UNIVERSITA' DEGLI STUDI DI PISA

FACOLTA' DI INGEGNERIA
CORSO DI LAUREA SPECIALISTICA IN INGEGNERIA BIOMEDICA
&
EUROPEAN PATENT OFFICE

Tesi di Laurea

"STATE OF THE ART INVESTIGATION IN MEDICAL ULTRASOUND DIAGNOSTICS USING PATENT PUBLICATIONS DATABASE"

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Chapter 4: Three Dimensional Imaging with ultrasound

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INTRODUCTION

Patents are now an integral part of global economy. The creation of the world trade system has also redefined the value of intellectual property protection and generated an unprecedented demand for patent protection that is no longer limited o the traditionally patent-oriented economies of Europe, Japan and the USA.

Countries like China, India and Korea, and Singapore and Israel too, are just some of the new players heavily involved in patent-driven innovative competition.

Patents protect technical inventions. An invention can, for example, be a product, process or apparatus. Inventions are only patentable if they are novel, industrially applicable and involve an inventive step, but even then patent protection is not ranted automatically. The application must be accompanied by a full technical description of the invention, which the Office then examines for compliance with the European Patent Convention.

Patents give their owners the right to prevent others from using their invention, and are thus of major economic importance. They also help to recoup research costs, allowing the inventor to reinvest in research and development.

The publication requirement allows competitors to build on patented inventions and come up with even better technical solutions. In doing so, patents boost the innovation which Europe badly needs to keep up with other economies, and contribute to the further development of a knowledge

society. The 56 million or so patent documents contained in the public EPO database constitute a vast trove of technical information.

The field of medical device, IPC class A61, according to European Patent Office Annual Report of 2005, is one of the technical fields with the most filings.

Anmeldestärkste technische Gebiete
Technical fields with the most filings
Domaines techniques dans lesquels le plus grand nombre de demandes ont été déposées

IPC-Klassen IPC classes Classes de la CIB		2004 Anzahl Number Nombre	2004 %	2005 Anzahl Number Nombre	2005 %	Veränderung 2004/2005 Change 2004/2005 Changement 2004/2005 Anzahl Number Nombre	%
A 61	Medizin oder Tiermedizin; Hygiene Medical or veterinary science; hygiene Sciences médicales ou vétérinaires ; hygiène	13 761	11.1	14 688	11.4	927	+6.7
H 04	Elektrische Nachrichtentechnik Electric communication technique Technique de la communication électrique	12 139	9.8	12 843	10.0	704	+5.8
G 06	Datenverarbeitung Computing Traitement des données	8 213	6.6	8 664	6.7	451	+5.5
H 01	Elektrische Bauteile Basic electric elements Eléments électriques	7 379	6.0	7 541	5.9	162	+2.2
C 07	Organische Chemie Organic chemistry Chimie organique	6 246	5.0	6 570	5.1	324	+5.2
G 01	Messen; Prüfen Measuring; testing Métrologie et essais	6 686	5.4	6 525	5.1	–161	–2.4
B 60	Fahrzeugtechnik Vehicles in general Véhicules	3 907	3.2	4 175	3.2	268	+6.9
C 12	Biochemie; Gentechnik Biochemistry; genetic engineering Biochimie ; génie génétique	3 967	3.2	4 098	3.2	131	+3.3
C 08	Org. makromolekulare Verbindungen Organic macromolecular compounds Composés macromoléculaires organiques	3 129	2.5	3 331	2.6	202	+6.5
F 16	Maschinenelemente Engineering elements Eléments de technologie	3 242	2.6	3 278	2.5	36	+1.1
	Zwischensumme Sub-total Total partiel	68 669	55.5	71 713	55.7	3 044	+4.4
	Andere Others Autres	55 106	44.5	56 966	44.3	1 860	+3.4
	Gesamt Total Total	**123 775**	**100.0**	**128 679**	**100.0**	**4 904**	**+4.0**

This state of the art investigation, performed using the patent publications database, is focused on the field of diagnostic ultrasound, a field that thanks to its non ionizing nature and low cost is a very high growing area and a lot of scientific research is made.
Scope of this work is to provide an useful tool that allows to check the level of the ultrasound technology and to indicate the future direction of this technique.
Scope of this work is also to provide information to all the researchers and inventors who want to set out a patent procedure of an invention. As known, the patent procedure, from the filing day until the decision of granting the patent is quite expensive, this work could be used as a primary consultation tool before to present a patent application. All chapters of this work contains an introduction that explain the technical problematic of a field and in the subsequent sections the solutions are described.

In the **first chapter** of this work the European Patent Office and the world of patents is introduced. A special attention is revolted to several articles of the EPC (European Patent Convention) and to the classification system adopted by the EPO. Some statistics about European patent application filed in 2005 are illustrated and the difference between the first to invent system adopted by EPO (and by the majority of countries) and the first to invent system (adopted by U.S.A.) will be treated at the end of this chapter.
In the **second chapter** the basics of ultrasound are illustrated with particular attention to the physics principles that are at the base of ultrasound devices described in this state of the art investigation.
The state of the art is divided in 5 chapters, from 3 to 7, each chapter is about a specific technique. In the **third chapter** the ultrasound contrast agents are introduced and their main diagnostic application are disclosed.
The **fourth chapter** is about three dimensional imaging, this field is divided in 4 section: mechanical, free-hand, 2D arrays and catheters.
In the **fifth chapter** the technique of elastography and its application is described focusing on the stimulation protocols and methods.
The **sixth chapter** is directed to all the devices that allow to study the blood flow inside vessels and arteries and the **seventh chapter** treats about the

ultrasound catheters and their characteristics. At the end of each chapter statistics about the trends in European patent application in the last 25 years will be illustrated.

In the conclusion of this work the future developments field of ultrasound technique will be illustrated.

CHAPTER I

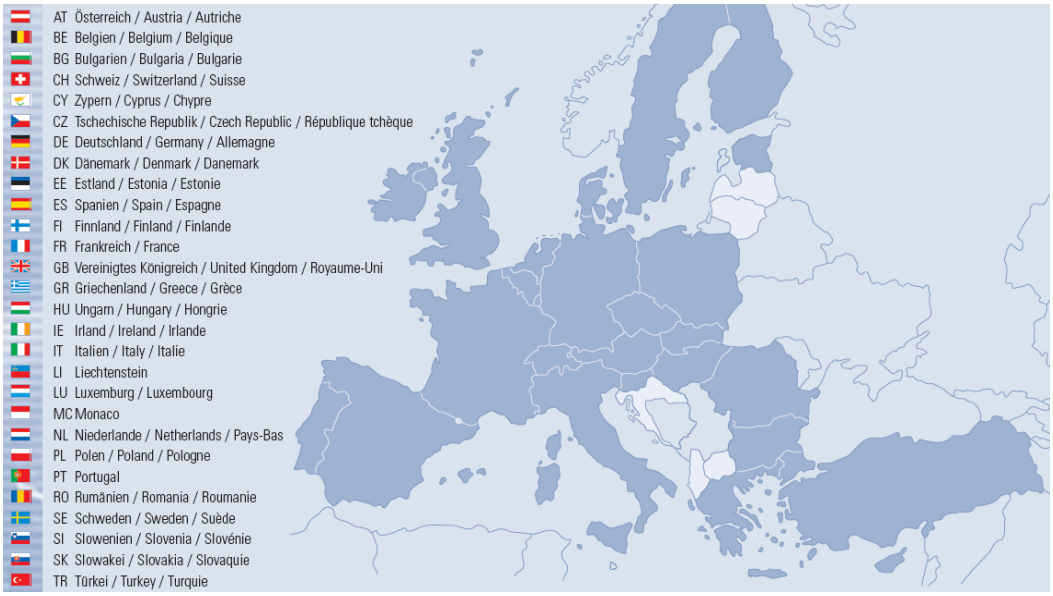
THE EUROPEAN PATENT OFFICE

& THE STATE OF THE ART

The mission of the EPO
– the patent granting authority for Europe –
is to support competitiveness and
economic growth
for the benefit of the citizens
of Europe

1.1 INTRODUCTION

The European Patent Office (EPO) grants European patents for the contracting states to the European Patent Convention (EPC), which was signed in Munich on 5 October 1973 and entered into force on 7 October 1977. It is one of the big three patent offices (with USA and Japan) and it is the executive arm of the European Patent Organisation, an intergovernmental body set up under the EPC, whose members are the EPC contracting states. The contracting states are 31, in the course of the year 2005, Latvia became the European Patent Organisation's 31st member state. The contracting states of EPO are (Fig. 1.1):



Contracting states

AT	Austria	FR	France	MC	Monaco
BE	Belgium	GB	United Kingdom	NL	Netherlands
BG	Bulgaria	GR	Greece	PL	Poland
CH	Switzerland	HU	Hungary	PT	Portugal
CY	Cyprus	IE	Ireland	RO	Romania
CZ	Czech Republic	IS	Iceland	SE	Sweden
DE	Germany	IT	Italy	SI	Slovenia
DK	Denmark	LI	Liechtenstein	SK	Slovakia
EE	Estonia	LT	Lithuania	TR	Turkey
ES	Spain	LU	Luxembourg		
FI	Finland	LV	Latvia		

Figure 1.1 The contracting states to the EPC

The EPO is not an EU organization, and is wholly self financing. The activities of the EPO are supervised by the Organisation's Administrative Council, composed of delegates from the contracting states

In view of the increasing interest in obtaining patent protection in central and eastern European countries, the European Patent Organisation has concluded bilateral agreements with Albania, Croatia, Lithuania and the former Yugoslav Republic of Macedonia, allowing the protection conferred by a European patent to be extended to these countries at the applicant's request. In October 1999 the EPO began negotiations to introduce a similar system for validating European patents outside Europe.

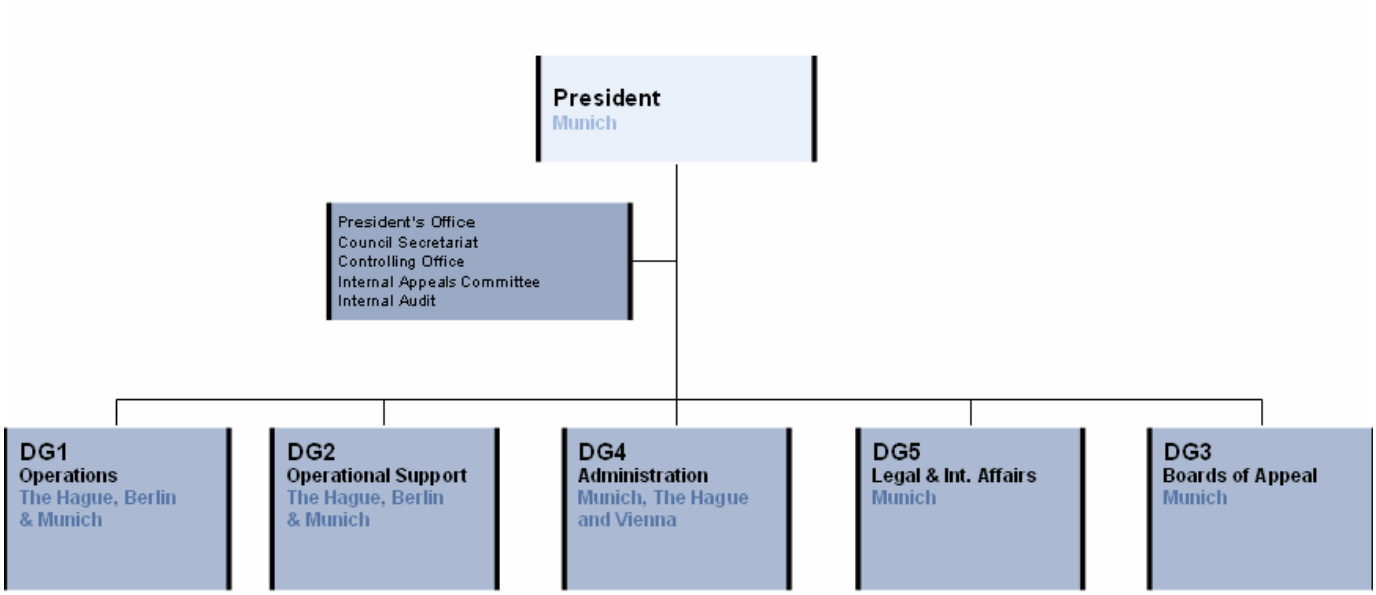


Figura 1.2: European Patent Office organigram

The location of the European Patent Office and the staff are:

- MUNICH

DG 3

Boards of Appeal

DG 4

Administration

DG 5

Legal and Int. Affairs

- THE HAGUE

DG 1

Operations

DG 2

Operational Support

- BERLIN

DG 1

Operations

DG 2

Operational Support

- VIENNA

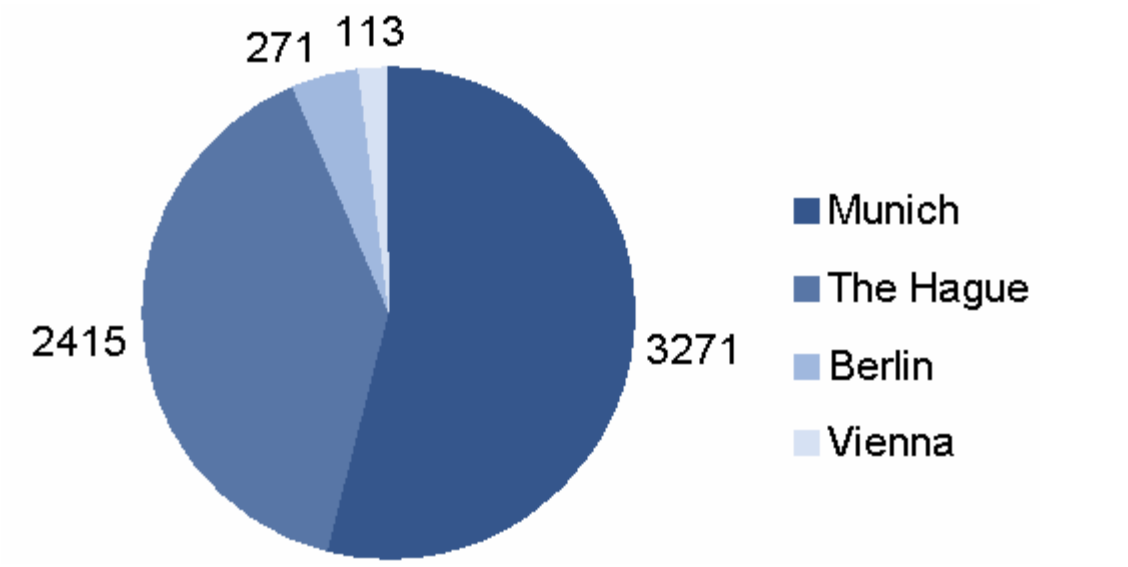
DG 4

Patent information

DG 2

Operational Support

- EPO STAFF BY LOCATION



1.2 STRUCTURE OF AN EUROPEAN PATENT

A patent is an exclusive entitlement to an invention and allows to forbid other people from using it for commercial purposes within a certain area of jurisdiction.

A patents protect the inventor against others taking advantage of the invention without payment.

The European Patent is divided in 3 parts

- Description
- Figures
- Claims

The first page of a patent contains some FIELDS of a patent like the publication date, the inventor name, the title etc. The layout of the first page is shown in figure 1.3

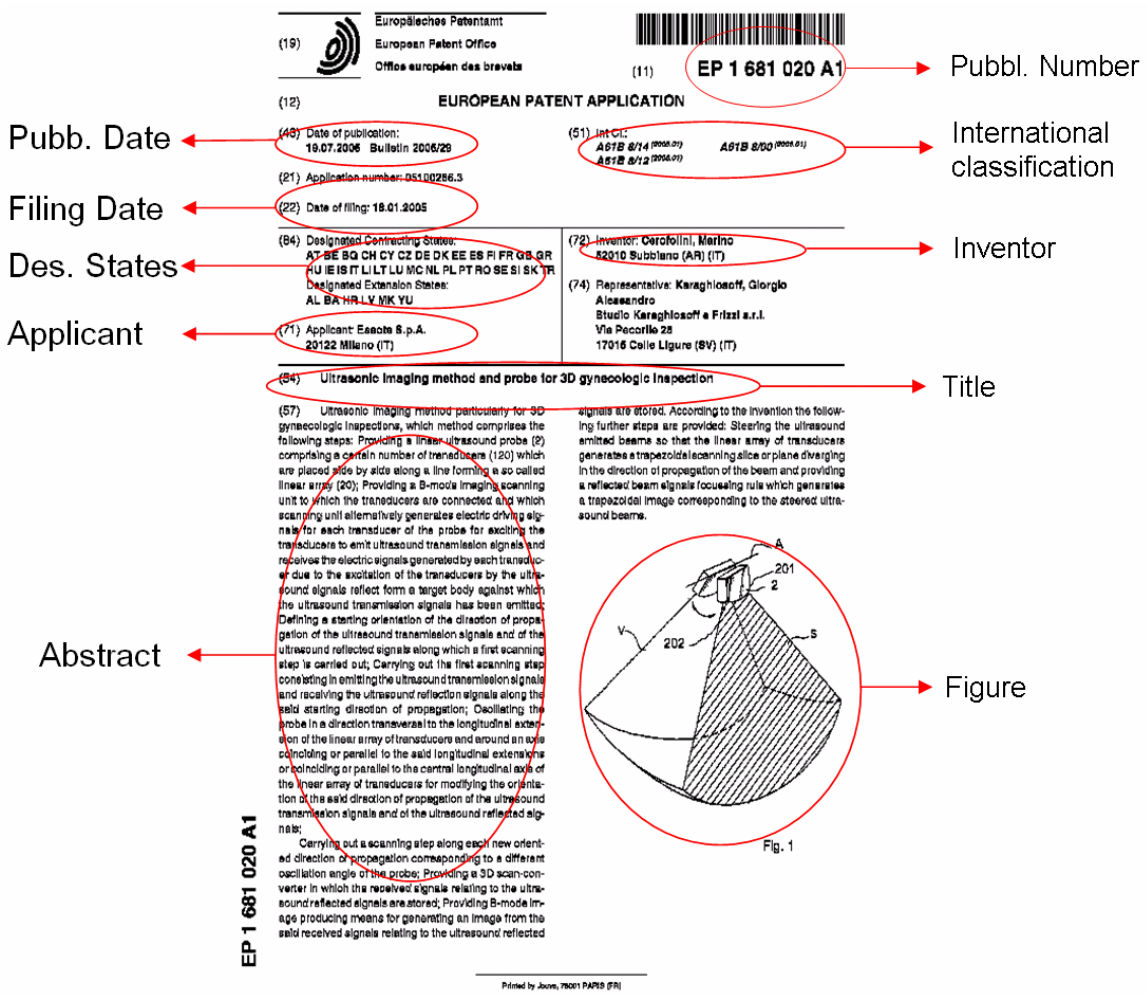


Figure 1.3 First page of a patent

The DESCRIPTION and the FIGURE are useful to understand the technical problem and the solution provided by the inventor.
The most important part of a patent are the CLAIMS. The claims are in the last part of the patent after the description.

Claims

1. Ultrasonic imaging method particularly for 3D gynaecologic inspections, which method comprises the following steps:

Providing a linear ultrasound probe (2) comprising a certain number of transducers (120) which are placed side by side along a line forming a so called linear array (20);
Providing a B-mode imaging scanning unit to which the transducers are connected and which scanning unit alternatively generates electric

Figure 1.4 Claims

The protection of the patent is guaranteed ONLY on what is written on the claims.

1.3 IPC, THE INTERNATIONAL PATENT CLASSIFICATION

The IPC is a worldwide patent classification system, which is elaborated and published under the responsibility of WIPO (Geneva).

The IPC was established initially on request of the Council of Europe, The first edition was in force from September 1, 1968, to June 30, 1974. The second edition was in force from July 1, 1974 till December 31, 1979. Since then there is a new edition every 5 years. The actual edition (the 8th) is in force since January 1, 2005.

The IPC has a hierarchical structure:

SECTION	e.g.	A
CLASS		A01
SUBCLASS		A01B
MAIN GROUP		A01B1/00
SUBGROUP		A01B1/02

The IPC is divided into eight sections, The section titles are to be considered as a very broad indication of the content: they do not define the exact scope:

A: HUMAN NECESSITIES

B: PERFORMING OPERATIONS; TRANSPORTING

C: CHEMISTRY; METALLURGY

D: TEXTILES; PAPER

E: FIXED CONSTRUCTIONS

F: MECHANICAL ENGINEERING; LIGHTING; HEATING; WEAPONS; BLASTING

G: PHYSICS

H: ELECTRICITY

As described above each section is divided into classes, A class symbol consists of the section symbol, followed by a two-digit number, as for example:

A61 MEDICAL OR VETERINARY SCIENCE; HYGIENE

Classes comprise one or more subclasses. The subclass symbols consist of the class symbols followed by a capital letter.

A61B DIAGNOSIS; SURGERY; IDENTIFICATION

Subclasses are broken down into main groups. Each main group symbol consists of the subclass symbol followed by a one- to three-digit number, an oblige stroke and the number 00.

A61B8/00 Diagnosis using ultrasonic, sonic or infrasonic waves

Subgroups form subdivisions under the main groups. Each subgroup symbol consists of the subclass symbol followed by the one- to three-digit number of its main group, the oblique stroke and a number of at least two digits other than 00.

The subgroup title is often a complete expression, in which case it begins with a capital letter. A subgroup title begins with a lower case letter if it reads as a continuation of the title of the hierarchically higher group. The hierarchy among subgroups is determined solely by the number of dots preceding their titles.

1.4 ECLA, THE EPO CLASSIFICATION

Before 1968, the former “Institut International de Brevets” (IIB) used a classification system called “Indeling der Techniek” (IdT), developed by the Dutch Patent Office, and largely based on the “Deutsche Patentklassifikation” (DPK).

After the first edition of the International Patent Classification (IPC) had entered into force, the IIB decided to convert its search documentation from IdT to a system based on IPC. This classification system would later become the ECLA classification system.

In view of the big differences between both systems, and in order to guarantee the quality of the system, it was decided to transfer the documents gradually, by “closing” the IdT at a certain date (different per technical field), and “opening” ECLA at the same time. New documents were from then on classified according to ECLA, the “backlog” being reclassified systematically or “ad hoc”, e.g. during searches. More than 95% of the classified documentation is now classified according to ECLA. Since 1991 all the new documents are only classified according to ECLA.

The structure of ECLA is similar to that of the IPC described in section x.2, IPC Guidance Headings are only used to identify parts of subclasses relating to the same subject matter. They do not define the scope of groups as such.

Internal subgroups have the same symbol as an IPC group, the text of these internal subgroups is put between **[N:]**.

A61B8/00 Diagnosis using ultrasonic, sonic or infrasonic waves, (imaging of objects using sonar G01S15/00)

A61B8/08 . Detecting organic movements or changes, e.g. tumours, cysts

A61B8/08F . . [N: using mammography (mammography by transillumination, X-ray mammography; detection of breast cancer)]

A61B8/08F2 . . . [N: with suspended breasts, e.g. patient in prone position]

1.5 THE STATE OF THE ART

The state of the art is the highest level of development, as of a device, technique, or scientific field, achieved at a particular time.

First used in 1910 and in the context of the European Patent Convention, the term "state of the art" is a very important concept in the process of assessing and asserting *novelty* and *inventive step*, and is a synonym of the expression "prior art".

Before to define the term "state of the art", the terms novelty and inventive steps should be defined. The ART 54 of the European patent convention establish that:

Novelty, Art 54 of EPC

(1)An invention shall be considered to be new if it does not form part of the state of the art.

(2)The state of the art shall be held to comprise everything made available to the public by means of a written or oral description, by use, or in any other way, before the date of filing of the European patent application.

(3) Additionally, the content of European patent applications as filed, of which the dates of filing are prior to the date referred to in paragraph 2 and which were published under Article 93 on or after that date, shall be considered as comprised in the state of the art.

(4) Paragraph 3 shall be applied only in so far as a Contracting State designated in respect of the later application, was also designated in respect of the earlier application as published.

(5) The provisions of paragraphs 1 to 4 shall not exclude the patentability of any substance or composition, comprised in the state of the art, for use in a method referred to in Article 52, paragraph 4, provided that its use for any method referred to in that paragraph is not comprised in the state of the art.

Inventive step, Article 56 of EPC

An invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art. If the state of the art also includes documents within the meaning of Article 54, paragraph 3, these documents are not to be considered in deciding whether there has been an inventive step.

"The state of the art shall be held to comprise everything made available to the public by means of a written or oral description, by use, or in any other way, before the date of filing of the European patent application" according to Art 54(2) EPC. Due account should be taken of Art. 54(3) as well, but merely for the examination of novelty.

The expression "background art" is also used in certain legal provisions, has the same meaning. The expression "internal state of the art" is used to describe the state of the art merely on possession of the (patent) applicant, but not in the public domain.

One of the most important articles of the Convention, Article 52(1) EPC, entitled "*Patentable inventions*", states:

"*European patents shall be granted for any inventions*

- *which are susceptible of industrial application*
- *which are new, and which involve an inventive step*

This article constitutes the basic, central patentability provision under the EPC.

However, the EPC provides further indications on what is patentable, by introducing exceptions. There are exceptions by virtue of the nature of the patent system (Article 52(2) and (3)) and exceptions by virtue of policy(Articles 52(4) and 53).

First, discoveries, scientific theories, mathematical methods, aesthetic creations, schemes, rules and methods for performing mental acts, playing games or doing business, programs for computers and presentations of information are not regarded as inventions and are excluded from patentability only to the extent that the invention relates to those areas *as such*. These exceptions, by virtue of the nature of the patent system, have been introduced as a way to illustrate what cannot be patentable due to the nature of the patent system, i.e. a patentable subject-matter should usually be directed to some physical product or process. The European Patent Office interprets this as requiring that the features providing the inventive step must be outside those areas.

The second set of exceptions, the exceptions by virtue of policy, include:

- **methods for treatment of the human or animal body by surgery or therapy, and diagnostic methods practiced on the human or animal body.**
- inventions contrary to "*order public*" or morality
- plant or animal varieties and essentially biological processes for the production of plants an animals.

In patent law, industrial applicability or industrial application is a patentability requirement according to which a patent can only be granted for an invention which is susceptible of industrial application, i.e. for an invention which can be made or used in some kind of industry. In this context, the concept of "industry" is far-reaching: it includes indeed agriculture for instance.

The industrial application requirement is closely related to the requirement of sufficiency of disclosure, in fact a patent application must disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

The utility in patent law, is a patentability requirement. Today, the utility requirement is the lowest bar and is easily met. Largely utility is used to prevent the patenting of inoperative devices such as perpetual motion machines.

European patent law does not test utility. Instead, it requires that to be patentable an invention must have industrial applicability.

In most patent laws, **prior art** or **state of the art** is all information that has been made available to the public in any form before a given date. If an invention has been described in prior art, a patent on that invention is not valid.

Information kept secret, for instance as a trade secret, is not usually prior art. Generally, this means that a patent will be granted on the invention despite the fact that someone else knew of the invention. A person who used an invention in secret may in some jurisdictions be able to claim "prior user rights" and thereby gain the right to continue using the invention. As a special exception, earlier filed and unpublished patent applications do qualify as prior art in certain circumstances.

The term "state of the art" is mainly used in the patent field. Patents disclose to society how an invention is practiced, in return for the right (during a limited term) to exclude others from manufacturing, selling, offering for sale or using the patented invention without the patentee's permission. Patent offices deal with prior art searches in the context of the patent granting procedure. To assess the validity of a patent application, patent offices explore the prior art that was disclosed before the invention occurred (in the United States and all first-to-invent patent systems) or before the filing date (in Europe and all first-to-file patent systems).

1.6 FIRST TO FILE V.S FIRST TO INVENT PATENT SYSTEM

First to file and **first to invent** are legal concepts that define who has the right to the grant of a patent for an invention. The first to file system is used in the majority of countries, with the notable exception of the United States, which operates a first to invent system.

In a *first to file system*, the right to the grant of a patent for a given invention lies with the first person to file a patent application for protection of that invention, regardless of the date of actual invention.

The United States uses a *first-to-invent* system, unlike most other countries in the world. Invention is the U.S. generally defined to comprise two steps: (1) conception of the invention and (2) reduction to practice of the invention. When an inventor conceives of an invention and *diligently* reduces the invention to practice (by filing a patent application, by practicing the invention, etc), the inventor's date of invention will be the date of conception. Thus, provided an inventor is diligent in reducing an application to practice, he or she will be the first inventor and the inventor entitled to a patent, even if another files a patent application (reduces the invention to practice) before the inventor.

However, the first applicant to file has the *prima facie* right to the grant of a patent. Should a second patent application be filed for the same invention, the second applicant can institute interference proceedings to determine who was the first inventor and thereby who is entitled to the grant of a patent. This can be an expensive and time-consuming process.

The debate as to which system is better is long-running and unlikely to reach a single conclusion. There are arguments for and against both systems.

The **first to file** system leads to procedural certainty as the filing date of an application can very rarely be challenged. In contrast, the first to invent system leads to uncertainty as the right to grant of a patent can be challenged by a second party and can only be finally determined by extensive consideration of the making of the invention.

It is said, however, that the first to file system favors large companies who can afford to rapidly file patent applications, thereby gaining an advantage over smaller companies who are slower to file due to cost restraints. The first to invent system is therefore said to be beneficial in encouraging the growth of smaller companies. A potential problem with this argument is that a smaller company, filing second, would have to rely on interference proceedings to claim their patent, which may be beyond their economic reach and they are therefore no better off.

Concluding this section we can cite the change made in 1989 by Canada, in fact they change from a first to invent system to a first to file invention priority system leaving U.S.A and Philippines as the only countries that continue to grant patents on the basis of a first to invent system.

1.7: HOW TO SEARCH A PATENT INTO DATABASE

At EPO to perform the research of a patent it is possible to use the SEA (Search Examiners Application).

Three tools in particular are particularly useful:

- Internal
- X-Full
- Viewer

Internal is a tool that allows to search in all the fields of a patent, in the title and in the abstract.

```
?  ..fi epodoc

Selected file: EPODOC

Search statement  1

?  a61b8/00/ec
** SS 1: Results 1.984
```

```
?  ultrasound
** SS 3: Results 16.404

Search statement  4

?  contrast 4d agent
** SS 4: Results 2.593
```

Figure 1.5 Snapshots from Internal

X-Full is a tool that allows to search in the whole text of a patent. The desired word (or words) is written in the QUERY field as shown in figure 1.6

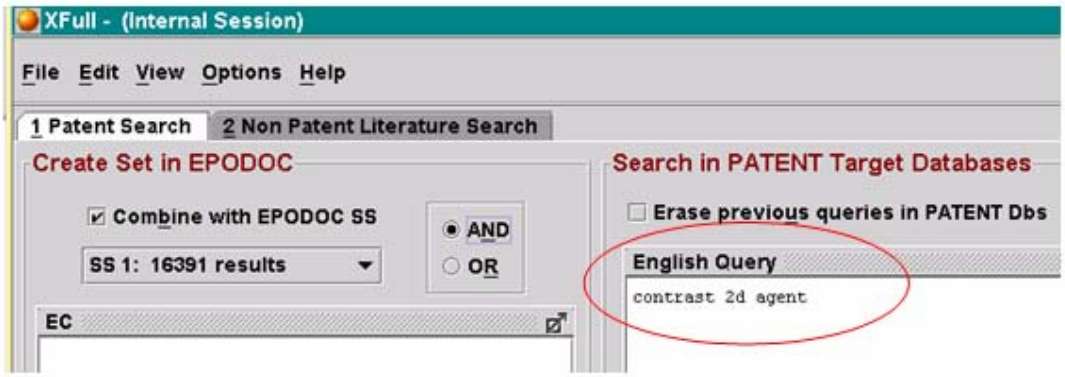
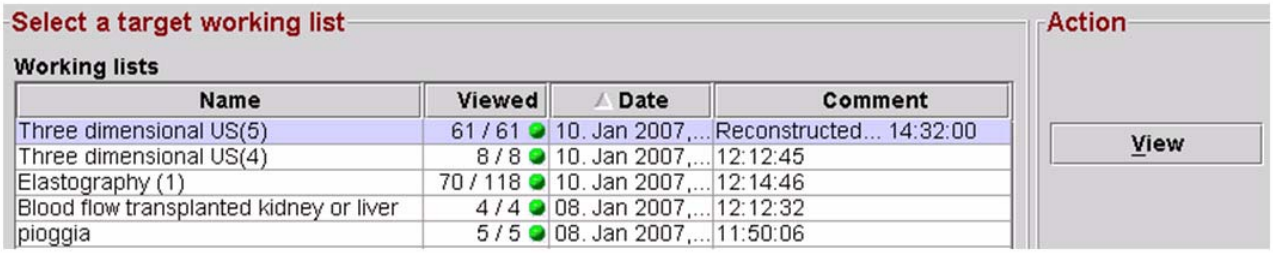


Figure 1.6 Snapshots from XFull

White X-Full it is possible to combine the results from internal with the desired query.

When the research is finished and the desired patent or patents are individuated it is possible to visualize them whit the VIEWER.

After saving the results of the research in a working list is possible to visualize the results.



Name	Viewed	Date	Comment
Three dimensional US(5)	61 / 61	10. Jan 2007,...	Reconstructed... 14:32:00
Three dimensional US(4)	8 / 8	10. Jan 2007,...	12:12:45
Elastography (1)	70 / 118	10. Jan 2007,...	12:14:46
Blood flow transplanted kidney or liver	4 / 4	08. Jan 2007,...	12:12:32
pioggia	5 / 5	08. Jan 2007,...	11:50:06

Figure 1.7: Snapshot from VIEWER (Working List Selection)

The patents are then displayed and it is possible to highlight some words in different colors that helps the user to individuate the most interest part of the patent and visualize all the images.

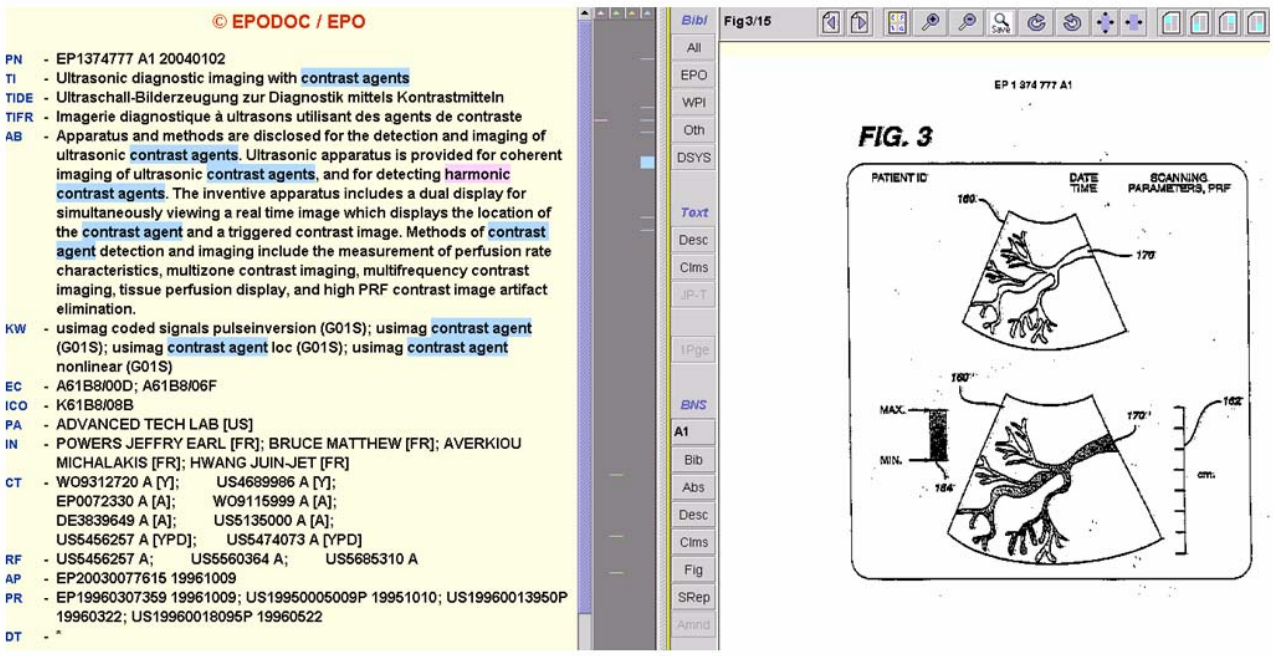


Figure 1x.8: Snapshot from VIEWER

CHAPTER II

ULTRASOUND OVERVIEW

Introduction

A typical medical ultrasound device sends ultrasound waves into the tissue and analyze the reflecting waves in order to obtain images of the region of interest or mechanical parameters of the tissue.

2.1 TRANSDUCERS AND THEIR CONFIGURATIONS

An ultrasound transducer generates acoustic waves by converting magnetic, thermal, and electrical energy into mechanical energy. The most efficient technique for medical ultrasound uses the piezoelectric effect, which was first demonstrated in 1880 by Jacques and Pierre Curie [Curie and Curie, 1880]. They applied a stress to a quartz crystal and detected an electrical potential across opposite faces of the material. The Curies also discovered the inverse piezoelectric effect by applying an electric field across the crystal to induce a mechanical deformation. In this manner, a piezoelectric

transducer converts an oscillating electric signal into an acoustic wave, and vice versa.

- **Material**

Ferroelectric materials strongly exhibit the piezoelectric effect, and they are ideal materials for medical ultrasound. For many years, the ferroelectric ceramic lead-zirconate-titanate (PZT) has been the standard transducer material for medical ultrasound.

Recent evolution in material technology allows to combinine the PZT and epoxy in different ratios and spatial distributions to create Polyvinylidene difluoride (PVDF).

PVDF is a ferroelectric polymer that has been used effectively in high-frequency transducers.

- **Scanning with array transducers**

The arrangement of the transducers is a very important aspect of ultrasound devices. An important step for ultrasound technology was the development of linear-array transducers. Previously, ultrasound systems had made an image by manually moving the transducer across the region of interest.

Linear array transducers were designed to electronically steer and focus the beam in a region of interest.

First developed for radar, sonar, and radio astronomy after world war II, in the first part of ’70 they were is formed by a large number of piezoelectric elements arranged like in figure 2.1. They can be activated at different times in order to obtain different wave-forms.

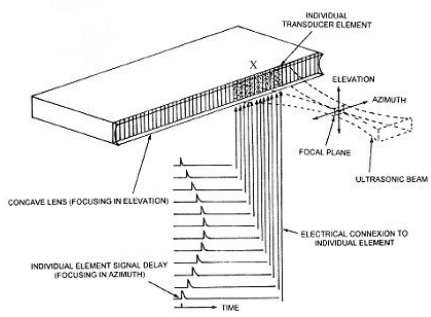


Figure 2.1: Linear Array

The possible piezoelectric elements configurations in linear array are:

- Linear Sequential Arrays;
- Curvilinear or convex Arrays;
- Phased Arrays;
- 2D Phased Arrays.

In sequential liner arrays the scanning lines are directed perpendicular to the face of the transducer; the acoustic beam is focused but not steered as shown in figure 2.2

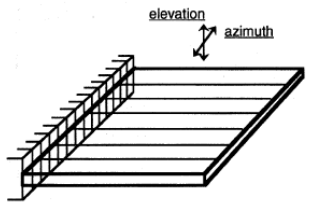


Figure 2.2 Linear Sequential Array

Curvilinear or convex arrays have a different shape than sequential linear arrays, but they operate in the same manner. The scan lines are directed perpendicular to the transducer face, the field of view is wider because of the convex shape

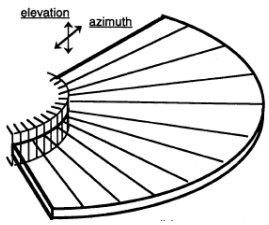


Figure 2.3: Curvilinear Array Configuration

In a phased array all the elements are used to transmit and receive each line of data. As shown in figure 2.4 the scanner steers the ultrasound beam through a sector-shaped region in the azimuth plane.

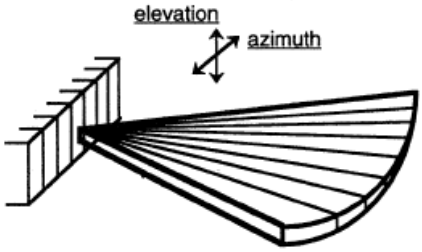


Figure 2.4: Phased array Configuration

A 2D phased-array has a large number of elements in both the azimuth and elevation dimensions. Therefore, 2D arrays can focus and steer the acoustic beam in both dimensions. A 2D array can scan a pyramidal region in real time to produce a volumetric image.

2.2 ULTRASONIC IMAGING MODALITIES

There are 3 different imaging modalities in ultrasound

- A-Mode;
- M-Mode;
- B-Mode.

In **A-Mode** an ultrasound signal is send into the body and the backscattered signal is shown usually on oscilloscopes. This modality is now obsolete.

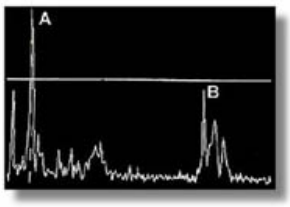


Figure 2.5 A-Mode view
www.ultrasound.net

A single beam in an ultrasound scan can be used to produce an **M-mode** picture where movement of a structure such as a heart valve can be depicted in a wave-like manner.

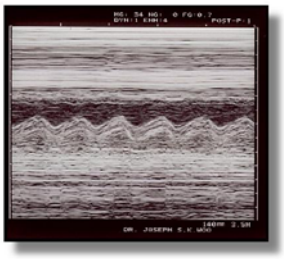


Figure 2.6 M-Mode view
www.ultrasound.net

In **B-Mode** the transducer is swept either mechanically or electronically over many directions to build up two-dimensional views (B-mode or 2D).

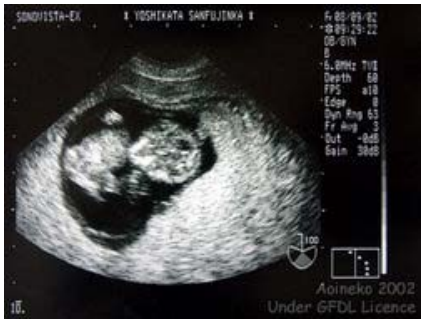


Figure 2.7 B-Mode view
www.ultrasound.net

2.3 DOPPLER EFFECT

The Doppler effect is a change in the frequency of a wave, resulting from motion of the wave source or receiver or in the case of a reflected wave, motion of the reflector. In medicine, Doppler US is used to detect and measure blood flow, and the major reflector is the red blood cell. The Doppler shift is dependent on the insonating frequency, the velocity of moving blood, and the angle between the sound beam and direction of moving blood, as expressed in the Doppler equation:

$$Df = \frac{2 f v \cos q}{c},$$

The angle of incidence between the ultrasound beam and the estimated flow direction (parallel to the long axis of the vessel) is the Doppler angle.

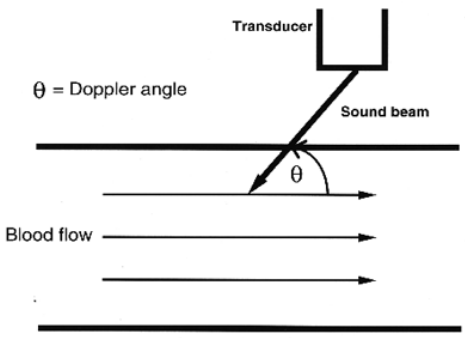


Figure 2.8 Doppler Angle

Df is the Doppler shift frequency (the difference between transmitted and received frequencies), *f* is the transmitted frequency, *v* is the blood velocity, *c* is the speed of sound, and *q* is the angle between the sound beam and the direction of moving blood. The equation can be rearranged to solve for blood velocity, and this is the value calculated by the Doppler US device:

$$V = \frac{Df\, c}{2 f \cos q}.$$

Current ultrasonic imaging systems operate in a pulse-echo (PE) or continuous-wave (CW) intensity mapping mode.

In continuous wave the ultrasound signal is continuously transmitted into the body, and the reflected energy is analyzed. The main limitation of CW is that it is not possible to separate Doppler signals arising from different points along the transmitted ultrasound beam. With PE it is possible to overcome this limitation.

Range resolution in pulsed Doppler is achieved by transmitting a short burst of ultrasound. The backpropagation signal reaches the transducer after a delay (*2t)*, where *t* is the time that the ultrasound wave needs to reach the sampling volume. Thus the sampling volume can be moved to different positions along the beam by altering this delay.

Right now there are 2 different imaging modalities called Color Doppler and Power Doppler. In Color Doppler the shift of frequency is used for calculate the velocity, the direction of flow information extracted by the electronics from the sequence of returning echoes is included in the velocity images, normally red denote flow toward the transducer and blue away from the transducer (see figure 2.9a).

In power Doppler the amplitude of the signal is analyzed in order to calculate the number of moving cells in the sample volume. Power Doppler images are relatively straightforward to interpret: the power level at each pixel is presented as

a level of brightness. Since the power at each pixel is fairly similar (see figure 2.9 b), the images have a uniform brightness except perhaps at vessel walls or in turbulent areas. The main attraction of Power Doppler Imaging is that it is a sensitive technique which is good for depicting flow in small vessels, it therefore gives more complete images of vascularity than Doppler Velocity Imaging *[Mc Dicken et al 2002]*.

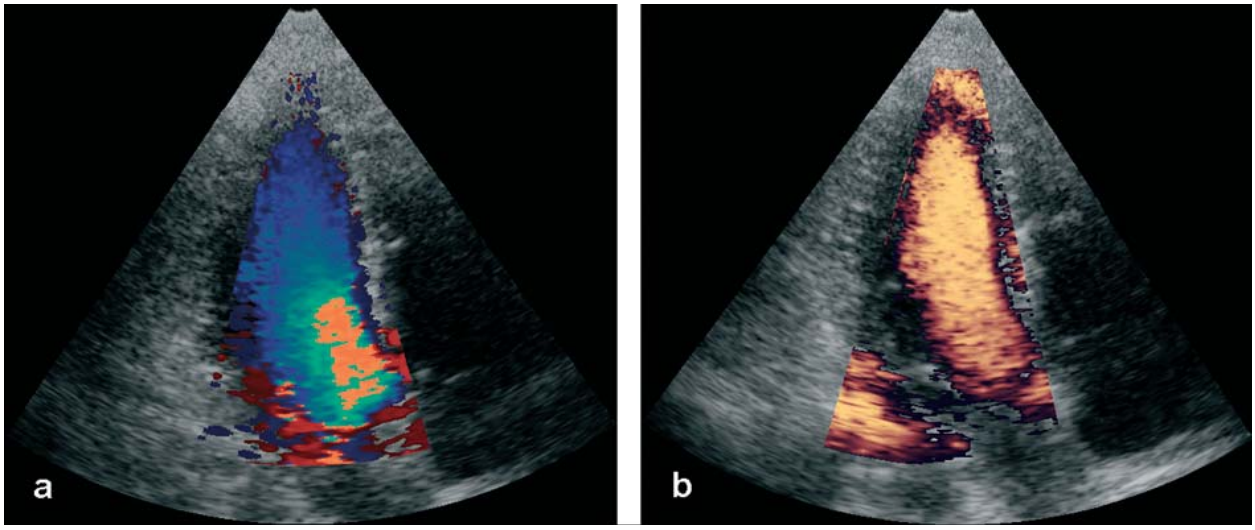
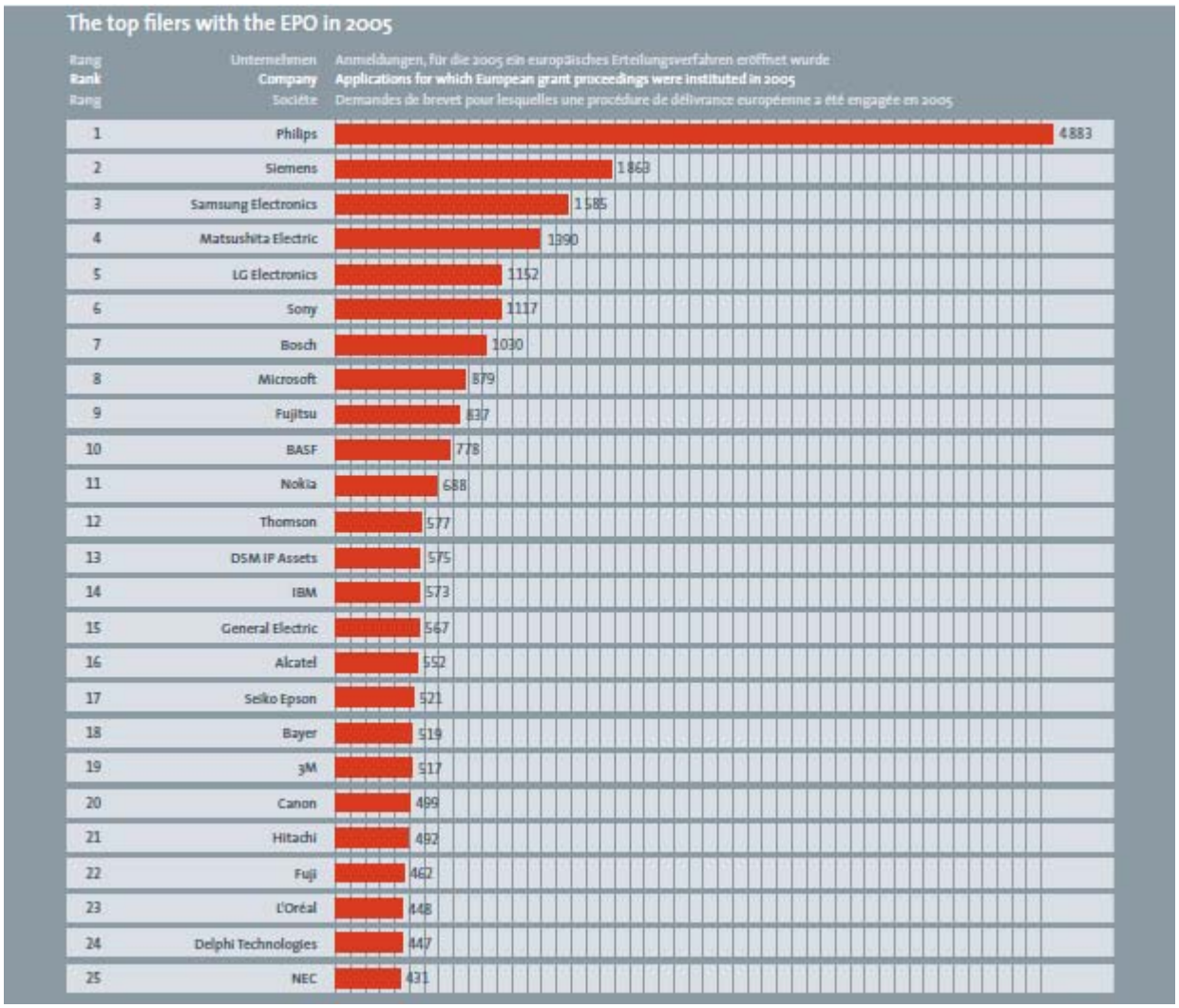


Figure 2.9 (a) Colour Velocity Doppler image of blood flow in the left ventricle, (b) a Power Doppler image of blood flow in the left ventricle.
[Mc Dicken et al 2002]

2.4 STATISTICS

As cited in the introduction, the field of medical device, IPC class A61, is one of the technical fields with the most filings. In the top filers with the EPO we find companies that are involved in medical field e.g. Philips, Siemens, and General Electric etc.

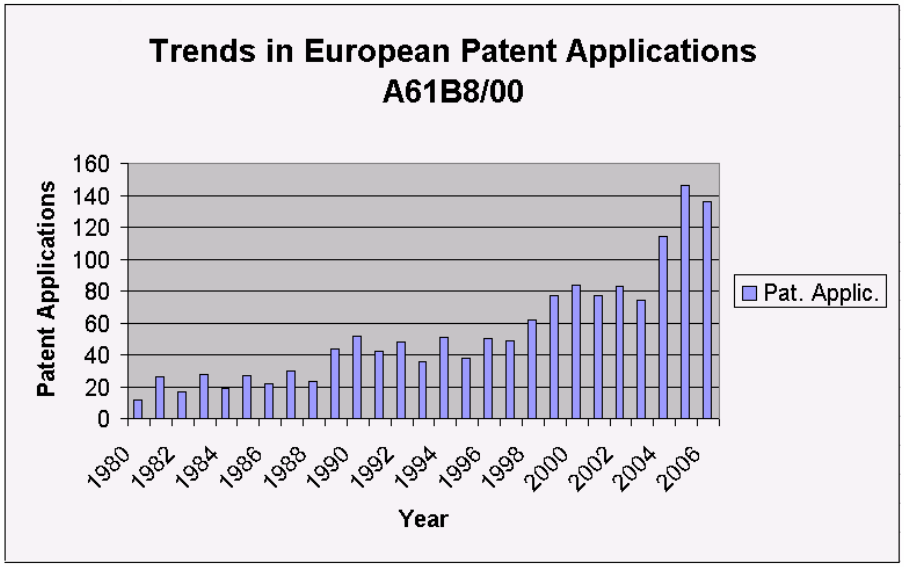


The majority of patents and patent applications consulted in this work can be found in the main group A61B8/00, Diagnosis using ultrasonic, sonic or infrasonic waves.

The statistics of this chapter (and also of the other chapters) are directed only to EUROPEAN PATENT APPLICATION and the research is based on the publication date. The publication date of the patents is assumed to be the date that reflects best the time that a technology is available to the

public. The figures of 2006 maybe are underestimated because of the backlog in classification.

	Total	Pat. Applic.
1980	23	12
1981	49	26
1982	66	17
1983	94	28
1984	113	19
1985	140	27
1986	162	22
1987	192	30
1988	215	23
1989	259	44
1990	311	52
1991	353	42
1992	401	48
1993	437	36
1994	488	51
1995	526	38
1996	576	50
1997	625	49
1998	687	62
1999	764	77
2000	848	84
2001	925	77
2002	1008	83
2003	1082	74
2004	1196	114
2005	1342	146
2006	1478	136



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CHAPTER III
PERFUSION WITH ULTRASOUND CONTRAST AGENTS (USCA)

3.1 INTRODUCTION TO USCA

Ultrasonic diagnostic imaging techniques enable imaging and measuring the anatomy and physiology within the body in a non-invasive manner. With the use of ultrasound contrast agents (USCA) it is possible to obtain additional information about perfusion in a minimally invasive way.

These substances are introduced into the body to enhance ultrasonic diagnosis quality *[Harvey et al. 2004]*. They strongly interact with ultrasonic waves and are bio-compatible, so they have no or little side-effects for the patient *[Wei et al. 1997].*

The first European patent application in this field was filed in 1984, but, as it is discussed in the statistics section, only in the last 6 years there has been a significant increase of patent applications.

An USCA is composed of tiny bubbles (called microbubbles) filled with air or other gas *[Wei et al. 1997].* During a typical USCA investigation a suspension of microbubbles is infused into the patient body in a continuous manner or as a bolus. The microbubbles are 1-7 microns in diameter and they are capable of surviving the passage through the capillaries.
The physics of the interaction between the USCA and the acoustic wave is very complex and it depends on a great number of parameters, including the type of gas inside the shell, the material of the shell and the acoustic pressure of the ultrasonic wave. The following properties of USCAs are of particular interest in the context of ultrasound diagnosis:

- The high difference in acoustic impedance of the gas/fluid interface results in a strong response to the ultrasonic signal (High Echogenity);
- High intensity sound impulses destroy the bubbles with the result of a high-intensity broadband signal produced by their collapse *[Harvey et al. 2004];*
- Air bubbles in the sound field reverberate and return sound with harmonic frequencies. This phenomenon can be used in "harmonic imaging" *[L.Dalla Palma et al. 1999].*

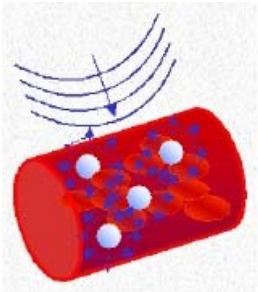

Figure 3.1 interaction between US wave and microbubbles, *http://www.mecheng.ucl.ac.uk*

Today a variety of contrast agents is available on the market. They differ by the type of gas and shell (stabilization), table 3.2 summarises the most current ones.

Microbubble	Gas	Stabilization	Company
First-generation vascular			
Agitated saline	Air	None	N/A
Echovist[a]	Air	None	Schering
Second-generation vascular			
Levovist (SHU 508 A)[a]	Air	Galactose/palmitic acid	Schering
Albunex[b]	Air	Sonicated albumin	Mallinckrodt
Third-generation vascular			
Optison (FS069)[a]	Perfluoropropane	Sonicated albumin	Mallinckrodt/Nycomed
Echogen (QW3600)	Dodecafluoropentane	Liquid droplet, surfactant	Sonus/Abbott
QW7437	Perfluorocarbon	Liquid droplet, surfactant	Sonus
Sonovue (BR1)	Sulphur hexafluoride	Phospholipids	Bracco
Aerosomes (Definity, MRX115, DMP115)	Perfluoropropane	Phospholipids	Du Pont Merck
PESDA	Perfluorobutane	Sonicated albumin	University of Nebraska
Quantison	Air	Dried albumin	Andaris Ltd.
Imavist (Imagent, AFO150)	Perfluorohexane	Surfactants	Alliance Pharm./Schering
Liver-specific agents			
Levovist (SHU 508 A)	Air	Galactose/palmitic acid	Schering
Sonavist (SHU 563 A)	Air	Cyanoacrylate shell	Schering
Sonazoid (NC100100)	Perfluorocarbon	Surfactants,	Nycomed
BR14	Perfluorobutane	Phospholipids	Bracco

Table 3.2: Most current ultrasound microbubbles [Harvey et al. 2004]

Blood is not very echogenic and perfusion images with good resolution and penetration are difficult to obtain. This problem is overcome thanks to the high echogenity of the USCA that allows tracking blood flow through vessels and organs with ultrasound transducers.

- SPECIAL WAVEFORM STIMULATION

It is possible to further enhance the quality of the image by coupling the USCA with special waveform stimulation like pulse inversion, codec excitation or chirp waveform.

In **pulse inversion** two signal 180° out of phase are sent to the tissue as shown in figure x.3

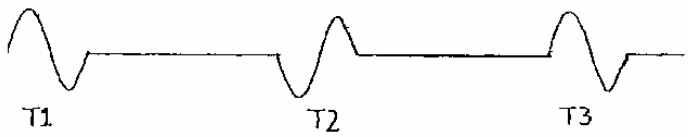

Figure 3.3: Pulse Inversion Stimulation *(EP0913704)*

Due to the non linearity of the tissue and microbubbles response the two received signals are not symmetric as the emitted pulses are.

In fact odd-ordered harmonics (fundamental, 3rd, 5th etc.) remain 180° out of phase, whereas even-ordered harmonics (2nd, 4th, etc.) are in phase.

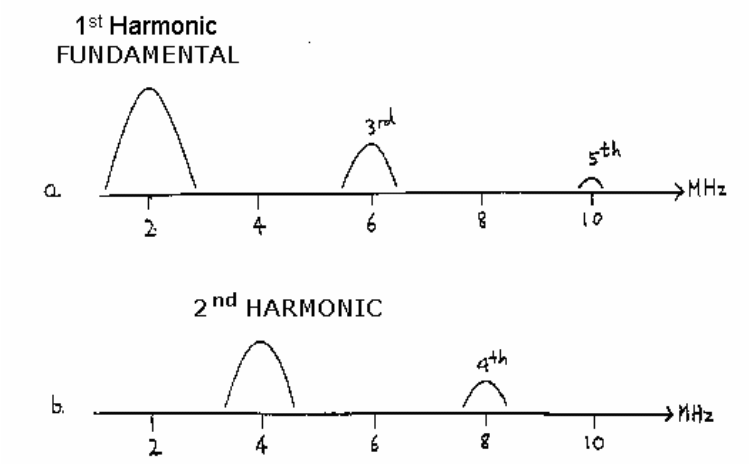

Figure 3.4: Odd-ordered harmonics and even-ordered harmonics *(EP0913704)*

However, it must be remembered that ultrasonic imaging transducers have finite pass bands, so the array will typically reproduce only the fundamental and the second harmonic; higher order harmonics will be eliminated by the upper cut-off of the transducer.

The two received echoes are processed by an adder:

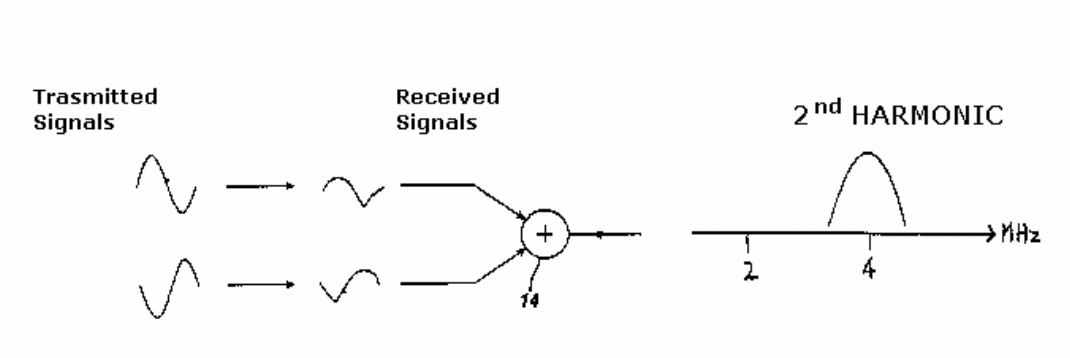

Figure 3.5: Elimination of the fundamental frequency components

As a result of this combination, the fundamental frequency components, being of opposing phases or polarity will cancel out. The second harmonic frequency components, being in phase, will reinforce each other; so a second harmonic signal is produced. If a subtractor is used instead of the adder, the harmonic components will cancel and the fundamental (linear) components will reinforce each other to produce separated fundamental frequency components.

Codec excitation has gained increasing attention in medical ultrasound over the last 10 years as a way of improving the SNR and consequently

increasing the observation depth and/or axial resolution *(Chiao and Mao,2005).*

The physics and formation of codec excitation is relatively complex and is beyond the scope of the present study, only the basic principle will be described.

Codec excitation relies on transmitting, instead of a short Gaussian pulse as in the case of conventional ultrasound, a longer pulse train of higher energy, having a particular ("coded") modulation of frequency and/or phase. At reception this particular modulation is identified (i.e. decoded or compressed) with a (matched) filter which enables to recover the system response of the tissue.

The codec excitation technique can also be combined with second harmonic imaging, thereby effectively cancelling out the acoustic response of media having linear response *(Chiao and Mao,2005);* and it has also been investigated for imaging with USCA *(Boobson et al. 2005).*

Another way to enhance the bubble nonlinear response is to stimulate the microbubble with **chirp waveform.** The chirp waveform is a combination of :

1. Low frequency wave that compress the bubble and initiate its dynamic (see figure x.6,first wave component);
2. High frequency wave (see figure x.6,second wave component) to produce an enhanced bubble nonlinear response

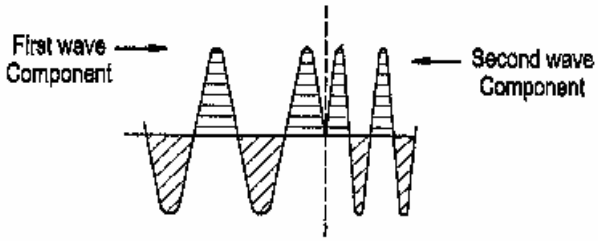

Figure 3.6: Chirp Waveform *(EP1406096)*

By adjusting the centre frequency, amplitude, and bandwidth for the two wave components of the stepped-chirp waveform and their relative phase, frequency, switch time (the time point where the waveform changes from one frequency to another) and the time delays in between, the nonlinear response of the bubble is enhanced.

3.2 USCA TECHNOLOGY AND APPLICATION IN LOW MECHANICAL INDEX IMAGING

This part addresses patents and patent applications directed to Low Mechanical Index (MI) imaging with USCA. The previously addressed characteristics of USCA, harmonic effect, high echogenity, can be exploited without breaking the microbubbles.

- BLOOD DYNAMICS INVESTIGATIONS

As already observed Blood without USCA has a very low echogenity so it is very difficult to obtain information about blood flow with ultrasound. USCAs are very useful for this purpose, since their high echogenity allows to obtain a stronger signal from the blood vessels.

As shown in several patent applications as for example *US2004087858* the contrast-to-tissue ratio (see glossary for the definition) is improved while the contrast agent is continuously infused.

To distinguish the blood flow from the surrounding tissue it is possible to perform subtraction imaging as shown in patent application *US2002028994* where two images of the same region of interest are acquired before and during USCA infusion and then subtracted raster by raster (A Raster defines values for pixels occupying a particular rectangular area of the plane) to discriminate the blood flow from the surrounding tissue.

USCA can be used to perform Power Colour Doppler imaging *(US2001009977)*. The microbubbles are used to improve the distance resolution, sensitivity, and increase the frame rate in power Doppler.

Similar imaging protocol, i.e. injection of a bolus (or continuously) of USCA and imaging how it flows through the vessels, can be implemented with special waveforms such as chirp wave-form as explained in patent application *EP1406096.*

- TISSUE ABLATION VISUALIZATION

Cardiac arrhythmia is a group of conditions in which the contraction of the heart is irregular or is faster or slower than normal. This pathology is

caused by electrical impulses that do not correctly spread trough myocardium causing the irregular contraction.
A therapy provide to locate the source of an abnormal electrical activity and isolate this source from the coronary vessels (Ablation).
Successful treatment of cardiac arrhythmia requires that the ablation lesion have a sufficient extent and depth in the myocardium to effectively eliminate the source of the abnormal electrical activity associated with the arrhythmia. A contrast agent is injected into an artery that feeds blood to tissue surrounding an ablation lesion *(US2003208123)*. During and after contrast agent injection, the ablation lesion and surrounding tissue is imaged.

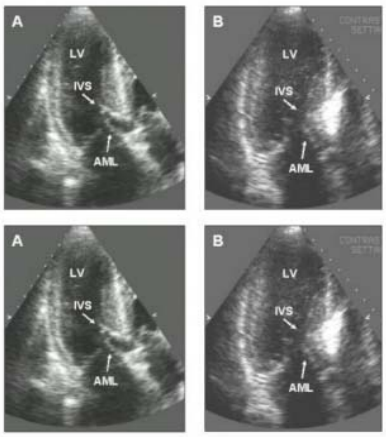

Figure 3.7 ***Echocardiogram A: ground level, B: after inj. of 1 ml of Levovist (350 mg/ml)***

The open capillaries in the living tissue allow the contrast agent to perfuse therein, while the closed capillaries in the nonviable tissue of the ablated lesion prevent the contrast agent from perfusing therein therefore it is possible to discriminate the living tissue from the ablated one and visualize the extent and depth of ablation lesions and decide whether the treatment is successful or not.

- DIAGNOSTIC IMAGING FOR DETECTING LESIONS OF THE LIVER

Blood flow to the liver comes from two sources: the hepatic artery and the portal vein. The liver receives 20% of its total supply of blood from the aorta and hepatic artery and 80% of its blood supply from the inferior vena cava and the portal vein. So is possible from literature and medical investigation to establish a curve that describes liver perfusion for normal patients.

It has been found that the vasculature developed by a tumour like hepatocellular carcinoma (HCC) is supplied primarily from the hepatic artery. Because the contrast agent first appears in the liver by way of the hepatic artery, this means that one of the initial sites of contrast agent detection in the liver after a bolus injection is the locus of an HCC lesion. If no lesion is present, only the usual hepatic artery and normal vessels supplied by it will appear with contrast present.

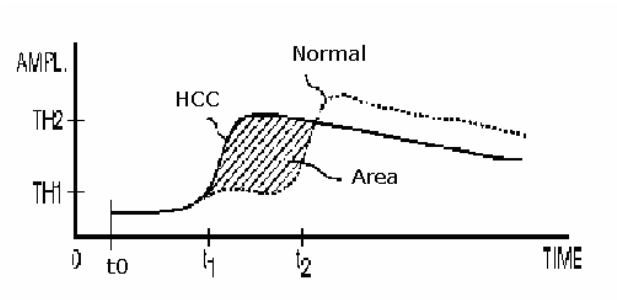

Figure 3.8: Normal and pathologic curve *(WO2006090309)*

As explained above most of the flow of blood with contrast agent in the normal liver is delayed because its passage through the kidneys. If a bolus of USCA is injected at t0, it reaches the liver at a time t2 (see figure 3.8). However the flow of blood with contrast agent in the hepatic artery and into the vasculature developed around an HCC lesion will appear earlier (t1<t2 as shown in figure 3.8). It is therefore the function of a pixel classifier to identify pixel or voxel data which is characteristic of the cross-hatched area between curves registered with the USCA and the normal statistical curve *(WO2006090309)*

- ULTRASOUND COMPARISON IMAGES

Tumours develop a complex vascularisation. Treatment of tumours involve destruction of their vascularisation, e.g. radiotherapy or chemotherapy. Successful treatment requires that the whole area affected by the tumour is isolated. A contrast agent is injected into the region of interest before and after treatment and its flow is observed with an ultrasound scanner (*US2005187475).* If the treatment is successful the contrast agent is prevented from flowing into the tumour through the vessels like shown in figure 3.9

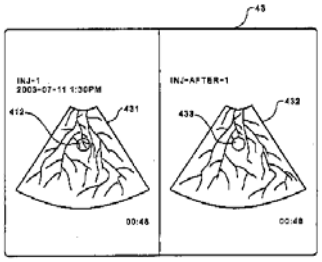

Figure 3.9: Pre and post treatment images *US2005187475*

3.3 USCA TECHNOLOGY AND APPLICATION IN HIGH MECHANICAL INDEX IMAGING

This part addresses patents and patent applications directed to High Mechanical Index (MI) imaging with USCA, i.e. involving the destruction of bubbles with a high intensity ultrasound wave. The destruction of USCA can be exploited in order to obtain a stronger backward signal and higher brightness in the image (figure 3.10) as explained in patent *US6245019.*

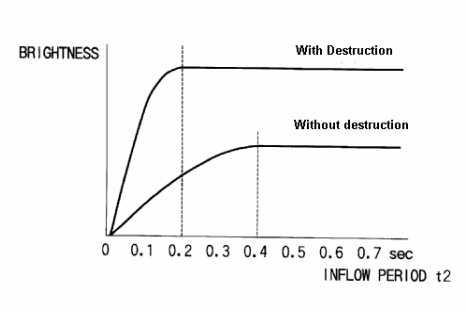

Figure 3.10: Comparison between High MI imaging and Low MI imaging *(US6245019)*

- REFILLING IMAGES OF A VESSEL OR ORGAN

The basic principle of perfusion studies with USCA is to have a **continuous injection of USCA**, destroy the agent in the area of interest (ROI) with an high mechanical index wave and see how it refills.

The refilling rate can be used to quantify the blood flow and this rate can be obtained by computing the intensity of the backscatter signal through time from the moment of transmitting the High MI pulse*(EP1514516)*. The blood flow is obtained by calculating the parameter □ (see figure x.11.)

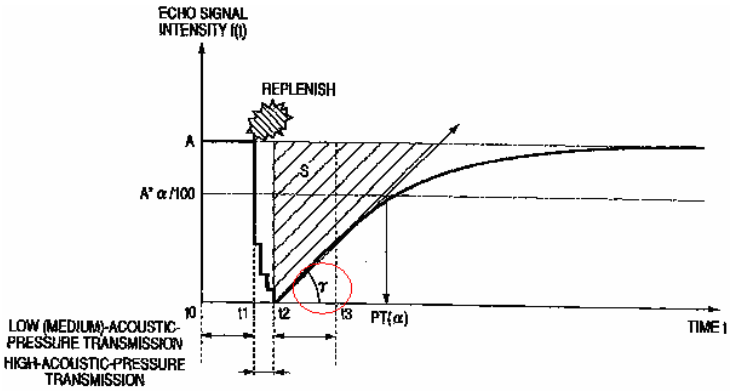

Figure 3.11: Time Intensity curve *(EP1514516)*

A similar protocol, i.e. transmitting an High MI pulse and subsequently imaging the refilling at regular intervals can be implemented with specific imaging approaches, such as pulse inversion *(EP0913704 & US6454714)* or codec excitation *(US2001044278)*.

- METHOD FOR MEASURING REAL TIME PRESSURE & FLUID DYNAMIC INSIDE MICROVESSELS

When insonifying a population of microbubbles with a pulse of a given power a certain amount of them is disrupted depending on the acoustic pressure of the pulse and their size.

It is possible to exploit the mechanical characteristics of USCA for real time measurement of the pressure in a region of interest *(WO0057792)*. The first step for this procedure is to introduce into a cavity a composition of microbubbles with a variety of diameters corresponding to predetermined fragility thresholds. Bigger microbubbles are more instable than the smaller ones.

After a pulse of a given pressure some microbubbles collapse and from the ultrasound backscatter response we can determinate the population of intact and failing microbubbles in the region of interest and the intensity of this signal is inversely proportional to the internal pressure.

By selectively destructing of microbubbles of a particular size range it is also possible to investigate the dynamic in small vessels (*EP1354555).*

In fact with sequentially transmitting pulses of increasing intensity it is possible to destroy selectively a fraction of bubbles (first the bigger, than the smaller) and observe how the smaller microbubbles flow into small cavity that bigger microbubbles can not reach.

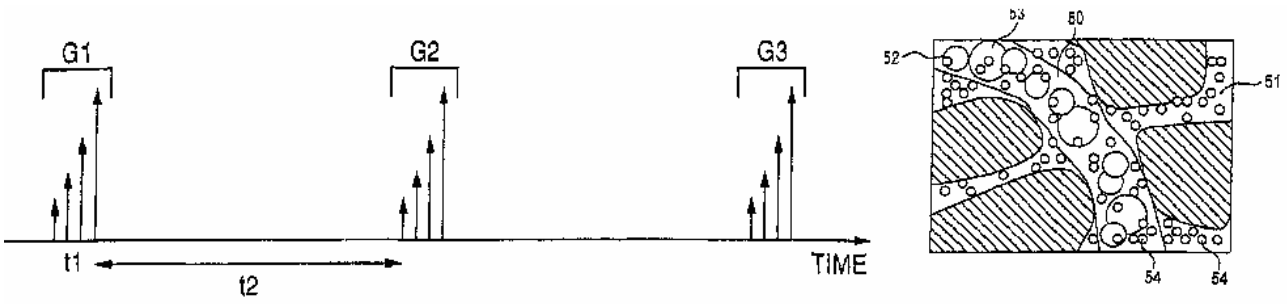

Figure 3.12 Stimulation protocol (*EP1354555)*

3.4 STATISTICS

In the field of USCA about 110 European patent application have been found *(see annex for the search procedure)*. The majority of these patent applications are classified as A61B8/00D:

"Diagnosis using ultrasonic, sonic or infrasonic waves by tracers, e.g. microbubbles introduced into the bloodstream"

As mentioned in the introduction, the first European patent application in this field was from 1984 *(EP0072330, FUJITSU LTD, filing date 06.08.1984,addressing pressure measuring with ultrasonic waves,)*. Since then this technique has been used in several other applications. In the successive years, especially from the beginning of nineties, an increase of patent applications in this field it's observed.

	Total	Pat. Applic.
1980	0	0
1981	0	0
1982	0	0
1983	0	0
1984	2	2
1985	2	0
1986	2	0
1987	2	0
1988	2	0
1989	4	2
1990	4	0
1991	5	1
1992	8	3
1993	10	2
1994	15	5
1995	17	2
1996	23	6
1997	28	5
1998	38	10
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2000	59	12
2001	67	8
2002	74	7
2003	78	4
2004	90	12
2005	101	11
2006	110	9

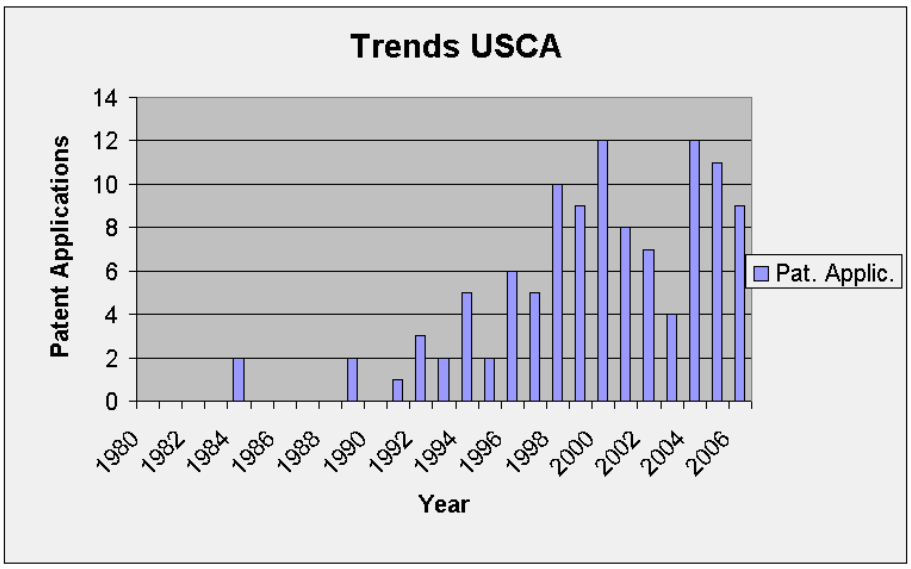

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Figure 3.13: Trends in European Patent Application in USCA field

CHAPTER IV
THREE DIMENSIONAL ULTRASOUND

4.1 INTRODUCTION

In the last 10 years of research, investigators and commercial companies have advanced ultrasound imaging with the development of 3D ultrasound. The major reason for the increase in the use of 3D ultrasound is related to the limitation of 2D viewing of 3D anatomy using conventional ultrasound.
As observed in *[Fenster et al. 2000]* mentally combine 2D images by the operator to form an impression of 3D volume is a *sub-optimal* approach because:

- This approach is variable and subjective, it may lead to incorrect decisions in diagnosis and in the planning of the therapy;
- Diagnostic and therapeutic decisions often require an accurate estimation of organ or tumour volume, in conventional 2D ultrasound the volume is calculated by measuring height width and length in 2 views and assuming an idealized (e.g. ellipsoidal) shape. This method is variable and operator dependent;

- It is difficult to adjust the transducer in the same position of a previous examination for monitoring therapeutic procedures;
- Some 2D slices of an organ are impossible to achieve because of the restriction imposed by the patient anatomy, but they can be reconstructed from a volume of data.

In 3D ultrasound examination, 2D ultrasound images are combined by a computer to form an objective 3D image of the anatomy or pathology. This image can be manipulated and viewed by the physician to obtain views of the organ at any angle.
Moreover, unlike CT and MR imaging, in which 2D images are usually acquired at a slow rate as a stack of parallel slices, in a fixed orientation, ultrasound provides tomographic 2D images at a high rate (15–60 images/Sec), and in arbitrary orientations *[Gee et al.2003]*.
In 1974, *Greenleaf et al*. first published a technique called "Ultrasound Computed Tomography" (UCT) describing an acquisition and reconstruction technique for volumetric echography. Success with this modality was limited due to the limited availability of computational power in the 1970s.
Progress has been slow due to the enormous computational requirements which must be met in order to acquire, reconstruct and view 3D information in near real time on low-cost systems. Advances in computer technology and visualization techniques in the past few years have made 3D ultrasound imaging viable.

4.2 3D ACQUISITION PROTOCOLS, SCANNIG TECHNIQUE AND IMAGE RECONSTRUCTION

Most 3D ultrasound imaging systems make use of conventional 1D ultrasound transducers to acquire a series of 2D ultrasound images, and differ only in the method used to determine the position and orientation of these 2D images within the 3D image volume being examined. The production of 3D images without distortions requires that three factors be optimized *[Gee et al.2003]*:

- Fast scanning procedure in order to prevent artefacts caused by involuntary, respiratory or cardiac motion

- 2D images position must be known
- The apparatus must be simple and convenient to use

In the majority of systems, 3D ultrasound is acquired by sweeping a 2D imaging plane over the area of interest and stacking up the resulting B-scans to form a 3D volume. Figure x.1 shows the complete spectrum of possible approaches and the applications where the advantages of 3D ultrasound may be useful exploited.

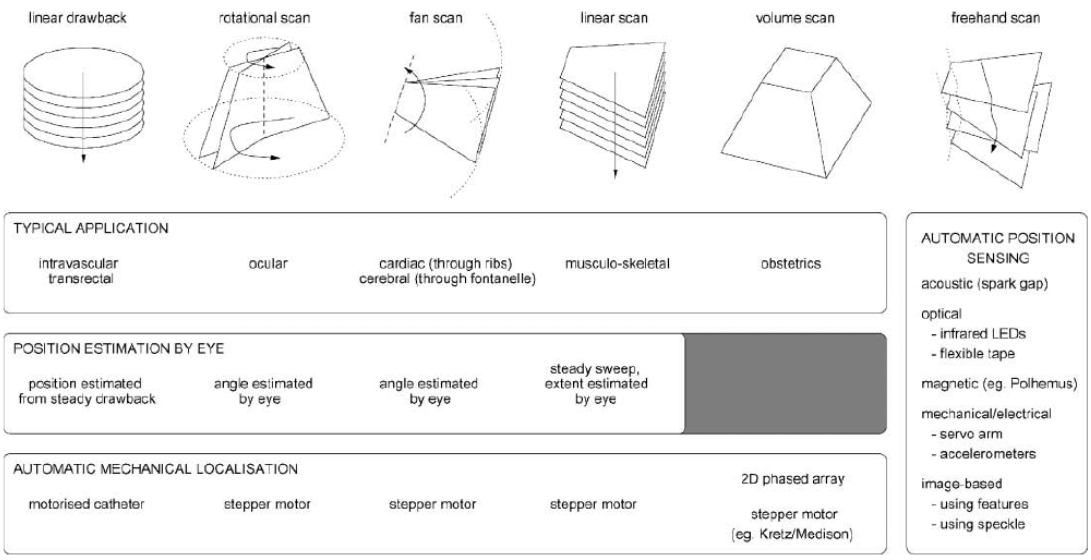


Figure 4.1: Ultrasound acquisition protocoles ***[Gee et al. 2003]***

Four different 3D ultrasound imaging approaches have been pursued *(fig 4.2)*:

- mechanical scanners;
- free-hand techniques with position sensing;
- free-hand techniques without position sensing (only in chatters);
- 2D array.

Scanning method	Image acquisition method	Disadvantages
Mechanical		
Linear	Acquired images are parallel to each other with equal spacing	Bulky device
Tilt	Acquired images are fan-like with equal angular spacing	Resolution degrades with depth
Rotational	Acquired images are propeller-like with equal angular spacing	Motion of axis of rotation results in artefacts
Free-Hand		
Acoustic	Measure time-of-flight of sound from spark gaps on transducer to microphones above patient	Line of sight required and sound velocity varies with humidity
Articulated arms	Measure angulation between movable arms	Scanning volume limited, flexing of arms
Magnetic sensor	Measure magnetic field generated by transmitter beside the patient with receiver on transducer	Ferrous metals distort magnetic field
Image correlation	Measure speckle decorrelation between adjacent images	Special computer processor required, compound motion is difficult to track
No position sensing	Distance or angle between images is assumed	Cannot measure distance
2D arrays	2D phased array transmits a diverging pyramidal beam and returned echoes are displayed in real time as multiple planes	System cost and signal/noise

Figure 4.2: Summary of 3D scanning methods *(Fenster et al. 2000)*

Image reconstruction refers to the process of generating a 3D representation of the anatomy by placing the acquired 2D images in their correct relative positions and orientations in the 3D image volume, and then using their pixel values to determine the voxel values in the 3D image.

Two methods have been implemented *[Fenster et al. 2000]*:

- Feature based reconstruction: The anatomical structures are determined in the 2D slices and then reconstructed in 3D images
- Volume based reconstruction: Each pixel of a 2D slice is placed in its correct 3D coordinates, first two coordinates based on the 2D coordinates and the third coordinate based on the position and orientation of the slice.

As observed in the introduction of this work, discussion of the reconstruction of techniques is beyond the scope of the present study.

4.3 MECHANICAL SCANNERS

In this approach the anatomy is scanned by using a motorized mechanical apparatus to translate, tilt or rotate a conventional transducer as it rapidly acquires a series of 2D ultrasound images spanning the volume of interest. Because the scanning protocol is predefined, the relative motion and orientation of each 2D image can be known accurately. The 2D images acquired during the scan are send to the computer and used to reconstruct 3D volume.

An application of this technique is breast tomography because the breast is immobile (so the time to translate or rotate the transducer is not a restriction), easy to access and homogenous.

Good acoustic coupling between the transducer and the body must be ensured at any time during the rapid, cyclic movement of the probe. This issue is conventionally solved by using a coupling fluid (e.g. gel). To perform ultrasound breast tomography the female subject has to suspend one of her breasts into a container filled with acoustical coupling.

The scanner placed into the housing rotates and translates while it acquires tomographic images *(US200464046, US2004068180 US20060173307, WO2005087110, US200609693, US 200468180)*.

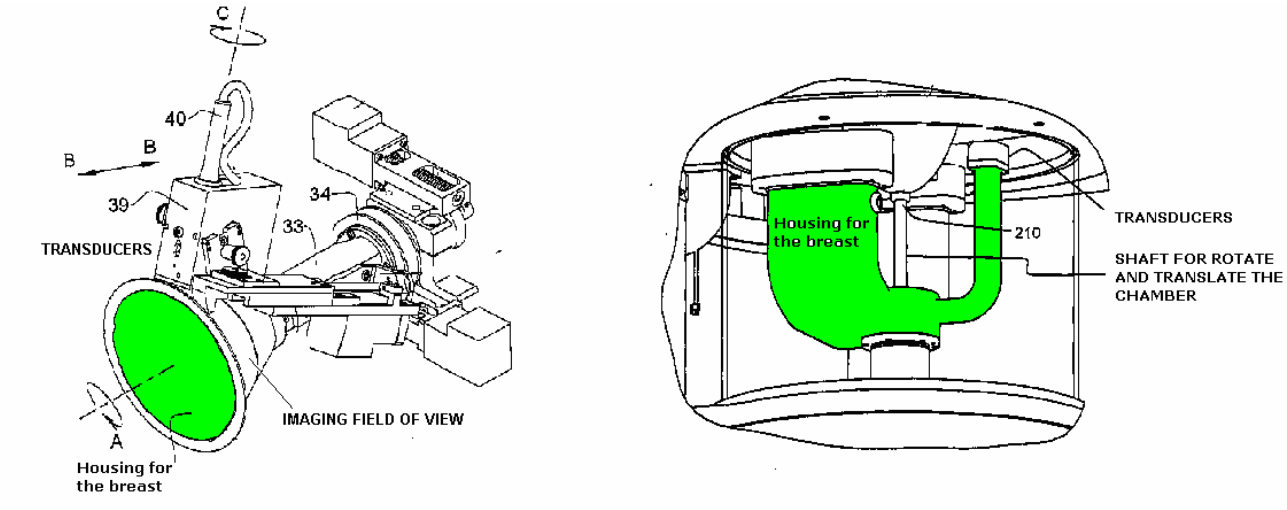


Figure 4.3 Mechanical Scanner for breast 3D imaging (*US20060173307 and US200609693)*

In figure x.3 two methods are shown, the device in the left side (*US20060173307)* The transducers array is mounted in a housing that can

be mechanically rotated in several direction(see fig. 4.3,letter a,b,c and number 40)in order to acquire 2D scans of the entire volume.

The device in the right side of figure 4.3 (*US200609693)* comprises a chamber filled with coupling fluid with the transducer mounted inside. Also in this device a system allows transducers to rotate and translate around the breast. The patient in this case has to lie in the prone position in a special bed.

The rotation of the ultrasonic transducer around the breast can cause turbulences in the coupling fluid and this can cause distortion in the tomographic image. This problem is solved using 2 chambers, one stationary in which the breast is immersed and one movable containing the transducers *(US2004064046)*

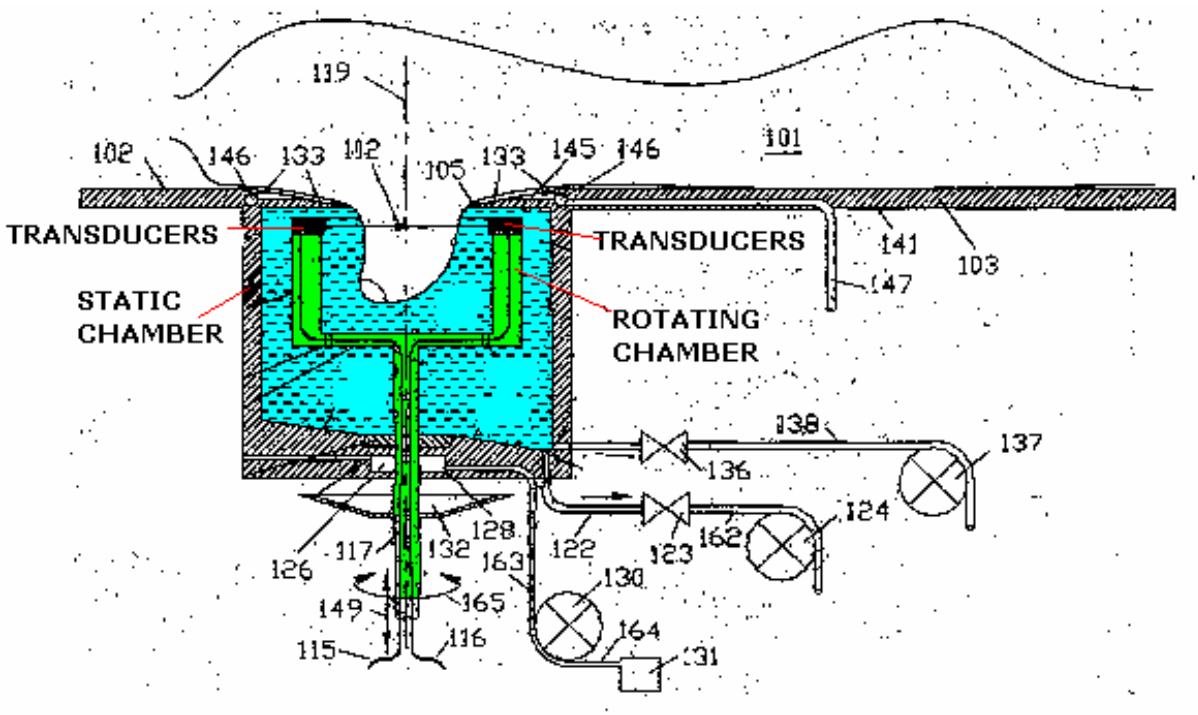


Figure 4.4: Double Chamber Device *(US2004064046)*

The fluid during the scan has the possibility to flow from the movable to the stationary chamber. The communication between the 2 chambers reduces turbulences during the scanning process. To perform a tomographic scan of the breast the rotating chamber (in which the transducers are mounted) is rotated and a first 2D slice is created then the rotating chamber is incrementally lowered and another slice is acquired (Fig. 4.5)

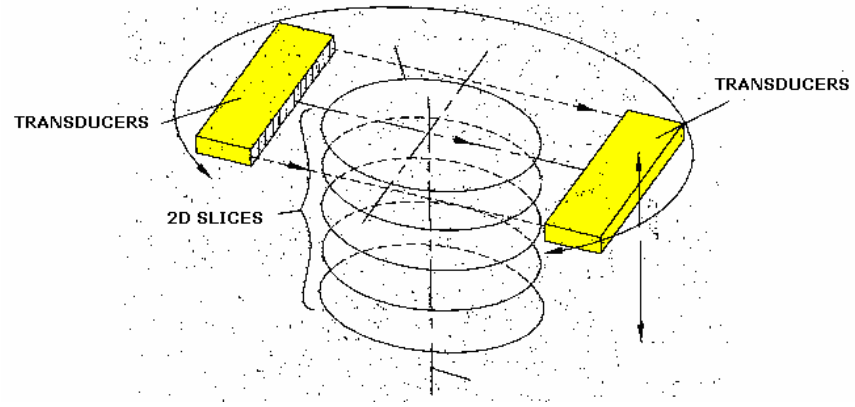


Figure 4.5 Acquisition of a volume *(US2004064046)*

When all the region of interest is scanned the 2D slices are processed by the computer and the 3D volume is created.

Some of these devices can also be coupled with an invasive therapeutic or diagnostic procedure *(WO200607423)* involving a needle localized with ultrasound which can be used for injecting drug (e.g. chemotherapeutic agent) into a tumour or used for biopsy *(US200609693)*.

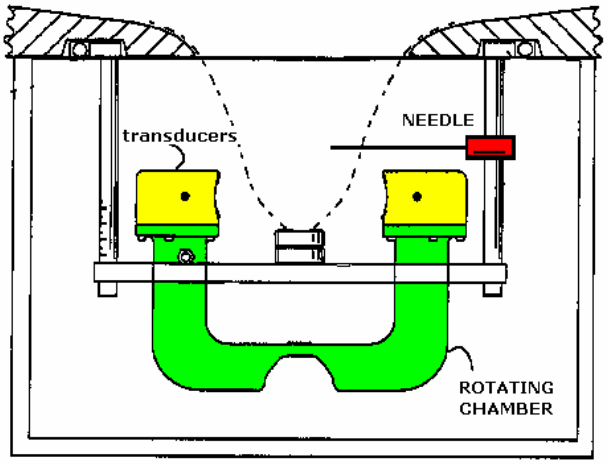


Figure 4.6: Mechanical Scanner coupled with needle *(US200609693)*

The time necessary for the mechanical movements required for the scan are a physical limitation for this kind of devices, hence only static tissue without cyclic artefacts can be scanned with the scanners described above. To avoid this limitation and obtain 3D image sets of moving organs the image can be acquired with an ECG gated device *(DE19723053 and US5871019)*.

As is well known the ECG is a record of the electrical activity of the heart. the so callad "R-Peak" correspond to the maximum of the electrical activity during the contraction of the ventricles and is easily discernible on the ECG(see figure 4.7) Each 2D slice is acquired at the same period of the cardiac cycle and then reconstructed to create the 3D volume of the heart

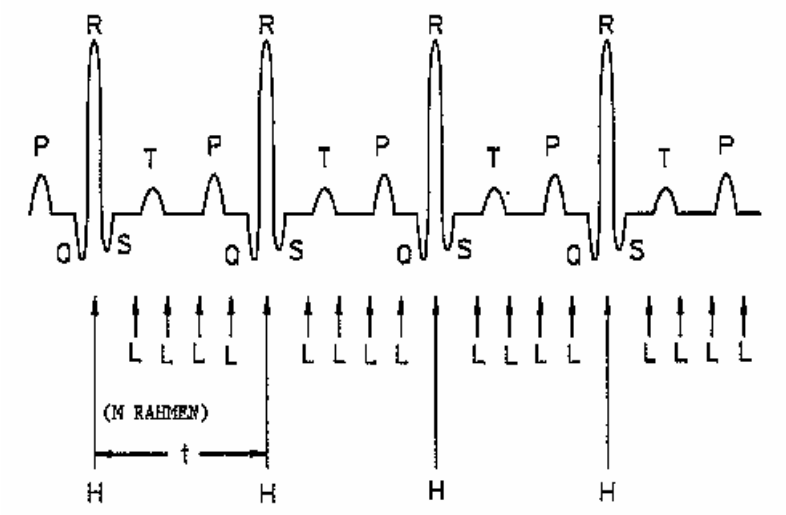


Figure 4.7: ECG - gated scanning procedure

Mechanical scanners have also several applications in the IVUS (intra-vascular ultrasound) and are described in the section 4.6.

4.4 FREE HAND SCANNERS

The mechanical scanning allows to obtain relatively short imaging times, high-quality 3D images and fast reconstruction times. However, the bulkiness and weight of the scanning

apparatus sometimes make it inconvenient to use, and large structures are difficult to scan. To overcome this problem, free-hand scanning techniques that do not require a motorized fixture have been developed by many investigators *[Fenster et al. 2000]*.

In these approaches, a sensor is attached to the transducer to measure its position and orientation. While the transducer is being manipulated, the acquired 2D images are stored by a computer together with their positions and orientations. This information is then used to reconstruct the 3D image. However the operator must ensure that the sets of 2D images have no significant gaps.

- **Free hand with articulated arm**

Position and orientation sensing can be achieved by mounting the ultrasound transducer on a multiple-jointed mechanical arm system. Potentiometers located at the joints of the arm provide the information necessary to calculate the relative position and orientation of the acquired 2D images *(US5806521)*.

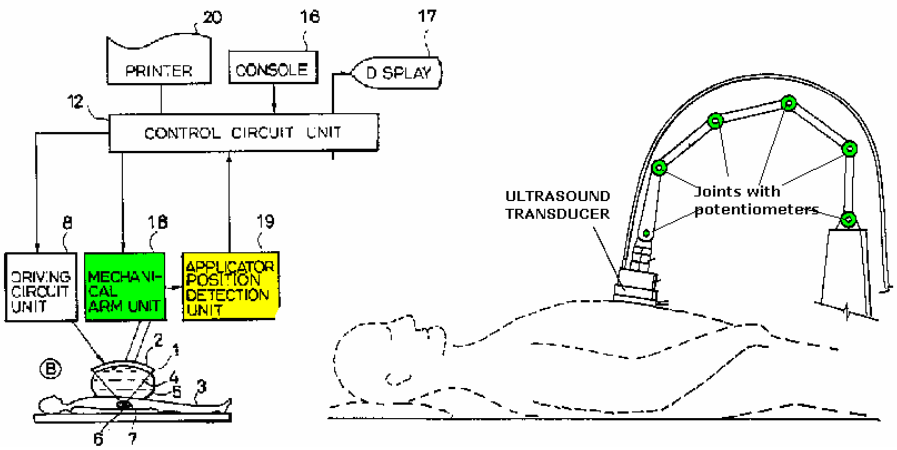


Figure 4.8 Free Hand with articulated arm ***(US5806521)***

- **Free hand with magnetic field sensors**

Magnetic field sensor can be used do determine the position of the transducer. The transmitter is placed beside the patient and the receiver is mounted on the hand-held transducer *(US6775404, EP0487339).* The position is calculated based on the received magnetic field
The main problem with magnetic field sensors are interference from sources such as CRT monitors, ac power cables and electrical signals from the transducer itself which can compromise the tracking accuracy.

- **Free hand with optical sensors**

To prevent artefacts induced by the environment optical sensor can be used as shown in patent application *US2004167402*. The basic principle is the same as in an optical mouse of the computer.

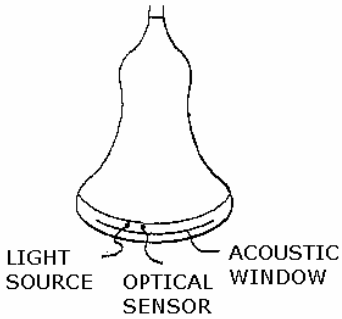


Figure 4.9: Free Hand Transducer with optical sensors *(US2004167402)*

The optical sensor allows to measure relative movement of the transducer over the skin and the signals from the sensor are used to determine the relative position of each image.

- **Free Hand with optical fibre**

A new technology that shows promising results in the area of 3D imaging is an optical system where optical fibres are run through the machine *[Pagulatos et al. 2005]*

The spatial localizer consists of a flexible tape with optical fibre sensors along its length. The curvature along the cable is measured using the optical fibres and integrated to give the location and orientation of the probe.

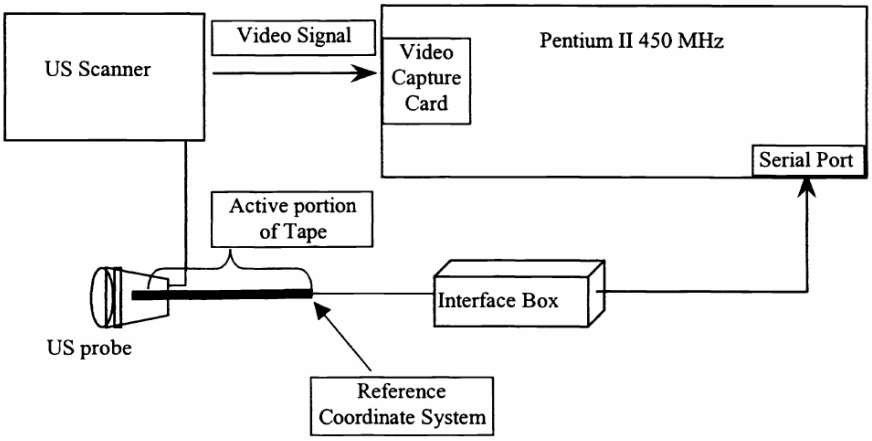


Figure 4.10 Free Hand system with optical fibre *[Pagulatos et al. 2005]*

The position tracking is insensitive to the scanning environment, the main limitation of this technique is that the location and orientation of the probe with practically long cable is not yet sufficiently accurate.

- Free hand with speckle decorrelation

An alternative technique, not requiring any device, uses the acquired images themselves to extract their relative positions. This can be accomplished using the phenomenon of speckle decorrelation. If two images are acquired from the same location, then the speckle pattern will be the same, so that there will be no decorrelation. However, if one of the images is moved with respect to the first, then the degree of decorrelation will be proportional to the distance moved, the exact relationship depending on the beam width in the direction of the motion *(US20030114755)*

This technique is used in obstetrics imaging to quantify volume and weight of the foetal and have some images of the foetal aspect. The accuracy of this technique is not very high and the effort required to obtain high quality 3D ultrasound images often overweight the potential benefits *[Fenster et al. 2000].*

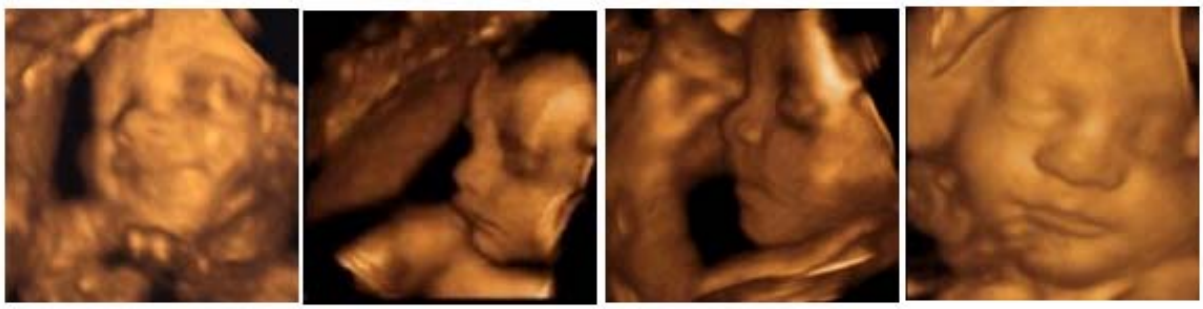


Figure 4.11 3D images of foetal

4.5 2D ARRAYS

The mechanical and free-hand scanning approaches for 3D ultrasound images described in the paragraph 4.3 and 4.4 all involve acquiring 2D ultrasound images with a conventional transducer (1D array).

The limitations of the 1D array described above are:

- Low acquisition speed (e.g. mechanical movement);
- Low accuracy (e.g. free hand with speckle decorrelation);
- Relative movement between probe and patient.

To overcome these limitations 2D array have been developed in the recent years. A 2D phased array is formed by a large number of ultrasound piezoelectric transducers steered electronically in order to insonify a pyramidal volume of interest.

With 2D array there are no moving parts and the acquisition of a pyramidal volume is almost instantaneous *[Fenster et al. 2000].* There is no relative movement between the probe and the patient and the image accuracy is high.

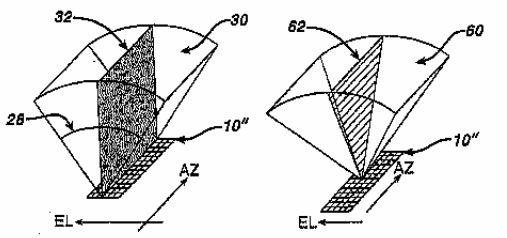


Figure 4.12 2D arrays *(EP1242991)*

The main problem of 2D arrays is the large number of piezoelectric elements that has to be steered at the same time in order to create the pyramidal beam. All the information from each piezoelectric element has to be send to the analyzing processor so there is also the problem of cables for connecting the array to the computer. These problems are reflected in high costs and so their commercial availability is yet limited *[Fenster et al 2006].*

A 2D array is showed in patent application *EP1242991.* The array described is formed by more than 3000 transducers arranged in a dodecahedral shape as shown in figure 4.13

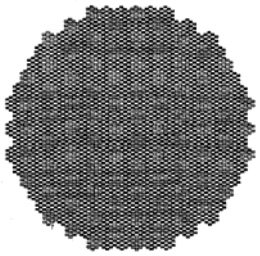


Figure 4.13: 2D array *EP1242991*

The transducers in the central part of the array (about 750) create the pyramidal beam, the others are used only for the received echo.

Since a cable with more than three thousand conductors is not currently practical,

(Such a cable would be impractically large, bulky and inflexible) the array is arranged in groups of 12 transducers. This reduces the number of conductors to 256.

For every transducer a complex microelectronics is dedicated as shown in figure 4.14

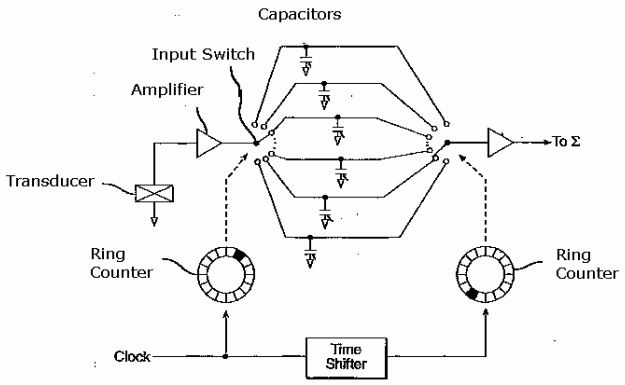


Figure 4.14: Microelectronics under each transducer *EP1242991*

This microelectronics allows to rapidly elaborate the signal for each group of 12 transducer and send the resulting signal to the analysing processor.

Other sub-array arrangement and division aiming at the reduction of the bulkiness of the device are shown in patent *US6013032* and patent application, *US20060106307* and *US2003220569.*

4.6 3D ULTRASOUND CATHETERS

Due to the miniaturization of ultrasound transducer, the harmless character of an echographic acquisition as well as a very good resolution obtained at high frequencies, ultrasound has become a technique of choice in endovascular imaging or intra-vascular ultrasound (IVUS).

This field has benefited from the advances in 3D ultrasound imaging, and catheters offering 3D ultrasound acquisition have been developed since the middle of the 90's.

The techniques used in the field of 3D IVUS follow a similar pattern as in conventional 3D echography addressed in the previous section with some particularities related to the specific application. Catheters for 3D imaging can be classified in 3 categories:

- Mechanical;
- Free-Hand;
- 2D array.

The mechanical approach involves sweeping or rotating the 1D array with a motorized system (e.g. an electrical motor). An example of 1D phased array rotated in order to cover a 3D volume is described in patent application *WO9856296*

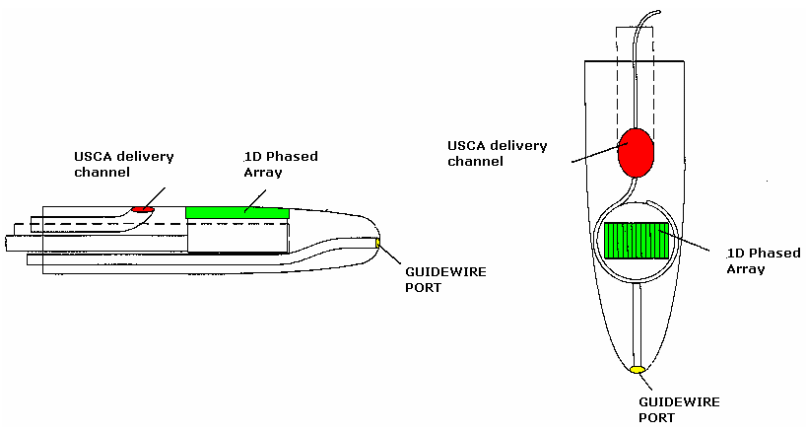


Figure 4.15 Catheter with mechanical rotating phased array *WO9856296*

The rotating array showed in figure 4.15 produces a sets of 2D images from which a 3D volume is reconstructed (fig 4.16). The guide-wire guides the catheter to the desired destination.

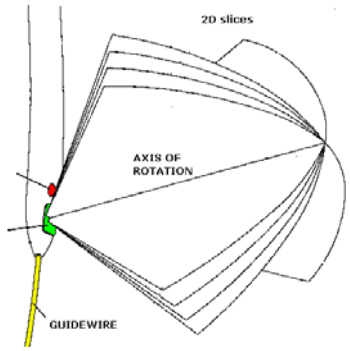


Figure 4.16 2D slices *WO9856296*

Patent application *WO9856296* describes in addiction a channel for delivering USCA (see figure 4.16). As indicated in *Forsberg et al 2002* delivering USCAs into the field of view of the ultrasound transducer allows to obtain flow information from smaller vessels associated with tumours.

Another possible arrangement for the array is described in patent application *US2003229286.* The transducers are disposed on the entire circumference of the catheter as shown in figure 4.17

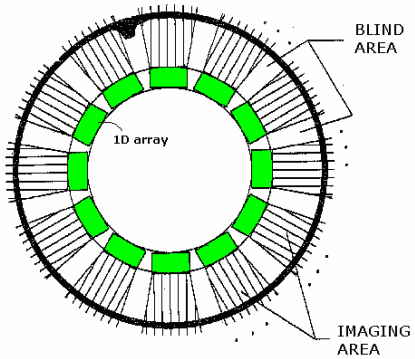


Figure 4.17: Cross section of the catheter (*US2003229286)*

1D array transducers are arranged in cluster, during imaging each cluster is tilted (over 60° or 90°) to cover a pyramidal volume.

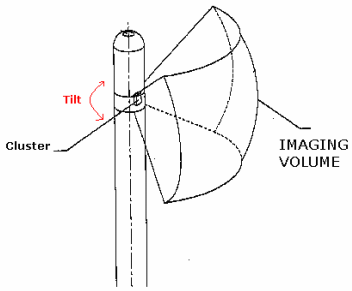


Figure 4.18: Scanning volume of a cluster with 60° tilt (*US2003229286)*

The integration of all the contributions of each cluster allows to have a whole volume image as shown in figure x.19

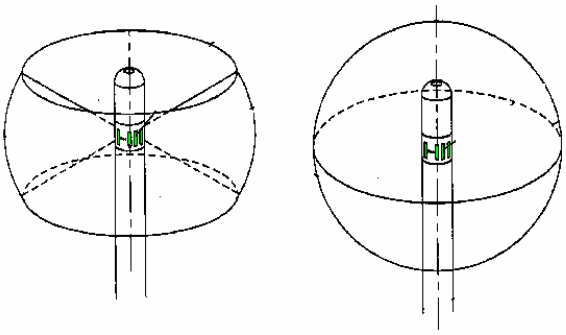


Figure 4.19: Scanning volume obtained from integration of all cluster with 60° tilt (right) and 90° (left) (*US2003229286)*

As described in section 4.3, also in catheters with mechanical scanners the images are hampered by cyclic artefacts. A solution is proposed in patent application *WO9811823* where ECG-Gated 3D IVUS Image Acquisition is described. In the present application 360° IVUS images are acquired immediately after consecutive R-peaks. however in order to avoid distortions caused by abnormal cardiac cycles, an image is rejected if the R-R interval does not meet a predefined range. After each accepted 360° acquisition the catheter is pulled to its next position for the acquisition of the next image.

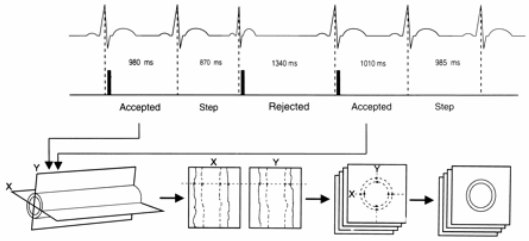


Figure 4.20 ECG-Gated IVUS acquisition *[Van Bingelen et al. 1997]*

With this catheter it is possible to image the coronary arteries without imaging artefacts produced by cyclic changes in vascular dimension.

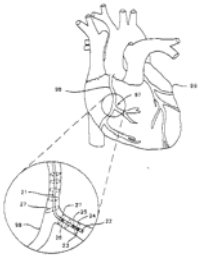


Figure 4.21 ECG-Gated IVUS investigation of coronary arteries *WO9811823*

A system for free hand IVUS for 3D imaging of a target organ is described in patent application *EP1717758*. The catheter comprises a 1D phased array, a magnetic field position sensor and an electrode that can be used to map the electrical activity of the heart.

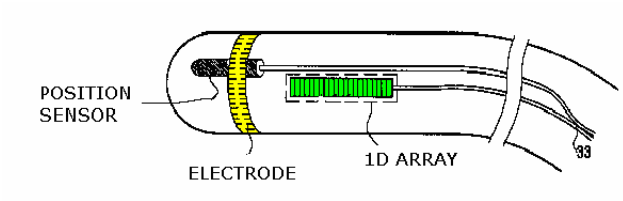


Figure 4.22: Free hand Catheter *EP1717758*

The 1D array acquires 2D images of the target organ and sends them to the image processor unit with location and orientation coordinates. The catheter is then translate or rotated manually by the physician in order to obtain a set of 2D images of the volume of interest without gaps.

Free hand IVUS 3D imaging is also possible without position sensing, but the catheter must be pulled at constant velocity by the physician so each 2D slice is separated from the next one by the same distance.

The advantages of 2D arrays in 3D imaging described in the previous section can also be exploited in catheters. Microelectronics and miniaturization of piezoelectric elements has allowed the use of 2D array also in IVUS. These devices offer the possibility of real time 3D intra vascular imaging of moving organs e.g. heart *[Light et al. 2001]* with high axial resolution (with catheters deep penetration is not required so higher frequencies can be used as observed in chapter 7.1).

In patent applications *US200328107* and *US2005119572* a 2D array catheter is described. As for 2D arrays described in section x.5 the main problem to resolve is the number of piezoelectric element that have to be connected and steered at the same time. The solution described is similar to the one proposed in patent application *EP1242991* (chapter 4.5), a sub-array division is made and each subarray has a dedicated microelectronic circuit to compute the signal received and to send information to the main computing system.

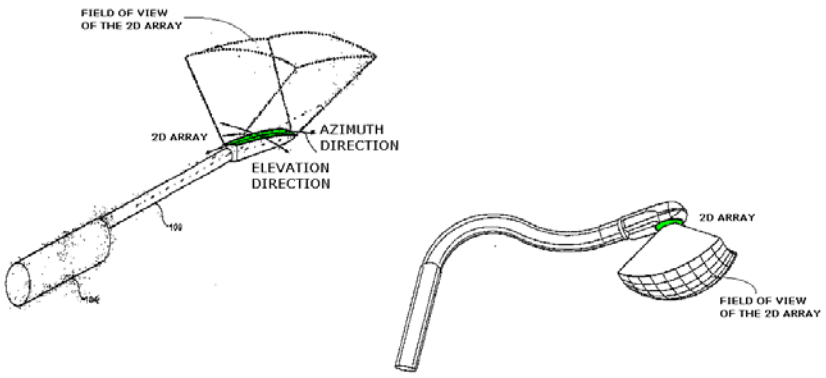


Figure 4.23: Pyramidal Beam produced by the 2D array (*US2005119572 right)* (*US200328107 left)*

The handiness of the transducer is also an important characteristic. The catheter described in patent application *US200328107* is equipped with a flexible region that allows to drive the catheter and to adapt the field of view to the region of interest.

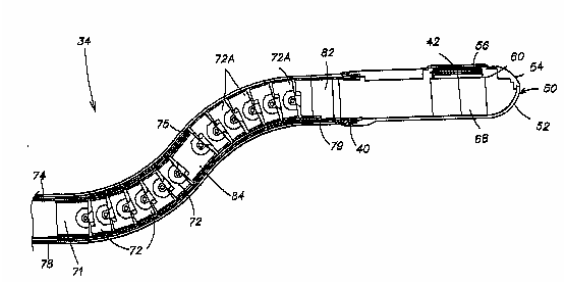


Figure 4.24: Flexible region of the catheter (*US200328107)*

4.7 STATISTICS

Patents about this field can be founded in the following classes:

A61B8/13 . Tomography

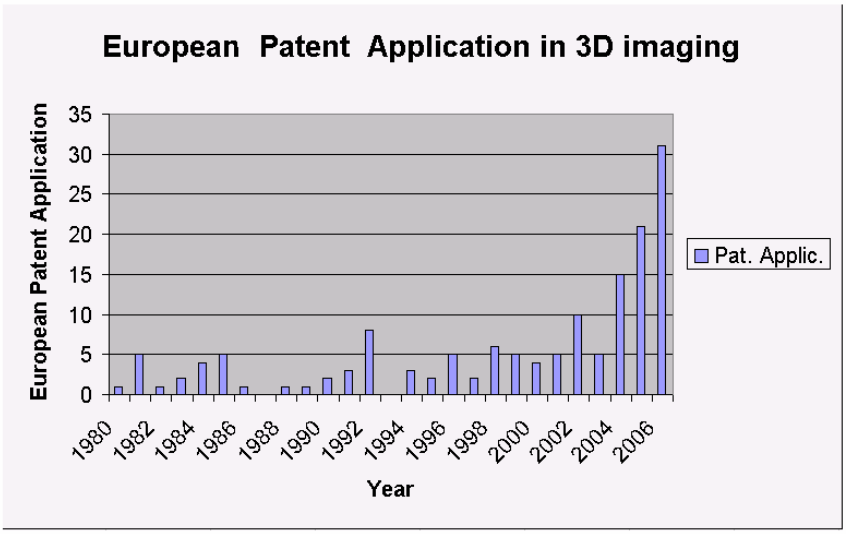
A61B8/14 . . Echo-tomography

A61B8/15 . . Transmission-tomography

And using the following key word:

Z61B8 imaging three dimensional

	Total	Pat. Applic.
1980	2	1
1981	7	5
1982	8	1
1983	10	2
1984	14	4
1985	19	5
1986	20	1
1987	20	0
1988	21	1
1989	22	1
1990	24	2
1991	27	3
1992	35	8
1993	35	0
1994	38	3
1995	40	2
1996	45	5
1997	47	2
1998	53	6
1999	58	5
2000	62	4
2001	67	5
2002	77	10
2003	82	5
2004	97	15
2005	118	21
2006	149	31



Europäische Patentamt

European Patent Office

Office européen des brevets

Figure 4.25: European Patent Application in three dimensional imaging with ultrasound

CHAPTER V
ELASTOGRAPHY

5.1 INTRODUCTION

It has been proved that pathological conditions often produce changes in biological tissue stiffness. The different mechanical characteristic of the tumour's tissue from the surrounding tissue is the basic principle of palpation [Krouskop et al 1998].

However, a lesion, in the prostate or in the breast in particular, may or may not possess echogenic properties and it would be difficult to detect it with conventional diagnostic ultrasound imaging systems[B.S. Garra et al. 1997].

As the echogenity and the stiffness of tissue are in general uncorrelated, Garra et al. observe it is expected that imaging the mechanical properties of the biological tissue will provide new information related to the pathological conditions, facilitating the diagnosis process.

The imaging modality that facilitates the display of mechanical properties of biological tissue is called **elastography** and is a sort of evolution of the palpation technique.

The purpose of elastography is to display an image of the distribution of a physical parameter related to the mechanical properties of the tissue for clinical applications.

The general principle of ultrasound elastography involves the following steps:

1. Acquiring a pre-compression ultrasound image of the region of interest;
2. Applying compression to the tissue;
3. Acquiring a post-compression image of the same region;
4. Evaluating the mechanical and elastic properties of the same region by comparing the pre and post-compression images (or signals), usually with correlation techniques.

Ultrasound is a common imaging modality for this method because it is non-invasive, safe (Radiofrequencies RF are non-ionizing radiation), inexpensive and portable.

Elasticity imaging applications can be divided into 3 categories depending on the nature of tissue stimulation:

- Mechanical stimulation;
- Wave stimulation;
- Physiologic stimulation.

5.2 SIGNAL PROCESSING

Strain is defined as the deformation of an object normalized to its original shape. In a one-dimensional (1D) object (i.e. an infinitesimally thin bar), the only possible deformation of the object is lengthening or shortening. This is illustrated in Figure 1(a). The relative amount of deformation is defined as strain. Strain, for which the symbol ε is used, can thus be written as:

$$\varepsilon = \frac{L - L_0}{L_0},$$

With L the length of the object after deformation and $L0$ its original length.

When the length of the object is not only known before and after deformation but also *during* the deformation process, the *Lagrangian (or Instantaneous strain*) strain can be defined:

$$\varepsilon(t)=\frac{L(t)-L(t_0)}{L(t_0)},$$

With *L* (*t*) the length of the object at time instance *t* and *L* (*t*0) =*L*0 its initial length.

Strain rate is the speed at which deformation (i.e. strain) occurs. It is represented by the symbol ε' and has the unit *1/s*. Although the unit is in fact the same as Hz, it is preferable to use s^{-1} since Hz is normally used to express a periodic change. Clearly, in the most general situation, strain (and thus strain rate) does not necessarily have a cyclic nature, as one can only deform an object once *(D'Hooge et al. 2000).* The instantaneous natural strain rate can be calculated as:

$$\dot{\varepsilon}_N(t)=\frac{L'(t)}{L(t)},$$

With *L*'(*t*) the rate of deformation and *L* (*t*) the instantaneous length of the object.

A method for quantifying the strain and the strain rate is the *Cross Correlation Method*. In this technique a RF signal line is acquired before and after deformation of an object.

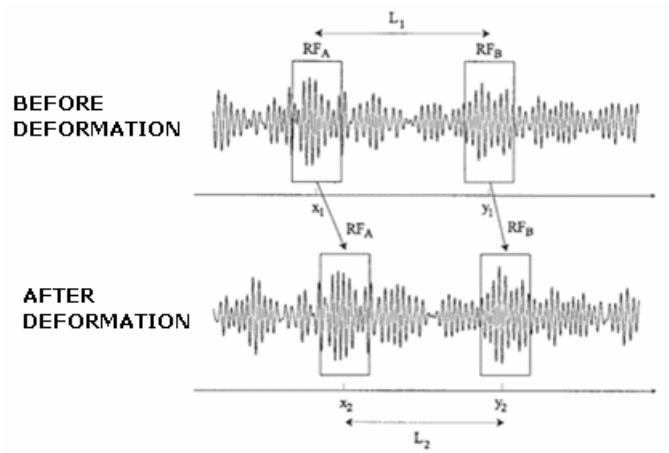


Figure 5.1: Cross correlation method

The regional motion is estimated by tracking a local radio frequent signal-pattern (resulting from a specific distribution of scatterers) between two subsequent acquisitions by means of the cross-correlation function, which is a measure for the similarity of two signals as a function of their relative phase.

Then the strain is obtained by dividing by the initial length *(L1).*The strain rate can be obtained by calculating the temporal derivative of the strain .

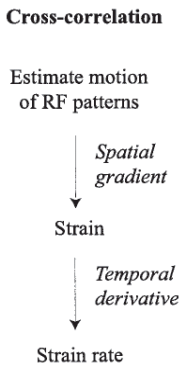


Figure 5.2 Schematic overview of operations in cross-correlation method

Strain rate can also be expressed as the difference in velocities at both ends of an object of initial length *L*1, this is the base of the **Velocity gradient method**. In accordance to the signal of figure x.1 the strain rate can also be defined as:

$$\dot{\varepsilon} \approx \frac{v_2 - v_1}{L_1}.$$

Where *v2* is the velocity of the second pattern and *v1* is the velocity of the first pattern. The local instantaneous velocities are measured with Doppler.

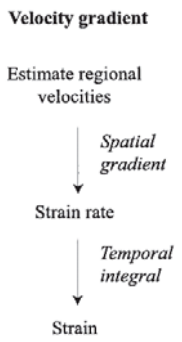


Figure 5.3 Schematic overview of operations in velocity gradient method

From the strain rate, the strain can be obtained by integration over time.

5.3 ELASTOGRAPHY WITH MECHANICAL STIMULATION

Elastography with mechanical stimulation or Static Elastography is the most frequently used elastography technique. In this application, a compressive force is applied to the tissue. The force can be applied either using motorized compression fixtures or using the ultrasound imaging transducer itself. The images obtained before and after compression are recorded to estimate the local motions using a correlation methods. The estimated motion valves along the ultrasound propagation direction represent the axial displacement map of the tissue and are used to determine the axial strain map. The strain map can then be displayed as a gray scale or colour-coded image and is called **elastogram.**

- FREE HAND SCANNING

the simplest approach is to perform compression ultrasound imaging by a conventional transducer while applying freehand, periodic, gentle axial loading and unloading to the tissues of interest with the same transducer as depicted by the arrow in fig. 5.4 *(US2005283076 & US6508768)*.

Figure 5.4: Free Hand Technique *(US2005283076)*

In this case the strain imaging capability may be added to a standard clinical ultrasound platform as a software up-grade without the need of new hardware addition.

In order to obtain a meaningful value of the strain the pressure applied by the physician must be known. This information is acquired with pressure sensors *(WO0139668)* located in the transducer housing.

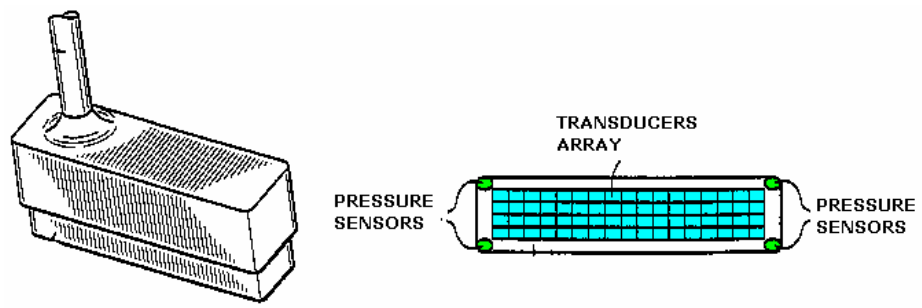


Figure 5.5: Ultrasound Array with Pressure Sensors *(WO0139668)*

The compression of the tissue can also be done by a probe inserted percutaneously during catheterization into the tissue to be measured. The physician drives the probe in the region of interest and applies the compression with the catheter *(EP148502)*. The transducer placed in the catheter (or alternatively outside) is used for pre and post-compression imaging. The scan must be done in a period of minimal periodic physiological motion (i.e. breathing).

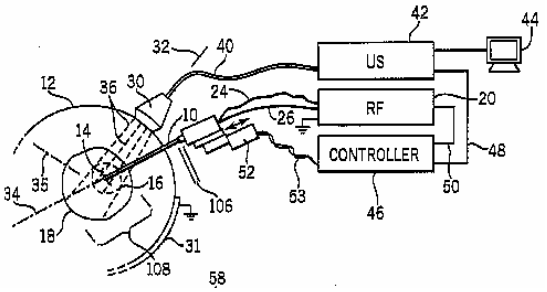


Figure 5.6 Block Diagram of catheter compression device

- MECHANICAL SCANNING

The use of devices that provide a mechanical stimulation to the tissue has the advantage that the compression intensity can be well controlled.

The stress is applied by a motorized compression fixture. Patents and patent applications describing this approach include *US5107837, US6270459, US6514204, WO9746160, US6558324* and *EP0958785*.

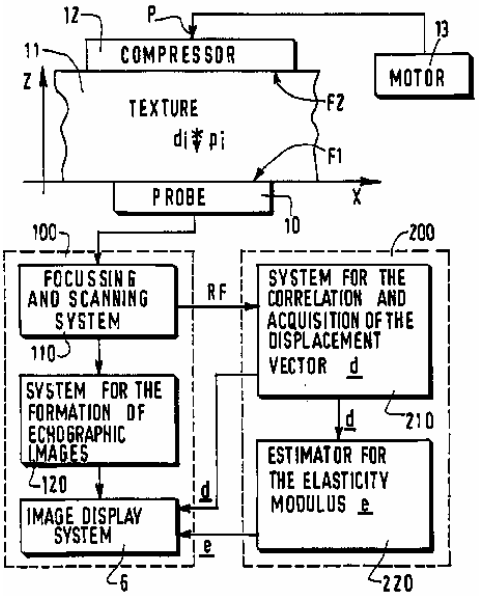


Figure 5.7 block diagram of a mechanical compression systems *EP0958785*

The differences among these patents are mainly in the construction of the apparatus and the display of the results.

With mechanical stimulation it is also possible to measure biomechanical properties of joints and other movable structures of the human body *(GB2404024)*

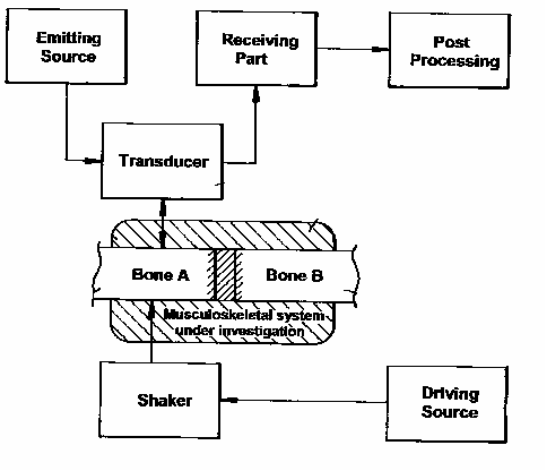


Figure x.8 Schematic diagram of the system for evaluating biomechanical properties of joints *(GB2404024)*

A shaker is used for inducing impulsive stimulation to the target structure. More rigid components or target structures, such as bones will be displaced according to forces transmitted to them through the surrounding soft tissue, which will generally exhibit resilient elastic or plastic properties. The rigid components will reflect any ultrasound pulses directed at them, which provides detailed information regarding their precise displacement as a function of time. In turn, this will reveal information regarding the surrounding medium through which the externally generated physical displacement excitation has been transmitted.

5.4 ELASTOGRAPHY WITH WAVE STIMULATION

The tissue motion can also be induced by a propagating wave. The basic principle is to stimulate the tissue with low frequency waves and image the region of interest with higher ultrasound frequency pulses. Different types of waves can be applied in order to obtain different tissue responses.

- LONGITUDINAL WAVE STIMULATION

In patent *US5919139* an audio transducer transmits vibrational energy into an area of a subject to be scanned. The vibrational energy transmitted by the audio transducer induces palpable vibrations in the tissue medium of the area being scanned. Simultaneously an ultrasound transducer transmits ultrasound pulses into the area. The amplitude and frequency variance of the observed mechanical properties of the tissue are derived from the amplitude and frequency variance of the observed vibrations

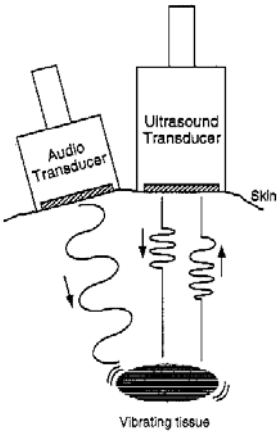


Figure 5.9: Audio/Ultrasound transducer *(US5919139)*

The audio transducer and the ultrasound transducer are coupled to each other through a duplex probe bracket which holds both transducers and allows the audio transducer to be pivoted relative to the ultrasound transducer.

A similar technique is applied in patent *US6068597* where a vibration of a wide range of frequencies is transmitted to the tissue with an audio amplifier. In this way it is possible to analyze the tissue response for a wide spectrum of frequencies and different pathologies can be diagnosed

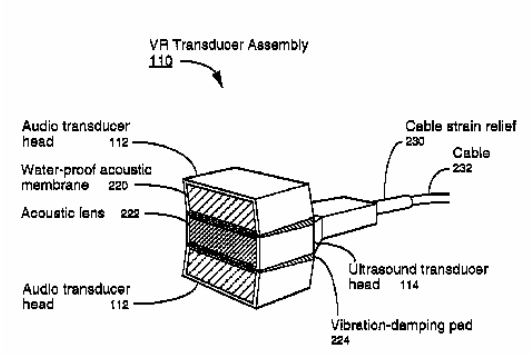


Figure 5.10: transducer assembly *(US6068597)*

AS observed in *Ophir et al. (2000)* the main application of Elastography is tumours investigation. However elastography can also be used for a blood vessel and cardiac tissue investigation *(US2004167403)*.

A first low power (1-10 W/cm^2) tracking pulse is transmitted by the transducers to the tissue. After that a pushing pulse of high energy (1000-10000 W/cm^2) is transmitted by the same transducer and immediately afterwards a second tracking signal is sent to the target region.

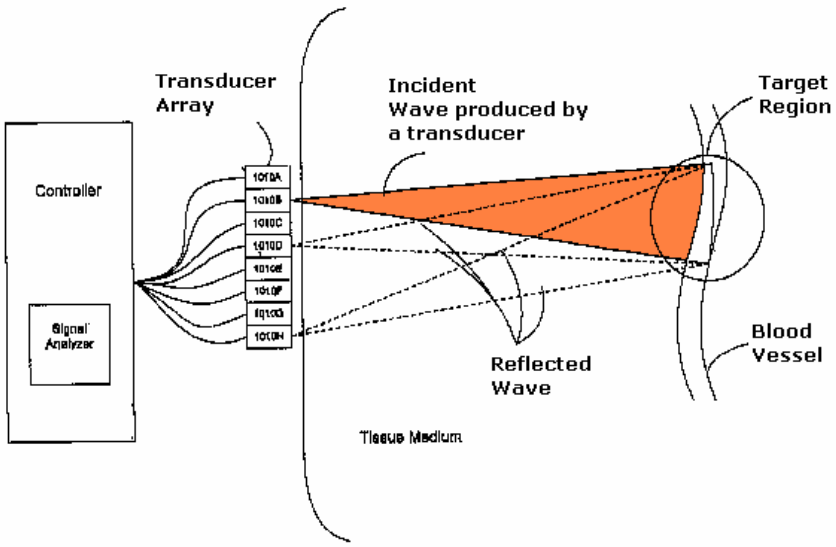


Figure 5.11: Schematic diagram of the system for evaluating blood vessel or cardiac tissue *(US2004167403)*

Comparing the backscattered signal received before and after the pushing pulse it is possible to evaluate the mechanical characteristics of the blood

vessel or cardiac tissue. This procedure can be repeated sequentially to provide a series of cycles

When deriving the mechanical properties of the medium from US observation a model of the tissue is always assumed. An elaborate representation of the tissue was proposed in patent application *US200511956* where different layers of the tissue are modelled as separated interconnected elements.

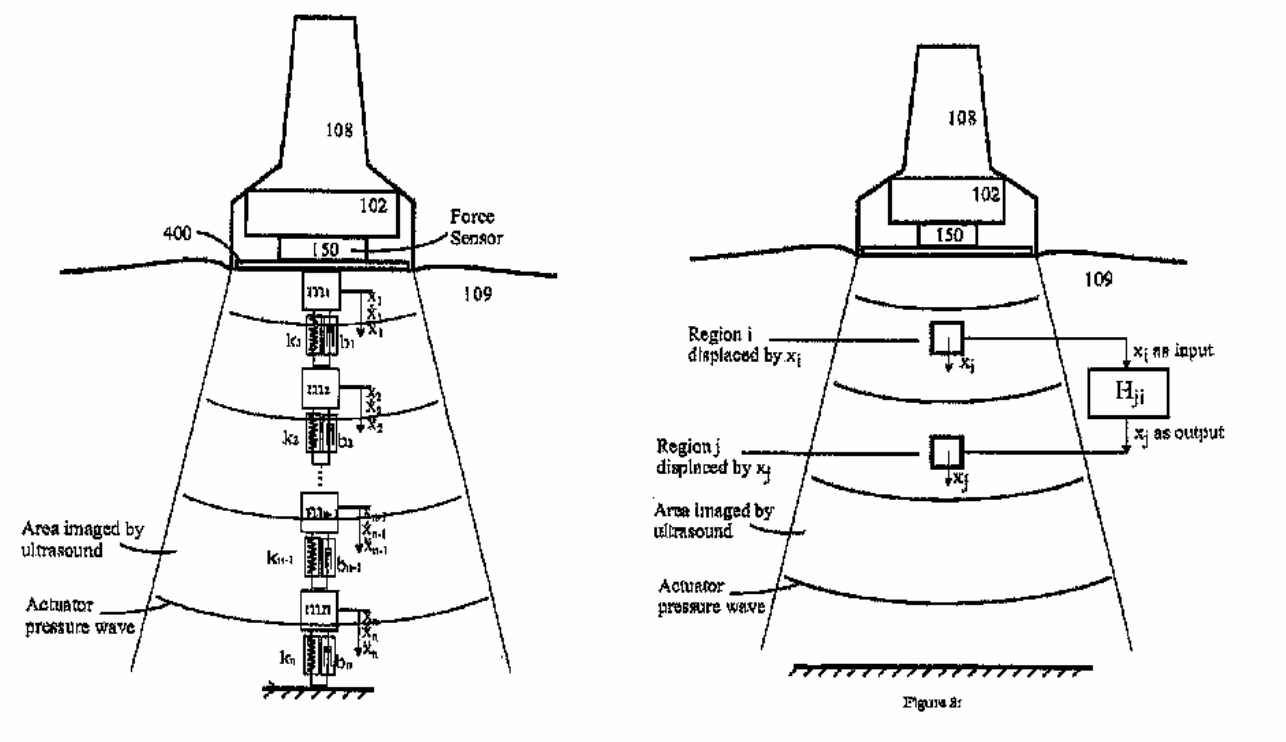


Figure 5.12: Tissue Models for calculate viscoelastic parameters *(US2005119568)*

The different parameters of the model are then obtained by minimizing the error between the real measurement and the calculated model response.

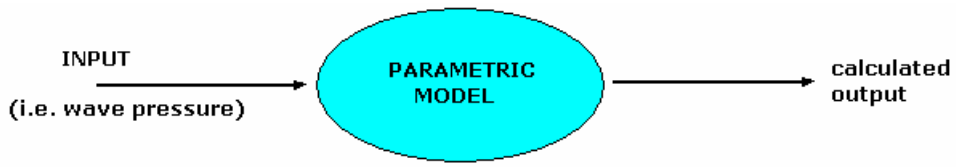


Figure 5.13 Schematic of the process

Several models are described and these include representing elements as spring & dampers (fig 5.12 left) or as black boxes where each tissue layer is identified with a specific transfer function (fig 5.12 right).

- SHEAR WAVE STIMULATION

First described in patent *US5810731* (filed March 4, 1997), Shear wave elasticity imaging (SWEI) is a new approach to imaging and characterizing tissue structures based on the use of shear acoustic waves remotely induced by the radiation force of a focused ultrasonic beam.
Transmission of an ultrasound pulse with a conventional transducer generates almost exclusively longitudinal waves, i.e. waves in which the deformation propagates along the direction of motion of the tissue. However a portion of tissue displaced in the axial direction can be itself a "virtual source" communicating its movement to the neighbouring portions of tissue and inducing a secondary shear wave in the direction orthogonal to the propagation of the original wave.

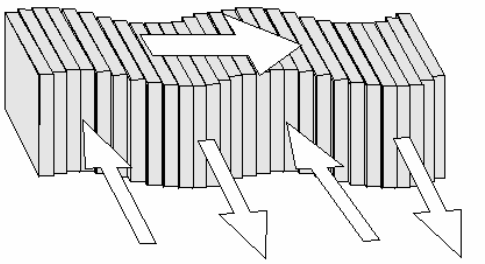


Figure 5.14: shear wave travelling to the right and perpendicular deformation
http://pubs.usgs.gov

In patent application *US200468184* ultrasound energy is transmitted by an ultrasound transducer into the tissue in a first direction to provide a **virtual** extended shear wave source. The virtual extended shear wave source generates an extended shear wave that propagates orthogonally to the first direction.
To generate this particular wave the axial component of the shear wave source is strengthened by adding another wave with opposite polarity near the first one.

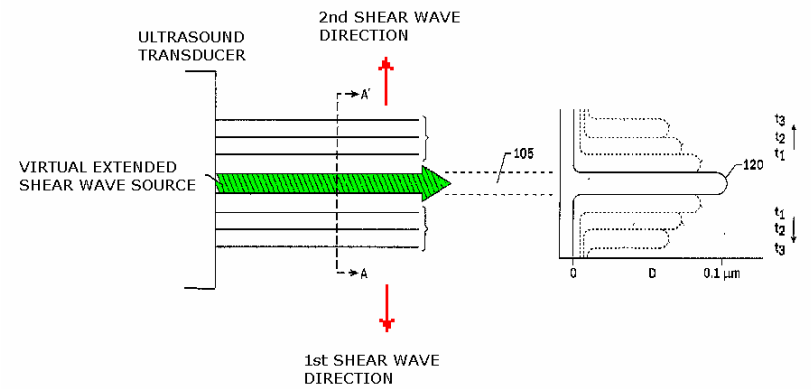


Figure 5.15: Virtual Shear Wave source and shear wave propagation through the tissue *US200468184*

The ultrasound system can be programmed to excite selected transducer elements of the ultrasound transducer array that can generate ultrasound energy to provide the virtual extended shear wave source.

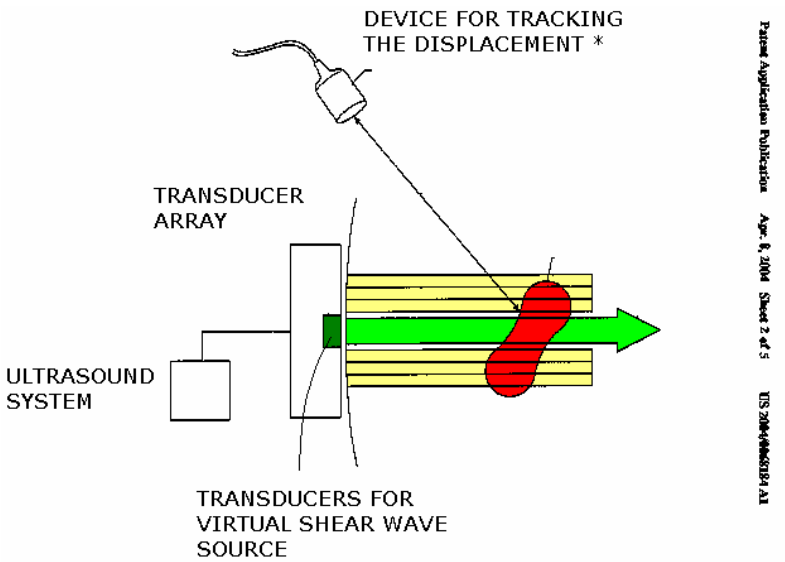


Figure 5.16: Ultrasound imaging method for tracking the displacement *US200468184*

The displacement of tissue is tracked (receiving reflected ultrasound energy from the tissue) by an ultrasound transducer. The ultrasound transducer is used to generate the virtual extended shear wave source and, later, the same transducer (or another one as shown in fig. 5.16) is used to track the movement of the tissue caused by the propagation of the extended shear waves.

5.5 ELASTOGRAPHY WITH PHYSIOLOGIC EXCITATION

The mechanical properties of the tissues can be observed exploiting where possible their natural movements instead of stimulating them externally. With this technique it is possible to calculate the mechanical parameters of organs like heart and arteries.

- CARDIAC STRAIN MEASUREMENTS

The non-invasive quantification of regional myocardial function is an important goal in clinical cardiology. Myocardial thickening/thinning indices are one method of attempting to define regional myocardial function *[D'Hooge et al. 2000]*. The basic technique is the same as used for elastography with external excitation, i.e. a region of interest is scanned before and after compression and signal are post-processed (real time or off-line) for calculating the mechanical indices. Scanning can be performed in the apical or parasternal view as shown in figure 5.17.

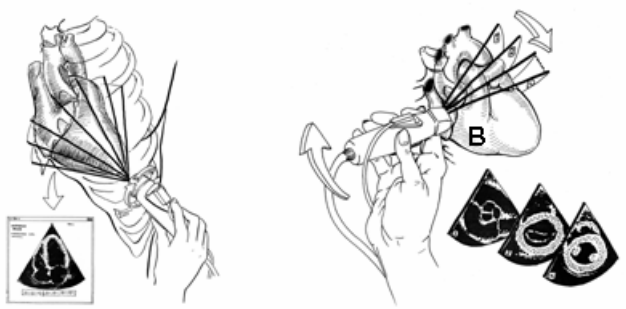


Figure 5.17: Apical view (left) and Parasternal view (right)
http://depts.washington.edu/cvrtc/imgac.html

The scanning position information is important for transformation of data in the transducer coordinate system into the heart coordinate system

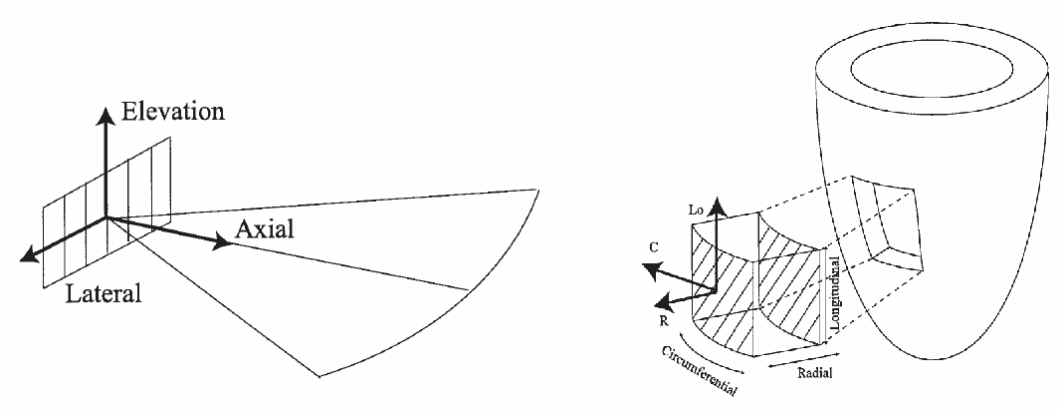


Figure 5.18 Transducer and heart coordinates system

For example, if a scan is performed in the apical view the axial direction of the transducer corresponds to the longitudinal axes in heart coordinates, whereas if the scan is performed into parasternal view, the transducer's axial direction is the corresponds to the radial direction of the heart.

- 1D Measurement

In cardiac strain estimation, cross correlation or gradient velocity methods described in paragraph x.2 are used to estimate 1D strain along the axial direction of the transducer.

The first approach is presented in patent application *US2003113043* and the latter in patent and patent applications *US2004092766 US6099471, WO9917660*

Some devices provide information about mechanical characteristic in real time *(US2004288989,US6099471)*

- 2D Measurement

A major drawback of the approaches described above is that they are limited to making only a one-dimensional measurement. Indeed, only the strain (rate) along an image line can be assessed *[D'Hooge et al. 2001]*. This limitation causes the technique to be angle dependent *[Castro et al 2000]*. As a result the deformation information is incomplete and this could limits its application in quantifying the cardiac function.

To overcome this limitation a method for calculate longitudinal and radial strain rate is described in patent application *WO2006124603* and *EP1079240*.

Scanning is performed in the parasternal view. The strain in the radial direction (axial of the transducer) is calculated with the velocity gradient method, the strain in the longitudinal direction (lateral for the transducer) is estimated by tracking the movement of RF patterns from a line to another.
To do this, the scan angle of the transducer is narrow (about 10 degrees) and the number of RF image lines is set at low value (12 images instead of 60). This allows to have:

- Images not much decorrelated in the longitudinal direction
- High number of frames per second

In patent *US6527717* motion tracking and Doppler information are used for the determination of a two-dimensional motion field and it is represented with vectors superposed on a B-mode image.

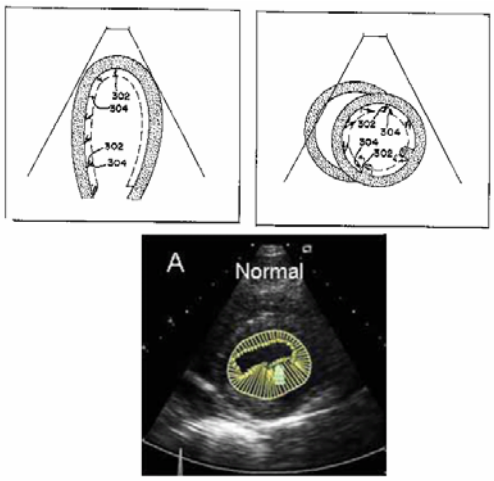


Figure 5.19 Motion vectors (*US6527717) & www.medical.siemens.com*

Where tissues are moving in different directions within a scanned region, a plurality of local determinations of two-dimensional motion vectors provides accurate estimates of motion throughout a scan region.

- INTRAVASCULAR ULTRASOUND ELASTOGRAPHY

The composition and morphology of the atherosclerotic lesion (i.e. the plaque) are considered as an important determinants of acute coronary ischemic syndromes. When a lesion is unstable, it may rupture and cause a thrombosis reaction. A rupture prone-plaque contains a large lipid pool covered by a thin fibrous cap and intravascular ultrasound elastography has been suggested to be a good technique to assess the presence of lipid pools and identify regions of high mechanical stress *[De Korte et al. 2002]*.

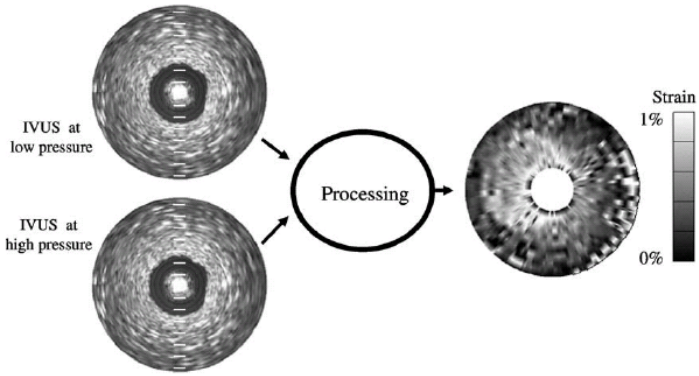


Figure 5.20: Vascular elastography measurement procedure ***[De Korte et al. 2002]***

For intravascular purposes, the intraluminal arterial pressure is used as the excitation force *(EP1713398)*. The radial strain of the tissue is obtained by cross-correlation techniques on the radio frequency (RF) signal as already describes The strain is colour-coded and plotted as a complimentary image to the IVUS echogram.

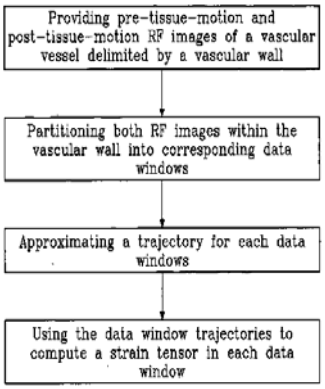


Figure 5.21: Flowchart of vascular elastography ***(EP1713398)***

The method described in patent application *EP1713398* can also be adapted using high resolution ultrasound devices for non-invasive vascular ultrasound elastography (NIVE) to non-invasively characterize **superficial vessels** such as carotid, femoral arteries, etc. NIVE is of clinical values for the purpose of diagnosis and follow-up of vascular pathologies. The method can further be adapted for non-invasive vascular ultrasound micro-elastography (MicroNIVE) for characterizing small superficial vessels in humans and animals.

5.6 STATISTICS

Patents about this field can be founded in the following classes:

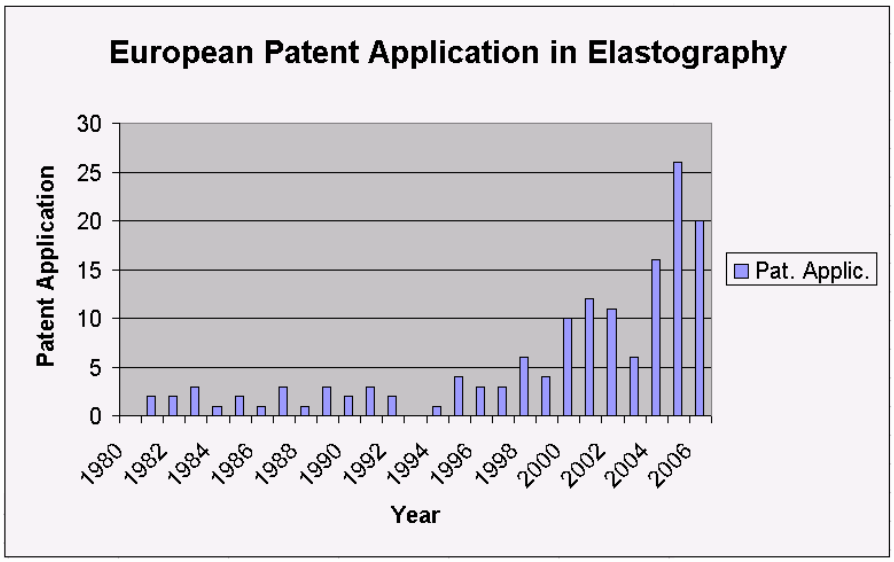
A61B8/08 . Detecting organic movements or changes, e.g. tumours, cysts

A61B8/08B . . [N: using Doppler signals (special applications of sonar systems for mapping or imaging]

And using the following key word:

Z61B8 imaging strain

	Total	Pat. Applic.
1980	2	0
1981	4	2
1982	6	2
1983	9	3
1984	10	1
1985	12	2
1986	13	1
1987	16	3
1988	17	1
1989	20	3
1990	22	2
1991	25	3
1992	27	2
1993	27	0
1994	28	1
1995	32	4
1996	35	3
1997	38	3
1998	44	6
1999	48	4
2000	58	10
2001	70	12
2002	81	11
2003	87	6
2004	103	16
2005	129	26
2006	149	20



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CHAPTER VI

BLOOD FLOW DOPPLER

6.1 INTRODUCTION

In blood velocity estimation, the goal is not simply to estimate the mean target position and mean target velocity. The goal instead is to measure the velocity profile over the smallest region possible and to repeat this measurement quickly and accurately over the entire target. Therefore, the joint optimization of spatial, velocity, and temporal resolution is critical. In addition to the mean velocity, diagnostically useful information includes the volume of blood flowing through various vessels, spatial variations in the velocity profile, and the presence of turbulence.

The figure below summarize the environment of an ultrasonic blood velocity.

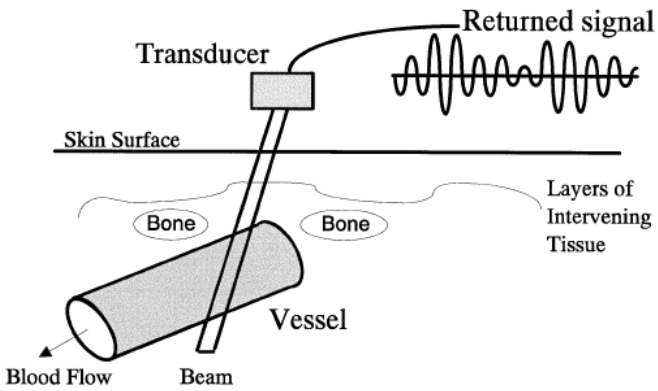

Figure 6.1: Blood Flow measurement environment
(Handbook of biomedical Engineer, Bronzino J.D. CRC Press. Inc , 2000)

The movement of blood cells causes a change in the frequencies of reflected sound waves (Doppler effect). If there is no blood flow, the frequency does not change. Information from the reflected sound waves can be processed by a computer to provide graphs or pictures that represent the flow of blood through the blood vessels.

Current ultrasonic imaging systems operate in a pulse-echo (PE) or continuous-wave (CW) intensity mapping modes as explained in chapter 2 (ultrasound overview).

As shown in the previous chapters, the Doppler effect is a widely used technique in diagnostic ultrasound, there are examples in USCA, 3D imaging and Elastography.

The applications of Doppler effect described in this chapter can be divided in 4 category:

- Blood flow in vessels and arteries;
- Blood flow in the heart ;
- Application of Doppler effect in pregnancy;
- Transcranial Doppler.

6.2 DETECTION OF BLOOD FLOW

A typical Doppler device is described in patent application *EP0933063*, the ultrasonic echo signals are computed by a phase shift detector (see figure 6.1, 30) and the blood stream velocity is calculated. The brighter or darker color is displayed according to the blood velocity in the vessel.

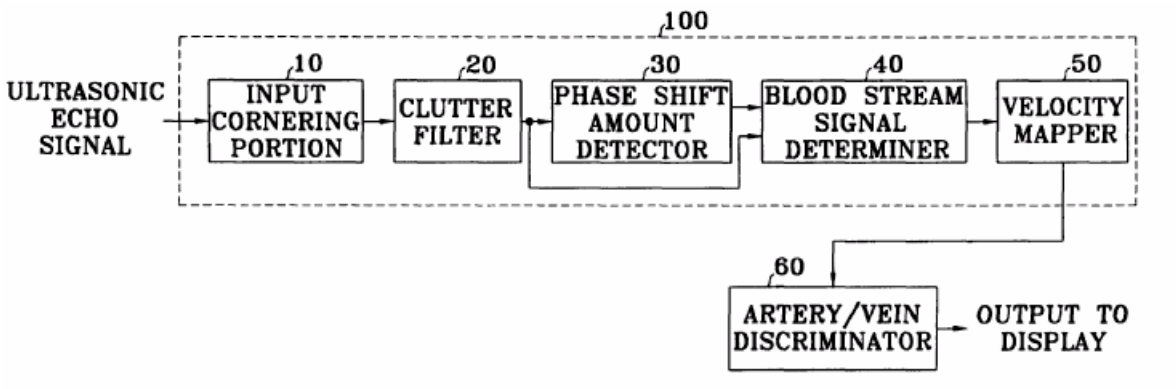

Figure 6.1: Blood Flow device block diagram *EP0933063*

The information about the blood flow can provide to the physician new information about the condition of the vessel and the presence of blood clots. A method for detecting arterial stenosis is described in patent application *EP1363539*. The detection of blood clots and blocked or narrowed blood vessels in almost any part of the body, especially in the neck, arms, and legs is a very important information for the physician. Blocked or narrowed arteries of the neck can cause dizziness, loss of vision, paralysis, weakness, numbness, or other symptoms of a stroke. Blood clots in the deep veins of the leg can cause leg pain and swelling and can increase a person's risk of pulmonary embolism.

To prevent artifacts caused by the motion of arteries induced by cardiac pressures the device is ECG gated as the devices described in chapter 4 such as *US5871019 and DE19723053*

After selecting a reference point the physician scans a region of interest with the transducer. The device is coupled with an articulated arm that measures accurately the relative angle between the reference point and the scanner which allows calculation of the velocity.

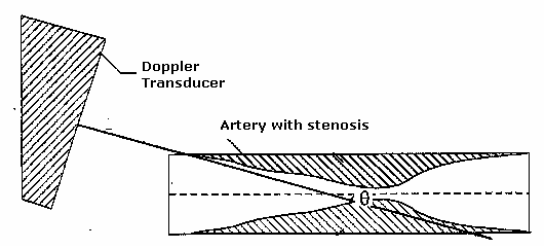

Figure 6.3 Doppler device (*EP1363539)*

The Doppler ultrasound system detects the velocity profiles of blood flow through a selected area of interest and creates a series of velocity profiles within the area of interest. These velocity profiles are then used to reconstruct the path of the artery and calculate the change of velocity along the length of the artery (delta curve).

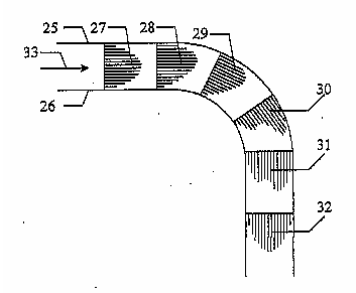

Figure 6.4 Velocity profiles along the artery (*EP1363539)*

Certain parameters indicative of potentially stenotic segments are automatically identified by analyzing the velocity and the delta curve of the segment of the artery. The parameters are:

- the average velocity of the velocity profile;
- the peak change in velocity across the velocity profile;
- the presence and degree of blunt flow found in the velocity profile;
- the presence and degree of turbulence found in the velocity profile;
- the degree of skew in the velocity profile;
- the width of the velocity profile.

All these parameters allow to make a diagnosis of a potentially stenotic area as shown in figure 6.5

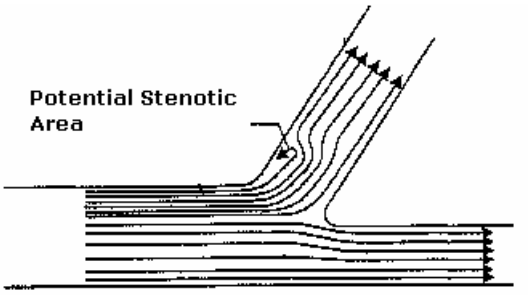

Figure 6.5 Potential stenotic area (*EP1363539)*

One problem in measuring blood flow is to calculate the relative angle θ between the transducer and the blood direction.

In patent application *EP1693004* this problem is solved by dividing the transducer in two parts, the first part sends the signal and the other part receives the reflected wave. The computer analyze the reflected signal, calculate the shift in frequency and the angle between the incident and reflected wave. When all these parameters are obtained it is possible to calculate the blood flow velocity.

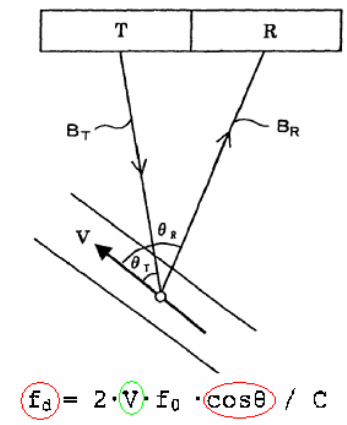

Figure 6.6 Doppler device (*EP1693004)*

A solution to this problem is also proposed in patent application *EP1221895.* The idea is to divide the transducer in two parts as described in *EP1693004 (*first patent application described in this chapter) but use each part of the transducer to transmit and to receive the ultrasound signals. The angle of blood flow or tissue motion is automatically calculated by comparing the reflected signals .

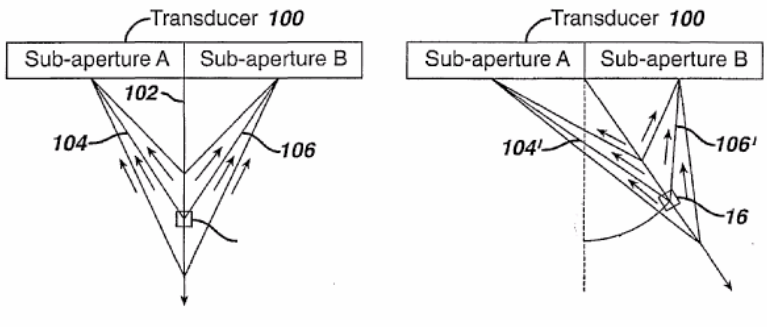

Figure 6.7 Doppler device (*EP1221895)*

Another solution to the problem of the relative angle is described in patent application *US2006241459.* The ultrasonic beam is electronically rotated as shown in figure 6.8, thereby enabling to the image of the artery under different angle.

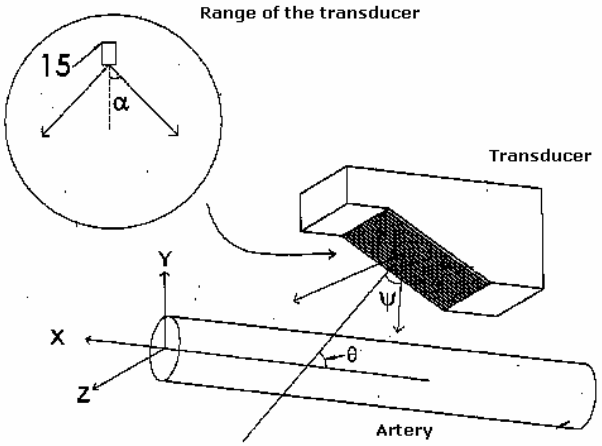

Figure 6.8 Doppler transducer (*US2006241459)*

Furthermore, the device continuously controls the direction of the ultrasound beams to achieve maximum return signal amplitude. Then, the condition and trend of the blood flow of the scanned region is recorded and displayed.

The same problem is addressed in patent *US5844140*. The transducer is mounted in a fluid filled housing with a magnetic rotor that allows to move the transducer in the desired position using magnetic coils. Hall effect sensors mounted in the housing allow to determine the position of the rotor

and of the transducer. Like in the patent application *US2006241459* the Doppler signals are analyzed by a computer and the best alignment is automatically calculated

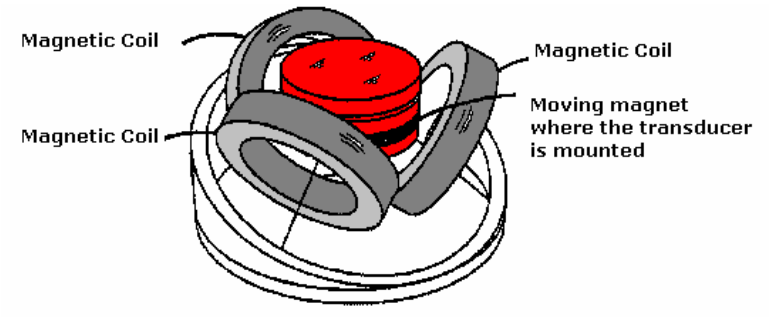

Figure 6.9 Magnetic Driving System (*US5844140)*

This device can be used for several application like carotid-tracking and also for transcranial Doppler ultrasound TCD, that will be described in the next section

The Doppler effect is also used in first aid devices like defibrillators as described in patent application *EP1463562.* The transducer array is mounted on an adhesive patch to detect the pulse of the patient in the carotid artery. The device is also equipped with ECG detection system. If no signal of blood flow and no ECG signal is present the defibrillator is "armed" and it is possible to provide the electrical shock to the patient.

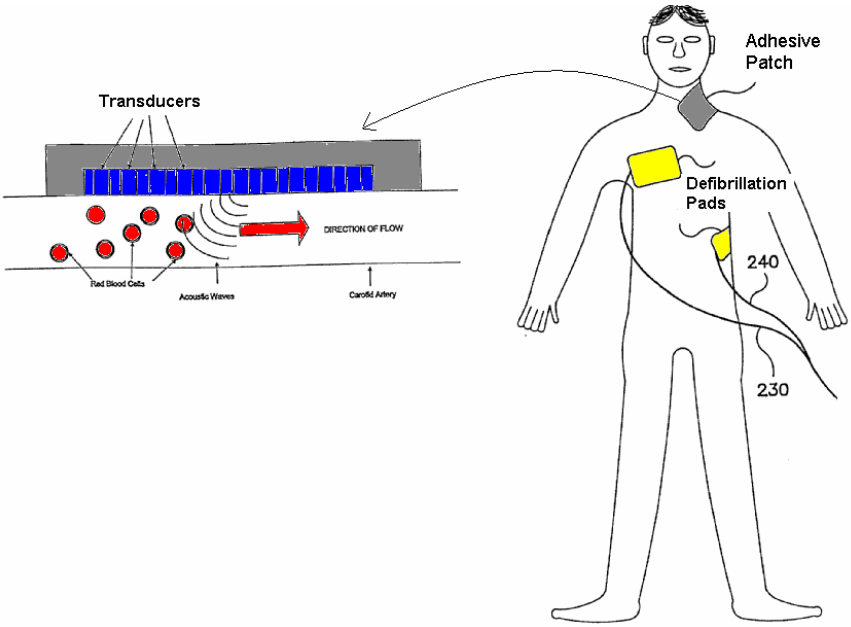

Figure 6.10 Cardiac Resuscitation System with perfusion detection system (EP*1463562)*

Another application of Doppler device is the diagnosis of male impotence. The system described in patent *US6251076* analyze the blood flow in the cavernosal artery of the penis. The housing allows a fixed orientation with respect to the artery while the ultrasound signals are acquired.

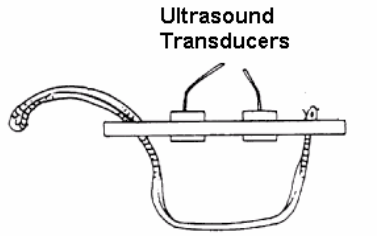

Figure 6.11 Male impotence diagnostic system *(US6251076)*

As widely known, tumours are able to develop a very complex vascularisation. By analyzing the type of vascularisation it is possible to discriminate a benign tumour from a malignant one, as described in patent application *WO2005004726.*

After imaging an area where a tumour is present the blood flow is calculated and by analyzing the velocity profiles of blood it is possible to calculate the vascular resistance to blood flow. If the level of vascular resistance is lower than a threshold value the tumour is a malignant, if is higher the tumour is benign (see table, figure 6.12).

parameter	malignant	benign	ROC curve area
average velocity difference	0.22 ± 0.07	0.14 ± 0.07	0.723 (P=0.0011)
minimal average velocity	0.24 ± 0.06	0.17 ± 0.04	0.808 (P<0.0001)
angle parameter, β	17° ± 18°	32° ± 33°	0.740 (P=0.0009)
high-to-low velocity ratio	0.38 ± 0.21	0.69 ± 0.34	0.786 (P<0.0001)
DVD_S	1.90 ± 1.33	9.21 ± 5.34	0.983 (P<0.0001)
SVD_S	0.97 ± 1.38	1.46 ± 4.57	0.507 (P=0.4727)

Figure 6.12 Values of the parameters which characterize the velocity spectrum (*WO2005004726)*

The availability of micro and nano-technologies has made possible the development of portable devices in the last years, such as watches that can provide information of the blood flow as described in patent *US6758816* and portable device that allows to measure the blood rheology non invasively *(US2003032869)* .

In patent *US6758816* the transducers, a transmitter and a receiver, are placed inside the watch strap and they acquire information of blood flow during the whole day. The information about flow can be stored and then analyzed.

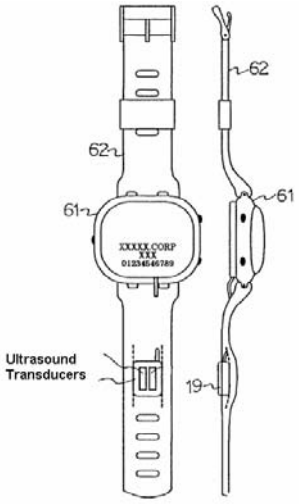

Figure 6.13 Pulse wave watch detector *(US6758816)*

In patent application *US2003032869* a rheology measuring apparatus is described. Rheology is the study of the deformation and flow of a substance (blood) under the influence of an applied stress.

The ultrasound transducers are mounted into a button of a normal pc-mouse, the blood-flow of the artery in the right(or left) forefinger is analyzed before and after clicking the button and the information are analyzed by a microprocessor that allows to calculate the mechanical characteristics of blood.

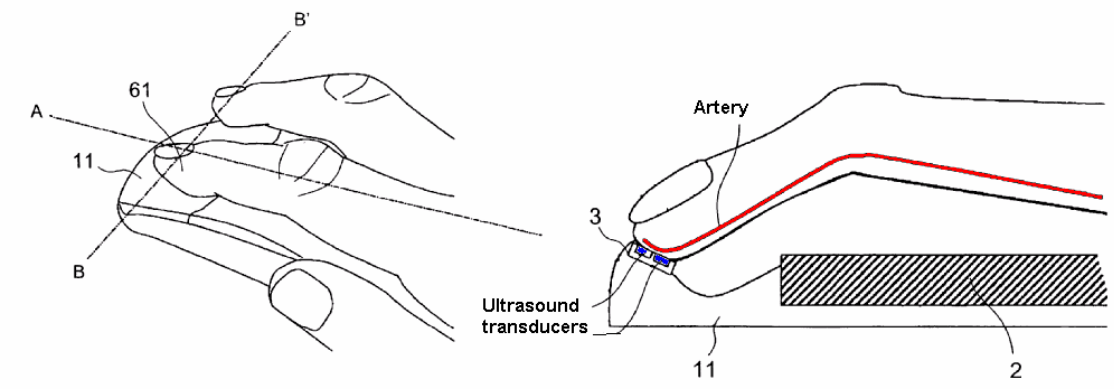

Figure 6.14 Rheology measuring apparatus *(US2003032869)*

6.3 BLOOD FLOW IN THE HEART

As described in chapter 5 (Elastography) the Doppler effect is widely exploited to measure the movement of heart walls. This is not the only possible application of Doppler effect in heart diagnosis. By analyzing the blood flow inside the chambers of the heart or immediately after it leaves the aortic valve it is possible to recognize the condition of the cardiac valves.

The device described in patent application *EP1601291* is a Doppler device for monitoring the blood flow through a cardiac valve. By selecting the time delay of the signal it is possible to obtain information about the blood flow immediately after the cardiac valve. The transducer array is placed is so that an apical view of the heart is obtained (see figure 6.15). The blood flow calculated from the Doppler signals is then visualized and abnormalities of blood flow caused by diseased condition of the cardiac valve are detected.

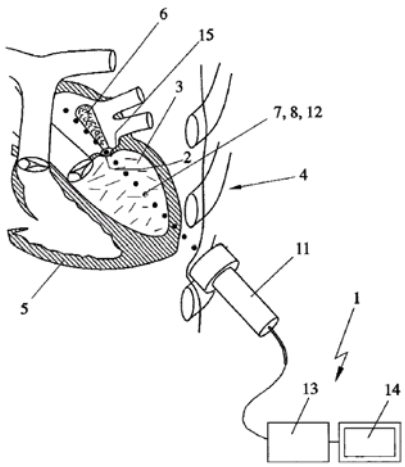

Figure 6.15 Ultrasonic device for monitoring the condition of flow through a cardiac valve *(EP1601291)*

A cardiac valve that is diseased or defective can be surgically excised and replaced with an artificial valve.

Once the valve has been replaced, it will be desirable to carefully monitor the condition of the valve, to ensure that it continues to function properly. While it is possible to externally examine a patient and reach diagnosis concerning the condition of a replacement valve and its proper functionality, an external examination may fail to identify incipient problems. If the valve subsequently fails catastrophically, the patient may die before surgery can correct the problem.

To prevent this event a system for monitoring the condition of flow through a cardiac valve is described in patent *US6398734.*

The ultrasound transducer are built with flexible piezoelectric material that allows to mount the transducers or within the wall of an artificial cardiac valve or around a cuff that wraps around aorta. The blood flow is continuously monitorized and if some abnormalities are revealed the device can send an alarm signal to a computer or to a cell phone .

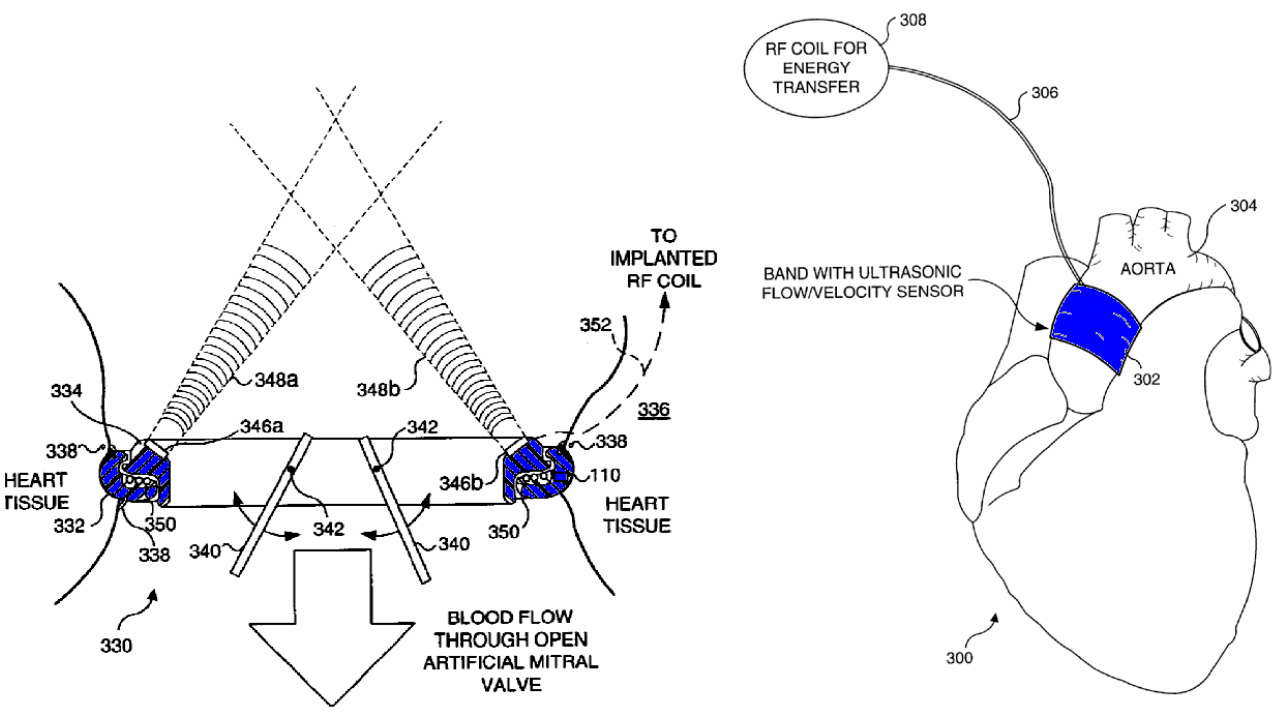

Figure 6.16 Ultrasonic device for monitoring the condition of flow through a cardiac valve *(US6398734)*

6.4 DOPPLER EFFECT IN PREGNANCY

An important information that can be obtained with the Doppler effect is the heartbeat frequency of fetus. It is known that heartbeat frequency of a fetus is higher than the frequency of the mother, and this difference in frequencies is exploited for calculate the fetal heartbeat rate in patent *US5630418.*

The Doppler signal that is received by the transducer contains components of the frequencies from the mother (low frequencies) and from the fetus (high frequencies), the signal is filtered with an high-pass filter which eliminates the low frequencies and the fetal heart rate is calculated by Fourier transform.

Another method for the calculation of the heartbeat frequency is presented in patent application *DE10345717*. The process comprises 3 steps:

1) The coefficient of the frequency of harmonic analysis of the signal at a certain time is calculated for several periods;

2) The Auto-correlation function of the previous coefficients is determined;

3) The fetal heartbeat frequency is calculated from the position of the maximum of the auto-correlation function obtained in the second step.

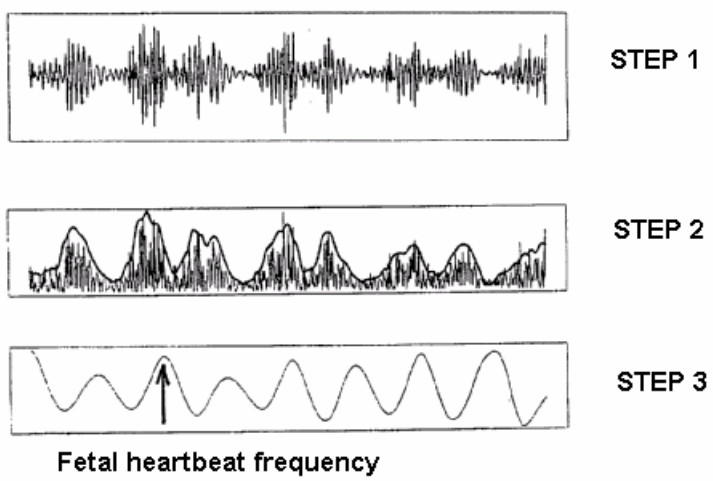

Figure 6.17 Detection of fetal heartbeat frequency *(DE10345717)*

6.5 TRANSCRANIAL DOPPLER ULTRASOUND (TCD)

Transcranial Doppler (TCD) ultrasound is a non-invasive method for the estimation of the blood flow velocities in the intracranial vessels. Using established TCD techniques, sections of the internal carotid artery (ICA), middle cerebral artery (MCA), anterior carotid artery (ACA), posterior cerebellar artery (PCA) and the basilar and periorbital arteries can be examined *[Markus 1993]*. TCD typically uses a 2 MHz pulse ultrasound positioned as shown in figure 6.18

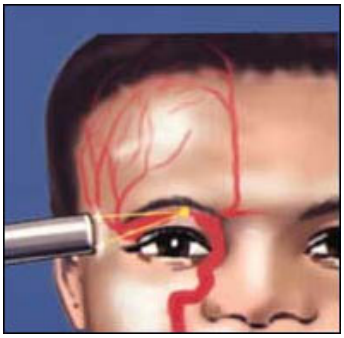

Figure 6.18 Positioning of the transducer in a TCD examination
http://www.mcg.edu/neurology

A TCD system is described in patent application *US2002103436*. The system comprise a bi-temporal probe hanger where the transducers are mounted as shown in figure 6.19

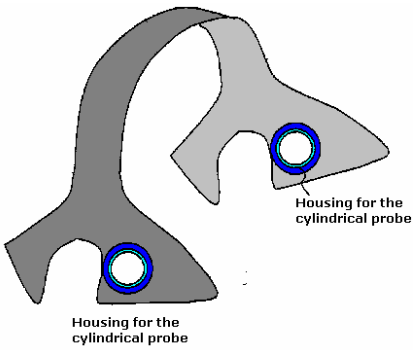

Figure 6.19 Bi-temporal probe hanger (*US2002103436)*

The ultrasound transducers are placed on the skin overlying the temporal bone (temple). The ultrasound transducer is connected with 2 roller balls that allow the physician to tilt the transducers in the desired direction as shown in figure x.18.

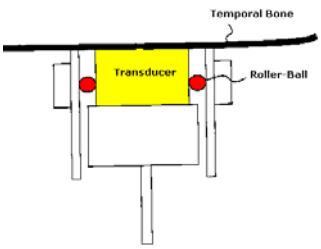

Figure 6.20 Probe Housing (*US2002103436)*

The intensity of the reflecting waves can be used for detecting circulating emboli, in fact the proportion of ultrasound reflected at the interface between two materials, such as that between blood and an embolus, is proportional to the difference in acoustic impedances of the two materials. Acoustic impedance itself depends on density; therefore, the greater the difference in density between the two media, the greater the amount of ultrasound reflected, and the greater the intensity of the received signal.

A crucial point in the diagnosis of thromboembolic event is the time between the diagnosis and the administration of life-saving thrombolityc therapy. The system described in patent *US6486219* is an implantable transcranial Doppler device with a drug delivery system connected with an external handheld computer. This device can be implanted in patients with high risk of stroke.

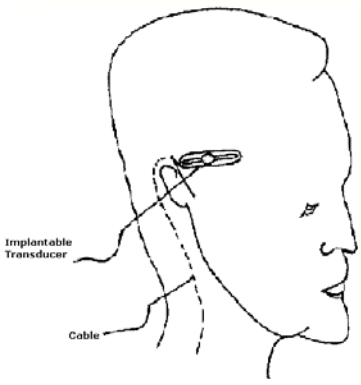

Figure 6.21 Implantable doppler device for TCD (*US6486219)*

The ultrasound transducer is placed in a flexible silicone probe housing. The housing contains also a reservoir for the therapy drug.

The analysis of the Doppler signals is done by the handheld computer that is telemetric connected with the transcranial Doppler device. Some threshold parameters(e.g. flow velocity) are configured in order to allow

automatic diagnosis and if a an emboli is detected the computer sends a signal to the implantable device to cause the infusion of thrombolityc and neuroprotective agents into the vein of the patient.

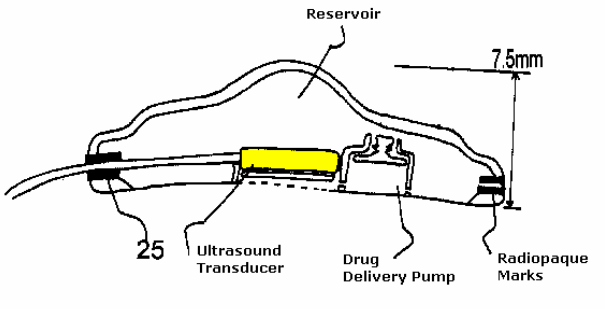

Figure 6.22 Implantable probe with drug delivery pump (*US6486219)*

The height of the probe housing is chosen such that it does not protrude sideways to alter the side profile of the patient's head and is well within the area covered by the hairline no cosmetic defect are produced by the implantation of the probe housing.

With TCD it is also possible to monitor the intracranial pressure (ICP). Elevated intracranial pressure not only reduces blood flow to the brain, but it also affects the normal metabolism of cells within the brain. Under some conditions, elevated intracranial pressures may cause the brain to be mechanically compressed, and to herniate. Before the TCD technique the conventional ICP monitoring devices were epidural catheters, subarachnoid screws and ventriculostomy catheters. All of these methods are invasive and must be performed in hospitals.

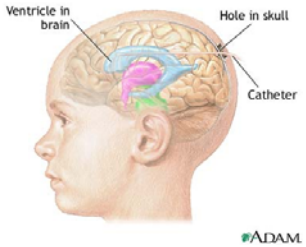

Figure 6.23 Invasive TCP measurement
http://www.pennhealth.com

With the device described in patent application *US2006079773* non invasive ICP measurements are possible thanks to the application of elastography to TCD.

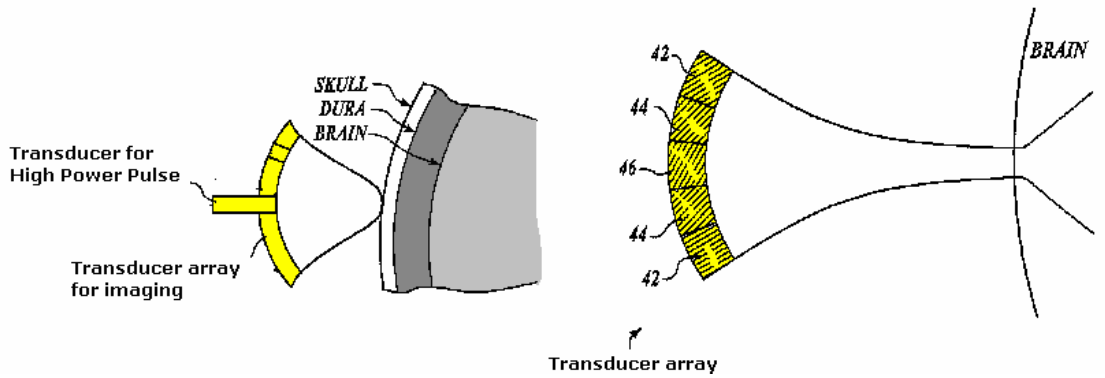

Figure 6.24 TCD for monitoring ICP (*US2006079773)*

The general principle of this technique is the similar as in elastography

5. Acquiring a pre compression ultrasound image of the region of interest (Brain);
6. Applying compression to the tissue with high power ultrasound pulse;
7. Acquiring a post compression relaxing signals of the same region;
8. Evaluating the ICP of the same region by analyzing the post compression relaxing signal as shown in figure 6.25

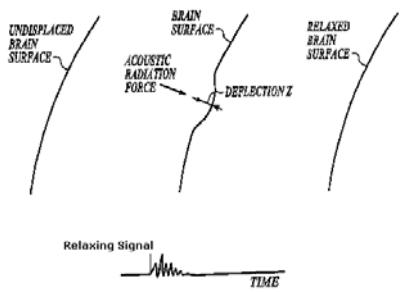

Figure 6.25 Procedure for monitoring ICP with TCD (*US2006079773)*

6.6 STATISTICS

Patents about this field can be founded in the following classes:

A61B8/02 . Measuring pulse or heart rate

A61B8/02B . . (186) [N: of a foetus]

A61B8/06 . Measuring blood flow

A61B8/06B . . [N: to determine blood output from the heart]

A61B8/06F . . [N: combined with B-scan, e.g. tomography]

A61B8/08P . . [N: Devices for detecting pregnancy]

	Total	Pat. Applic.
1980	6	6
1981	11	5
1982	12	1
1983	20	8
1984	24	4
1985	37	13
1986	49	12
1987	57	8
1988	62	5
1989	77	15
1990	94	17
1991	104	10
1992	112	8
1993	117	5
1994	128	11
1995	135	7
1996	138	3
1997	145	7
1998	153	8
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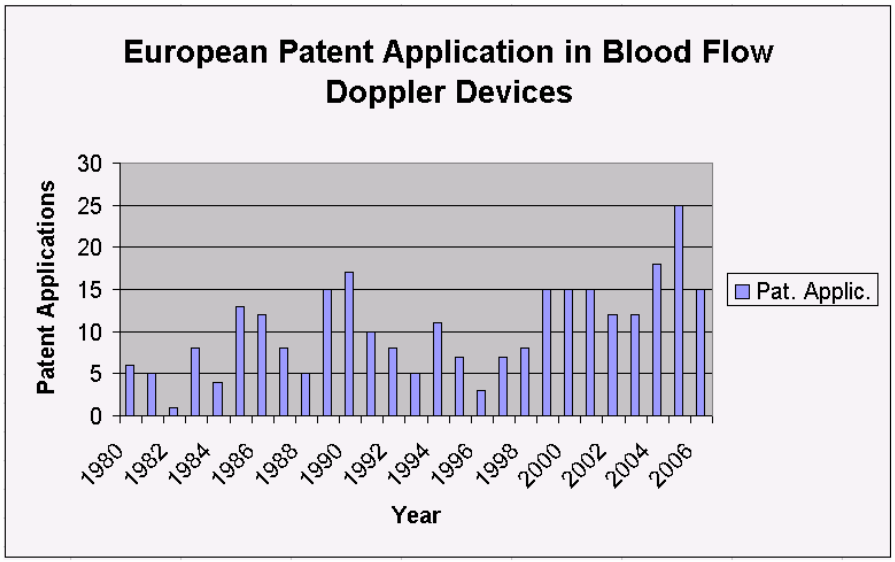
2000	183	15
2001	198	15
2002	210	12
2003	222	12
2004	240	18
2005	265	25
2006	280	15



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CHAPTER 7
ULTRASOUND CATHETERS

7.1 INTRODUCTION

Miniaturization is a continuing trend in technology toward ever-smaller scales for first mechanical, then optical and most recently electronic devices.

In the last year also ultrasound devices have exploited this trend in technology and ultrasound catheters started to be utilized in hospitals. The major advantage of the use of ultrasound catheters is that it is possible to utilize higher frequencies because a deep penetration of the beam is not necessary. Thanks to the use of higher frequencies higher axial resolution is reached.

Ultrasound catheters can be utilized for trans-esophageal echography (TEE), intravascular ultrasound (IVUS) and trans-rectal echography.

Their application range is very wide, from 3D imaging of organs (chapter x, par. 6), to special technique such as vascular elastography (chapter x, par. 5) and tissue ablation visualization with USCA (chapter x, par. 4).

One of the most important characteristic of a catheter is the handiness, some solution are provided in order to drive the catheter or at least the ultrasound transducer inside the body.

7.2 MECHANICAL ROTATION OF ULTRASOUND CATHETERS

In mechanical catheters the ultrasound transducer is coupled with a mechanical driving system that allows the physician to rotate, tilt or translate the transducer. As shown in figure x.1 the surgeon rotates the endoscope shaft (that is inside the body) by turning the control wheel *(US2004176691)*

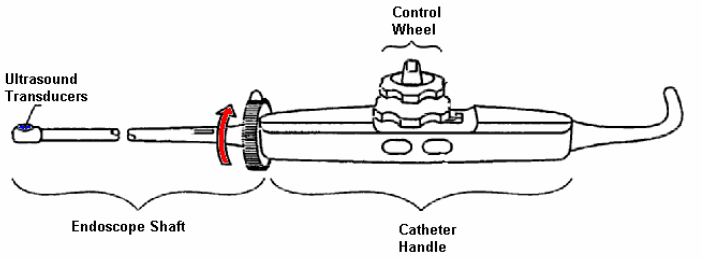


Figure 7.1 Ultrasound catheter (*US2004176691)*

A similar solution is proposed in patent application *EP0580304* the catheter is mechanically tilted by a mechanical motor driven by the surgeon and the 3 transducers (A,B,C) can be rotated as shown in figure x.2 in order to obtain a wider field of view

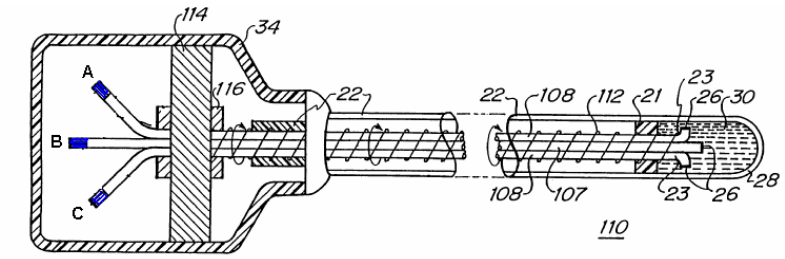


Figure 7.2 Ultrasound catheter (*EP0580304)*

In patent application *EP1691690* once that the catheter reached the desired position the transducer can be mechanically moved in order to obtain different views of the organ investigated.

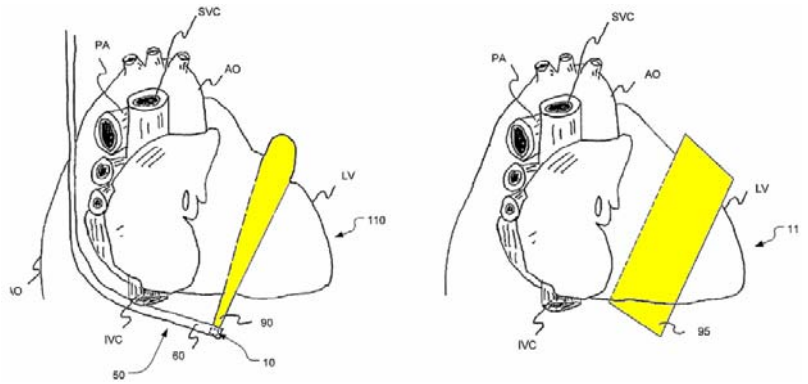


Figure 7.3 Ultrasound catheter (*EP1691690)*

7.3 MECHANICAL ROTATION OF ULTRASOUND TRANSDUCER

The same results obtained by rotating the whole catheters can be reached by rotating only the distal end of the probe or at least the transducer.

In patent application *DE4207577* the 1D array is mechanically rotated as shown in figure 7.3. The cone beam obtained by rotating the array can be used to perform 3D images

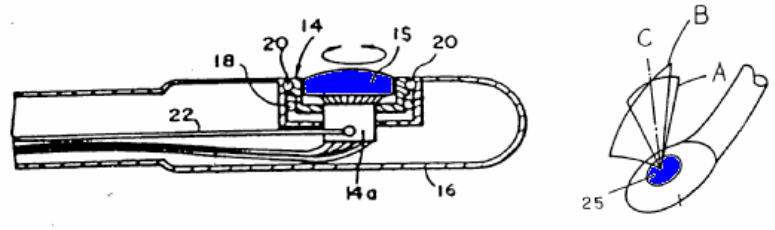


Figure 7.4 Ultrasound catheter (*DE4207577)*

In patent application *EP1208801* the probe is equipped with a curvilinear array mounted on the distal end of the catheter. The array is linked to a mechanical motor that allows to tilt it as shown in figure x.5

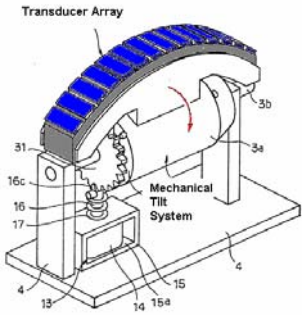


Figure 7.5 Transducer array and mechanical tilt system mounted in the distal end of a probe (*EP1208801)*

Similar solution are proposed in patent application *EP1535574* where the transducer array is connected to a system of cables (Driving Cable) that allows the rotation.

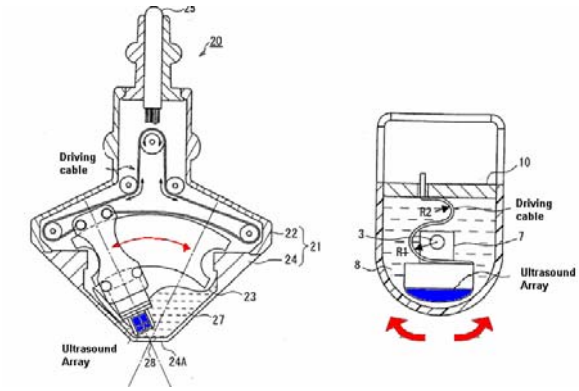


Figure 7.6 Catheters mechanical driving system (*EP1535574)*

A different solution is provided in patent application *EP1659951*. The array and the probe are fixed, the only part that is mechanically rotated is a mirror that reflects the ultrasonic wave in the desired direction (fig. x.7)

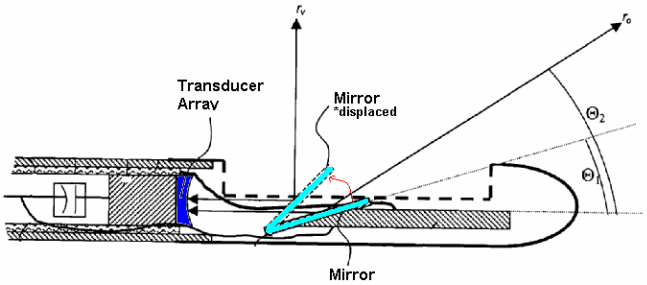


Figure 7.7 Catheter with mirror (*EP1208801)*

It is possible also to rotate only the last part of the catheter as shown in patent application *DE19926708*. This particular catheter is also equipped with a channel for delivering drugs or USCA into the field of view of the catheter.

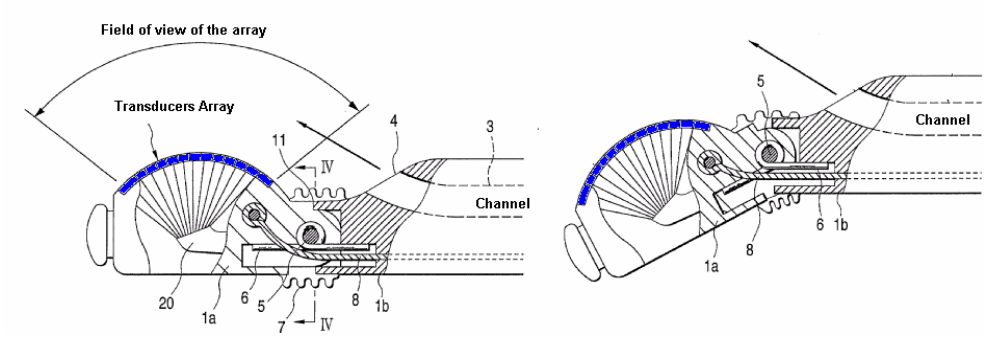


Figure 7.8 Catheter with fluid channel *(DE19926708)*

7.4 OTHER SOLUTIONS

2D (two-dimensional) images typically do not provide desired accuracy of structures/features within a body. In applications where a relatively high level of imaging accuracy may be critical, such as biopsy needle guidance through or in proximity to sensitive bodily structures which may need to be avoided by the needle, linear array transducer probes may not be practical. In patent application *EP0955010* a "biplane" ultrasound catheter is described, this catheter is equipped with 2 transducers array mounted in the distal end of the probe in order to obtain 2 perpendicular imaging planes

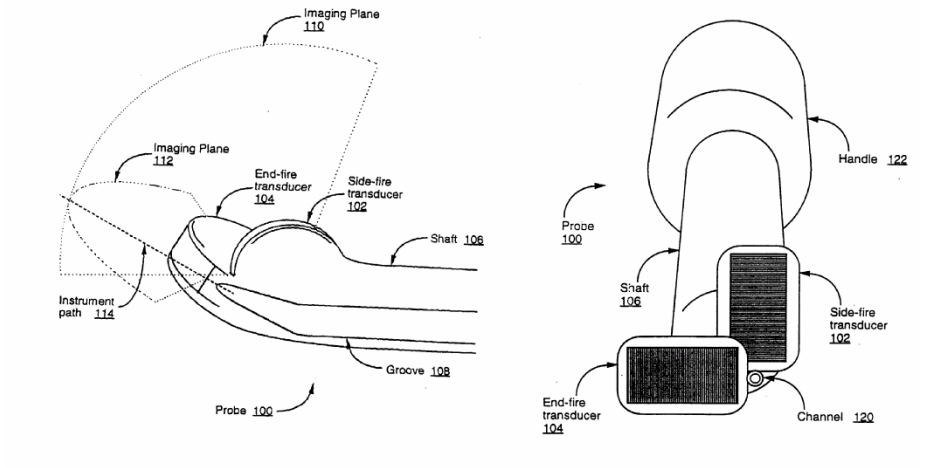


Figure 7.9 Biplane ultrasound catheter (*EP0955010)*

The biplane ultrasound catheter can also be equipped with a puncture needle for performing biopsy as shown in patent *US6238336.*

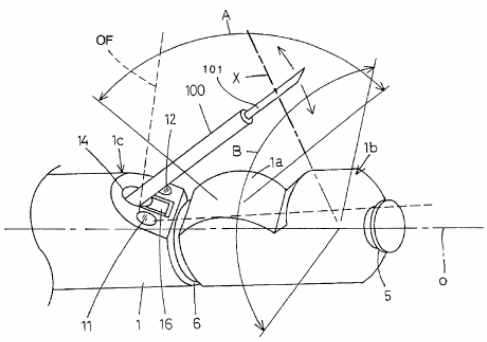


Figure 7.10 Biplane ultrasound catheter with needle (*US6238336)*

Also catheters with one transducer array can also be equipped with a puncture needle for performing biopsy*(US6149598)*. See figure x.11

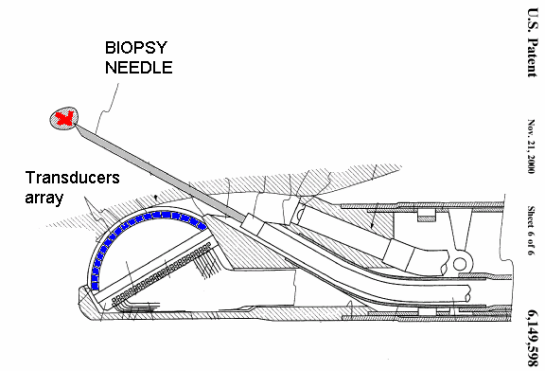


Figure 7.11 Ultrasound Catheter with needle (*US6238336)*

In patent application *EP1059878* an optical-acoustic imaging catheter is described. The device comprises a single-mode optical fiber with a Bragg grating surrounded by a piezoelectric jacket in polyvinyldiene fluoride (PDVF).

An electrical generator transmits ultrasound impulses to both the Bragg grating and to the tissue where the catheter is located, e.g. the blood. The backward signal causes deformation in the PDVF jacket, and also in the Bragg grating.

If mechanical deformations appear inside the optical fiber, they cause modulation of light reflected backward, which is received by the electronic instruments.

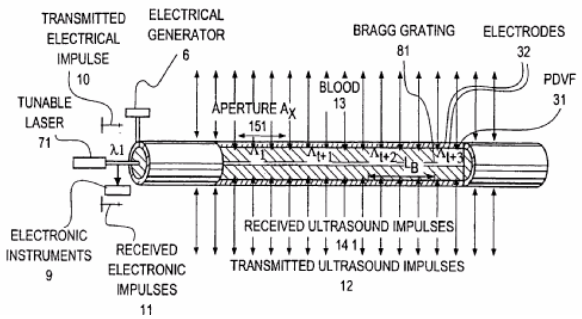


Figure 7.10 Optical acoustic imaging catheter *(EP1059878)*

7.5 MINIMALLY INVASIVE CATHETERS

A limitation of all the catheters is that the surgeon does not have tactile sense of the surgical field. This limitation can be exceed with the fingertip ultrasound medical instrument described in patent application *EP1596717*, a minimal invasive ultrasound surgical instrument mounted on the surgeon's fingertip. The device is also equipped with a pressure sensor (fig x.11)

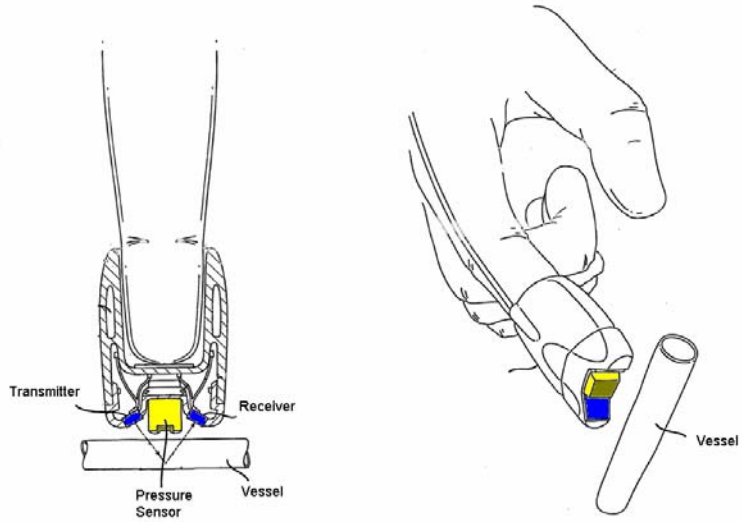


Figure 7.11 Fingertip ultrasound device (*EP1596717)*

A similar solution is proposed also in patent application *WO0165537*. The miniaturized ultrasound transducer (fig 7.12) is mounted at distal end of the flexible cable (fig. 7.12)

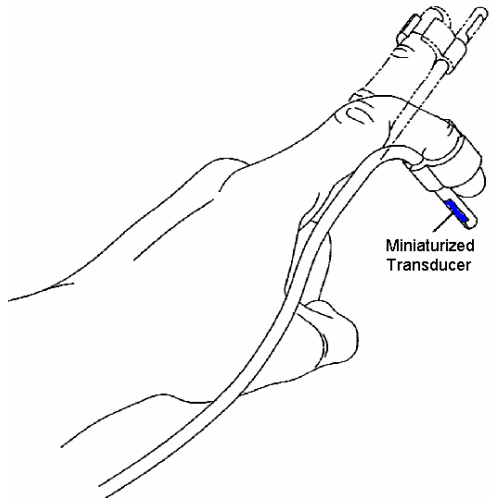


Figure 7.12 Miniaturized catheter (*EP1596717)*

The less invasive catheter is described in patent application *EP1529483.* The capsule endoscope can be swallowed by the patient and then naturally ejected. The transducer can be rotated without causing rotation in the capsule. This allows to image all the digestive system without introducing a trans esophageal catheter inside the patient.

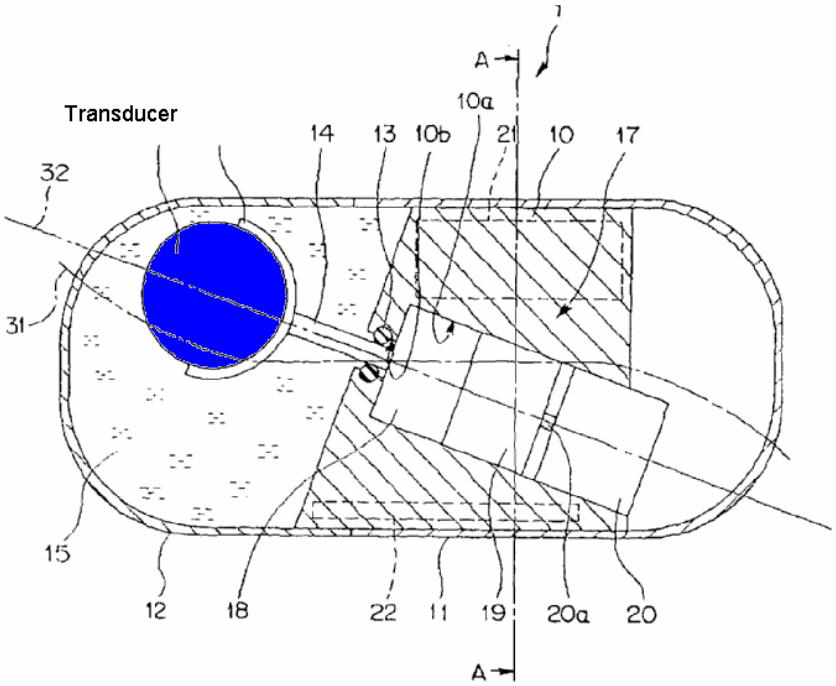
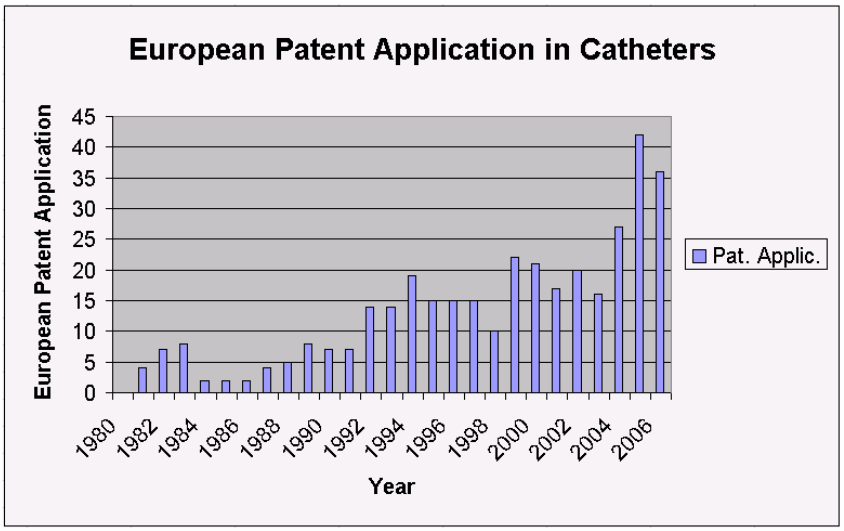


Figure 7. 13 capsule endoscope (*EP1529483)*

7.6 Statistics about ultrasound catheters

	Total	Pat. Applic.
1980	0	0
1981	4	4
1982	11	7
1983	19	8
1984	21	2
1985	23	2
1986	25	2
1987	29	4
1988	34	5
1989	42	8
1990	49	7
1991	56	7
1992	70	14
1993	84	14
1994	103	19
1995	118	15
1996	133	15
1997	148	15
1998	158	10
1999	180	22
2000	201	21
2001	218	17
2002	238	20
2003	254	16
2004	281	27
2005	323	42
2006	359	36



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CHAPTER IIX
CONCLUSIONS

After having analyzed a vast number of patents and patent application it is possible to indicate the future trends in the field of diagnostic ultrasound.
What is possible to see is that there is a trend toward miniaturization and to telemedicine, the term telemedicine is the delivery of medicine at a distance. The necessity to have small portable devices that allow checking the patient's condition even at home is one of the future direction of develop of this technology. As cited in patent and patent applications *US6390979*, *US2003225335* and *DE20318977* the device for monitor and analyze blood flow are connected wireless with the cell-phone of the patient and they can send an alarm to a caregiver if the signal presents some abnormalities.
Monitoring a patient at home using known devices like blood flow monitors and transferring the information to a caregiver is a fast growing emerging service. These remote monitoring solutions has a focus on current high morbidity chronic diseases.
The miniaturization of components in recent years has made possible to create portable device that provide an overall solution in terms of ergonomics, ease of use by those having limited experience with ultrasound diagnostic equipment, imaging acquisition and processing capability, image display quality, and user localization, such as watches that can provide

information of the blood flow and portable imaging device like the system described in patent US6436040.

Thanks to the miniaturization of components, ultrasound catheters started to be used in hospitals. The major advantage of the use of ultrasound catheters is that it is possible to scan the region of interest with high frequencies because a deep penetration of the beam is not necessary. Thanks to the use of higher frequencies higher axial resolution is reached. Ultrasound catheters can be utilized for trans-esophageal echography (TEE), intravascular ultrasound (IVUS) and trans-rectal echography.

As described in chapter 7, now it is possible to have minimally invasive catheters such the one described in patent application *EP1596717* and the capsule endoscope described in patent application *EP1529483*, that allow to have images of the gastrointestinal tract. The Natural peristalsis moves the capsule endoscope smoothly and painlessly throughout the gastrointestinal tract.

In the next future, 3D ultrasound imaging will represents the highest level of us technology. With these device it is possible to obtain new views and a whole organ approach allows to quantify without limitations some important parameters like the volume etc.

At the moment, these device are not very expanded due to the high cost and the fact that the new information provided must be validated before these device will be very common in hospitals. The only application of these device at the moment is to obtain 3D images of the foetal. The increasing number of patent application in this field allows to affirm that in the next years these device will be common in hospitals.

Another recent application of ultrasound is the elastography. The different mechanical characteristic of the tumour's tissue from the surrounding tissue is the basic principle of palpation. However, a lesion, in the prostate or in the breast in particular, may or may not possess echogenic properties and it would be difficult to detect it with conventional diagnostic ultrasound imaging systems. The imaging modality that facilitates the display of mechanical properties of biological tissue is called elastography and is a sort of evolution of the palpation technique.

The purpose of elastography is to display an image of the distribution of a physical parameter related to the mechanical properties of the tissue for clinical applications.

Finally, after having analyzed the number of European patent application in the diagnostic ultrasound field from 1980 until 2006 we observe a positive trend, especially in the field of 3D imaging.

ANNEX 1: Ultrasound contrast agents

Annex to ultrasound contrast agent patent applications statistic.

OPEN INTERNAL

..fi epodoc

Selected file: EPODOC

Search statement 1

ep/pn

** SS 1: Results 1.723.429

Search statement 2

..lim 1

** SS 2: Results 1.723.429

Search limited to 1723429 documents

Limitation starting with SS 2

Search statement 3

? ultrasound

** SS 3: Results 1.642

MOVE TO X-FULL (run with the limitation)

Query : (contrast) 5d (agent or microbubble)

299 document selected

Save the Xfile and go back to internal

110 documents avaible in internal,

Limitation active now on this 110 documents, start the classification by priority date:

```
? pd<1980-01-01
** SS 29: Results 0
```

until:

Search statement 51

```
? pd<2006-01-01
** SS 51: Results 101
```

Search statement 52

```
? pd<2007-01-01
** SS 52: Results 110
```

ANNEX 2: Three Dimensional Ultrasound.

Above are shown the search procedures for find the documents used in my state of the art investigation.

1st research

internal

..fi epodoc

ultrasound & tomography

pd>2000-01-01

90 reusults send to the viewer,10 patents application selected in the drawer after reading title and abstract of the invention of all 90 results

2nd research

internal

..fi epodoc

ultrasound

pd>2000-01-01

..lim 3 (ultrasound & pd) *(9183 results)*

move to x full (run with limitation) *(all databases avaible selected)*

Query: (three or 3 or dimension) 3d (scanner or tomography)

75 results send to the viewer,12 patents application selected in the drawer after reading title and abstract of the invention of all 75 result

3rd research (mechanical scanners)

internal

..fi epodoc

ultrasound

pd>2000-01-01

..lim 3 (ultrasound & pd) *(9183 results)*

move to x full (run with limitation) *(all databases avaible selected)*

Query: (Three or 3 or dimension) 3d (mechanical or scanner)

112 results send to the viewer,11 patents application selected in the drawer after reading title and abstract of the invention of all 112 results

4th research (free hand)

internal

..fi epodoc

ultrasound

pd>2000-01-01

..lim 3 (ultrasound & pd) *(9183 results)*

Free 2d hand

9 results send to the viewer,1 patents application selected in the drawer after reading title and abstract of the invention of all 9 results

5th research (Catheters and Probes with 3D US)

internal

..fi epodoc

ultrasound

pd>2000-01-01

..lim 3 (ultrasound & pd) *(9183 results)*

move to x full (run with limitation) *(all databases avaible selected)*

Query: (catheter or probe) 3d (volum+ or tomograph+ or three or dimension)

80 results send to the viewer, patents application selected in the drawer after reading title and abstract of the invention of all 80 results

ANNEX 3 ELASTOGRAPHY

Search 1

Internal:

..fi epodoc

Selected file: EPODOC
    Search statement 1

ultrasound
SS 1: Results 16.176

X-full
Query: Elastography

70 results send to viewer

Search 2

Internal

..fi epodoc

Selected file: EPODOC
    Search statement 1

ultrasound
SS 1: Results 16.176

X-full
Query: (cardiac or myocardial) 3d strain

22 Documents send to viewer,

Search 3

Internal

..fi epodoc

Selected file: EPODOC
Search statement 1

z61b5/kw
** SS 1: Results 30.872

X-full
Query: elastography

36 Documents send to viewer,

ANNEX 4: BLOOD FLOW DOPPLER

Patents about this field can be founded in the following classes:

A61B8/02 . Measuring pulse or heart rate

A61B8/02B . . (186) [N: of a foetus]

A61B8/06 . Measuring blood flow

A61B8/06B . . [N: to determine blood output from the heart]

A61B8/06F . . [N: combined with B-scan, e.g. tomography]

A61B8/08P . . [N: Devices for detecting pregnancy]

I used a limitation in the database by publication date:

pd>2000-01-01

ANNEX 5: STATISTICS

All the information used in the statistics at the end of each chapter are found in the EPODOC database.

For the statistics the database is limited to the European Patent Application. After limited the database to the interesting patents I started the classification by priority date:

? pd<1980-01-01
** SS 1: Results xx

until:

Search statement 26

? pd<2006-01-01
** SS 26: Results xx

Search statement 27

? pd<2007-01-01
** SS 27: Results xx

- **Chapter 2: Statistics about A61B8/00**

All the European patent application classified as A61B8/00, diagnosis using ultrasonic, sonic or infrasonic waves.

- **Chapter 3: Statistics about ULTRASOUND CONTRAST AGENTS**

All the European patent application classified as A61B8/00D, Diagnosis using ultrasonic, sonic or infrasonic waves by tracers, e.g. microbubbles introduced into the bloodstream.

- **Chapter 4: Statistics about 3D IMAGING**

All the European patent application classified as A61B8/13, Tomography; A61B8/14, Echo-tomography; A61B8/15, transmission-tomography.

All the European patent application with the KEY WORD: Z61B8 imaging three dimensional.

- **Chapter 5: Statistics about ELASTOGRAPHY**

All the European patent application classified as A61B8/08, Detecting organic movements or changes, e.g. tumours, cysts; A61B8/08B Detecting organic movements using Doppler signals special applications of sonar system for mapping or imaging.

All the European patent application with the KEY WORD: Z61B8 imaging strain.

- **Chapter 6: Statistics about BLOOD FLOW DOPPLER**

All the European patent application classified as A61B8/02, Measuring pulse or heart rate; A61B8/02B Measuring pulse or heart rate of a foetus; A61B8/06, Measuring blood flow; A61B8/06B Measuring pulse or heart rate to determine blood output from the heart; A61B8/06F Measuring pulse or heart rate combined with B-scan, e.g. tomography; A61B8/08P, Measuring pulse or heart for detecting pregnancy.

- **Chapter 6: Statistics about ULTRASOUND CATHETHERS**

All the European patent application classified as A61B8/06D, imaging of objects using sonar in body cavities or body tracts by using a catheter.

ANNEX 6: ECLA, Main-group A61B8

According to the ECLA classification system all the patents about diagnosis using ultrasound are classified in the sub-class A61B8. In this annex the hierarchical structure of the patent classification system is showed.

SECTION:

HUMAN NECESSITIES	**A**

CLASS:

MEDICAL OR VETERINARY SCIENCE; HYGIENE	**A61**

SUBCLASS:

DIAGNOSIS; SURGERY; IDENTIFICATION (analysing biological material G01N, e.g. G01N33/48; obtaining records using waves other than optical waves, in general G03B42/00)	**A61B**

MAIN GROUP

Diagnosis using ultrasonic, sonic or infrasonic waves (imaging of objects using sonar G01S15/00)	**A61B8**

All the patent cited in this work can be classified in one of the following sub-groups. The classification is divided in two tables.

Diagnosis using ultrasonic, sonic or infrasonic waves (imaging of objects using sonar G01S15/00)	**A61B8**
	A61B8/00
[N: Details of transducer positioning, e.g. by a coupling medium]	A61B8/00B
[N: by tracers, e.g. microbubbles introduced into the bloodstream]	A61B8/00D
Measuring pulse or heart rate	A61B8/02
[N: of a foetus (measuring heart rate of a foetus in general A61B5/024B)]	A61B8/02B
Measuring blood pressure	A61B8/04
Measuring blood flow (measuring volume flow in general G01F, e.g. G01F1/66, G01F1/72; measuring speed of fluids in general G01P5/00)	A61B8/06
[N: to determine blood output from the heart (in general A61B5/029)]	A61B8/06B
[N: by devices introduced into the body, e.g. catheters (in body cavities in general A61B8/12)]	A61B8/06D
[N: combined with B-scan, e.g. tomography]	A61B8/06F

Diagnosis using ultrasonic, sonic or infrasonic waves (imaging of objects using sonar G01S15/00)	**A61B8**
	A61B8/00
Detecting organic movements or changes, e.g. tumours, cysts, swellings (A61B8/02 to A61B8/06 take precedence)	A61B8/08
[N: using Doppler signals (special applications of sonar systems for mapping or imaging G01S15/89)]	A61B8/08B
[N: using echo-encephalography]	A61B8/08D
[N: using mammography (mammography by transillumination A61B5/00P2; X-ray mammography A61B6/00D3; detection of breast cancer A61B10/00G)]	A61B8/08F
[N: with suspended breasts, e.g. patient in prone position] [N0002]	A61B8/08F2
[N: Devices for detecting or locating foreign bodies (devices for detecting or locating foreign bodies in general A61B5/06; by radiation A61B6/12; instruments for taking a cell sample or for biopsy A61B10/00C; markers, echogenic devices A61B19/00R)]	A61B8/08H
[N: Measuring tissue layers, e.g. skin, interfaces]	A61B8/08J
[N: Devices for detecting pregnancy, e.g. by foetal movements]	A61B8/08P
[N: of bone material (A61B5/103R takes precedence)]	A61B8/08R
Eye inspection	A61B8/10
in body cavities or body tracts, e.g. by using catheters [N: (A61B8/06D takes precedence; catheters per se A61M25/00)]	A61B8/12
[N: using mechanical scanning, e.g. by micro-motor (mechanical steering of sound beams G10K11/35)] [C9807]	A61B8/12B
[N: using electronic scanning, e.g. by phased array (electrical steering of transducer arrays G10K11/34)]	A61B8/12D
Tomography ([N: A61B8/06F], A61B8/10, A61B8/12 take precedence; tomography for radiation diagnosis A61B6/02)	A61B8/13
Echo-tomography	A61B8/14
Transmission-tomography	A61B8/15

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PATENT BIBLIOGRAPHY

Chapter 3: Ultrasound Contrast Agents (USCA)

PATENT NUMBER	CHAPTER	DATE OF FILING	DATE OF PUBBLICATION
EP0913704	3	01/10/1998	06/05/1999
EP1406096	3	23/09/2003	24/07/2004
US2004087858	3	01/11/2002	06/05/2004
US2002028994	3	31/01/2001	07/05/2002
US2001009977	3	05/01/2001	26/07/2001
EP1406096	3	23/09/2003	07/04/2004
US2003208123	3	26/05/2002	06/11/2003
WO2006090309	3	16/02/2006	31/08/2006
US2005187475	3	27/12/2004	25/08/2005
US6245019	3	30/04/1999	12/06/2001
EP1514516	3	10/09/2004	16/03/2005
EP0913704	3	01/10/1998	06/05/1999
US6454714	3	20/10/2000	24/09/2002
US2001044278	3	04/06/2001	22/11/2001
WO0057792	3	31/03/1999	05/10/2000
EP1354555	3	26/12/2000	04/07/2002
EP0072330	3	06/08/1982	16/02/1983

Chapter 4: Three Dimensional Imaging with ultrasound

PATENT NUMBER	CHAPTER	DATE OF FILING	DATE OF PUBBLICATION
US200464046	4	27/06/2003	01/04/2004
US2004068180	4	04/10/2002	08/04/2004
US20060173307	4	03/02/2006	31/08/2006
WO2005087110	4	15/03/2005	22/09/2005
US200609693	4	17/12/2005	01/06/2006
US 200468180	4	12/03/2004	23/09/2004
WO200607423	4	14/05/2006	03/11/2006
US200609693	4	05/05/2006	16/11/2006
DE19723053	4	02/06/1997	12/02/1998
US5871019	4	22/09/1997	16/02/1999
US5806521	4	26/03/1996	15/09/1998
US6775404	4	15/03/2000	10/08/2004
EP0487339	4	21/11/1991	27/05/1992
US2004167402	4	20/02/2003	26/08/2004
US20030114755	4	12/11/2005	05/05/2006
EP1242991	4	24/08/2000	28/02/2002
US6013032	4	13/03/1998	11/01/2000
US20060106307	4	12/05/2006	23/11/2006
US2003220569	4	28/03/2003	27/11/2003
WO9856296	4	13/06/1997	17/12/1998
US2003229286	4	19/05/2003	11/12/2003
WO9811823	4	15/10/1997	26/03/1998
EP1717758	4	25/04/2006	02/11/2006
US200328107	4	08/07/2002	12/03/2003
US2005119572	4	02/05/2005	04/01/2007
EP1242991	4	14/08/2001	14/12/2005
US200328107	4	26/05/2002	06/11/2003

Chapter 5: Elastography

PATENT NUMBER	CHAPTER	DATE OF FILING	DATE OF PUBBLICATION
US2005283076	5	16/06/2005	22/12/2005
US6508768	5	17/10/2001	21/01/2003
WO0139668	5	01/12/1999	07/06/2001
EP1614388	5	09/07/2004	11/01/2006
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Chapter 6: Blood Flow Measurement

PATENT NUMBER	CHAPTER	DATE OF FILING	DATE OF PUBBLICATION
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EP1363539	6	28/02/2002	15/09/2002
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Chapter 7: Ultrasound Catheters

PATENT NUMBER	CHAPTER	DATE OF FILING	DATE OF PUBBLICATION
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EP0580304	7	01/07/1993	26/01/1994
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GLOSSARY

Acoustic impedance: In an analogy to transmission line impedance, the acoustic impedance is the ratio of pressure to particle velocity in a medium; more commonly, it is defined as $Z=\rho c$, where ρ=density and c=speed of sound in a medium [the units are kg/(m2 ·sec) or Rayls].

A-mode: The original display of ultrasound measurements, in which the amplitude of the returned echoes along a single line is displayed on an oscilloscope.

Angular response: The radiation pattern versus angle for a single element of an array.

Attenuation: The reduction of signal amplitude that occurs per unit distance travelled. Some attenuation occurs in homogeneous media such as water due to viscous heating and other phenomena, but that is very small and is usually taken to be negligible over the 10- to 20-cm distances typical of imaging systems. In inhomogeneous media such as soft tissues, the attenuation is much higher and increases with frequency. The values reported for most soft tissues lie around 0.5 dB/cm/MHz.

Axial resolution: The ability to distinguish between targets aligned in the axial direction (the direction of acoustic propagation).

Azimuth dimension: The lateral dimension that is along the scanning plane for an array transducer.

Backscatter: That part of a scattered signal that goes back toward the transmitter of the energy.

Baseband signal: The received signal after the center frequency component (carrier frequency) has been removed by demodulation.

B-mode or 2D: The current display mode of choice. This is produced by sweeping the transducer from side to side and displaying the strength of the returned echoes as bright spots in their geometrically correct direction and distance.

Carrier frequency: The center frequency in the spectrum of the transmitted signal.

Clutter: An unwanted fixed signal component generated by stationary targets typically outside the region of interest (such as vessel walls).

Complex envelope: A signal expressed by the product of the carrier, a high-frequency component, and other lower-frequency components that comprise the envelope. The envelope is usually expressed in complex form.

CNR: Contrast signal to Noise Ratio. This gives the ratio of the signal power scattered from the contrast agent in a region to the noise power in that region. This ratio is often referred to as sensitivity.

CTR: Contrast signal to Tissue signal Ratio. This gives the ratio of the signal power scattered from the contrast agent in a region to the signal power scattered from the tissue in that region. This ratio is often referred to as specificity.

Electrical matching networks: Active or passive networks designed to tune out reactive components of the transducer and/or match the transducer impedance to the source and receiver impedance.

Elevation dimension: The lateral dimension that is perpendicular to the scanning plane for an array transducer.

Grating lobes: Undesirable artefacts in the radiation pattern of a transducer; they are produced at a location where the path length difference to adjacent array elements is a multiple of a wavelength.

Heart Coordinate System: The radial (R) axis: perpendicular to the epicardium.
The longitudinal (Lo) axis: perpendicular to the radial axis, tangent to the epicardium. The circumferential (C) axis: perpendicular to both the radial and longitudinal axis. Figure G.1 illustrates the coordinate system.

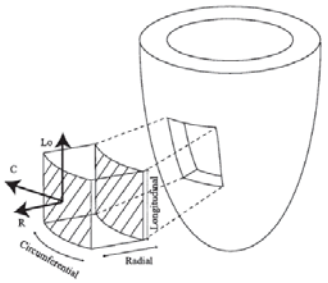

Figure G.1: Heart Coordinate System ***[D'Hooge et al. 2000]***

Lateral modes: Transducer vibrations that occur in the lateral dimensions when the transducer is excited in the thickness dimension.

Lateral resolution: The ability to distinguish between targets in the azimuth and elevation dimensions (perpendicular to the axial dimension).

Maximum likelihood: A statistical estimation technique that maximizes the probability of the occurrence of an event to estimate a parameter. ML estimate is the minimum variance, unbiased estimate.

M-mode: Followed A-mode by recording the strength of the echoes as dark spots on moving light-sensitive paper. Objects that move, such as the heart, caused standard patterns of motion to be displayed, and a lot of diagnostic information such as valve closure rates, whether valves opened or closed completely, and wall thickness could be obtained from M-mode recordings.

Real-time imaging: A real time image is a digital image in which all the operations to the signal are made between two acquired samples.

Reflection: Occurs at interfaces between large regions (much larger than a wavelength) of media with differing acoustic properties such as density or compressibility. This is similar to the reflection of light at interfaces and can be either *total,* like a mirror, or *partial,* like a half-silvered mirror or the ghostlike reflection seen in a sheet of glass.

Scattering: Occurs when there are irregularities or inhomogeneities in the acoustic properties of a medium over distances comparable with or smaller than the wavelength of the sound. Scattering from objects much smaller than a wavelength typically increases with frequency (the blue-sky law in optics), while that from an object comparable to a wavelength is constant with frequency (why clouds appear white).

Strain: Deformation of an object normalized to its original shape. The symbol used for strain is ε and can be written as:

$$\varepsilon = \frac{L - L_0}{L_0},$$

With L (t) the length of the object at time instance t and L (t0) =L0 its initial length.

Strain Rate: **S**peed at which deformation (i.e. strain) occurs. It is represented by the symbol ε' and has the unit *1/s*. The instantaneous strain rate can be calculated as:

$$\dot{\varepsilon}_N(t) = \frac{L'(t)}{L(t)},$$

With $L'(t)$ the rate of deformation and L (t) the instantaneous length of the object.

Ultrasound Coordinate System: The ultrasound coordinate system has axial, lateral and elevation axes which are, respectively, along the image line, perpendicular to image line and within the image plane and perpendicular to the image plane like shown in figure G.2.

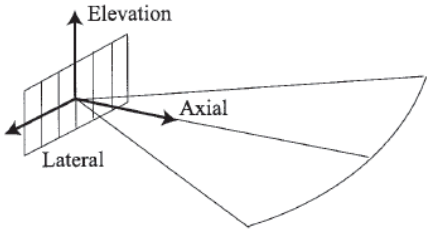

Figure G.2 Ultrasound Coordinate System ***[D'Hooge et al. 2000]***

Patent organization glossary

AIPLA – American Intellectual Property Law Association

ASEAN – Association of South East Asian Nations

ANASE – Association des nations de l'Asie du Sud-Est

CIS – Commonwealth of Independent States

GUS – Gemeinschaft Unabhängiger Staaten

CEI – Communauté des Etats indépendants

EAPIC – Europe-Asia Patent Information Conference

EAPO – Eurasian Patent Organization

EPC – European Patent Convention

EPI – Institute of Professional Representatives

EPLA – European Patent Litigation Agreement

EUROTAB – European Round-Table on Patent Practice

IPC – International Patent Classification

IPO – Intellectual Property Owners Association

JIPA – Japan Intellectual Property Association

JPO– Japan Patent Office

OAPI – Organisation africaine de la propriété intellectuelle

OHIM – Office for Harmonization in the Internal Market

HABM – Harmonisierungsamt für den Binnenmarkt

OHMI – Office de l'harmonisation dans le marché intérieur

OMPI – Organisation Mondiale de la Propriété Intellectuelle

PATINNOVA – European Commission conference on patents and innovation

PCT – Patent Cooperation Treaty

Rospatent – Russian Agency for Patents and Trademarks

SACEPO – Standing Advisory Committee before the EPO

SCP – Standing Committee on the Law of Patents

SIPO – State Intellectual Property Office (Chinese Patent Office)

SPLT – Substantive Patent Law Treaty

UNICE – Union of Industrial and Employers' Confederations of Europe

USPTO – United States Patent and Trademark Office

WIPO – World Intellectual Property Organization

AKNWOLEDGMENTS

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