\rho_0} \left( p_0 + \frac{\pi S_e}{3 \gamma r} \right)}$$

Where $p_0$ signifies the ambient fluid pressure, $\rho_0$ the density of the ambient fluid, $\gamma$ is the adiabatic gas constant, and $S_e$ the experimentally determined shell’s elasticity [18].

1.4.3 UCAs investigation methods.

- **Population studies:** In most studies, the UCAs are studied in high concentrations, where a large number of microbubbles are insonified and the backscattered pulse is compared to a reference microbubbles free backscattered signal. With this method, we are not able to distinguish the real response of a single bubble due to multiple scattering [18].

- **Optical studies:** After the introduction of fast acquisition cameras such as the Brandaris 128 which allows 128 images to be taken with a frame rate of 25 MHz, the optical observation of an insonified microbubble was possible. This way the radial oscillations and thought them the acoustic emissions and the frequency response of the microbubbles can be calculated [18].

- **Single bubble studies:** This is the technique used in the presented study, where echoes from single microbubbles each one insonified alone and not on a populations. This way we can be certain that the observed response is a result of the behavior of the microbubble itself and not an artifact from intervening implications such as multiple scattering [18].
1.5 Safety of ultrasound

Because of the vast exposure of the general population to diagnostic ultrasound, any question of the possibility of harmful effects becomes very important. This is especially true for exposures of the fetus to ultrasound. In 1991, the US Government’s Food and Drug Administration (FDA) began allowing the intensity of ultrasound used to scan the fetus to increase to 7.7 times its previous value, if manufacturers agreed to build new output displays into the ultrasound systems. While scientists have conducted many studies to try to determine whether there are any effects of ultrasound on the fetus, virtually all of these studies are of people exposed to ultrasound before the output levels were allowed to increase. Based on their concerns about the theoretical effects of ultrasound on the developing fetus, researchers have conducted epidemiological studies looking for associations between ultrasound exposure and various traits, particularly with problems in brain development, growth, and childhood cancers. Even when an increase in a particular trait is associated, or linked, with ultrasound exposure in an epidemiological study, does not necessarily mean that ultrasound is the cause of the increase in the trait. So far, there is published data on whether or not in utero ultrasound scans can be linked to any of these traits: low Apgar scores at birth, birth defects, speech or hearing disorders, diminished height or weight in childhood, birth defects, chromosomal abnormalities, childhood cancers, and developmental problems including learning disabilities. There is no conclusive evidence that any of these traits were caused by the in utero ultrasound exposure experienced by these children. However, there is evidence from some of these studies linking some of these traits to ultrasound exposure—evidence which needs further investigation in order to be sure that the more intense ultrasound used today could not be causing these effects. Many of the epidemiological studies only tracked a small number of people, rendering their conclusions less powerful. One way to get a bigger picture in cases like this is to review a whole group of studies that track a particular trait, in order to increase the number of people under consideration. In one review of more than 100 studies on ultrasound exposure, scientists grouped the studies of each trait in order to try to get a clearer picture of which traits might be linked to ultrasound. Grouping the three studies that looked at whether children were right or left-handed, they found slightly more left-handedness among boys exposed to ultrasound in utero. Grouping the four studies on childhood cancer, they found no association between cancer and in utero ultrasound exposure. Out of eleven studies that looked at birth weight, two studies found an association between in utero ultrasound exposure and a small reduction in birth weight. Low birth weight is linked with various health risks to the newborn. But another study actually associated ultrasound with an increase in birth weight. Even when there appears to be an association between ultrasound and a trait such as low birth weight, this does not prove that ultrasound is causing the trait. In some of these studies, women may have had more ultrasound scans because they already knew or suspected that there was some type of a problem with the fetus, and so these babies may be more likely to have problems, independent of their exposure to ultrasound. For instance, if the fetus does not seem to be growing enough, the mother may get ultrasound scans to check on the health of the fetus. If these babies are then born with low birth weights, it may be from a growth problem that predated the ultrasound exposure, and not a result of the ultrasound exposure. In other words, a statistical link
between ultrasound exposure and a particular trait does not prove that ultrasound is causing that trait: there could be what scientists call a confounding variable [11].

One of the largest studies to date of in utero ultrasound exposure followed over 15,000 women in Australia. There was no reported increase in birth defects. However, the study was not designed to study birth defects, but to show that ultrasound screening decreases the incidence of health problems in newborns. So while reassuring, most scientists would not find this study conclusive. Another large study was designed to show that ultrasound screening in Canada would help to prevent prematurity. In this study, 1,415 women received ultrasound scans at five different points in their pregnancies, between 18 and 38 weeks. The other group of 1,419 women received only one ultrasound scan at 18 weeks. In the course of the study, they found that the offspring of the group that received more ultrasound scans had slightly lower birth weights. One study found that 72 children with delayed speech had a higher rate of in utero ultrasound exposure than 144 children who did not have speech delays. However, the study did not describe why these children had been exposed to ultrasound, or the intensity or duration of the exposure. It is possible that they had ultrasound scans because of some other problem that also caused the speech delay. Once again, the association between ultrasound and speech delay does not necessarily mean that the ultrasound is the cause of the speech delay. The cause may well have been some third factor. And other studies have shown no association between ultrasound and speech delay. Nevertheless, the authors of this study recommended caution in using prenatal ultrasound. Reviewing all the studies of the human population published so far, there are individual studies that found associations between diagnostic ultrasound and low birth weight, dyslexia, and delayed speech development. However, the NCRP found that there is insufficient evidence, even in these cases, to conclude that diagnostic ultrasound is the cause of any of these adverse effects, or any adverse effects whatsoever. The inability to find convincing proof of an effect does not preclude the possibility of it happening. Part of the challenge in determining the effects of ultrasound is that researchers cannot, ethically, conduct laboratory experiments on human beings. The NCRP recommends that scientists conduct more studies in laboratory animals in order to identify any specific, subtle harmful effects that might be caused by ultrasound, and might arise in humans. Then, epidemiologists may be able to design bigger and better studies which could be targeted specifically to reaffirm that ultrasound, as it is used today, is not having any such subtle, harmful effects on the human population.

1.5.1 Ultrasound Systems Estimate Risks

Diagnostic ultrasound systems now come with displays meant to warn the system operator when there may be a risk to the patient (or fetus) from the heat or mechanical effects caused by ultrasound. The system displays numbers that provide crude measures of the risk. The Thermal Index (TI) is an estimate of risk from heat, and the Mechanical Index (MI) is an estimate of risk from the nonthermal effects of ultrasound. Manufacturers began incorporating these displays into ultrasound systems in order to meet the US government’s 1991 new regulations allowing them to increase ultrasound system outputs. If they used the Index displays, they could increase outputs. When the MI is above 0.5 or the TI is above 1.0, the NCRP recommends that the risks of ultrasound be weighed against the benefits. As ultrasound waves pass through the body, their
energy is converted into heat—heat absorbed by the tissues of the body. In general, the denser the tissue, the more heat is absorbed, as the ultrasound waves cannot pass through dense tissue as easily. So fluid does not heat up very much, soft tissues heat up somewhat more, and bone heats up the most. If the ultrasound waves are passing through soft tissues, as is the case when scanning a fetus in the first trimester, the Thermal Index is calculated one way, known as the Soft Tissue Thermal Index, or TIS. If the ultrasound is focused near bone inside the body, as is the case for a fetus in the second or third trimester, the Thermal Index is calculated another way, known as the Bone Thermal Index or TIB. However, the physician or technician who is using the ultrasound system must interpret these numbers in order to weigh the risks against the benefits of getting a better ultrasound image. Getting a better image may mean assuming greater risks. And in some cases the system operator needs to take into account the way that the ultrasound waves pass through that particular patient. For instance, the calculation of risk may be affected by whether the patient is thin or obese, whether or not they have a full bladder, or whether or not there are gas bubbles in the scanned part of the body. The NCRP recommends that this system of assessing risk be improved in a number of ways. Scientists should continue to refine the formulas used to calculate the TI and MI estimates. Manufacturers should design ultrasound systems to automatically minimize the acoustic power and pressure while still yielding the desired images. Independent laboratories should conduct spot-checks of ultrasound systems to ensure that the information supplied by manufacturers about the output of the system is correct. And ultrasound operators should receive more education in evaluating risks and benefits. This training should be part of the process of ultrasound laboratory accreditation. During the past decade the diagnostic capabilities and applications of ultrasound have increased dramatically. Part of the improvement in diagnostic capability is due to the higher acoustic intensity allowed for ultrasound by the US government, starting in 1991. At the same time, scientific knowledge of the biological effects of ultrasound has expanded. The medical community recognizes that they are responsible for maintaining the excellent safety record of diagnostic ultrasound. It is up to ultrasound technicians and doctors to evaluate the risks and benefits of diagnostic ultrasound in each case. The recommendations in this report are designed to bring as much information as possible to the physicians and ultrasound technicians faced with making these decisions [11].

Unlike ionizing radiation, there has been little international safety standard on the clinical use of ultrasound or standard for the calibration of output from diagnostic equipment. There is a large body of scientific literature on bioeffects but it is difficult to interpret much of the early work in the context of the safety of diagnostic ultrasound as the exposure conditions used were not clinically relevant. It is difficult to find biological endpoints that were sufficiently sensitive to respond since modest acoustic outputs were used. Difficult to find biological endpoints that were sufficiently sensitive to respond since modest acoustic outputs were used [16].
1.5.2 Standardization in diagnostic ultrasound

It is very important the subject of standardization in diagnostic ultrasound. The International Electrotechnical Commission (IEC) is included since it is the parent world standards organization. The IEC Subcommittee 29D (Ultrasonics Working Group on Medical Applications) is currently circulating a draft standard entitled “Methods of Measuring the Performance of Ultrasonic Pulse-Echo Diagnostic Equipment.”

There are basically three types of standards:
1) Fundamental standards,
2) Engineering standards, and
3) User oriented operational standards.

1) Fundamental Standard:
Measurements of fundamental quantities such as the peak and average acoustic intensity in an ultrasound beam are often very difficult to perform. However, such measurements are presently being made at a number of institutions and should soon result in calibrated secondary standards for engineering measurements. There is no unanimity about the best method for measuring ultrasound intensity. Currently, the following techniques are being examined.

- Radiation Force: a method for measuring average intensity which uses the change in force (typically measured in micrograms) recorded as the deflection of a reflecting or absorbing target with incident ultrasound.
- Calorimetry: a classical method for measuring average power using the change in temperature due to ultrasound absorption in a fluid.
- Capacitive Transducers: a method for measuring both peak and average intensities using the modulation of the spacing of a charged parallel plate capacitor by an incident sound wave.
- Transducer Reciprocity Calibration: well-known method in sonar which allows a simple measurement of peak and average intensities provided the reciprocity parameters are known and are not seriously complicated by the near field diffraction pattern.
- Optical Diffraction: a method for measuring the peak and average intensity using the Debye-Sears effect.

Since no single technique is clearly superior, it seems certain that, some combination of these methods will result in calibrating secondary standard piezoelectric transducers for research and engineering measurement.)

2) Engineering Standards:
These standards are normally intended for measurements on subsystems to be performed by manufacturers and calibration centers. Traditional engineering methods and standards for measuring gain, bandwidth, noise level, electrical leakage, etc., are available. With the exception of the ultrasonic transducer and its radiation pattern, this area of standardization
is well advanced, although the measurements can become tedious and, therefore, may be neglected unless mandated by law.

3) User-Oriented Operational Standards:
Methods for checking the performance of complex ultrasound systems on a daily or weekly basis may literally be a matter of life or death. Whereas an oscilloscope out of calibration may mean the repeat of a test for an engineer, it may result in missed diagnosis with irretrievable results for the physician. Standards for use by the hospital technologist must be simple and easy to use since they will often be used by people with little or no background in science or engineering (in many larger hospitals, biomedical engineering technicians are just now filling this gap). The test must use a simple low cost device and should test the whole system as a “black box” to avoid manufacturers’ complaints. The traditional method in medicine is to employ a “phantom” or a standard object to be scanned [32].
Chapter 2
“Brain anatomy and Glioblastoma Multiforme”

2.1 Introduction

Living creatures are made up of cells. Groups of cells are similar in appearance and with the same functions from tissues. Cancer is a disease defined by unregulated growth of abnormal cells. These abnormal cells grow into/ around parts of the body and interfere with their normal functioning. Also these cells are spread to distant organs in the body.

The brain is a soft mass of supportive tissues and nerve cells connected to the spinal cord. Nerves in the brain and spinal cord transmit messages throughout the body. The brain and spinal cord together form the central nervous system (CNS). The central nervous system is the core of our existence. Of course learning about the normal workings of brain and spine helps us to understand the symptoms of brain tumors, how they are diagnosed and how they are treated [1].

2.2 Basic anatomy of brain.

2.2.1 Main parts of brain.

![The brain](image)

Figure 2.1: The brain.

The human brain is a complex organ that allows us to think, move, feel, see, hear, taste and smell. It controls our body, receives information and stores information (our memories). The brain produces electrical signals, which, together with chemical reactions let the parts of the
body communicate. Nerves send these signals throughout the body. The adult human brain weights on average about 1.5 kg and is very soft.

The three main components of the brain are:

- the cerebrum
- the cerebellum
- the brain stem

The cerebrum is the largest and most developmentally advanced part of the human brain. It is responsible for several higher functions. The cerebrum is divided into a right and a left hemisphere and four main lobes. The left hemisphere controls the majority of functions on the right side of the body, while the right hemisphere controls most of functions on the left side of the body. The crossing of nerve fibers takes place in the brain stem [22]. The four main lobes are:

- **The frontal lobe**: is located at the front of the brain and is associated with reasoning, motor skills, higher level cognition and expensive language. At the back of the brain receives information from various lobes of the brain and utilizes this information to carry out body movements [23].

- **The parietal lobe**: is located in the middle section of the brain and is associated with processing tactile sensory information such as pressure, touch, and pain. A portion of the brain known as the somatosensory cortex is located in this lobe and is essential to the processing of the body's senses [23].

- **The temporal lobe**: is located on the bottom section of the brain. This lobe is also the location of the primary auditory cortex, which is important for interpreting sounds and the language we hear. The hippocampus is also located in the temporal lobe, which is why this portion of the brain is also heavily associated with the formation of memories [23].

- **The occipital lobe**: is located at the back portion of the brain and is associated with interpreting visual stimuli and information. The primary visual cortex, which receives and interprets information from the retinas of the eyes, is located in the occipital lobe [23].
Also the layers of the cerebrum of the brain are:

The entire cerebrum is composed of two layers, the gray and white matter.

- **The gray matter** (or cerebral cortex): is the 20-millimeter thick outermost layer and contains the centers of cognition and personality and the coordination of complicated movements. The gray matter is also organized for different functions [22].

- **The white matter**: is a network of fibers that enables regions of the brain to communicate with each other [22].
The cerebellum is the second largest area, is responsible for maintaining balance and further control of movement and coordination [22]. It lies on top of the pons, behind the brain stem. The cerebellum is comprised of small lobes and receives information from the balance system of the, inner ear, sensory nerves; the auditory and visual systems. It is involved in the coordination of motor movements, as well as, basic facets of memory and learning. Also, the cerebellum is similar to the cerebrum in that it has two hemispheres and has a highly folded cortex [23]. The cerebellum has three main general parts:

- **The archicerebellum**: is associated with the flocculonodular lobe and is mainly involved in vestibular and eye movement functions. It receives input from the inferior and medial vestibular nuclei and sends fibers back to the vestibular nuclei, creating a feedback loop that allows for the constant maintenance of balance [24].

- **The paleocerebellum**: controls proprioception related to muscle tone (constant, partial muscle contraction that is important for the maintenance of posture). The paleocerebellum receives its inputs from the posterior and anterior spinocerebellar tracts, which carry information about the position and forces acting on the legs. The paleocerebellum then sends axonal projections to the deep cerebellar nuclei [24].

- **The neocerebellum**: receives input from the pontocerebellar tract and projects to the deep cerebellar nuclei. The pontocerebellar tract originates at the...
pontine nuclei, which receive their input from the cerebral motor cortex. Thus, the neocerebellum is associated with motor control, in particular, the coordination of fine finger movements such as those required by typing [24].

The **brain stem** is the final pathway between cerebral structures and the spinal cord. It is responsible for a variety of automatic functions such as control of respiration, heart rate and blood pressure, wake-fulness, arousal and attention [22]. The brain stem is comprised of the hindbrain and midbrain:

- **The hindbrain:** is the structure that connects the spinal cord to the brain and contains structures including medulla, the pons and the reticular formation. The medulla is located directly above the spinal cord and controls many vital autonomic functions such as heart rate, breathing and blood pressure. The pons connects the medulla to the cerebellum and helps coordinate movement on each side of the body. The reticular formation is a neural network located in the medulla that helps control functions such as sleep and attention [23].

- **The midbrain:** is the smallest region of the brain that acts as a sort of relay station for auditory and visual information. The midbrain controls many important functions such as the visual and auditory systems as well as eye movement. Portions of the midbrain called the red nucleus and the substantial nigra are involved in the control of body movement. The darkly pigmented substantial nigra contains a large number of dopamine-producing neurons are located. The degeneration of neurons in the substantial nigra is associated with Parkinson’s disease [23].
2.2.2 Main cells of brain.

The brain and spinal cord are made up of many cells, including neurons and glial cells. Neurons are cells that send and receive electro-chemical signals to and from the brain and nervous system. There are about 100 billion neurons in the brain. There are many more glial cells. They provide support functions for the neurons, and are far more numerous than neurons.

- **Neurons**: There are many types of neurons. They vary in size from 4 μm to 100 μm in diameter. Their length varies from a fraction of an inch to several feet. The neuron consists of a cell body (or soma) with branching dendrites (signal receivers) and a projection called an axon, which conduct the nerve signal. At the other end of the axon, the axon terminals transmit the electro-chemical signal across a synapse (the gap between the axon terminal and the receiving cell). The axon, which is a long extension of a nerve cell, and take information away from the cell body. Bundles of axons are known as nerves or, within the CNS (central nervous system), as nerve tracts or pathways. Dendrites bring information to the cell body. Myelin coats and insulate the axon (except for periodic breaks called nodes of Ranvier), increasing transmission speed along the axon. Myelin is manufactured by Schwann's cells, and consists of 70-80% lipids (fat) and 20-30% protein. The cell body (soma) contains the neuron's nucleus (with DNA and typical nuclear organelles). Dendrites branch from the cell body and receive messages. A typical neuron has about 1,000 to 10,000 synapses (that is, it communicates with 1,000-10,000 other neurons, muscle cells, glands, etc.) [25]. The main types of neurons are:

  i. **Sensory neurons or bipolar neurons**: carry messages from the body's sense receptors (eyes, ears, etc.) to the CNS. These neurons have two processes. Sensory neuron account for 0.9% of all neurons. (Examples are retinal cells, olfactory epithelium cells) [25].

  ii. **Motoneurons or multipolar neurons**: carry signals from the CNS to the muscles and glands. These neurons have many processes originating from the cell body. Motoneurons account for 9% of all neurons. (Examples are spinal motor neurons, pyramidal neurons, Purkinje cells) [25].

  iii. **Interneurons or pseudopolare (Spelling) cells**: form all the neural wiring within the CNS. These have two axons (instead of an axon and a dendrite). One axon communicates with the spinal cord; one with either the skin or muscle. These neurons have two processes. (Examples are dorsal root ganglia cells) [25].
• **Glia:** commonly called neuroglia or simply glia (Greek for "glue"), are non-neuronal cells that maintain homeostasis from myelin and provide support and protection for the brain's neurons. In the human brain, there is roughly one glia for every neuron with a ratio of about two neurons for every three glia in the cerebral gray matter. Glias are commonly known as the glue of the nervous system; however, this is not fully accurate. The four main functions of glial cells are to surround neurons and hold them in place, to supply nutrients and oxygen to neurons, to insulate one neuron from another, and to destroy pathogens and remove dead neurons. They also modulate neurotransmission [26]. The main types of glia are:

i. **Microglia:** are like specialized macrophages capable of phagocytosis that protects neurons of the central nervous system. They are derived from hematopoietic precursors rather than ectodermal tissue; they are commonly categorized as such because of their supportive role to neurons. These cells comprise approximately 15% of the total cells of the central nervous system. They are found in all regions of the brain and spinal cord. Microglial cells are small relative to macroglial cells, with changing shapes and oblong nuclei. They are mobile within the brain and multiply when the brain is damaged. In the healthy central nervous system, microglia processes constantly sample all aspects of their environment (neurons, macroglia and blood vessels) [26].

ii. **Macroglia:**

→ **Astrocytes:** are located in central nervous system. The most abundant type of macroglial cell, astrocytes (also called astroglia) has numerous projections that anchor neurons to their blood supply. They regulate the external chemical environment of neurons by removing excess ions, notably potassium, and recycling neurotransmitters released during synaptic transmission. The current theory suggests that astrocytes may be the predominant "building blocks" of the blood-brain barrier. Astrocytes may regulate vasoconstriction and vasodilatation by producing substances such as arachidonic acid, whose metabolites are vasoactive. Astrocytes signal each other using calcium. Extracellular release of ATP, and consequent activation of purinergic receptors on other astrocytes, may also mediate calcium waves in some cases. In general, there are two types of astrocytes, protoplasmic and fibrous, similar in function but distinct in morphology and distribution. Protoplasmic astrocytes have short, thick, highly branched processes and are typically found in gray matter. Fibrous astrocytes have long, thin, less branched processes
and are more commonly found in white matter. It has recently been shown that astrocytes activity is linked to blood flow in the brain, and that this is what is actually being measured in fMRI [26].

- **Oligodendrocytes**: are located in central nervous system. Oligodendrocytes are cells that coat axons in the central nervous system (CNS) with their cell membrane forming a specialized membrane differentiation called myelin, producing the so-called myelin sheath. The myelin sheath provides insulation to the axon that allows electrical signals to propagate more efficiently [26].

- **Ependymal cells**: are located in central nervous system. Ependymal cells, also named ependymocytes, line the cavities of the CNS and make up the walls of the ventricles. These cells create and secrete cerebrospinal fluid (CSF) and beat their cilia to help circulate that CSF and make up the Blood-CSF barrier. They are also thought to act as neural stem cells [26].

- **Radial glia**: are located in central nervous system. Radial glia cells arise from neuroepithelial cells after the onset of neurogenesis. Their differentiation abilities are more restricted than those of neuroepithelial cells. In the developing nervous system, radial glia functions both as neuronal progenitors and as a scaffold upon which newborn neurons migrate. In the mature brain, the cerebellum and retina retain characteristic radial glial cells. In the cerebellum, these are Bergmann glia, which regulate synaptic plasticity. In the retina, the radial Müller cell is the principal glial cell, and participates in a bidirectional communication with neurons [26].

- **Schwann cells**: are located in peripheral nervous system. Similar in function to oligodendrocytes, Schwann cells provide myelination to axons in the peripheral nervous system (PNS). They also have phagocytotic activity and clear cellular debris that allows for regrowth of PNS neurons [26].
Satellite cells: are located in peripheral nervous system. Satellite glial cells are small cells that surround neurons in sensory, sympathetic and parasympathetic ganglia. These cells help regulate the external chemical environment. Like astrocytes, they are interconnected by gap junctions and respond to ATP by elevating intracellular concentration of calcium ions. They are highly sensitive to injury and inflammation, and appear to contribute to pathological states, such as chronic pain [26].

Enteric glial cells: are located in peripheral nervous system. Are found in the intrinsic ganglia of the digestive system. They are thought to have many roles in the enteric system, some related to homeostasis and muscular digestive processes [26].
2.3 Brain tumor basics.

2.3.1 What a brain tumor is and the basic categories.

A brain tumor is a mass of unnecessary cell growing in the brain. There are two basic kinds of brain tumors:

- **Primary brain tumors**, those start and tend to stay in the brain.
- **Metastatic brain tumors**, those begin as cancer elsewhere in the body and spreads to the brain.

When doctors describe brain tumors, they often use the words “benign” or “malignant”. Those descriptions refer to the degree of malignancy or aggressiveness of a brain tumor.

→ **Benign brain tumors**: a benign brain tumor consists of very slow growing cells, usually has distinct borders and rarely spreads. When viewed under a microscope the cells have an almost normal appearance. Surgery alone might be an effective treatment for this type of tumor. A brain tumor composed of benign cells, but located in a vital area, can be considered to be life threatening, although the tumor and its cells would not be classified as malignant.

→ **Malignant brain tumors**: are both primary and metastatic brain tumors [1].

A malignant brain tumor is usually rapid growing, invasive and life- threatening. Malignant brain tumors are often called brain cancer. However, since primary brain tumors rarely spread outside the brain and spinal cord, they do not exactly fit the general definition of cancer. Malignant brain tumors that are cancerous can spread to other parts of the body. They lack distinct borders due to their tendency to send “roots” into nearby normal tissue. They can also shed cells that travel to distant parts of the brain and spine by way of the cerebrospinal fluid. Some malignant tumors, however, do remain localized to a region of the brain or the spinal cord. Cancer cells that begin growing elsewhere in the body and then travel to the brain form metastatic brain tumors. For example, cancers of the lung, breast, colon and skin (melanoma), frequently spread to the brain via the bloodstream or a magnetic- like attraction to the other organs of the body [1].
2.3.2 Tumor grading.

Tumors are graded to facilitate communication, to plan treatment and to predict outcome. The grade of a tumor indicates its degree of malignancy. This grading is done by WHO (World Health Organization) [1].

Grade is assigned based on the tumor’s microscopic appearance using some or all of the following criteria:

- Similarity to normal cells.
- Rate of growth (mitotic index).
- Indications of uncontrolled growth.
- Dead tumor cells in the center of the tumor (necrosis).
- Potential for invasion and/or spread (infiltration) based on whether or not it has a definite margin (diffuse or focal).
- Blood supply (vascularity).

Using the WHO grading system:

→ **Grade I**: tumors are the least malignant and are usually associated with long-term survival. The tumors grow slowly and have an almost normal appearance when viewed through a microscope. Surgery alone might be an effective treatment for this grade of tumor.

→ **Grade II**: tumors are relatively slow growing and have a slightly abnormal microscopic appearance. Some can spread into nearby normal tissue and recur. Some of these tumors recur as a higher grade.

→ **Grade III**: tumors are, by definition, malignant although there is not always a sharp distinction between grade II and grade III tumor. The cells of a grade III tumor are actively reproducing abnormal cells which grow into brain tissue. These tumors tend to recur, often as a higher grade.

→ **Grade IV**: the most malignant tumors. They reproduce rapidly, can have a bizarre appearance when viewed under the microscope and easily grow into surrounding normal brain tissue. These tumors form new blood vessels so that they can maintain their rapid growth. They also have areas of dead cells in their center. The glioblastoma multiforme is the most common example of a grade IV tumor [1].

Tumors often contain several grades of cells. The highest or most malignant grade of cells determines the grade, even if most of the tumor is a lower grade. Some tumors undergo change. A benign growth might become malignant. In some tumors, a lower-grade tumor might recur as a higher-grade tumor [1].
2.4 Glioblastoma multiforme (GBM).

2.4.1 General information about GBM.

Figure 2.4: Glioblastoma Multiforme in 59-year old male [13].

“Glioblastoma”, “Glioblastoma multiforme”, “Grade IV astrocytoma” and “GBM” are all names for the same tumor. Glioblastomas arise from astrocytes, which are star-shaped cells supporting the other cells in the brain [2]. Any tumor that arises from the glial or supportive tissue of the brain is called a “glioma”. One type of glioma is the astrocytoma. Astrocytomas are named after astrocytes, the star shaped cells from which they grow. Grade IV astrocytoma is glioblastoma [3]. These are infiltrating tumors located in the deep white matter or in the deep gray matter neighboring white matter, mainly in cerebral hemispheres [4]. These tumors represent about 20% of all primary brain tumors and about 50% of the gliomas. They are more common in older adults and affect more men than women. Only nine percent of childhood brain tumors are glioblastomas [2].

Glioblastomas are generally found in the cerebral hemispheres of the brain, but can be found anywhere in the brain or spinal cord. Because glioblastomas can grow rapidly, the most common symptoms are usually due to increased pressure in the brain and can include headache, nausea, vomiting and drowsiness. Depending on the location of the tumor, patients can develop a variety
of other symptoms. Such as weakness or sensory impairment on one side of the body, seizures, memory of language impairment and visual changes [2].

Glioblastomas may arise from a lower grade astrocytoma (grade II or III) or start as a grade IV tumor. Regardless of their origin, all glioblastomas are grade IV tumors because they have several features of rapidly growing tumors, abnormal and numerous blood vessels, as well as dead tissue called necrosis. Since these tumors arise from normal brain they easily intermingle with the normal brain tissue as well as invade and migrate away from the main tumor. However, glioblastoma will rarely spread elsewhere in the body. In addition, several clusters of cells may be resistant to radiation and chemotherapy. All of these factors make these tumors a challenge to treat [2].

Many differentiating characteristics from diffuse astrocytomas are prominent microvascular proliferation, tumor necrosis, increased mitotic activity and more cellular and nuclear pleomorphism. Giant-cell variant of GBM constitutes 5% of all GBMs. It has multinuclear and amorphous cellular structure. Its differentiating properties are its firmness due to excessive stroma formation and well definition. GBMs located in the posterior fossa may cause diverse cerebellar symptoms like headache, gait disturbances, ataxia, nausea and vomiting. These findings can suggest the existence of a mass lesion in the posterior fossa. However, none of these are specific for GBM [4].

2.4.2 Cause of glioblastomas (molecular genetics mainly).

The cause of these tumors, as well as, other types of brain tumors is unknown. Scientists have identified abnormalities on chromosomes 10 and 17 which may play a role in the development of these tumors. However, what causes those abnormalities is still uncertain. Scientists are conducting, occupational and familial, generic research to identify common links among patients [3].

Several genetic disorders are associated with increased incidence of gliomas (for example tuberous sclerosis, neurofibromatosis type I and II, Turcot Syndrome, Li-Fraumeni Syndrome. An association exists between ionizing radiation and astrocytomas. Children who receive low dose intracranial radiation have a 2 to 6 fold increase in prevalence of astrocytomas and prophylactic whole-brain radiation therapy in patients with acute lymphocytic leukemia increased the incidence of astrocytomas 22 fold [21].

Other suspected risk factors, such as electromagnetic radiation and cellular telephone use, are yet to be substantiated by large epidemiologic studies. However, researchers reviewed 16
published studies that looked at cell phone use and the risk of brain cancers are concluded that using cell phones for more than 10 years gives a consistent pattern of increased risk of at least 2 types of brain cancer, such as acoustic neuroma and gliomas. The risk is significantly higher for the ipsilateral exposure (tumor on the same side of the brain as cell phone exposure) [21].

Glioblastoma Multiforme (GBM) exceeds in its occurrence and mortality beyond any other brain tumor in adults. On the molecular level, human brain tumors manifest a complex interplay of multiple, nonrandom genetic events that encompass activation of proto-oncogenes and inactivation of tumor suppressor genes, which in turn leads to aberrant expression of growth factor receptors and their ligands. Genetically glioblastomas display loses in parts of chromosomes 6, 9, 10, 13, 17, 19 and 22 as well as gains or amplifications of chromosomes 1, 5, 7, 8, 11 and 22. Mutations of tumor suppressor genes such as CDKN2, PTEN/MNAC1, DMBT1 and TP53 as well as overexpression of EGFR, N-myc, PDGFR, MDM2 and gli have also been identified [14].

Two discrete subsets of glioblastomas derived from astrocytic lineage have been recognized on the basis of the chemical and genetic makeup of the tumor. In the following table 2.1 we can see clinical and genetic differences between primary and secondary Glioblastoma Multiforme of Astrocytic Lineage.

<table>
<thead>
<tr>
<th>Clinical History</th>
<th>Primary GBM de novo &lt;2 months</th>
<th>Secondary GBM &lt;4.5 yrs from LGA</th>
<th>Secondary GBM ~2 yrs from AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ratio (M:F)</td>
<td>1.4</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Mean age at diagnosis (yrs)</td>
<td>55</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>TP53 mutation</td>
<td>10%</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>EGFR amplification</td>
<td>40%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>MDM2 amplification</td>
<td>5%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>p16 deletion</td>
<td>35%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>PTEN mutation</td>
<td>30%</td>
<td>5%</td>
<td></td>
</tr>
</tbody>
</table>

Table 2.1: Clinical and genetic differences of GBM [14]

Primary or de novo, type occurs most commonly in elderly patients. The glioblastoma cells are often small undifferentiated, showing a high proliferative index. They exhibit overexpression (in approximately 80% of cases) or amplification (in 40% of cases) of the EGFR gene, which is located on the short arm of chromosome 7. Other genetic alterations include over expression of the MDM2 (murine double minute 2) gene, loss of P16 and mutation of PTEN (phosphate and tensin homology deleted) from chromosome 10 and retinoblastoma (Rb) genes on chromosomes 12, 9, 10 and 13, respectively. Deletions in primary GBMs usually involve the CDKN2/p16 gene and three mutations have been described in primary GBMs with allelic loss of chromosome 9p. Homozygous deletion of the CDKN2 genes has been shown to be associated with EGFR amplification and higher proliferative indices [14].
Close association of EGFR amplification and CDKN2 deletions, occurring primarily in elderly patients with primary glioblastomas without a TP53 mutation, may contribute to the worse prognosis of elderly GBM patients. PTEN alteration is also more common in primary glioblastomas and is found in 30%-40% of astrocytomas with chromosomes loss. The pattern of genetic alterations in pediatric glioblastomas is distinct from that of adult GBMs: Kraus et al found no CDKN2A deletions and no amplification of EGFR, CDK4, or MDM2 proto-oncogenes in a recent study. Overall, these alterations occur randomly and nonsequentially and thus no genetic history can be constructed for patients with de novo tumors.

The secondary type, on the other hand, afflicts a younger population that shows histologic progression from a previously known low-grade astrocytoma. Numerous genetic alterations accumulate and become linked together sequentially to parallel malignant progression. Inactivation of TP53 gene and overexpression of PDGF ligands and receptors play a crucial role in the initial steps of the evolution. The subsequent loss of chromosomes 1, 9p, 13q and 19q is considered to be major events in tumor progression. Finally the transition from anaplastic astrocytoma to secondary glioblastoma requires loss of chromosome 10q, where the PTEN gene resides, although this event does not occur as frequently as in the primary glioblastoma [14].

Another form of GBM, as illustrated in figure 2.4, arise from pre-existing oligodendroglioma in response to losses of chromosomes 1p and 19q initially, followed by inactivation of PTEN/MMAC1 and p16/CDKN2A and amplification of the EGFR gene. Most cases belong to the de novo type and the alterations in genes between the groups appear to be mutually exclusive, especially with respect to Rb, EGFR, TP53 and chromosome 19q. Prognostic values for GBM based on genetic markers have received mixed opinions. Some studies have established a poor prognosis associated with overexpression of EGFR oncogenes and improved outcome in relation to TP53 inactivation, whereas others could not substantiate the results. Previously, only age and histologic grade have generally been considered to be independent predictors of survival, but recent results suggest that loss of heterozygosity in 9p and p16 deletions may prove to be objective molecular standards for the diagnosis of high grade gliomas. Poorer survival was also associated with either the deletion of p16 or the loss of heterozygosity in 9p or 10q; however, the absence of these markers was nonprognostic. PTEN and p53 mutations have been associated with reduced and prolonged survival, respectively. In several studies, detection of EGFR expression and amplification has been linked to higher Ki-67 labeling indexes and decreased survival in patients with glioblastoma. In a study by Kraus et al, two comparable groups of GBM patients (all with de novo GBM, age-and gender- matched) but with different clinical outcome showed no impact of EGFR, PTEN, TP53 and CDNK2A tumor suppressor genes on their overall survival.

It appears, however, that of an accurate prognosis to be established, the functional status of specific genetic markers in question must interface with a subgroup of patients according to their age and certain other parameters. A better understanding of the classification of genes is thus crucial for this purpose [14].
Figure 2.5: Tumorigenesis in Glioblastoma Multiforme [14].
2.4.3 Histological components of a GBM.

The starting point of any discussion of GBMs is a clear understanding of their histological anatomy. In the past decade, there has been a significant increase in our knowledge of the molecular biology of these tumors, including how they arise from astrocytic tumor cells or their precursors. More important for surgical management, however, is the fact that GBMs have clearly defined histological components.

Many times, the GBMs are described according to pathological analyses of serial stereotactic biopsies taken from MR imaging-defined areas within GBMs as we can see in the below figure 2.6. They found that there are three contiguous regions of a GBM:

- The contrast-enhancing portion on T1-weighted MR images that corresponds to the tumor cell mass without intervening brain parenchyma.
- The hypointense area found in the center of the enhancing mass in many but not all GBMs that represents necrotic tumor cells.
- Areas of increased signal (hypertensity) on T2-weighed MR images surrounding the contrast enhancing region which represent isolated tumor cell infiltration into the brain parenchyma.

On T1-weighed images these latter areas appear as nonenhancing hypointense regions. The density of infiltrating cells may vary in these areas from nearly all tumor cells to rare scattered cells with a predominance of edema. This anatomy is important to surgical discussions of GBM because surgical resections are typically aimed at removing the enhancing portion of the tumor (along with its area of central necrosis, if present). This means that all resections of GBMs leave behind nonenhancing infiltrative tumor cells that reside away from the primary tumor mass.
Figure 2.6: The histological anatomy of a GBM [14].
Chapter 3

“Intraoperative Neurosurgical Ultrasound”

3.1 Introduction

Intracranial localization is a major challenge in neurosurgery and a precise sense of complex three-dimensional anatomic relationships has to be maintained in order to successfully perform any operation. The art of surgical navigation has traditionally been taught in such a way that specific landmarks had to be identified that could then be used as touchstones during operations. Venturing deeper into subcortical parenchyma has demanded from the neurosurgeon distinctive skill, judgment, experience and apprenticeship. Modern mainly computer-based technology should be introduced into the operating room in order to assure the best neurosurgical intervention possible for the patients entrusted to our treatment. Different approaches have been chosen to define neuronavigator systems that are supposed to be universal, intuitive, accurate and robust and allow the surgeon to register different medical images one to another and to the physical space of the patient’s head. Their aim is to help surgeons to use multimodality data in a rational and quantitative way for purposes of surgical localization. This aim does not serve as an end in itself but it is supposed to aid to improve the quality of the intervention to the benefit of the patient. Thus it should result in:

- making it easy to simulate and plan a part of the intervention,
- increasing the accuracy of the approach thus making it less invasive and more safe,
- decreasing the intervention length (at the price of a potentially longer and more rigorous preparation),
- the possibility to consider new interventions which were unrealizable up to now, and
- the possibility to validate a protocol for therapeutic approach, as the employed computers allow precise recording of the preoperatively chosen strategies and comparison with the obtained clinical results.

Surgical intervention remains the mainstay of diagnostic and therapeutic management of primary brain tumors. It provides the means of obtaining at least a biopsy sample for pathological assessment of tumor type and grade, of achieving effective cytoreduction and of guiding focused brachytherapy or radiosurgery. The challenges presented to the neurosurgeon especially by glial neoplasms include their often deep-seated location within ‘eloquent’ parenchyma, their irregularly shaped outlines, and their ill-defined margins due to parenchymal invasion. Throughout the text, the reader should keep in mind that interactive image-guided neurosurgery systems are only surgical tools, not substitutes for surgeons’ knowledge or expertise and that they cannot solve basic problems that are due to the nature of the treated tumors [28].
For the management of patients with suspected or confirmed intracranial tumors imaging of the brain is often indicated at different stages and usually has a significant role in each of them. Several stages of management may be considered although they are in practice often integrated:

- Detection or confirmation that a structural abnormality is present
- Localization and assessment of the extent of any abnormality
- Characterization of the abnormality: distinction of neoplasms from non neoplastic processes
- Assessment of the nature of any tumor
- Facilitation of additional diagnostic procedures, and planning for surgery or other types of therapy
- Intraoperative control of resection progress
- Monitoring of response to therapy

Computerized tomography is a good screening method for the demonstration of supratentorial abnormalities, because it is accurate and the imaging method most often available. It is still considered as the basic radiologic study since it gives sufficiently specific information for the management of brain tumors and is only minimally invasive. If it comes to surgery most often additional MR imaging sequences are acquired for its superior anatomical distinction.

Several criteria are important for the differential diagnosis of brain tumors:

- Signal contrast with normal brain
- Tumor structure
- Tumor margins
- Presence, absence, and extent of perifocal edema
- Indirect tumor signs
- Relation of tumor to blood vessels, richness of tumor blood supply
- Degree of contrast enhancement

Tables 3.1a, b, c summarize the advantages, capabilities and limitations of CT, MR imaging (MRI) and intraoperative ultrasonography (IOUS).
Table 3.1a [28]

<table>
<thead>
<tr>
<th>Advantages and capabilities</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CT</strong></td>
<td></td>
</tr>
<tr>
<td>- shorter imaging time than MRI</td>
<td>- imaging of posterior fossa lesions is limited due to bone artifacts</td>
</tr>
<tr>
<td>- lower costs than MRI</td>
<td>- poor definition of the extent of edema</td>
</tr>
<tr>
<td>- good definition of extra-axial brain tumors</td>
<td>- acquisition of only one plane</td>
</tr>
<tr>
<td>- (acoustic neuromas, meningioma)</td>
<td>- need for the calculation of reconstructions</td>
</tr>
<tr>
<td>- better anatomical resolution than IOUS</td>
<td>- intraoperative usage possible only at a few university centers</td>
</tr>
<tr>
<td>- superior in depicting the presence of calcification and bone abnormalities</td>
<td>- risks associated to the use of x-ray radiation</td>
</tr>
<tr>
<td>→ destruction, erosion, penetration, hyperostosis</td>
<td>- poor neuroanatomical definition compared to MRI</td>
</tr>
</tbody>
</table>

Table 3.1 b [28]

<table>
<thead>
<tr>
<th>Advantages and capabilities</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MRI</strong></td>
<td></td>
</tr>
<tr>
<td>- higher sensitivity in the demonstration of edema compared to CT</td>
<td>- no signal return from calcification</td>
</tr>
<tr>
<td>→ earlier detection of tumors</td>
<td>- differentiation between tumor and surrounding edema is often not possible</td>
</tr>
<tr>
<td>- more accurate definition of the extent of surrounding edema</td>
<td>- only pre- and postoperative imaging (intraoperative imaging is at the stage of a clinical trial)</td>
</tr>
<tr>
<td>- better detection of mass effects and atrophy</td>
<td>- restricted availability</td>
</tr>
<tr>
<td>- high neuroanatomical definition</td>
<td>- lower spatial fidelity than in CT images</td>
</tr>
<tr>
<td>→ best identification of brain stem structures</td>
<td></td>
</tr>
<tr>
<td>- superior depiction of anatomical relationship</td>
<td></td>
</tr>
<tr>
<td>→ more accurate distinction between a vascular structure and adjacent parenchymal bone artifacts</td>
<td></td>
</tr>
<tr>
<td>- ease of imaging in any plane</td>
<td></td>
</tr>
<tr>
<td>- direct visualization of different planes</td>
<td></td>
</tr>
<tr>
<td>→ more accurate description of shape</td>
<td></td>
</tr>
<tr>
<td>- possibility of obtaining high resolution data sets within a reasonable amount of time</td>
<td></td>
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</tbody>
</table>
The generally purpose is to show which possibilities exist nowadays to exploit the information being inherent to the three-dimensional volumetric data sets to the benefit of the surgeon and, therefore, to the benefit of the patient he or she is operating on. The principle of interactive image-guided neurosurgery is to keep the imaging data as long as possible in its original digital format by transferring it to a computer workstation dedicated to the operating room and allowing a direct interaction with the data. With the help of the computer and an intraoperative position sensing system reconstructed images can be presented allowing for accurate, dynamic, interactive, three-dimensional localization of surgical targets and trajectories. Computer-interactive surgery, as this field is also sometimes called, pursues the idea of real-time visualization of the preoperative imaging data, on the one hand creating the possibility to see just what is relevant to the actual operating situation at a viewing distance of the operating site but, on the other hand, minimizing the interference with the procedure itself [28].

Glioblastoma Multiforme (GBM), the most common and aggressive adult brain tumor, is characterized by pleomorphic, highly mitotic and widely invasive tumor cells whose treatment by necessity includes surgery, radiation therapy and chemotherapy. Although surgery is usually the initial intervention, the choice of aggressively resecting GBMs- rather than performing biopsy or limited subtotal resections-has been one of the most controversial debates among neurosurgical oncologists. Whereas in other areas of oncology, surgery aims at complete tumor extirpation along with wide margins of normal tissue, the invasive nature of GBMs virtually precludes obtaining a margin of normal brain around the primary tumor mass. Because even the most aggressive resections leave tumor cells, many surgeons pot against anything more than a biopsy, whereas other neurosurgeons advocate radical removals to minimize tumor burden. Although this controversy could be settled by a randomized trial, such a trial is probably not possible. Nevertheless, in the last decade there has been an increasing awareness among neurosurgeons regarding the value of aggressively resecting GBMs not only for cytoreduction, but also for symptom control and accurate diagnosis. This changing perspective has been due, at least in part, to recent studies demonstrating the value of aggressive surgery in diagnosis and on
patient survival and to the implementation of image-guided surgical techniques and functional brain mapping, both of which have made radical resections safer and more feasible [14].

The main and great challenge is to provide more accurate perspective on the surgical management of GBMs. Because a clear understanding of the cellular components of a GBM is critical to understanding surgical management, the stage that must be firstly reviewed is the histological anatomy of GBMs and then describe the goals of surgery, including a rationale for aggressive surgical resection based on experience with GBMs at a large cancer center and review the modern surgical techniques used to safely accomplish these goals [14].

3.2 History of intraoperative brain ultrasound

![Intraoperative Ultrasound](image)

Figure 3.1: Intraoperative Ultrasound [15].

The first experiments to exam brain tissue specimens were performed in 1947 by Dussik et al. and in 1950 French et al. successfully localized brain tumors using a one-dimensional A-mode transducer with 15 MHz. They found that the texture of neoplastic cerebral tissue is such that the ultrasonic response is approximately twice that of normal cerebral tissue. In post mortem investigations they were able to locate with ultrasonography subcortical cerebral neoplasms, and in animal experiments they showed that the pulsed ultrasonic vibrations from their transducer did not produce demonstrable damage in the animal brains. Neurosurgeon William Peyton used the ultrasound transducer for the first time in 1951 in brain surgery to localize a parietal
glioblastoma. In 1963, two-dimensional B-mode ultrasonography which gives the intensity of the returning echo by the brightness of the pixel became available facilitating the use of this imaging modality and providing better information about ventricular size and intracranial relationships. Kurze et al. reviewed in 1965 the early history of ultrasound use in neurosurgery. They also reported on 159 cases of their own stating that its use was rapid and harmless with immediate and reproducible results. Hill gave in 1973 a more complete overview on the history of ‘medical ultrasonics’ emphasizing that although ultrasonography it may be fairer to judge it as a slow developer with promise of considerable talent.’

The next major advance was the advent of real-time B-mode sector scanning. The first preliminary reports on intraoperative use of this technique appeared in the beginning of the 1980’s almost simultaneously from three different research groups). The real-time B-mode provided better images than were available before, and it substantially contributed to the operation of subcortical lesions essentially simplifying the localization process and allowing image-guided biopsy. Chandler et al. reported two years later, in 1982, on 21 neurosurgical procedures employing intraoperative real-time ultrasonography. In their opinion, the technique proved to be extremely useful in localizing small subcortical neoplasms, as well as delineating solid and cystic portions of deep lesions. They claimed that they were able to clearly identify and localize the pathology in every case. Additionally, they thought the ultrasonography to be very useful for finding the shortest route of access to the tumor. This reduced unnecessary surgical dissection as stressed by Knake et al. [28].

To overcome the shortcomings of two-dimensionality and to improve lateral resolution, already in the early 1980s, Koivukangas and co-workers studied methods of ultrasound holographic imaging (UHB). The presented method allowed acquiring better images especially from curved or rounded structures that were difficult to obtain with the usual real-time B-mode scanners because of deflection at an oblique angle. Later, the UHB system was used to acquire three-dimensional volume images. At the same time, the Oulu clinic was among the first to implement real time B imaging intraoperatively. Furthermore, different approaches for the interaction with the three-dimensional data were tested: a) a stereopair technique where a computer program produced a pair of complex images which were typically rotated five or six degrees with respect to each other producing the stereo optic effect useful in the study of internal structures, b) projection graphics allowing to envision the outline e.g. of a tumor and some selected details of the surrounding structures being a valuable tool for the neurosurgeon during the operation, and c) the vibrating mirror method where a computer displayed rapidly in sequence adjacent parallel sections of ultrasound-tomograms in virtual image space behind a synchronously vibrating mirror allowing the observer to interact in real-time and on-line with the display employing a three-dimensional pointer to selectively identify, enhance, remove and/or measure features of interest in the displayed volume.

Another approach to achieve three-dimensional images with a B-mode scanner was presented by Trobaugh et al. who affixed light-emitting diodes to the ultrasound probe for tracking its position. With a three-dimensional rendering algorithm they were able to create near real-time
three-dimensional volumes. They applied their technique in neurosurgery for the comparison to oblique preoperative CT/MR images to assess

Kumar et al. reported in 1993 on a prospective clinical study including inter alia 40 supratentorial gliomas. They found the ultrasonography to be extremely helpful in quickly and easily locating a small, deep seated supratentorial lesion while it did not significantly add to operating time. As further advantage they mentioned in accord with earlier reports that the learning curve with the use of the instrument was short [28].

### 3.3 Why we use intraoperative ultrasound

**Generally description mainly use for localization and biopsy**

![Image of ultrasound](image)

**Figure 3.2:** Use of intraoperative ultrasound for localization [15].

Safe and effective resection of GBM involves correct positioning of the craniotomy and accurate identification of the contrast enhancing portion of the lesion and the corresponding sulci. Various surgical adjuncts are available to improve the surgeon’s ability to localize and identify the tumor intraoperatively, it provides a method for visualizing tumors below the surface of the brain including high-resolution intraoperative ultrasound; image guided frameless stereotaxis and intraoperative CT or MR imaging [14], [10]. Localization and characterization of intracranial masses during an operation are major problems for neurosurgeons. The brain is a
solid object so the neurosurgeon must either cut into it or to retract it to visualize masses within or under the brain. We use intraoperative ultrasonography to determine to image the abnormalities and their extension during operations [5].

With ultrasound a lesion can easily be seen and its position precisely verified intraoperatively. Biopsy probes can be attached to a sector scanner and the position of the probes relative to the patient is under the control of operator, unencumbered by a rigid frame. Ultrasound sector scanners are generally portable and can easily function in an operating room [7]. The ability to locate precisely a deeply situated intracranial lesion intraoperatively can reduce the risk of damage to normal tissue, assist in determining the extent of tumor resection and reduce the time of surgery. Intraoperative ultrasound holds great promise. Deep intracranial neoplasms may produce no visible changes on the brain surface to help the surgeon localize a tumor at the time of operation. Intraoperative ultrasound provides a unique, nonradiative, safe way to image beneath the brain surface to determine the depth of the lesion, characterize it as complex, fluid-filled or solid and delineate the relationship of the intracranial mass to the adjacent anatomic structures. This increased surgical precision promoted the efficiency of the surgical procedure and shortened the intraoperative time [8]. It is important the fact to predict intraoperatively the pathological nature of the lesions [13]. The borders of malignant tumors have features different from those of benign tumors and they can be easily detected by ultrasonography [14].

The unit is portable, self-contained device with a viewing monitor connected to a sector scanner. Adjustments in intensity and frequency allow for alterations in image quality and depth of penetration [14]. The ultrasound transducer can be put into practice repeatedly at different stages of the operation to determine whether or not further tumor remains after initial resection and if so its site, size and accessibility. Furthermore, intraoperative ultrasonography allows for detection of intraoperative brain and/or tumor shift resulting from cerebrospinal fluid drainage and from decompression of the tumor area. Another approach to achieve removal of tumor tissue to a considerable extent was the volumetric resection method for subcortical lesions presented by Kelly et al. . . . He used a CT-based stereotactic system — introduced in a later section — placing stainless steel reference balls at 5 mm intervals through the tumor along the surgical viewline providing a means of detecting subsequent intracranial shifts on lateral teleradiographs. Koivukangas and Kelly reported in 1986 on the first application of intraoperative ultrasound imaging to the stereotactic removal of subcortical brain tumors, thus, combining the Kelly system for stereotactic computer-assisted laser resection of intra-axial brain neoplasms with ultrasonography. The ultrasound transducer was mounted on a stereotactic frame as pioneered by Backlund et al. in 1975 with an A-scan and Heilbrun et al. in 1983 with a real-time B-scan for stereotactic tumor biopsy. Applying a successive scanning procedure that defined a box-shaped stereotactic volume all points in space was assigned Cartesian coordinates. The result was ultrasound-guided stereotactic surgery. The chief benefits of this combination were the supplementary data on the tumor itself offered by the ultrasonography, and the possibility of real-time imaging to follow the effects of tumor removal at successive stages of the procedure.
In 1990, Koivukangas and Louhisalmi reported on a further development of their three-dimensional ultrasound-guided stereotactic approach to malignant gliomas. They fed the three-dimensional stack of two-dimensional real-time B-mode ultrasound images into a computer, outlined the tumor with a computer-mouse and programmed a computer-driven laser to perform layer-by-layer resection of the tumor. The neurosurgeon only visually controlled the movement of the laser beam and interacted with the surgical field with suction-irrigation and hemostasis maneuvers. Already in the same report they indicated that they were devising a neuronavigator to replace the stereotactic frame.

The intraoperative localization of intracranial anatomical structures and pathological processes and of a minimally invasive navigational approach to the lesion with the aid of the neuronavigation system and simultaneous intraoperative ultrasonography were the main goals pursued by the introduction of the Leksell Index System into brain tumor surgery. According to the plan a skin incision and a craniotomy were created taking care that during the process of drilling holes into the skull and completion of the craniotomy the head did not slip within the Mayfield head holder. The system was completed by carefully positioning the sterilized adapter piece on the end segment of the neuronavigator arm so that sterility was preserved. Thereafter, the five different end instruments could be interchanged freely, with the navigator itself recognizing each through magnetic detectors. After the instrument exchange the computer always required a prompt for approval. Communication with the workstation was possible by the use of a foot pedal and two push-buttons on the arm, thus there was no need to use the computer mouse or even the keyboard. New landmarks could be established as reference points, e.g. around the site of craniotomy, allowing to monitor whether accuracy was sustained, a feature that was not used very often. Before the opening of the dura the ultrasound transducer was used to identify anatomical landmarks and confirm the accuracy of the system in all cases. For thorough comparison to the reformatted MR images both images were frozen and for the purpose of documentation snapshots of the computer screen and Polaroid images of the ultrasound image could be taken. After opening the dura the gyri and sulci could be identified and a sulcal, microsurgical approach even to very small lesions could be chosen avoiding unnecessary dissection of brain tissue. At this stage, usually the end instrument was the suction tip, thus the neuronavigator did not introduce any extra instrument into the surgical field. During the resection of the lesion the suction could be used as a pointer to identify the ‘tumor margins’. Intraoperative ultrasonography was applied from time to time to assure that the preoperative imaging data was still valid or to establish a new correlation between reality and image space and for multimodality information. As coupling agent sterile saline was employed. Finally, before closure of the dura completeness of resection was checked on ultrasound images [28].

Although the principal function of intraoperative ultrasound is localization and characterization of lesions, it also provides a precise means of placing a needle within a lesion for biopsy or aspiration. An accurate and reliable needle a guide is commercially available (Advanced Technology Laboratories, Bothel, Washington, USA) and keeps the biopsy needle within the plane of the ultrasound image. The depth of the desired guide is then preset such that the exact point will be reached. The approach of the needle, the aspiration and the post-needle removal is all monitored in real-time so that if the lesion is pushed aside by the needle or if
bleeding occurs, this can be easily recognized. Virtually any region of the cerebrum, cerebellum or brainstem can be accurately biopsied with this technique. With few exceptions, we have used intraoperative ultrasound via a craniotomy rather than a trephine. Although imaging through a trephine is adequate, it does not allow room for simultaneous passage of the biopsy [27].

Figure 3.3: Biopsy of a high-grade astrocytoma (GBM) [27].

Since the margins and internal characteristics of tumors can be identified during surgery, biopsy procedures or resections can be tailored to each case. Multiple biopsy passes can be made to sample all parts of a tumor. An entire core biopsy is also possible to perform using this technique. Biopsy specimens can be obtained with a minimum of trauma to the brain. Sometimes for the biopsy are required to sample multiple areas of the lesions. The biopsies are performed usually with a Dorsey Cannula (3.5 mm diameter hollow tube containing a stylet). When the stylet was removed and the cannula was advanced, a sample care of tissue was obtained through the entire lesion [5].

Ultrasound is relatively inexpensive and easy to implement and allows identification of tumor location and biopsy. The ultrasound can be helpful for assessing intraoperatively the extent of tumor resection; total resection of the echogenic mass seen by ultrasound generally corresponds to resection of the enhancing mass seen on MR imaging [14]. Also, this method provides an additional measure of safety to the patient [27]. It is obviously a useful adjunct during neurosurgical operations [5]. Compared to other methods of localization, ultrasound has the advantage of imaging in real time. Changes in the tumor and shifts in the surrounding brain can be examined as the resection proceeds [14]. In certain cases, ultrasonography allow to the neurosurgeons to obtain additional valuable information during the operation. Also it allows evaluating the operative field at the time of operation. This gives him better access and hence improves the safety and thoroughness of the procedure [5].
3.4 Procedure

3.4.1 Application

- Incision and coupling

Ultrasound examinations of the brain have largely been restricted to infants and young children. In adults the bony calvarium acts as a severe obstacle to ultrasound transmission but once the bone has been removed, the underlying brain can easily be scanned [7]. Since ultrasound does not propagate efficiently in air the space between the surface of the transducer and the brain must be filled with acoustic medium. Different techniques were applied as long as the transducers could not withstand sterilization. Nowadays, physiological saline solution is added between the surface of the brain and the transducer or the surgical defect is filled with it to establish the acoustic coupling. The data were acquired after craniotomy, but before opening the dura mater [28]. Imaging is accomplished with equal clarity either through the dura or directly on the brain surface [27]. The US probe, covered by a sterile condom, was gently positioned at the dura mater, using sterile gel to ensure a good acoustic coupling with minimal applied force. Thus, the probe positioning did not cause any significant deformation of the dura mater. When a satisfying cross-sectional image of the tumor was obtained, the probe was kept in a fixed position during data acquisition [15].

The doubly draped scanhead is then usually applied directly to the surface of the dura matter for scanning. According to the occasion a special water path is created in order to evaluate the near path. The skull is filled with sterile saline. The tip of the scanhead is placed into the saline providing a water path. The water path every time is constructed with different ways. It is constructed generally by attaching an adhesive Steri-Drape to the perimeter of the craniotomy site. The drape contained a central hole that was approximately the size of the craniotomy. Around this hole, there was adhesive material on the surface of the drape. The drape can therefore be attached to the perimeter of the craniotomy while the edges of the drape, which contain no adhesive, can be lifted away from the skull. A through was filled with saline and the tip of the scanhead was dipped into the fluid. There is some leakage around the base of the drape, making repeated filling of the cavity necessary but we are able to visualize the surface of the brain easily using this technique [5], [6], [7].
• Navigation systems

With more modern methods of application the intraoperative localization of intracranial anatomical structures and pathological processes and of a minimally invasive navigational approach to the lesion with the aid of the neuronavigation system and simultaneous intraoperative ultrasonography were the main goals pursued by the introduction of the Leksell Index System into brain tumor surgery. The surgeon held the probe by hand or the pre-mentioned system, supported at the wrist to minimize artificial probe movements. The data were subsequently transferred to a computer for off-line processing. According to the plan a skin incision and a craniotomy were created taking care that during the process of drilling holes into the skull and completion of the craniotomy the head did not slip within the Mayfield head holder. The system was completed by carefully positioning the sterilized adapter piece on the end segment of the neuronavigator arm so that sterility was preserved. Thereafter, the five different end instruments could be interchanged freely, with the navigator itself recognizing each through magnetic detectors. After the instrument exchange the computer always required a prompt for approval. Communication with the workstation was possible by the use of a foot pedal and two push-buttons on the arm, thus there was no need to use the computer mouse or even the keyboard. New landmarks could be established as reference points, e.g. around the site of craniotomy, allowing to monitor whether accuracy was sustained, a feature that was not used very often. Before the opening of the dura the ultrasound transducer was used to identify anatomical landmarks and confirm the accuracy of the system in all cases. For thorough comparison to the reformatted MR images both images were frozen and for the purpose of documentation snapshots of the computer screen and Polaroid images of the ultrasound image could be taken. After opening the dura the gyri and sulci could be identified and a sulcal, microsurgical approach even to very small lesions could be chosen avoiding unnecessary dissection of brain tissue. At this stage, usually the end instrument was the suction tip, thus the neuronavigator did not introduce any extra instrument into the surgical field. During the resection of the lesion the suction could be used as a pointer to identify the ‘tumor margins’. Intraoperative ultrasonography was applied from time to time to assure that the preoperative imaging data was still valid or to establish a new correlation between reality and image space and for multimodality information. As coupling agent sterile saline was employed. Finally, before closure of the dura completeness of resection was checked on ultrasound images [28]. In the following figure 3.1 we can see intraoperative use of the Leksell Index System combined with intraoperative use of ultrasonography to give time multimodality imaging.
Sterilization

It is of course, an absolute requirement that the equipment used for intraoperative scanning maintain a high level of sterilization at all times. In the most optimal circumstances, the probes themselves are sterilized prior to the examination. In the past, we have successfully used gas sterilization with ethylene oxide for some of the intraoperative probes, but many manufacturers do not support this type of gas sterilization, fearing that the high temperatures during the aeration process might damage the transducer skin. This wasn’t found to be a problem over many years of use, but there are other problems with ethylene oxide gas sterilization, including a 24-hour turnaround time due to the prolonged aeration cycle. Currently, is used a gas-plasma sterilization technology, the Sterad system, which utilizes low temperature sterilization and is more environmentally acceptable. This still requires a prolonged turnaround time of several hours [34]. Obviously, rapid sterilization using an autoclave is not feasible for this sensitive electronic equipment. Some institutions will allow prolonged immersion in glutaraldehyde, but this is not deemed sufficiently effective sterilization for internal intraoperative use at our institution. There are also environmental issues with glutaraldehyde fumes and there have been some reported adverse patient reactions to contact with glutaraldehyde, if it has not been sufficiently rinsed off prior to the scans. Sterile probe covers are probably the simplest means of achieving adequate sterilization for intraoperative use. Both the transducer itself and the transducer cord must be covered in sterile sheaths. Optimally, one should use a sheath specifically designed to fit snugly over the probe in use.
Some of these have long extensions to cover the transducer cord, but if not, standard endoscopic sheaths can also be utilized for this purpose in combination with the transducer probe sheath [34]. Applying the sterile sheath and cord covers takes an additional one to two minutes of OR time in order to maintain meticulous sterile technique while covering the probes with these sheaths. Acoustic coupling must be applied to the transducer while covering the probes with these sheaths. Acoustic coupling must be applied to the transducer prior to insertion into the sheath, using either sterile gel or sterile fluid. If sterile probe covers are used as the principal means of protection, it is necessary to soak the probes in some sterilizing solution, such as glutaraldehyde or bleach. For 30 minutes prior to the intraoperative scan. The specific solutions must be cleared with the manufacturer of the equipment in order to avoid damage to the ultrasound probes [34]. Different techniques were applied as long as the transducers could not withstand sterilization [28]. The surgeon held the probe by hand or the pre-mentioned system, supported at the wrist to minimize artificial probe movements. The data were subsequently transferred to a computer for off-line processing.

- **Data acquiring**

  The data were acquired after craniotomy, but before opening the dura mater. The US probe, covered by a sterile condom, was gently positioned at the dura mater, using sterile gel to ensure a good acoustic coupling with minimal applied force. Thus, the probe positioning did not cause any significant deformation of the dura mater. When a satisfying cross-sectional image of the tumor was obtained, the probe was kept in a fixed position during data acquisition. The surgeon held the probe by hand, supported at the wrist to minimize artificial probe movements. The data were subsequently transferred to a computer for off-line processing [15]. The data were acquired after craniotomy, but before opening the dura mater [28].
3.4.2 Scanners and transducers that are mainly used

- **Modes**

**Applications of A-mode:**
One of the most useful and widespread applications of A-mode ultrasound has been echoencephalography. Using a simple time-base display allows position measurement of prominent brain structures such as the septum pellucidum, third ventricle and lateral ventricles. Echoencephalography is also used to detect space occupying lesions such as a tumor (which also displaces these structures).

**Application of B-Mode:**
B scanners use an A-mode unit together with transducer position sensors and intensity or Z-axis modulated display to map out the reflectors in a two-dimensional direction. The areas of the body accessible to contact B-scanning are limited to those with targets lying under a smooth large area of the skin without a large amount of intervening obstructions, such as bones or bowel gas. With a long water path between the transducer and the patient, the requirement for a smooth area is somewhat relaxed.

**Applications of M-Mode:**
M-mode uses a standard A-mode instrument with a modified display. The M-mode display resembles the B-mode or intensity-modulated display with the exception that the horizontal axis is a slow time sweep with the vertical axis a fast time sweep corresponding to the distance from the transducer (pulse propagation time). The M-mode is useful for mapping moving objects such as heart structures or arterial walls. Gray scale displays are fairly common in M-mode instruments [32].

- **Transducers**

Current US devices are equipped with two-if not more- multifrequency transducers. These are chosen on the basis of their frequency as well as their shape and footprint in relation to the area to be explored. It is important to exploit the different frequencies available and to modify them during the examination and vary the position of focal zone. A variation in the frequency and focus zone enables the insonation characteristics to be adapted to the built of patient, while at the same time performing an optimal exploration of all the superficial and deep portions of the organ [38].

While standard ultrasound probes used for daily scanning in the ultrasound department can also be used for intraoperative ultrasonography, it is preferable to utilize probes specifically designed for intraoperative use. The larger size and configuration of standard ultrasound probes can make it difficult to gain complete access to the target organs, due to
the confined spaces available during intraoperative scanning. The ability to flex and extend the scanning surface is an absolute requirement in order to maintain acoustic contact with the target organ. Many probes also offer a left-to-right deflection, which can also be useful, but is not an absolute necessity. Scanning technique will vary with the choice of transducer and the target organ being studied [34]. The high spatial resolution achievable with high frequency transducers is far superior to other imaging modalities [38]. Whenever the study of deeper structures is required or the effective width of a superficial but voluminous lesion needs to be defined, a lower frequency transducer should be used (2-7 MHz), despite the consequent loss of resolution. Study of the area of interest should be conducted as much as possible according to different and combined approaches, with scan planes performed at different angles [38].

With present day real time sector scanners, it is possible to localize lesions routinely and to characterize their internal contents as well [5]. Often for the transducer it is advantageous to image a lesion at various frequencies. A variety of probes have been developed for different intraoperative uses. For neurosurgical use, both in the head and in the spine, once again end-fire probes are most optimal, sometimes with frequencies ranging from 7 to 10MHz [27]. For intraoperative ultrasound brain imaging especially end-fire probes in the 5 to 7.5MHz range is required. Specially designed small footprint probes are available for imaging through very small craniotomy sites or burr holes, but standard endoluminal end-fire probes can also be successfully utilized for imaging and interventional guidance [34]. Very small end-fire probes have been developed for intracranial use to allow successful scanning through entry sites as small as a burr hole [34]. Cerebral, cerebellar and brainstem lesions are generally best imaged with a 5 or 3MHz transducer but occasionally a 7.5MHz transducer is used for very superficial lesions [27]. Often for the transducer it is advantageous to image a lesion at various frequencies.

Intraoperative A-mode ultrasound imaging of the brain has been described, but the use of intraoperative real time B-mode brain scanning appears to be relatively rare. Intraoperative B-mode scanning might prove valuable, especially in tumor localization, biopsies and other stereostatic procedures [7]. The real-time conical transducer can make a better contact with the surface of the brain or with the intact dura than the rectangular transducer, but it had a poor near field overview. Both scanners are without an overt mechanical vibration, which is an important consideration in scanning the delicate tissues of the brain. The 3.0 and 5.0 MHz frequencies that are used appear to be appropriate for this application. Images are well defined from the area of contact at the craniotomy site to the opposite side of the skull, especially when using the linear array transducer. The entire width of the intracranial contents could be defined in any given plane by appropriate placement of the transducer. Using a 3.0 MHz transducer with the sector scanner, the width of the brain was also well identified. When the 5.0 MHz transducer is used, the lesion itself is better resolved, but at the expense of demonstrating the deeper anatomic structures. This particular sector scanner is bulky and it also lacked a near field so that the immediate surface of the brain cortex was not apparent. This can be overcome if a 7.5 MHz transducer is available.

Ultrasound images that are suitable for diagnostic purposes are obtained by placing the transducer lightly on the surface of the brain after the dura is opened. Because the surface of the brain is convex and no overt pressure was exerted on the brain, the flat rectangular
transducer surface did not make complete contact at all points along the transducer face. Nevertheless, where the contact is made, the images are of excellent quality. The methodology can be improved with further modifications of the transducers that produce high resolution images of varying depth penetrations will allow smaller cranial defects to be utilized. The ability to allow the transducer to lie in a disinfecting solution prior to use would eliminate the need for encasing the transducer and cables in sterile shields [8].

In most cases ultrasonography was performed using some of the following scanners and transducers:

- ATL Neurosector with a specially adapted in line scanhead (which contained elements of 3.0, 5.0, 7.5 MHz)
- ATL III Sector scanner with scanheads (3.0, 5.0 MHz)
- ATL Mark III real-time sector scanner was used with 5 MHz transducer.
- ATL rotating sector scanner with 3 MHz transducer was used. All scans were performed with the transducer applied directly to the dura.
- ADR Corporation linear array real-time unit equipped with a 3.0 MHz transducer delineated the features of the intracranial anatomy. The surface of the rectangular transducer measured 9.2x 2cm.
- ATL Mark III unit sector scanner with a conical shaped transducer (725A). The transducer could be used at 3.0 or 5.0 MHz, both of medium focus.
- A conventional color-coded duplex ultrasound system equipped with a 3.5~7.5 MHz phase-array transducer (B&K Medical, Denmark) was used in all cases. The 7.5 MHz transducer is used for shallow or small regions and 3.5~5 MHz transducer is adjusted for deep-seated lesions or a wide area survey.
- All tumors were evaluated using a Tosbee real-time ultrasound scanner (Tosbee, Toshiba). A 3-5 MHz transducer was used.
- The ultrasound imager is an Echo Camera SSD-650 (Aloka Co. Ltd., Japan). A small 5-MHz convex ultrasound probe can be connected directly to the neuronavigator arm of the Leksell Index System. The ultrasound imager was used in all cases immediately after craniotomy.
- A mechanical ultrasound sector scanner with individually selectable transducers of differing frequencies and local lengths was used (ATL Neurosector, Advanced Technologies Laboratories, and Bellevue, Washington). The scanhead contains transducers of 3.0 MHz (long focus), 5.0 MHz (medium focus) and 7.5 MHz (short focus). Most examinations of adults used the 3.0-5.0 MHz transducer [5], [6], [7], [8], [9], [10], [13], [28].

To conclude in the most of the cases, it is necessary to use a transducer that will give optimal resolution and deep penetration with excellent biopsy capabilities. Also must be easily attached to different systems and arms. The shape must be slim in order to make it easy to hold and facilitates locating and viewing tumors. This is particularly useful in helping determine how a craniotomy should be performed in relation to a deep-seated tumor [12]. In the figure 3.5 below, we can see many different types of intracranial transducers.
3.5 Acoustical properties of tissues

Sound waves can produce an image of the brain because of the different densities present in the tissue of the brain, blood or tumor. Matter of different density reflects or echoes the sound waves differently, allowing the machine to distinguish between the structures. Also, Matter of different density reflects or echoes the sound waves different densities present in the tissue of the brain, blood or tumor.

3.5.1 Bioeffects of ultrasound

When ultrasound propagates through human tissue, some early research workers identified irreversible interactions between ultrasound and living systems. The human body exhibit tremendous complexities in its interaction with sound. The mechanism of this interaction was often only qualitatively investigated. There are potential biological effects or bioeffects [32]. Biological effects are changes in living systems caused by exposure to ultrasound. Ultrasound exposures used for diagnostic imaging are designed to minimize the interaction of the sound field with the tissue such that potential biological effects are avoided. Knowledge of the acoustic mechanisms for the interaction of ultrasound with tissues is required to maintain the safe use of diagnostic ultrasound and to facilitate the design of diagnosing applications of biomedical ultrasound. Absorption of ultrasound results in the conversion of ultrasonic energy to heat. Ultrasound-induced temperature rise is dependent on several factors, including tissue properties (e.g., absorption coefficient, density, perfusion, etc.), ultrasound exposure parameters [e.g., frequency, pressure amplitude, pulse duration, pulse repetition frequency (PRF), etc.], and beam
and scanning configurations. Thus, the generation of heat in tissues can typically be controlled through proper exposure design [34]. Brain tumors have acoustic properties different from those of normal brain tissues [5]. The potential bioeffects of ultrasound result from two major mechanisms, thermal and mechanical (nonthermal) [16], [29], [30], [32].

Biophysical effects of ultrasound are traditionally separated into:

- Thermal caused by continuous wave exposure (e.g. heating including increased metabolic activity and blood flow)
- Non-thermal (mechanical) effects caused by pulsed exposure (e.g. acoustic cavitation and its associated effects, radiation forces, radiation torque, acoustic streaming)
- Effects that are either thermal or non-thermal (e.g. insonation)

It is incorrect to assume that only one effect is present at any time and that physical diagnosis may be classed as either thermal or nonthermal. The reality is that the two effects are not separable and indeed it is rarely true that one class of effects may be ignored completely. A notable exception is extracorporeal lithotripsy, which causes exclusively mechanical bioeffects. For all other situations, it is best to assume that nonthermal effects will always be accompanied by some heating because the interaction between ultrasound and tissue is simultaneously thermal and mechanical and there is insufficient evidence as to whether there is a true threshold for bioeffects resulting from either mechanism. Conversely, acoustic fields that give rise to heating are always accompanied by nonthermal effects. With Pulsing the ultrasound beam reduces the temperature rise proportionately to the pulsing ratio; it does not eliminate heating [33].

- Thermal effects of ultrasound:

Heating for example, are dependent upon the acoustic energy delivered per unit time (acoustic power, measured in joule/s = watt) to a particular tissue area (i.e. the acoustic intensity (see intensity of sound), measured in watts/cm²) [30]. Some early research workers identified irreversible interactions between ultrasound and living systems. The mechanism of this interaction was often only qualitatively investigated. It was apparent that absorption coefficients for tissue and biological systems were such that thermal damage could be produced [32]. The best indicator of the amount of heat delivered to a tissue by ultrasound, is the spatial peak temporal average intensity, which is the maximum intensity occurring in the ultrasound beam averaged over the pulse repetition period (for pulsed ultrasound, the time from the beginning of one pulse to the beginning of the next). The heating of the tissue is also dependent upon how fast heat is removed from the tissue by perfusion or conduction. Factors affecting heat deposition in a tissue are the absorption coefficient of the particular tissue, the transducer frequency, focusing of the ultrasound beam, whether the ultrasound transmission is pulsed or continuous, and
examination time. Beneficial effects of heating such as pain relief, resolution of inflammatory infiltrates, and increase in blood flow are exploited in ultrasound therapy. Extensive heating will destruct tissues, and high-intensity focused ultrasound may be used in tumor ablation. Heat also has a teratogenic effect. Experimental animal studies in mice and guinea pigs have shown that continuous ultrasound with an intensity of more than 100 mW/cm² applied to the fetus for an uninterrupted period of more than 10 minutes may affect the fetus significantly. In medical diagnostic use of ultrasound, the heating effect is normally well below a temperature rise that would be considered potentially dangerous (e.g. 12°C). Doppler applications may, however, have intensity (ISPTA) that exceeds 100mW/cm², and should therefore be used with caution in fetal examinations [30].

Although there is evidence for insonation causing a rise in tissue temperature, the extent of tissue heating is dependent on a number of variables. Heating is intensity dependent. Reduced heating occurs for pulsed ultrasound as opposed to continuous ultrasound, the reduction being approximately proportional to the on: off pulse ratio. Homeostatic mechanisms will tend to counteract the rise in temperature of tissues exposed to heating. The success of homeostasis in restoring normal temperature depends on the balance between heat gain and heat loss. Any alteration in temperature automatically initiates a reaction in an effort to restore normal temperature. However, it is apparent that homeostatic control was unable to prevent the rise in tissue temperature recorded by Draper and colleagues. This is because local and general homeostatic mechanisms are only partially successful in quickly reversing the effect of a rise in temperature. The resultant tissue temperature following heating will primarily depend on the extent of conduction into surrounding tissues and dissipation by blood perfusion. Dissipation by blood perfusion is highly variable and difficult to estimate, but is known to be poor in fatty tissue and tendon [33]. As sound beam passes through tissue, it undergoes attenuation. A significant fraction of this attenuation is due to absorption. For low power ultrasound, the heat deposited is quickly dissipated. Some concern is warranted with pulsed Doppler and color flow imaging equipment where high power levels and time average intensities may result in large values in thermal index [16]. The mechanism of this interaction was often only qualitatively investigated. It was apparent that absorption coefficients for tissue and biological systems were such that thermal damage could be produced [32].

- Non-thermal (mechanical) effects of ultrasound:

Nonthermal effects have been divided by ter Haar into cavitation and other mechanical effects. She contended that the beneficial effects of ultrasound were due to —nonthermal interaction mechanismsl rather than heating. The term —cavitationl appears to have been first used by Sir John Thornycroft in the early 20th century and was defined as the formation and life of bubbles in liquids [34]. They divide these effects into two categories.
The first category is called acoustic cavitation.

The general term —cavitation— can be used to describe any bubble phenomenon, but it will be used here to denote acoustic cavitation: the behavior of bubbles within an acoustic field [33]. Cavitation, which was a grossly observed phenomena associated with high frequency sound fields in liquid media, was presumed to be responsible for irreversible changes [32]. Cavitation requires small, stable gas bubbles to be present in the tissues, and involves implosion (collapse) of the bubbles caused by the ultrasound. The sudden collapse results in mechanical damage and possible formation of free radicals [30]. It really includes generation, growth, vibration and possible collapse of microbubbles within the tissue. Experimentally, both macroscopic damage (rupture of blood vessels and cells) and microscopic damage (e.g. to chromosomes) have been found, and when gas bubbles of the appropriate size (in the order of microns or smaller) are present, mechanical damage may occur even at the low ultrasound intensities delivered by diagnostic ultrasound scanners. However, the intensity threshold for cavitation in man is much higher than that obtainable by commercial instruments (approx. 1 kW/cm²), and even though thermal and mechanical effects may act synergistically, no confirmed bioeffects in patients (or operators) have ever been observed [30].

There are two types of cavitation:

- Stable cavitation: creation of bubbles that oscillate with sound beam.
- Transient cavitation: process in which the oscillations grow so strong that the bubbles collapse violently producing very intense localized effects [16].

Therefore, cavitation may be more specifically defined as —the formation of tiny gas bubbles in the tissues as the result of ultrasound vibration. In addition to heat, scientists have begun to learn more about the various types of mechanical effects that ultrasound can have on the body [33]. Cavitation can occur when sound passes through an area that contains a cavity, such as a gas bubble or other air pocket. Ultrasound waves consist of cycles of compression and expansion that exert a positive and negative pressure. These cycles of pressure work on the molecules by pulling them together and pushing them away. During the negative cycle, given sufficient ultrasound intensity, cavities are introduced into the subjected body. While pure liquids have very high tensile bond strength that prohibit ultrasound waves from creating cavities, body tissue contains trapped gas in small solid particles that greatly reduce the tensile bond strength and enable ultrasound waves to create cavities. The small gas pockets are constantly being worked out by the ultrasound waves during positive and negative pressure cycles until they reach a critical size. The growth of the cavity mainly depends on the intensity of the ultrasound waves. A very high intensity ultrasound can cause the cavity to implode during a single pressure cycle while a low ultrasound intensity require several pressure cycles to reach the critical size [31].

Some tissues, most notably adult lung and intestine, do contain air bubbles, and are therefore more vulnerable to these cavitation effects. Microbubbles can be introduced intentionally into the body through the injection of gas-based ultrasound contrast agents [34]. Acoustic cavitation describes the interaction of a sound field with a gas bubble. The occurrence of cavitation thus requires the presence of a stabilized gas body or nucleus. Aside from tissues such as the lung and intestine, the presence of naturally occurring gas in tissues is typically rare. Several models exist
to explain the stabilization of gas nuclei in fluids. One model (the crevice model) assumes that gas nuclei are stabilized in crevices of hydrophobic impurities in the liquid. As the pressure in the liquid decreases, the gas in the crevice expands and may separate from the impurity to form a microbubble. If preexisting nuclei are present, gas bodies can be produced in tissues by a high-amplitude acoustic exposure, such as a lithotripter field or HIFU exposure. When exposed to an acoustic field, a bubble in a liquid will oscillate around an equilibrium radius. Various theoretical models can be used to predict the radius of a bubble as a function of time of exposure. The maximum response of a bubble to an acoustic field occurs when it is exposed at its resonance frequency. The resonance frequency is dependent on the initial size of the bubble, and for frequencies relevant to diagnostic ultrasound imaging, resonance size bubbles are on the order of a few micrometers in radius. Non-inertial cavitation (sometimes termed stable cavitation in earlier literature) describes a repetitive oscillation of a bubble over many acoustic cycles. The maximum expansion of a non-inertial cavity typically does not exceed twice the equilibrium radius. The response of the bubble can be nonlinear and is dependent on variables, including the acoustic pressure amplitude, exposure frequency, and size of the bubble. Bubble oscillations can be damped through viscous dissipation, sound radiation, and thermal conduction. A variety of physical phenomena can be associated with non-inertial cavitation. Rectified diffusion describes the slow growth of an oscillating bubble owing to a net flow of gas into the bubble over many acoustic cycles. Acoustically driven bubble oscillations can result in heat production, microstreaming of fluid near the bubble, and localized shear stresses. In a traveling wave field, radiation forces can produce bubble translation, whereas in a stationary acoustic wave, field radiation forces can cause bubbles to collect at pressure minima and maxima depending on their size. Interactions between bubbles and particles in a sound field can result in bubble coalescence or the attraction of nearby particles or cells to an oscillating bubble. At sufficiently high exposure amplitudes, a bubble may expand to a maximum radius greater than twice its initial radius and then collapse rapidly to a small fraction of its initial radius. This response of the bubble to the acoustic field is termed inertial cavitation (sometimes termed transient cavitation in earlier literature). Here, the motion of the bubble is highly nonlinear and the collapse is dominated by the inertia of the surrounding liquid medium. For appropriate exposure conditions, a single ultrasound pulse on the order of one microsecond in duration can cause a bubble to expand rapidly and collapse violently. The violence of the collapse of the inertial cavity is determined by various parameters, including acoustic frequency, pressure amplitude, and initial bubble radius. The response of an inertial cavity to an acoustic field is highly nonlinear, such that a small increase in acoustic pressure amplitude can change the bubble response from a non-inertial cavity to an inertial cavity. The acoustic pressure at which the transition occurs is often called the threshold for inertial cavitation. Extremely high temperatures and pressures can be achieved at the minimum radius of the inertial bubble collapse. Some models predict maximum collapse temperatures exceeding thousands of degrees Kelvin. These high temperatures and pressures are localized spatially near the collapsing bubble and are limited temporally to the duration of the collapse. In general, for a given bubble radius and pressure amplitude, as the frequency of exposure increases the maximum collapse pressure in the bubble decreases. Several interesting physical phenomena are associated with inertial cavitation. The production of high temperatures and pressures during inertial collapse can lead to the formation of free radicals. The field of sonochemistry explores the application of inertial cavitation to generate chemical species
or drive chemical reactions. Sonoluminescence describes the generation of light from activities associated with inertial cavitation. During inertial collapse, the motion of the bubble wall may become supersonic and generate a spherically diverging shock wave in the liquid medium surrounding the collapsing bubble. Bubbles undergoing inertial cavitation near solid boundaries can collapse asymmetrically. Asymmetric collapse can result in the formation of high-speed, fluid microjets that impinge on the solid boundary. Microjets can produce pitting of metals, such as aluminum foil, and likely play a role in the fragmentation of kidney stones with lithotripter shock waves [34].

In cavitation, the sound waves can cause the bubbles or air pockets to expand and contract rhythmically: in other words, to pulsate, or resonate. When they pulsate, the bubbles send secondary sound waves off in all directions. These secondary sound waves can actually improve ultrasound images because the secondary waves also reflect back to the transducer, and provide more information. Thus, doctors now sometimes inject artificial bubbles known as contrast agents into the body before taking ultrasound images, for instance, of the circulatory system. If the bubbles contract towards the point of collapsing, they can build up very high temperatures and pressures for a few tens of nanoseconds. These high temperatures and high pressures can produce highly reactive chemicals called free radicals, and other potentially toxic compounds which, although considered unlikely, could theoretically cause genetic damage. The rapid contraction of bubbles in cavitation can also cause microjets of liquid which can damage cells. When diagnostic ultrasound is focused on the lung or intestine of laboratory animals, which contain gas bubbles, these cavitation effects can cause ruptures in very small blood vessels. The NCRP’s safety guidelines for diagnostic ultrasound are designed to try to prevent cavitation effects, because these effects can be damaging. Restrictions on the pressure amplitude of the ultrasound pulse, in combination with awareness of whether or not there are gas bubbles in the tissue being imaged, can help to prevent cavitation. Other factors such as the length of the pulse, and the density of the liquid, also influence whether or not cavitation occurs. And if there are gas bubbles, the number, size and location of the bubbles also contribute to the effect [11].

The following figure 3.6 illustrates the growth process of a cavity under a low intensity ultrasound where the size grows and shrinks until it implodes. While the cavity goes through cycles of expansion and compression, the net effect is growth in size due to the fact that gas diffusion in the expansion cycle is greater than that of the compression cycle. This process continues until the cavity reaches a critical size where the cavity starts to grow rapidly due to high absorption capacity. The critical size mainly depends on the intensity of the ultrasound. Shortly after reaching the critical size, the cavity implodes [31].
The implosion of the cavities sets up the environment for unusual chemical reactions. This is mainly due to the extreme temperature created by the implosion that can reach up to 5,500 degrees. During the collapse, pressure inside the cavities can reach levels equivalent to thousands of atmospheric pressure. During the implosion stage, the cavity bursts and expels liquid traveling at roughly 400 km/h. This implosion is so extreme that it can send small particles with such a high speed and cause them to melt at the point of impact and reformat. In the following figure 3.7 we can see the imploding cavity [31].
These extreme conditions are responsible for several biological effects. One well-known effect is the cell suspension changes due to the implosion of cavities. Cavitations occur in the fluid suspending cells. Studies clearly shown the direct relationship between cavitations caused by ultrasound and distortion of cell’s membrane suspended by the fluid in which the implosion occurred. It is unclear; however, if the internal structure or function of the cell that survived a nearby cavity implosion is affected. Energy transported via ultrasound waves can be characterized by several terms depending on purpose. Generally, energy of ultrasound is described by pressure, temperature, density, and particle displacement. Developing a model for ultrasound waves requires a strong understanding of the wave’s nature. Specifically, for a bio-heat model of ultrasound waves, a special attention should be directed to the understanding of the attenuation, scattering, and absorption of ultrasound waves traveling through biological tissue.

![Figure 3.8: Zinc powder after a cavity implosion [31.]](image)

The second category includes changes in pressure, force, torque (causing things to rotate) and streaming (stirring of the liquid).

These changes, in turn, can cause audible sounds, electrical changes in cell membranes that make them more permeable to large molecules, movement, and redistribution of cells in liquid, and cell damage. When ultrasound passes through liquid, it causes a sort of stirring action called acoustic streaming. As the acoustic pressure of the ultrasound increases, the flow of liquid speeds up. This stirring action, in theory, could occur in fluid-filled parts of a patient’s body, such as blood vessels, the bladder, or amniotic sac. In experiments with animals, when streaming of the liquid comes near a solid object, shearing can occur, and this can damage platelets and lead to abnormal blood clotting (thrombosis). It is not clear to what extent this effect occurs in
humans exposed to diagnostic ultrasound. Some studies have linked ultrasound to increased movement of the fetus at the time of the scan. One theory to explain this is that the fetus moves because it actually hears sound caused by the pressure of the ultrasound beam on the bones of the fetal head. At present, there is no evidence that hearing sounds during the ultrasound scan causes any damage to the fetus [11].

Also techniques that employ radiation force are frequently used in methods to calibrate ultrasonic fields. The magnitude of the radiation force depends on characteristics of both the sound field and the object in the field. For the case of a plane wave incident normally on a perfectly absorbing target, the radiation force is equal to $W/c$, where $W$ is the total acoustic power and $c$ is the speed of sound in the propagating medium. The radiation force exerted by a plane wave on a perfectly reflecting target is twice that of a perfectly absorbing target. These plane wave approximations provide adequate estimates of radiation force. However, actual ultrasonic fields have finite beam widths, can be focused, and may be distorted by nonlinear propagation, all of which can influence radiation force. Radiation forces exerted on cells in a stationary wave field are more complex and can result in the banding of red cells at one-half wavelength intervals in a blood vessel in vivo. Radiation forces can also displace contrast agents to the wall of blood vessels in laboratory animals. Radiation force is the underlying mechanism for phenomena such as radiation torque, acoustic streaming, acoustic levitation, and acoustic fountain effects. Radiation torque can result in the rotation or spinning of symmetrical particles, whereas asymmetrical particles may rotate to a preferential orientation in the sound field. An acoustic field propagating in a fluid medium can give rise to a bulk fluid flow termed acoustic streaming. The streaming velocity is dependent on factors including the absorption coefficient, speed of sound, kinematic viscosity, intensity, beam geometry, and nonlinear propagation. The use of acoustic streaming produced by ultrasound may hold promise as a diagnostic technique to identify cysts noninvasively. Radiation forces have been demonstrated to stimulate cardiac and neural tissues [34].

→ The third category includes other mechanical effects.

Other mechanical effects are considered to be created by small oscillation of particles due to the movement of ultrasound waves through tissues. Any displacement, however, will depend on the acoustic pressure amplitude or intensity, which will be small. Consequently, small particle oscillation is usually not seen as a cause of the biophysical effects of ultrasound. Free radical formation has also been suggested as a potential source of cell damage with ultrasound. However, because there is no good evidence of cavitation occurring in vivo, the evidence for free radical formation secondary to ultrasonic cavitation in solutions in vitro is not relevant in this
context. Also these mechanical effects do not require the presence of bubbles in order to occur [34].

The human body exhibits tremendous complexities in its interaction with sound. Accurate physical measurements are often very difficult to make in the low Megahertz frequency range since the finite size of the measuring transducer often distorts the value of the very quantities being measured. In addition, measurements of tissues are generally difficult to obtain, particularly in the case of human patients where medical standards and protocols must be maintained. If measurements are made in vitro or with fixed tissue, the measurements must be compared with in vivo results to be biologically meaningful. These practical problems account for the present paucity of reliable, well-documented information in this area, which only now is receiving the much needed attention it deserves. In biological tissues, there is only a minor dependence of the sound velocity on frequency, at least, in the 1-20 MHz frequency range that covers most medical Applications at present. For example, a small dispersion amounting to approximately 0.15% velocity change for a 1-10 MHz frequency change has been recorded for beef hemoglobin. At present, it is unclear how even a small velocity dispersion effects or limits the resolution of various acoustic imaging systems. Accurate physical measurements are often very difficult to make in the low Megahertz frequency range since the finite size of the measuring transducer often distorts the value of the very quantities being measured. Since live human tissue is generally at a constant normal body temperature of 37°C, there is little need in present diagnostic regimes to consider effects of temperature on the acoustic properties of tissue. This is not to imply that such temperature effects should be ignored, since interesting possibilities utilizing temperature changes have been suggested for experimental studies with the aim of possible future medical applications [32].

Histologically, glioblastomas exhibit marked cytologic diversity, ranging from small-cell tumors with scant cytoplasm to ones composed of multinucleate giant cells. Mixed patterns are the rule. Mitoses, including atypical forms, are frequent but vary significantly in number within individual tumors. Exuberant vascular proliferation, often endothelial and pericytic, frequently accompanies necrosis.

Tissue culture studies of malignant gliomas have routinely shown that these tumors are among the most heterogeneous of all human tumors. Most consistent abnormalities are on chromosomes 7, 10, 17 and 22. Especially losses of heterozygosity for loci on chromosomes 10 and 17 are frequent. Changes on chromosome 10 appear to be more selective for glioblastomas compared to less anaplastic astrocytomas. In contrast, losses of heterozygosity for loci on chromosome 17 appear to occur in astrocytomas regardless of the degree of anaplasia. Oncogenes that code for growth factors such as EGF or their receptors such as EGF receptor are often activated in those tumor specimens. In summary, these findings support the theorem that glioblastoma multiforme often evolves from less malignant astrocytomas by malignant transformation as indicated by loss of tumor suppressor genes allowing the malignant cells to develop autostimulation processes. This fact was shown by
Laws et al. (1986) who found that 49% of 79 supratentorial low-grade astrocytomas recurred and was documented at surgery or autopsy as having changed to astrocytoma grade 3 or 4 [28]. Ultrasound users are expected to assess the risk/benefit ratio based on their interpretation of equipment output displays (including the thermal index, TI) and an understanding of the significance of biologic effects [29].

3.5.2 Echogenicity of living tissues

Sound waves can produce an image of the brain because of the different densities present in the tissue of the brain, blood or tumor. Matter of different density reflects or echoes the sound waves different densities present in the tissue of the brain, blood or tumor. Matter of different density reflects or echoes the sound waves differently, allowing the machine to distinguish between the structures.

Ultrasound imaging became a diagnostic tool in the 1970s with the introduction of the gray-scale ultrasonography. In this scale, the reflected echoes from tissues are nonlinearly compressed so that specularly reflected and diffusely scattered echoes can be captured to construct the image. Prior to that, only specularly reflected echoes were used as the primary building component of the ultrasound image. Recent research in the fundamental knowledge of ultrasound tissue interaction has lead to a better understanding of its mechanism and side effects. Studies were directed to the understanding of ultrasound scattering off tissues. Experimental methods for measuring scattering of ultrasound waves in tissue have been developed to generate models that characterize tissue-ultrasound interaction. These studies on tissue-ultrasound interaction revealed the nature of the undesired side effects of ultrasound therapy and imaging [31].

The depiction, which is produced by ultrasound, is mainly based on the echogenicity of the tissue. Echogenicity (misspelled sometimes as echogenicity) is the inability to bounce an echo, i.e. return the signal in ultrasound examinations. In other words, Echogenicity is higher when the surface bouncing the sound echo reflects lesser sound waves. With this way any inner part of the body that reflects sound waves and thus produces echoes that may be detected using ultrasound scanners [36]. The echogenic ultrasound waves are highly reflective waves which are shown as a white area in the scan. It could be increased by intravenously administering gas-filled microbubble contrast agent to the systemic circulation. This is because microbubbles have a high degree of echogenicity. When gas bubbles are caught in an ultrasonic frequency field, they compress, oscillate, and reflect a characteristic echo- this generates the strong and unique sonogram in contrast-enhanced ultrasound. Gas cores can be composed of air, or heavy gases like perfluorocarbon, or nitrogen. Heavy gases are less water-soluble so they are less likely to leak out from the microbubble to impair echogenicity Therefore, microbubbles with heavy gas cores are likely to last longer in circulation. During ultrasound examinations, sometimes echogenicity is higher in certain parts of the body and these parts are called hyperechoic regions and sometimes echogenicity is lower which means that these regions are hypoechoic [37].
In general the focus zone(s) should be placed at the level of or, better still, immediately below the area of interest. The signal coming from the tissues situated at the level of the focal zone of the transducer is in fact more intense than the signal of the tissues that are more superficial or deeper to it. The possibility of varying the position of the focus zones and transducers with a broad range of frequencies enables optimal exploration with greater lateral resolution. However occasionally focus zones are unable to create an effectively uniform transition between the different levels of depth and a single well-positioned focus zone may be better. Increasing the number of transmit focus zones narrows the beam profile, with improved lateral resolution but decreased temporal resolution. An excessively low gray gain can, for example make a markedly hypoechoic lesion appear anechoic. On the other hand, an excessive gain can create echogenic artifacts. The dynamic range is used to improve the echo display, making the low-amplitude echoes distinguishable. Nonetheless, increasing the dynamic range decreases the contrast [38].

Focal lesions can be characterized at ultrasound by a solid or liquid structure. Solid lesions are characterized by scattered echoes or varying intensity level and can be divided into four categories:

- **Solid homogenous lesions** - echoes similar in intensity and dimension, generally fine and uniformly distributed.
- **Heterogeneous solid lesions** - echoes with differing intensity and dimension, with varied distribution.
- **Solid lesions with acoustic shadowing** - homogeneous or heterogeneous but with beam attenuation.
- **Prevalently solid complex lesions** - the prevalently solid and usually heterogeneous portion is associated with minority fluid-filled portions.

Then on the basis of the intensity of the echoes, both solid lesions with homogeneous echotexture and those with heterogeneous echotexture can have a hyperechoic, isoechoic or hypoechoic ecostructure. Generally speaking, hypoechoic lesions have an elevated —waterl component, whereas hyperechoic lesions are characterized by a rich capillary network or a significant stromal component. The greater or lesser echogenicity should be defined as much as possible in relation to the adjacent parenchyma, which constitutes the background of the echoes. However, clearly a mass which does not develop within a parenchyma can easily be defined as hypoechoic or hyperechoic in the absolute sense. In addition, the characteristics of the parenchymal —backgroundl can clearly change: lesions which might appear hyperechoic in a normal liver can have a hypoechoic appearance in the setting of steatosis. The isoechoic lesion, which produces the same reflection of echoes as the surrounding parenchyma, clearly cannot be recognized as such and can be identified only in the presence of indirect signs such as the outline of an organ or the displacement of surrounding structures. In general tumors are hypoechoic,
being characterized by elevated cellularity and a limited stromal component and therefore by few interfaces which reflect the ultrasound [38].

The transmission of the acoustic signal through a lesion and posterior to it and therefore the posterior echogenicity, can be increased, normal or reduced. Beam attenuation (posterior acoustic shadowing) is the expression of the presence of intense reflection of the ultrasound beam resulting from, for example, calcifications, hyalinosis and fibrosis (including tumor stroma). Even a gaseous component can produce a similar effect, either as the only curved echogenic image with posterior attenuation or as individual attenuating nuclei. The posterior shadow may be only mildly visible or markedly apparent to the point of obstructing the visualization of the tissues immediately distal to the lesion or even the deep portion of the lesion itself. When instead the superficial interface of the lesion creates the artifact, the lesion itself can be concealed, especially its anterior portion. Beam attenuation to the point of producing posterior acoustic shadowing which conceals the deep portion of a lesion and/or healthy soft tissue immediately distal to this, can in the first instance orient the diagnosis towards malignancy.

Liquid lesions can also be divided into four categories:

- **Simple fluid-filled lesions** - homogeneous anechoic, none reflecting.
- **Reflective corpuscular lesions** - generally dense internal echoes, occasionally mobile with a shift in patient position, also identifiable with optimized gray gain.
- **Septated cystic lesions** - or with parietal polypoid lesions (solid sessile or pedunculated lesions with intraluminal development
- **Prevalently cystic complex lesions** – generally corpuscular, with a few solid components.

Septated lesions may have a variable number of internal septations, which may be partial or complete (in the latter case the formation may be described as multilocular) and thin and regular or thick and irregular. In general, good transmission of the ultrasound beam through a focal lesion, even to the extent of producing increased through-transmission, orients the diagnosis towards benignity, especially for superficial structures, although there are some notable exceptions. Lateral acoustic shadowing can therefore be present as occurs especially in fluid-filled lesions, or absent, especially in solid lesions [38].

There are various characteristics of focal lesions which need to be considered, both for defining the appearance of the lesion and for writing up the diagnostic report: shape, echostructure, margins, dimensions, number, site and relations with adjacent structures. It should also be borne in mind that in small lesions the morphologic appearance is poorly definable, with a greater overlap between benignity and malignancy than in larger lesion. The shape can be regular or irregular. Lesions with regular shape may be rounded (ratio between the two largest orthogonal diameters <1.5), oval (ratio between 1.2 and 2), elongated (ratio>2) or lobulated
(multiple lobulations formed by the confluence of more than one lesion or symmetrical growth in different directions, with a polycyclic appearance of the margins). A lesion with an irregular shape is instead particularly asymmetrical and therefore cannot be easily attributed to any of the above-mentioned typologies nor can its size be easily determined. The greater the irregularity in shape is, the higher the probability of a malignant nature of the lesion, although this is clearly a generalization [38].

The echotexture can be homogeneous or heterogeneous. The latter, which is also defined as “mixed” can be the result of components with different degrees of anaplasia, histologically different components, irregular divisions in the vascular supply, regressive phenomena (spontaneous or treatment-induced) and possible overlying infection. The complex echostructure illustrate above is the maximum expression of heterogeneity of the echotexture of the lesion, which cannot be classified as hypoechoic, isoechoic or hyperechoic. In absolutely general terms, the greater the heterogeneity of the echotexture is, the higher the probability of a malignant nature of the lesion. Clearly, however, the finding should be evaluated on a case-by-case basis. Necrotic phenomena tend to be hypoechoic or even anechoic, thus they can simulate cystic components. Hemorrhage can be expressed with a different echogenicity according to the time of the bleeding. Adipose components are usually hyperechoic [38].

The margins (borders) can be sharp and regular, ill-defined (indistinct), lobulated (both micro- and macrolobulated), angular (sudden variations in the profile) or speculated (fine bands irradiating around the lesion). The dimension of the lesions can be measured with electronic calipers of the device, by searching for the scan plane where the lesion appears at its widest and measuring the longest diameter and the largest perpendicular diameter on this image. The volume of the lesion can then be calculated by measuring the maximum length, width and height of a lesion on two scans obtained on orthogonal planes and applying the ellipsoid formula, by which the measurements are multiplied by 0.524 (an operation which is performed automatically by the software of the US device). Alternatively, the calculation can be based on measurements of the lesion perimeter. However, these are at least in part abstractions, since the measurements can be influenced by a number of factors, including the irregular shape of the lesion or ill-defined and infiltrating margins. Volumetric measurements performed in 3D are more accurate than those in 2D, with less interobserver variability and a greater repeatability. The measurements obtained are less dependent in the dimensions, morphology and echostructure of the lesion. The orientation of the lesion with respect to the skin surface and therefore the transducer should also be noted. Determining the deformability or otherwise of surface lesions through compression of the transducer is also important. Compressibility is in fact suggestive of a benign lesion, whereas malignant lesions tend to be hard and inelastic, also on palpation. Mobility with respect to the adjacent anatomic structures can suggest the absence of invasion. Occasionally variations IN compression make identification of isoechoic superficial lesions possible, which are identifiable due to the different compression characteristics with respect to the surrounding tissue. Compression with the transducer can help to define the generally hard consistency and tenderness, at least in surface lesions, which are useful elements for differential diagnosis. In the case of neoplastic lesions, the tenderness may be due to rapid
growth, infiltration of anatomic structures sensitive to pain and/or compression of adjacent structures. Running the transducer over the skin may also reveal an increased consistency or even a —bump‖, which may be useful for identifying masses that are immediately recognizable [38].

The transition between the lesion and healthy parenchyma may be sharp or mediated by a generally thin hypoechoic or hyperechoic halo. The halo, situated between the lesion and the parenchyma compressed by expansive growth, desmoplastic or inflammatory response of tissue. A peripheral hypoechoic halo can be the expression of perifocal compressive edema, perilesional vessels or a tumor component with active growth. The type of growth of the tumor can be expansive, with a well recognizable and measurable formation and overall regular shape, which causes a mass effect on the adjacent structures. In this case indirect signs may be apparent such as displacement/compression of vessels, ducts or other anatomic structures, or focal deformation of the profile of an organ. In the latter case the organ may display a bulge of its surface or a lesion which patently protrudes, with exophytic or even pedunculated development. In some organs the compresses perilesional parenchyma is transformed into a pseudocapsule. Alternatively, growth may be invasive, with poorly defined tissue which tends to encroach on rather than displace the surrounding structures, such as vessels and which deforms the organ in a broader sense, without a focal bulge but occasionally with diffuse enlargement which may respect the basic morphology of the organ. When the diffuse structural undermining of the organ is mild, it may go unrecognized. In contrast to expansive lesions, invasive lesions may produce retraction of a surface of an organ. Various changes to the surrounding tissues may occur; compression, distortion, ischemia (even from infiltration or compression of afferent vessels) and dilatation of ducts (e.g. lactiferous or biliary ducts). Lesions which tend to grow without developing fibrous septa, such as lymphomatous lesions, tend to encroach upon adjacent vessels rather than invade them, which instead is common among lesions with a significant stromal component. The presence of normal intralesional vessels which cross the area in question suggests either benignity or a malignant lesion with particular rapid invasive growth. In the latter case, however, it is more likely the vessels show signs of luminal thrombosis or stenosis. A characteristic of malignant lesions or the infiltration of adjacent structures by malignant lesions is the fixity with respect to structures which would normally show movement. Examples include reduced respiratory motion in pulmonary tumors invading the chest wall, or the absence of movement of invasive cervical tumors with respect to the act of swallowing [38].

Acoustic absorption plays a major role in all tissues. The sound intensity $I$ decrease with the distance of propagation $x$ according to:

$$I = I_0 e^{-2ax}$$

Where $I_0$ is the intensity at $x = 0$, and $a$ is the acoustic pressure absorption coefficient. The factor of 2 in the exponential results from transforming pressure into intensity, since under plane wave conditions the intensity is proportional to the square of the pressure. For tissue, absorption
is approximately proportional to frequency, whereas classical absorption mechanisms result in quadratic frequency dependence. Individual tissues may vary somewhat from this relation. Absorption in tissues is primarily related to the protein content, although there is component of absorption that is apparently related to other constituents. In general, it appears that acoustic absorption in tissue can be described by a relaxation process, in which acoustic energy is highly attenuated at certain particular frequencies, which are determined by the material's molecular properties.

Since most ultrasonic diagnostic equipment operates in a pulse-echo mode, it is important to consider the interaction of various acoustic pulse waveforms with tissue. A highly damped oscillatory waveform is typically generated. Thus short bursts of sound having significant amplitude for only a few cycles are transmitted through the tissue and undergo absorption loss described by. These short acoustic pulses are refracted, reflected, and scattered by structural details within the tissue. Because of relatively small velocity changes in various soft tissue media, refraction is generally not a serious problem. It is, of course, much more pronounced if bone is involved in the sound pathway. Velocities and directions of both longitudinal and shear waves are related in terms of Snell’s law. Soft, tissues are perhaps also isotropic, although piezoelectric action in cholesterol plaque and bone has been reported, which demands anisotropy.

In table 3.2 we can see a list of the absorption coefficients for similar materials and table 3.3 gives the reflection coefficients for some interfaces of importance in medical diagnosis.

<table>
<thead>
<tr>
<th>Material</th>
<th>Frequency MHZ</th>
<th>α (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>1.0</td>
<td>.10</td>
</tr>
<tr>
<td>Brain tumors (formalin fixed)</td>
<td>5.0</td>
<td>.73</td>
</tr>
<tr>
<td>Meningioma</td>
<td>5.0</td>
<td>.38</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>5.0</td>
<td>.50</td>
</tr>
<tr>
<td>Metastatic tumor</td>
<td>5.0</td>
<td>.44</td>
</tr>
<tr>
<td>Normal brain</td>
<td>5.0</td>
<td>.08</td>
</tr>
<tr>
<td>Fat</td>
<td>1.0</td>
<td>.13</td>
</tr>
<tr>
<td>Muscle</td>
<td>1.0</td>
<td>.19</td>
</tr>
<tr>
<td>Liver</td>
<td>2.0</td>
<td>.27</td>
</tr>
<tr>
<td>Kidney</td>
<td>2.0</td>
<td>.04</td>
</tr>
<tr>
<td>Blood</td>
<td>2.0</td>
<td>1.7</td>
</tr>
<tr>
<td>Bone (human skull)</td>
<td>1.2</td>
<td>2.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.5</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

Table 3.2: Absorption coefficients [32]
Acoustic parameter determination for normal and pathological tissues has yet to be extensively developed, which accounts in part for the paucity information in Tables 3.2 and 3.3. However, this area is extremely important. It appears that many types of normal and abnormal tissues can be uniquely classified in terms of their acoustical properties and that such a classification scheme could be incorporated into a diagnostic system. For example, recent studies have indicated that specific brain tumors can be uniquely classified according to their acoustic reflection patterns. Another study has suggested that the elastic properties of soft tissues are largely responsible for their echographic visualizability and that these properties are determined in some cases by structural collagen-containing compounds [32].

The surface of normal brain sulci is moderately echogenic while the deeper tissues are quite hypoechoic and homogenous. Frequently, a mass is associated with acute edematous swelling of the brain which makes the lesions appear even more echogenic and increases the conspicuity of tumors. The majority of benign and malignant primary brain tumors, as well as most metastatic brain lesions, are hyperechoic in comparison to the surrounding brain tissue. However, certain patients with longstanding brain tumors may develop a chronic edematous pattern, which may actually increase echogenicity of brain tissue and this can decrease the conspicuity of focal masses [34]. The most highly echogenic brain lesions are usually meningiomas and especially those with calcifications, which occur frequently. In every instance during intraoperative ultrasound imaging, the low-grade tumors have an increased echogenicity relative to the surrounding normal brain. This has allowed both identification of the tumor and a much better definition of its borders. Also for high-grade gliomas ultrasound is helpful to define the borders [27]. Glioblastomas and other primary brain tumors, as well as most metastases and even lymphoma tend to be hyperechoic and are usually well circumscribed and sharply marginated [34]. The solid portion (contrast enhancing region on MR images) of most GBMs is echogenic on ultrasound and can be delineated from surrounding infiltrative and edematous brain [14]. The more aggressive glioblastomas may have less well-defined margins as they infiltrate into surrounding brain parenchyma. Hypoechoic areas of fluid accumulation may be seen in brain
tumors due to liquefaction necrosis, but cystic spaces are also frequently seen in certain types of cystic astrocytomas. The cyst cavities, septations and solid components of the cystic tumors may be better depicted by intraoperative ultrasound. Low grade astrocytomas are often less echogenic less well marginated and hence, may be difficult to precisely identify and delineate with IOUS. Distortion of the sulcal groove pattern or compression of surface brain markings may help identify the tumor. Also the use of color flow or power Doppler, demonstrating deformity and displacement of vessels, may also be useful in defining the borders of these subtle lesions. Acute bleeding into a tumor or brain parenchyma will typically appear as single or multiple, small, hyperechoic foci, which may enlarge or become confluent over time [34].

The ventricles are a good centrally located landmark due to their homogenous hypoechogenicity. On the contrary, the sulci, the falx, and choroid plexus are heterogenously hyperechogenic, which can well demonstrate the midline and the boundary of the parenchyma. The white and gray matters of the parenchyma are homogenous hypotoisoechogenic, thus they are more difficult to delineate from each other. The brain stem is homogenously hypoechogenic due to the compact nerve bundles and nuclei, and can serve as an anatomical landmark in the basal skull. The heterogenous echogenicity of metastatic tumors and glioblastoma multiform (GBM) is dependent on the extent of tumor necrosis. In intraoperative sonographic examination, malignant perilesional areas were seen as two different echogenic zones. The tumors are surrounded many times by a first, very thin hypoechogenic zone. The echogenicity of the first zone was similar to brain tissue. The second zone is a vasogenic edematous zone. The ultrasonographic appearance of this zone was hyperechogenic and was similar to that of solid tumor parts. The ultrasonographic appearance of malignant glial tumors is hypoechogenic compared to the surrounding brain [10].

![Figure 3.9: Intraoperative ultrasound image of a GBMs typically appear as echogenic lesions with ultrasound. The boundary (black arrows) and the surrounding brain (darker region) are well seen][14](image)
On real-time B-mode images tissue that is more echogenic appears to be whiter on the screen; the least echogenic substance (cerebrospinal fluid) appears as dark. To display images of good quality the time-gain compensation curve must be set so that normal brain tissue is uniformly hypoechoic. For orientation normal landmarks such as the ventricular walls, choroid plexus, Sylvian cisterns, tentorium cerebelli, falx, and some prominent cortical sulci which are brightly echogenic are sought. The scanner can be used to measure the distance from the surface of the scanhead to the lesion as well as the diameter of the lesion. Those measurements are displayed on the screen. It can be of great value during the operation or subsequent follow-up to measure the size of a cyst, abscess or hematoma to determine the need for further aspiration and during tumor surgery to estimate the amount of tumor still being ahead.

Virtually all brain tumors are at least partly hyperechogenic. Diffuse calcification within a lesion, as e.g. in many meningiomas and oligodendroglioma, produces diffusely stronger echo patterns, while intratumoral cysts or areas of liquefactive necrosis appear as echo-free or echo-poor zones within tumor substance. The delineation of cystic and solid parts of a tumor as well as the differentiation between cyst and necrosis is even more distinct than on CT images. When looking at astrocytomas the higher-grade ones tend to be more locally invasive, a feature that is often reflected in the sonographic appearance of a zone of intermediate echogenicity. Aggressive astrocytomas are also more likely to contain echo-poor areas of tumor necrosis. Even edema can often be distinguished from the surrounding brain a feature that makes the ultrasonography a helpful adjunct to other imaging modalities. Koivukangas demonstrated in a clinical study of 27 brain tumors that the ultrasound imaging could serve to distinguish between tumor and edema in cases where the CT result was equivocal. This was confirmed by LeRoux et al. who showed the increased echogenicity to be due to diffuse tumor invasion or gliosis following previous surgical intervention. Therefore ultrasonography improved intraoperative delineation of tumor margins, thus maximizing the extent of resection. Later; Auer et al. compared in a large investigation preoperative CT and intraoperative ultrasonography results. Whenever there was a discrepancy between those two imaging modalities while examining gliomas the ultrasonography gave a more accurate image of the situation, as confirmed at operation [28].
### 3.6 Goals of surgical resection

The goals of surgical resection are to establish a histological diagnosis, relieve symptoms, provide tissue for continued studies of the disease and extend patient survival by achieving maximal cytoreduction without morbidity. Although modern imaging techniques, such as magnetic resonance spectroscopy, are improving diagnostic capacity, distinctions between Glioblastoma Multiforme, other primary brain tumors, brain metastases and abscesses cannot be made from radiographic studies alone. Thus a major goal of surgery is to provide adequate samples for correct histological diagnosis.

Despite arguments that stereotactic biopsy can be utilized to obtain tissue appropriate for diagnosis, the common practice of performing a stereotactic biopsy prior to the open craniotomy is generally not warranted unless a chemo- or radiosensitive neoplasm (e.g. lymphoma), an abscess, or another non-neoplastic lesion is highly suspected. In these cases, a stereotactic biopsy prior to the open craniotomy is generally not warranted unless a chemo- or radiosensitive neoplasm (e.g. lymphoma), an abscess, or another non-neoplastic lesion is highly suspected. In these cases, a stereotactic biopsy may eliminate the need for a craniotomy. However, when a Glioblastoma Multiforme or other glial neoplasm is the primary radiographic diagnosis, we generally advocate proceeding directly to open craniotomy. The advantage of this approach is that it avoids two procedures and that the histological diagnosis is usually more accurate when large amounts of tissue are provided to the neuropathologist. Specifically, in a study of 81 consecutive patients treated at the M. D. Anderson Cancer Center (MDACC), it was shown that even with expert neuropathological review, there is a 38% discrepancy between the diagnoses made from small biopsy specimens compared with that made from resected. Importantly, the incorrect diagnosis made by small biopsies would have affected therapeutic regimens in 26% of cases and prognostication in 38% of cases.

In our opinion, stereotactic biopsy should be reserved for those cases in which radical resection of the lesion are not considered desirable, e.g. in the case of a diffusely infiltrating “butterfly” or brainstem glioma. If a biopsy is the primary method form obtaining tissue, improvement in the diagnostic accuracy can be achieved with MR image-guided procedures and serial sampling through all areas of the tumor with particular attention to the contrast-enhancing portion of the lesion and its interface with the necrotic and surrounding hypointense regions. More recently, magnetic resonance spectroscopy has been utilized to guide stereostatic biopsies due to its potential ability to identify the most malignant portion of a neoplasm based on the elevation of the choline to creatine ratio and reduced level of N- acetylasparate found in malignant neoplasms compared with normal or cerebral edema.

There are two general approaches to the resection of Glioblastoma Multiforme. The first is an “inside-out” approach in which the surgeon enters the solid tumor as an initial step in the resection and then proceeds to perform a piecemeal removal directed towards the edge of the lesion. The edge is defined as the zone where more normal brain than tumor initially there is less chance of injuring surrounding brain and the critical edge that juxtaposes normal brain is encountered after much of the mass is removed. A major problem with this approach however, is
that the center of a GBM is usually the most vascular part of the tumor. These tumor vessels are also very fragile as they are neoplastic and not normal in their structure. Thus, with the inside-out approach the surgeon is often faced with significant bleeding from vessels that are difficult to coagulate and that can obscure vision and make identification of the borders of the lesion difficult. Moreover, the vessels that supply the tumor come from the sulci and these are identified only at the conclusion of the resection.

An alternative resection technique and one to which we espouse is circumferential or en bloc tumor removal. In this approach, the edges of the tumor are defined at the outset before any incision is made in the brain. The edge of the tumor is the border of the enhancing portion of the solid tumor mass (or beyond this point if the lesion is in noneloquent regions). In the past, we relied on visual inspection and intraoperative ultrasound to define this edge, but computer-assisted image-guided stereotaxis (see below) has revolutionized the surgeon’s capacity to precisely define the interface between the enhancing and nonenhancing portions of the tumor.

An important consideration of this approach is to define the edge relative to surrounding sulci. In our experience, the edge of the enhancing mass often forms one side the sulcal wall. These sulci can then be split allowing for identification of the feeding vessels and preservation of the mass branches. After the definition of the intended plane of dissection, the pia is located along the edge of the tumor. The different tissue consistency of these zones allows them to separate with gentle dissection. All feeding vessels to the tumor can be coagulated. Thus the en bloc specimen is typically attained.

The advantage of this approach is that the edge is defined early in the procedure and that bleeding is kept minimized because the center of the tumor, where the vessels are fragile and immature, is not entered, while enabling identification of the feeding vessels at their origin. In addition, vessels passing through the tumor can be preserved because they are identified before tumor can be preserved because they are identified before tumor resection commences. Importantly, one can preserve venous structures until the end of the resection so that arterial outflow is maintained until all the arterial feeders are detached from the mass.

It is our general preference to perform this type of en bloc resection whenever feasible. This approach is most difficult for deep lesions because the surgical corridors are often too small to allow the tumor to be removed as a single mass and so inside-out resections may be required. In these cases, an attempt is made to dissect circumferentially as much as possible before truncating the tumor. Sequential dissection and removal is then used to progressively resect the tumor.

In cases where the tumor is some distance from critical areas, resection of the lesion with wide margins may be possible. This is the most commonly done with lesions involving the frontal, temporal, or occipital lobes, where a lobectomy can be performed. The advantage of a lobectomy is that both the enhancing portion and a variable amount of the surrounding T2 changes on MR images will be resected [14].
3.7 Measurements

Some of the main characteristics that we can approximate with the use of Intraoperative Ultrasound are:

- Character of the lesion
- Position of the lesion
- Depth from the surface of the brain

The depth and location of masses relative to the craniotomy site could be determined before the intracranial portion of the operation which actually began [5]. The tumor location under the craniotomy the margins from the perilesional brain tissue, internal configuration and echogenicity, the changes in the peri-tumoral area and the location of the neuroanatomical structures such as the ventricle, falx and main arteries to the border of the lesions were also imagined. High-grade glial tumors generally have irregular margins. This feature reflects their invasive character. Surgical dissection of these tissues from the brain is extremely difficult. Necrotic components are dead parts of lesion and commonly found in malignant tumors. They do not have any vital metabolic reactions and blood circulation. The sonographic appearance of these parts is as low echogenic areas located somewhere in the tumor parenchymal [13]. Tumor depth and other measurements were made at the time of examination using digital electronic calipers incorporated into the scanner. Correction for sound velocity in the brain was not used in measuring distances within the brain and all depth measurements were made with an assumed velocity of sound transmission of 1540 meters per second [9]. The hypervascularity of a tumor can be well demonstrated on IOUS by color Doppler over the core of the tumor [10].

3.8 Results of intraoperative ultrasound application generally

Since the technique is dynamic and extremely flexible, it allows the neurosurgeon to study the brain in much greater detail than can be accomplished by most diagnostic techniques. Easily location lesions and biopsies can be under ultrasonic guidance. Most importantly ultrasound allows a direct approach through the brain when necessary with minimal cerebral tissue and it shows precisely the extent of tumor resection.

Many more cross sections through the brain can be rapidly obtained at a real-time frame rate than can be obtained with standard CT scanning. The excluded fluid collections were purely hemorrhagic. Because of the known time-dependent changes in the appearance of intracranial blood on both CT and ultrasound scans. We cannot correlate the ultrasonic findings with the CT
findings for example since at times there was a considerable interval. In contradistinction to CT intraoperative ultrasound accurately locates the lesion at the time of surgery and it defines the lesion at the time of surgery and it defines the lesion in any plane and determines the relationship of a lesion to adjacent brain tissue. In the future ultrasonic techniques have the potential to replace complicated CT stereotactic maneuvers in selected patients with intracranial lesions [8].

The extent of tumors after partial resection could be mapped to determine the amount and distribution of any residual mass [5]. In many times, there is a clear definition of the location, configuration, and tissue consistency of the mass [6]. Small lesions under 1cm in diameter are difficult to be located without ultrasonography. The ability to locate precisely a deeply situated intracranial lesion intraoperatively and the use of microsurgical techniques can minimize the risk of damaging normal cerebral tissue and reduce the length of surgery. Also it is especially valuable in preventing unnecessary damage to normal brain tissue during exploration. No infections or other complications have resulted from the use of the transdural intraoperative ultrasound [9]. The extent of resection and the site of tissue biopsy for pathologic examination can be chosen precisely on the basis of the ultrasonic localization.

Most of the intracranial lesions were hyperechoic, except those with a cystic component. It was also found that intraoperative Ultrasound is very sensitive for differentiating the solid part from the cystic portion [10]. The demonstrated features such as necrotic parts, perilesional edemas, irregular contour and contrast enhancement could be more of intraoperative help in orientation and consequent tumor removal than in differentiating between various histological effects [13]. The results show that the pulsation of the brain caused by the normal systole/diastole arterial pressure variation is sufficient for reliable strain calculation. This means that the surgeon only needs to hold the probe in a fixed position for a few seconds and the data acquisition thus implies no changes to equipment or procedures normally applied during US-guided neurosurgery. In the strain images, the brain tumors were associated with lower strain magnitude than the surrounding normal tissue. The strain imaging of the tumors showed overall good qualitative correspondence with the B-mode images; however, we also noticed smaller areas where the strain data might indicate tumor, whereas the conventional US did not. For the two cases investigated, rectification and subsequent smoothing of the strain images enhanced the visualization of the tumor borders. We conclude that vascular pulsation is sufficient for generation of elastograms of the brain and that this imaging modality can be used for tumor detection [15].

Image-guided neurosurgery increases surgical radicality for glioblastomas while at the same time minimizing surgical morbidity thus improving the patients’ quality of life and progression-free time of survival. Surgery will be in the future as today the mainstay for the treatment of patients harboring glioblastoma multiforme but the quality of surgical interventions will further be improved. Surgery will still be, at least for a while, the mainstay for the treatment of cerebral gliomas, but any other possibility for dealing with those especially highly aggressive tumors
needs to be evaluated carefully for its potential advantages and disadvantages because surgery cannot cure a neoplasm that extends far beyond its definable borders. Neuronavigation in brain tumor surgery is still in its infancy, and many neuronavigator systems are just developing into their second generation. New possibilities will open up in the forthcoming years leading neurosurgery into the next millennium and to completely new horizons especially for the treatment of brain tumor patients [28].

3.9 Drawbacks

Intraoperative ultrasound is limited by its relatively poor signal-to-noise ratio and its two dimensions, usually in an oblique orientation, both of which detract from its interpretability and value as an intraoperative adjustment [10]. The disadvantage of ultrasound includes inability to view tumors that are not echogenic and the inability to traverse bone and thus guide the positioning of the craniotomy. Also, in many cases of radiation necrosis and in some cases of recurrent tumors, the boundaries of the lesion are less well defined.

These neuronavigation systems allow the surgeon to navigate the brain based on the preoperative images and are useful for accurately localizing the lesion, permitting preoperative planning of the approach, placing the skin incision and craniotomy and defining the edge between the contrast enhancing region and surrounding brain. Despite its obvious advantages for localization, these neuronavigation systems suffer from the inability to update the image in real-time. Thus, they cannot account for brain shift as the tumor is resected or with release of cerebrospinal fluid. However the success of these systems may have been less than desirable. Consequently, all of these systems become less accurate as the procedure proceeds and we generally rely on standard intraoperative ultrasound as the resection progresses [14].
Chapter 4

“Analysis of Field II, Methodology, Results & Discussion”

4.1 Introduction

In order to achieve this kind of simulation we use Field II, a program which was created by a group of technical university of Denmark. Field II is a program for simulating ultrasound transducer fields and ultrasound imaging using linear acoustics. The program is capable of calculating the emitted and pulse-echo fields for both the pulsed and continuous wave case for a large number of different transducers. Also any kind of linear imaging can be simulated as well as realistic images of human tissue [42].

4.2 Materials and Methodology

4.2.1 Program analysis, organization and function.

The program consists of a C program and a number of MATLAB m-functions that calls this program. All calculations are performed by the C program and all data is kept by the c program. The Field program system uses the concept of spatial impulse responses as developed by Tupholme and Stepanishen in a series of papers. The approach relies on linear systems theory to find the ultrasound field for both the pulsed and continuous wave case. This is done through the spatial impulse response. This response gives the emitted ultrasound field at a specific point in space as function of time, when the transducer is excited by a Dirac delta function. The field for any kind of excitation can then be found by just convolving the spatial impulse response with the excitation function. The impulse response will vary as a function of position relative to the transducer, hence the name spatial impulse response.

The received response from a small oscillating sphere can be found by acoustic reciprocity. The spatial impulse response equals the received response for a spherical wave emitted by a point. The total received response in pulse-echo can, thus, be found by convolving the transducer excitation function with the spatial impulse response of the emitting aperture, with the spatial impulse response of the receiving aperture, and then taking into account the electro-mechanical transfer function of the transducer to yield the received voltage trace. Any excitation can be used, since linear systems theory is used. The result for the continuous wave case is found by Fourier transforming the spatial impulse response for the given frequency. The approach taken here can, thus, yield all the different commonly found ultrasound fields for linear propagation.

A number of different authors have calculated the spatial impulse response for different transducer geometries. But in general it is difficult to calculate a solution, and especially if
apodization of the transducer is taken into account. Here the transducer surface does not vibrate as a piston, e.g. the edges might vibrate less than the center. The simulation program circumvents this problem by dividing the transducer surface into squares and the sum the response of these squares to yield the response. Thereby any transducer geometry and any apodization can be simulated. The approach is described in.

The time for one simulation is also of major concern. As the squares making up the transducer aperture are small, it is appropriate to use a far-field approximation, making simulation simple. Another issue in keeping the simulation time down is to use a low sampling frequency. Often spatial impulse responses are calculated using sampling frequencies in the GHz range due to the sharp discontinuities of the responses. These discontinuities are handled in the Field programs by accurately keeping track of the time position of the responses and use the integrated spatial impulse response as an intermediate step in the calculations. Thereby no energy is lost in the response, which is far more important than having an exact shape of the spatial impulse response. Hereby the Field program usually does better using 100 MHz sampling and approximate calculations, than using the exact analytic expression and GHz sampling [41], [42].

Field II can simulate all kinds of transducers using linear acoustics. The calculation of the Spatial Impulse Response assumes linearity and any complex-shaped transducer can therefore be divided into smaller apertures and the response can be found by adding the responses from the sub-apertures. All kinds of ultrasound transducers control dynamically the focusing and the apodization of the transducers.

When the medium becomes complex, solving the wave propagation formula becomes impossible. Modeling becomes more complex inside the body because the ultrasound propagation speed is different for each tissue. It is important to know how the ultrasound wave is generated and the ultrasound wave beam shaped. The simulation method can be used for optimization of the array parameters in the design stage. The purpose of the program is to predict ultrasound fields and thereby make it possible to optimize the geometry, phasing and apodization of an ultrasound [40, 41, 42, 46, and 47].
### 4.2.2 Field II Simulation and Anatomic Phantoms

Field simulation generally follows this type of sequence:

- Define an array.
- Define the Impulse Response of a transducer element of that array.
- Define the waveform of the transmitted signal.
- Define targets that will be imaging.
- Calculate the scattered response from these targets for each image line position.
- Envelope detection and compress.
- Display the image [40, 43].
- Image analysis (Optical analysis of image, CNR contrast analysis of image).

The simulations of artificial phantoms are done by simulating and summing the field from a collection of point scatterers. A single RF line in an image can be calculated by summing the response from a collection of scatterers, in which the scattering strength is determined by the density and speed of sound perturbations in the tissue. Homogeneous tissue is, thus, made from a collection of randomly placed scatterers with a scattering strength with a Gaussian distribution. The variance of the distribution is determined by the backscattering cross-section of the particular tissue.

The phantoms typically consist of 100,000 or more scatterers, and simulating 50 to 128 RF lines can take several days depending on the computer used. It is therefore beneficial to split the simulation into concurrently run sessions. This can easily be done by first generating the scatterer's position and amplitude and then storing them in a file. This file can then be used by a number of workstations to find the RF signal for different imaging directions, which are then stored in separate files; one for each RF line. These files are then used to assemble an image. This is the approach used for the simulations shown here. For the 1 million scatterers it roughly takes 1 hour and 10 minutes for a 3 GHz Central Processing Unit (CPU) to generate one RF line, thus, simulating roughly 270 point scatterers per second. The image consists of 128 lines and splitting the simulation over 10 CPUs makes it possible to generate the image in a little over 12 hours. The 100 CPU Linux cluster can make the image in roughly 1 hour and 10 minutes.

The anatomic phantoms are attempts to generate images as they will be seen from real human subjects. This is done by drawing a bitmap image of scattering strength of the region of interest. This map then determines the factor multiplied onto the scattering amplitude generated from the Gaussian distribution, and models the difference in the density and speed of sound perturbations in the tissue. Simulated boundaries were introduced by making lines in the scatterer map along which the strong scatterers were placed. This is marked by completely white lines shown in the scatterer maps. The model is currently two-dimensional, but can readily be expanded to three dimensions. Currently, the elevation direction is merely made by making a 15 mm thickness for the scatter positions, which are randomly distributed in the interval. The scatterer map used in
This example was based on the optical photos from the Visible Human Project. They were created from scanning a human cadaver with CT and MRI scanners and then subsequently slicing the cadaver into 1 mm sections for taking photographs.

A phantom for a left kidney in a longitudinal scan has been made. 1,000,000 scatterers were randomly distributed within the phantom, and with a Gaussian distributed scatter amplitude with a standard deviation determined by the scatter map. The phantom was scanned with a 7 MHz 128 element phased array transducer with lambda/2 spacing and Hanning apodization. A single transmit focus 60 mm from the transducer was used, and focusing during reception is at 5 to 150 mm in 1 mm increments. The images consist of 128 lines with 0.7 degrees between lines [45], [50], [51], [52], [53], [54], [55].

4.2.3 Analysis of routines

The general diagram of the files that we use is below:

We have to mention that firstly we have to initialize Field II with the command field_init via MATLAB [54], [55], [56]. The routines that we have called after are:

- make_scatterers.m
  - human_brain_phantom.m
  - bmpread.m
    - brain_cut.bmp
    - pht_data.mat

- sim_brain.m
  - pht_data.mat
  - Rf_data

- make_polar.m
  - Rf-data
    - make_tables.m
    - make_interpolation.m
    - Final Picture
We have three mainly parts:

- **Creation of the phantom**

  In the first part we have to create the Phantom with the distributed scatterers (1000000 randomly distributed within the Phantom). We use a bmp (8bit) picture of brain. This picture has been created from the normalization according to the 6 different densities of 6 different parts of the brain (water, cerebrospinal fluid, white mater, gray mater, tumor and tumor boundary). So we have a bmp image of scattering strength of the region of interest. The file bmpread.m is used to read the bmp picture of brain from a disk and returns the indexed image X and associated MAP. The file human_brain_phantom.m creates the phantom. The file make_scatterers.m creates the target points (scatterers N=1000000) randomly distributed within the phantom and makes the file for the scatterers in the phantom with the name pht_data.mat.

- **Simulation**

  The second part contains the file sim_brain.m that makes the simulation. The simulation is performed and the data is stored in Rf_file (file Rf_data). The data for the scatterers are read from the file pht_data.mat. Here we define the transducer. Here are all the parameters that we need to define for the transducer:

  - fo = transducer’s frequency
  - f = focal point
  - N = number of elements
  - No_lines = number of lines of RF data

- **Final Image**

  The third part creates the images from the above procedures. The data from file Rf_data are processed to do the polar to rectangular mapping to yield the image. This is done by the routine make_polar.m that creates an image with a dynamic range of 50dB. The parameter that we have changed is the No_lines that must be the same with the number of elements. By calling the routine make_polar.m, this file uses the files make_tables.m and make_interpolation.m to work properly. With this procedure we have the picture.
4.2.4 Results

4.2.4.1 Results of Simulation in Field II

Before referring the results we have to mention that the experiments have been done according to the combinations of the parameters that can take specific values due to the bibliography, we have 8 experiments.

For $f_0 = 3\text{MHz, 7MHz}$

$N = 70, 128$

$f = 30\text{mm, 90mm}$

The combinations are:

- For $f_0=3\text{MHz, } f=30\text{mm, } N=70$
- For $f_0=3\text{MHz, } f=30\text{mm, } N=128$
- For $f_0=3\text{MHz, } f=90\text{mm, } N=70$
- For $f_0=3\text{MHz, } f=90\text{mm, } N=128$
- For $f_0=7\text{MHz, } f=30\text{mm, } N=70$
- For $f_0=7\text{MHz, } f=30\text{mm, } N=128$
- For $f_0=7\text{MHz, } f=90\text{mm, } N=70$
- For $f_0=7\text{MHz, } f=90\text{mm, } N=128$

So we have 8 different combinations:
Final Images

Figure 4.1

(Normalized Picture of Brain Before Simulation)
Figure 4.2
1. fo=3MHz, f=30mm, N=70

Figure 4.3
2. fo=3MHz, f=30mm, N=128

Figure 4.4
3. fo=3MHz, f=90mm, N=70

Figure 4.5
4. fo=3MHz, f=90mm, N=128
5. $f_0=7\text{MHz}$, $f=30\text{mm}$, $N=70$

6. $f_0=7\text{MHz}$, $f=30\text{mm}$, $N=128$

7. $f_0=7\text{MHz}$, $f=90\text{mm}$, $N=70$

8. $f_0=7\text{MHz}$, $f=90\text{mm}$, $N=128$
4.2.4.2 Results of CNR Analysis

Contrast-to-Noise-Ratio Resolution is the ability to distinguish between differences in intensity in an image. The measure is used in medical imaging to qualify the quality of acquired images. CNR is similar to the metric Signal-to-Noise-Ratio (SNR), but subtracts off a term before taking the ratio. So we can calculate signal intensity differences between two regions.

In order to calculate CNR we use the formula:

\[
\text{CNR} = \frac{|S_a - S_b|}{\sigma_o}
\]

Where:

- \(S_a\): is the average of the pixels’ values in region a (region with tumor)
- \(S_b\): is the average of the pixels’ values in region b (background)
- \(\sigma_o\): is the standard deviation of the values of the pixels in region b.

The regions in pixels that we have chosen from the pictures of our Results are:

- For region a:  
  i) 276:356
  j) 361:441

Figure4.10: Region a
• For region b:  i) 159:239

j) 409:489

Figure 4.11: Region b

The values of these pixels are the values that will give us the region for the test. In the table 4.1 below, we can see the results of calculations and the CNRs for every experiment. According to these results the best picture is Figure 4.9, which represents the final experiment.

**Calculations of CNR & Results**

Table 4.1

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</table>
4.3 Discussion

We depict the appearance and properties of b-scan ultrasound image from the distribution of point scatterers. Image simulation has been done by taking into account the densities of the tissues the geometry and the characteristics of the ultrasound probe. For example the transducer’s size and element number, it’s frequency etc.

They are presented the most of the real characteristics of an ultrasound image. This ultrasound image is estimated by the simultaneous study temporal ultrasound field and it’s interaction with the scatterers. The starting data is a picture extracted from a brain model. We have chosen a 2D slice where the pixel size is known. After we normalize this picture according to the density values of every tissue which is part of the part that we want to depict. According to the classification, densities are allocated to each image pixel. With this way we have a bmp image with specific pixel size. However, the main part of an ultrasound image consists of a speckle pattern. Speckles come from the signal reflected by tissue micro-in homogeneities. These micro-in homogeneities are generally simulated by randomly placed scatterers.

Geometry and characteristics of the ultrasound probe (focal point, transducer’s number and size, transducer’s frequency) are the input parameters. The main flow of the procedure of the simulation is below:

One of the most important parts is to analyze the influence that has every one of the parameters that we change in every experiment, on the final image. Below follows the analysis of the parameters that we change in every experiment:

- **Frequency influence:**
  The frequency influence can be seen in the results. This influence on the spatial resolution is easily perceptible on the images (page 98-99). Here we cannot discuss about change in penetration depth, because we have limits from the pixels.

- **Probe’s elements influence:**
There are experiments that have been produced with the same focal point and frequency but different elements (70 & 128). The number of the elements and their size has a direct impact on the lateral resolution of the simulated images.

- **Focal’s point influence:**
  Focal point is the point in a focused ultrasound beam with the highest intensity measured in a non-attenuating medium. The closer the structure of interest to the focal point, the better the resolution. We can see in the results that the most appropriate focal point is 90mm.

**Choice of the Best Experiment Combination**

→ **According to simple observation:**
As we can see from the comparison of the simulated images from pages 98, 99 the 8th experiment with parameters’ values $f_o=7\text{MHz}$, $f=90\text{mm}$, $N=128$ are the most appropriate as geometry and transducer characteristics for the ultrasound imaging.

→ **According to CNR analysis:**
With these values we can compare signal intensity differences. Improving CNR increases perception of the distinct differences between two clinical areas of interest. The low CNR of the system is often determined using objects having a very small difference from background. In this case because the signal (the difference from background) is so small, noise is a significant factor. In our case the bigger the CNR, the bigger difference between the tumor and the background, so we have better depiction. According to this we choose the same result with the previous simple observation the 8th experiment as the best result in our project.

$fo=7\text{MHz}$, $f=90\text{mm}$, $N=128$

![Figure 4.12: Final experiment. Optimal result.](image)
Real and Simulated Ultrasound Comparison

We wished to compare qualitatively a real ultrasound image found in the literature with a simulated one. In both cases the pulse frequency was 7 MHz (figure 5). Because the observed scene is different between the two images, the only ambition of this comparison is to present the mutual characteristics of both images but also the disparities between our model and a real ultrasound image. The real ultrasound image depicts a baby's brain.

![Real and Simulated Ultrasound Comparison](image)

Figure 4.13: Comparison between a real 7 MHz ultrasound image (left) and a simulated one (right).

Qualitatively, we find in the simulated ultrasound image some of the main characteristics of a real ultrasound image:

- The simulated ultrasound image is mainly produced by speckle patterns which are organized on concentric circles. The speckle size grows when the distance to the probe increases.
- The pulse frequency and the number of probe transducers seem to have the expected behavior on the simulation. Higher pulse frequencies give finer speckle in the axial direction and so enhance the spatial image resolution. A high number of transducers provides finer speckle in the lateral direction.
- The acoustical interface between tissues is well delineated. However, other ultrasound image characteristics have not been taken into account. This is the case for example of the signal attenuation by the medium absorption.

Ultrasound devices compensate this attenuation by amplification with a gain increasing with the depth. This gain has the effect to enhance the attenuated signal but also the noise. Other ultrasound image characteristics like acoustic shadow or mirror effect are totally absent on the simulated images. This lack comes directly from the used model where the wave propagation and reflection are not simulated explicitly; however, these effects are generally considered as artifacts on the real ultrasound images. But beyond these remarks, additional differences between
simulated and real images remain. Firstly we have not taken the operators pressure on the probe and the resulting organs deformation into account. Secondly, a great aspect difference is provided by our tissue microinhomogeneities model. Seeing that the main aspect of an ultrasound image is provided by the speckle, a more realistic modeling of tissue in inhomogeneities should enhance the realism of the simulated image. Concluding, Ultrasonic imaging is the most common medical imaging technique for producing elastograms.
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