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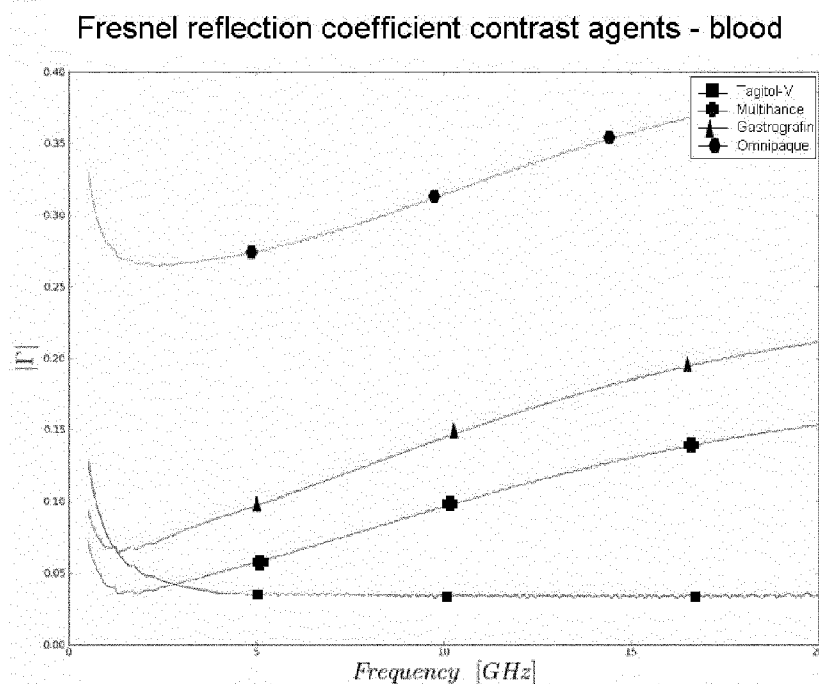


Figure 18

(57) Abstract: The present invention relates to the use of contrast agents in radar based imaging, particularly in medical imaging. The invention also relates to the use of contrast agents in diagnosis of various diseases using radar-based technology. An apparatus for radar-based imaging comprising a contrast agent is also disclosed.

- 1 -

Agents for Medical Radar Imaging

This invention relates to in vivo the use of agents or markers for medical diagnosis based on radar technology. One preferred aspect of the present invention relates to agents as contrast agents in medical imaging based on radar radiation.

Radar (Radio detection and ranging) is a system for detection of objects using specific electromagnetic waves. Radar systems are able to detect size, form, altitude, direction and speed of both fixed objects and moving objects. Typical moving objects can be cars and other vehicles, aircrafts and space shuttles. Use of radars today include both military use like air-defence systems and civil use like for example air traffic control, weather prognosis, geological radar mapping and various systems traffic monitoring systems. Most radar systems monitor objects in a far distance from the radar electromagnetic source and radar monitoring system. However, during the last years radar-based anti-collision systems for cars are able to monitor objects close to the cars.

Radar can also be used for medical diagnosis and radar-based medical imaging systems are in development. These systems might have a resolution of less than 1 cm maybe around 1 mm. US5,030,956 (Murphy) describes a radar tomography method and apparatus that generates a plurality of radar pulses in a transmitter and project them with an antenna toward a patient. Radar pulses reflected from the patient are picked up by the antenna and conducted to the receiver. The described system in US5,030,956 is also able to produce three-dimensional information. US2004/0249257 (Tupin) discloses an ultra-wide band radar known as micropower impulse radar that is combined with advanced signal processing techniques to provide a new type of medical imaging technology including frequency spectrum analysis and modern statistical filtering techniques to search for, acquire, track, and interrogate physiological data. US2004/0019282 (Mullen) describes hybrid lidar-radar system for medical diagnostics. The radar system can be used for detecting tumors within tissues by detecting reflected signals from tissue and discriminating the information related to the tumor from the undesirable backscattering of light created by the tissue itself. US2010/0234720 (Tupin) describes a system and method for extracting physiological data using ultra-wideband radar and improved signal processing techniques. US2010/0292559 (Hannemann) describes a radar-

- 2 -

equipped patient bed for a medical imaging apparatus and operating methods thereof. US2009/0192384 (Fontius) describes a medical unit which comprises a three dimensional radar array for detection of positional or movement data of objects in an examination space and a processing unit for the evaluation of the detected data, with the processing unit being connected to the medical unit and the three dimensional radar array, and with the evaluated data being used to control the medical unit or for post-processing data acquired by the medical diagnostic or therapeutic unit. WO2010/124117 (Lifewave) describes fetal and/or maternal monitoring devices, systems and methods using UWB medical radar. These devices and systems may include a UWB sensor providing high-resolution and reliable simultaneous monitoring of multiple indicators of fetal and/or maternal health, such as fetal heart rate, fetal heart rate variability, fetal respiration, fetal gross body movement and other parameters during pregnancy. Future use of radar medical imaging is also described by Yngve Vogt: Non-dangerous radar might replace X-ray in Appolon (University of Oslo), 2/2011 pages 36-37.

Thus, on the whole, radar technology might be used for diagnosis of disease based on mapping of diseases tissue and by monitoring the signal reflected from the human body. This signal has tended to be used in medical imaging to study natural events in which organ impedance changes occur (e.g. breathing, eating, blood flow, heart beating etc) with imaging optionally being assisted by artificially increasing the volume or fluid content of the organ under study, e.g. by administration of a meal, by increasing total blood volume, etc. Unlike diagnostic imaging modalities such as X-ray, MRI, ultrasound and scintigraphy however, there has as yet been no suggestion that EII might benefit from the use of contrast media, and in particular the use of parenterally administered contrast media, to improve organ or tissue contrast.

We now therefore propose the use of agents or markers for medical diagnosis based on radar technology. One preferred aspect of the present invention relates to agents as contrast agents in medical imaging based on radar radiation.

By "agents", "markers" and "contrast agents" is meant materials which on administration will serve to enhance the diagnostic information typically by enhancing the contrast in the resulting images by modifying the reflection of the

- 3 -

electromagnetic radiation from the tissue in those tissues, organs or ducts into which they distribute. Where such markers and contrast agents serve to modify the local reflection of tissue they will function as modifiers of the radiation reflection as a function of the concentration of markers or negative contrast agents in the tissue, organs or ducts where they are present. The terms agent, marker and contrast agent as used herein are synonymous and may be used interchangeably.

Such markers and contrast media may be administered enterally or, particularly preferably, parenterally. Preferred parenteral administration route is intravascular administration, more preferably intravenous administration.

Thus in one aspect the invention relates to the use of agents or markers for medical diagnosis based on radar technology. One preferred aspect of the present invention relates to agents as contrast agents in medical imaging based on radar radiation.

The present invention also relates to a method of diagnosis of (or imaging) a sample (e.g. a human or non-human animal subject) comprising a radar marker or radar contrast agent, said method comprising:

generating a radar-based signal or image of at least part of said sample (or subject), said marker or contrast agent being capable on dissolution or dispersion in water of yielding a fluid having an impact on the radar radiation signal in the sample (or subject).

By "having an impact" is meant that the marker or contrast agent interacts with radar radiation to a different extent than the medium of the sample in which it is located, such that the marker or contrast agent is detectable within the sample and capable of being rendered into an image showing its location within the sample.

One method of measuring the impact that a marker or contrast agent has on the radar radiation signal is by determining the Fresnel reflection coefficient of the marker or agent in a particular medium. A high Fresnel reflection coefficient is indicative of having high contrast in that medium.

The imaging method preferably comprises the step of administering the radar marker or radar contrast agent to said sample (or subject).

- 4 -

In the imaging method, the radar marker or radar contrast agent is optionally dissolved or dispersed in a physiologically tolerable liquid carrier medium.

- 5 The present invention therefore relates to a method of diagnosis of (or imaging) a human or animal subject which method comprises:
- administering to said subject a radar marker or a radar contrast agent, optionally dissolved or dispersed in a physiologically tolerable liquid carrier medium, and
- 10 generating a radar-based signal or image of at least part of said subject, said marker or contrast agent being capable on dissolution or dispersion in water of yielding a fluid having an impact on the radar radiation signal in the subject.

- In the method of the invention, the step of generating a radar based signal or image
- 15 of at least part of said sample (or subject) preferably comprises
- a. subjecting the sample (or subject) to radar radiation;
 - b. detecting the radar radiation that has interacted with the sample (or subject); and
 - c. processing the detected radar radiation to generate an image of the sample
- 20 (or subject).

Thus, viewed from another aspect, the invention relates to a method of producing an image of a sample containing a radar marker or radar contrast agent, said method comprising

- 25 a. subjecting the sample to radar radiation;
- b. detecting the radar radiation that has interacted with the sample; and
- c. processing the detected radar radiation to generate an image of the sample.

- In the method of the invention, the radar radiation is preferably emitted from a first
- 30 antenna (e.g. in step a.), and detected at a second antenna (e.g. in step b.). Preferably, an array of antennas is used, such that the signal emitted from each antenna is detected by the remaining antennas in the array.

- In the method of the invention, the step of generating a radar based signal or image
- 35 of at least part of said sample (or subject) preferably comprises:

- 5 -

- 5
- i. subjecting the sample (or subject) to radar radiation emitted from one or transmitters;
 - ii. detecting the effect of the contents of the sample (or subject) on the passage of the radar radiation through the sample (or subject) by recording two or more signals, each signal being associated with a different propagation path within the sample (or subject); and
 - iii. processing the detected radar radiation by aligning the signals to generate two or more aligned signals which are synthetically focused on a desired volume of the sample (or subject), and processing the aligned signals to generate part of the image of the sample (or subject).
- 10

Preferably, steps i., ii. and iii. are repeated until an image of the sample (or subject) has been generated.

15

Medical imaging using radar is known in the art and would be familiar to the skilled person. This type of imaging is sometimes referred to as microwave imaging, or ultrawideband (UWB) microwave imaging. The range of frequencies used in radar imaging typically varies from 0.1-40 GHz, preferably 0.5-20 GHz.

20

Step c. is typically done using a computer processor which generates an image of the sample (or subject) on a display device such as a computer screen. Algorithms to process signals detected from the one or more detecting antenna(s) are known in the art and would be familiar to the skilled person.

25

Step c. preferably comprises generating an image of the sample (or subject) showing the distribution of the contrast agent in the sample (or subject).

The method preferably further comprises the step of administering the contrast agent to the sample (or subject).

30

The method preferably further comprises the step of using the image of the subject to diagnose a disease in the subject, preferably a human or non-human animal subject.

- 6 -

The sample used in the method can be part of a human or non-human animal body, or alternatively a inanimate tissue sample which has been taken from a human or non-human animal body. Alternatively, the method may be carried out on a synthetic mimic of human or non-human animal tissue. Such synthetic analogues
5 are typically called "phantoms" in the art.

The terms "sample" and "subject" as used herein are generally interchangeable. The term subject is however generally used when referring to animate or live samples, such as human or non-human animals which are being imaged.

10

The present invention also relates to an imaging apparatus comprising
a radar contrast agent;
one or more antennas capable of emitting radar radiation to a defined
volume and receiving radar radiation that has passed through that volume; and
15 a computer processor for processing the signals received by the one or
more antennas to form an image of the defined volume.

Preferably, the defined volume is sized to accommodate a human body.

20 The apparatus of the invention preferably also comprises a sample which contains the radar contrast agent, wherein at least part of the sample is located in the defined volume. Preferably, the sample is inanimate (i.e. does not form part of a living organism).

25 The apparatus of the invention preferably also comprises a means for administering the radar contrast agent to a human or non-human animal, such as a syringe, a catheter or an enema kit.

Viewed from another aspect the invention provides the use of a physiologically
30 tolerable agents, markers and contrast agents which are capable of changing the reflection properties of radar radiation in the human body after administration of the agent, preferably in diagnosis of a disease in a human or non-human animal. Such diagnosis is preferably by mapping of disease tissue by radar and by monitoring the signal reflected from the human or non-human animal.

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- 7 -

The present invention also relates to contrast agents for use in diagnosis of a human or nonhuman animal by radar imaging.

5 In the imaging methodology of the present invention, the sample is preferably not located in an external (or applied) magnetic field.

A wide range of materials can be used as markers and contrast agents for radar-based medical diagnostic methods, but particular mention should be made of five categories of contrast agent: organic iodinated agents; metal chelates, gas,
10 magnetic iron oxide particles and inorganic salts.

Organic Iodinated Agents

Insofar as organic iodinated agents are concerned, particular mention should be
15 made of those agents already proposed in the literature for use as X-ray contrast agents. Examples of such materials include many compounds with low toxicity and compounds may be selected which distribute preferentially within the body, e.g. which congregate at particular tissues, organs or tissue abnormalities or which are essentially confined to the circulatory system and act as blood pool agents.

20

Examples of X-ray contrast agents suited for use according to the present invention include in particular the iodinated contrast agents, especially those containing one or more, generally one or two, triiodophenyl groups in their structure.

25 The most preferred organic iodinated compounds to be used as markers and contrast agents for radar-based medical diagnosis are water-soluble agents comprising one or two benzene rings each substituted with 3 iodine atoms.

The even more preferred agents are such agents without any charge in vivo; so-called non-ionic agents. These compounds have several alcohol groups to secure
30 that the substances have high water-solubility without being a salt.

Preferred agents are the following compounds: diatrizoic acid, ioxaglinic acid, iomeprol, iobitriol, iohexol, iopamidol, iopentol, iodixanol, ioforminol, ioxaglate,
35 ioxilan, iopromide, iotrolan, ioversol and iothalamate.

The even most preferred agents are the following compounds: iohexol, iopamidol, iopentol, iodixanol, ioforminol, ioxaglate, ioxilan, iopromide, iotrolan, ioversol and iothalamate. Iohexol is the most preferred organic iodinated agent.

5

Particular organic iodinated compounds useful according to the invention thus, for example, include compounds described in US5,993,780 (Nycomed), US5,958,376 (Nycomed), US5,958,375 (Nycomed), US5,882,628 (Nycomed), US7,754,920 (GE Healthcare), US7,662,859 (GE Healthcare), US7,592,482 (Bracco), US7,485,753 (GE Healthcare), US4,032,567 (Schering), US4,239,747 (Schering), US4,264,572 (Schering), US4,269,819 (Schering), US4,269,819 (Schering), US4,364,921 (Schering), US4,395,391 (Schering), US4,426,371 (Schering), US4,547,357 (Schering), US5,004,835 (Schering), US5,073,362 (Schering) US5,183,654 (Schering), US 5,232,685 (Schering), US4,139,605 (Bracco), US4,348,377 (Bracco), US4,352,788 (Bracco), US5,591,846 (Bracco), US5,628,980 (Bracco), US5,689,002 (Bracco), US5,856,570 (Bracco), US5,908,610 (Bracco), US5,911,972 (Bracco), US6,350,908 (Bracco), US6,420,603 (Bracco), US6,506,938 (bracco), US7, 115,778 (Bracco), US4,006,743 (Mallinckrodt), US4,125,599 (Mallinckrodt), US4,160,015 (Mallinckrodt), US4,396,598 (Mallinckrodt), US5,019,371 (Mallinckrodt), US5,075,502 (Mallinckrodt), US5,191,120 (Mallinckrodt), US5,356,613 (Mallinckrodt), US5,204,086 (Nycomed), US5,349,085 (Nycomed), US6,406,680 (Nycomed), US6,310,243 (Nycomed) and US2010322868 (Nycomed) . The disclosures of these and all other documents cited herein are incorporated herein by reference.

25

As mentioned above, the organic iodinated agents used in the present invention are preferably iodobenzene compounds (i.e. having iodine as a ring substituent on an aromatic C₆ ring), especially diiodo or more preferably triiodo benzene compounds, in particular diiodo and triiodo benzene compounds having the iodines at non-

adjacent ring positions. The iodobenzene ring is preferably also substituted by hydrophilic groups comprising one, two or three hydroxyl groups. Preferred hydrophilic groups include

30



35

wherein

- 9 -

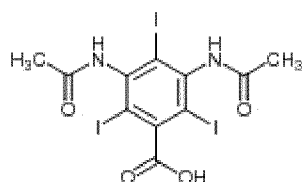
X is a C₁₋₆ alkylene group, especially an ethylene and more especially a propylene group;

R¹ is hydrogen or a methyl group; and

where n is 1, 2, or 3, preferably 2 or 3.

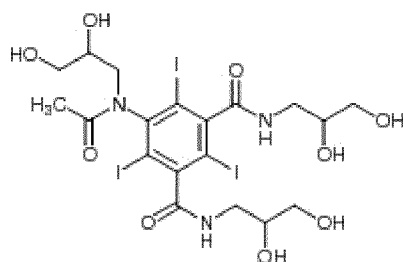
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The most preferred iodinated agents are;



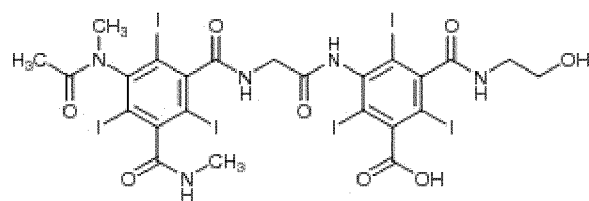
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Diatrizoic acid

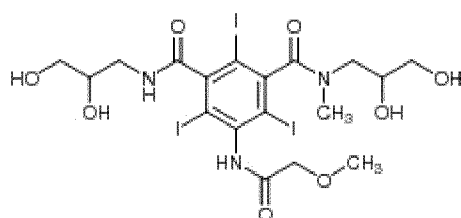


Iohexol

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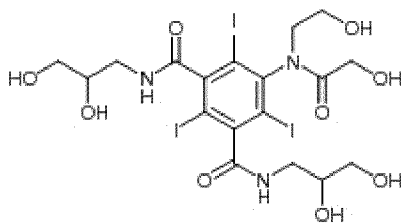
Ioxaglinic acid



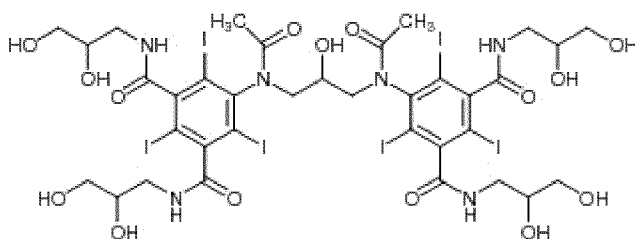
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Iopromide

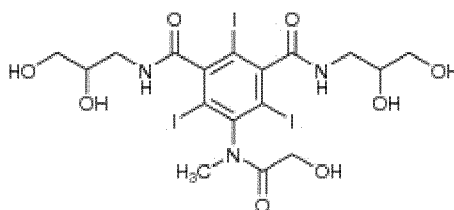
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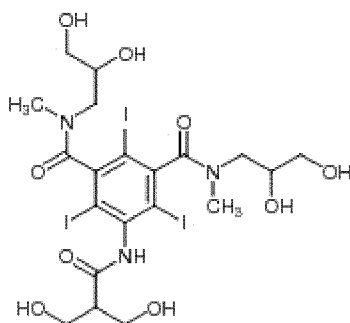
Ioversol



Iodixanol



Iomeprol



Iobitriol

Metal Chelates

- 15 Insofar as metal chelates are concerned, particular mention should be made of these agents already proposed in the literature for use as MRI contrast agents. Examples of such materials include many compounds with low toxicity and compounds may be selected which distribute preferentially within the body, e.g.

- 11 -

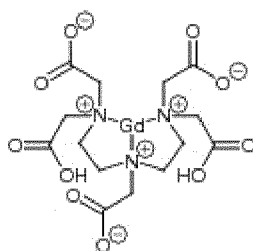
which congregate at particular tissues, organs or tissue abnormalities or which are essentially confined to the circulatory system and act as blood pool agents.

Examples of metal chelates suited for use according to the present invention include in particular paramagnetic chelates especially gadolinium chelates, dysprosium chelates, iron chelates and manganese chelates, especially those containing a chelating agent being an amino acid derivative like for example derivatives of EDTA, DTPA, DPDP, DOTA and DO3A.

The most preferred metal chelates to be used as markers and contrast agents for radar-based medical diagnosis are water-soluble agents comprising gadolinium (3+) or manganese (2+). Both non-ionic chelates and ionic chelates are among the most preferred chelates for use as markers and contrast agents for radar-based medical diagnosis.

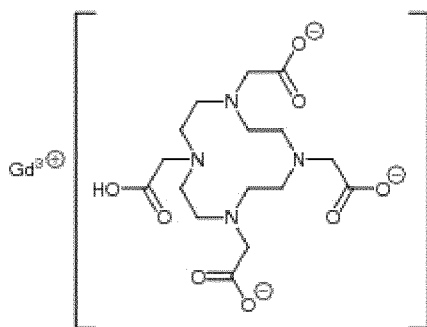
The even most preferred chelates are the following compounds: GdDTPA (gadopentetate dimeglumine), GdDOTA (gadoteric acid meglumine), GdDTPA-BMA (gadodiamide), Gd2HP-DO3A (gadoteridol), MnDPDP (mangafodipir), gadoversetamide, gadobenic acid, gadoxetic acid, gadofost, gadobutrol, gadocoletic acid, gadodenterate, gadomelitol, gadopentamide. Non-ionic chelates are used as pharmaceutically acceptable salts like sodium salt, potassium salt or meglumine salt.

The most preferred chelates are:

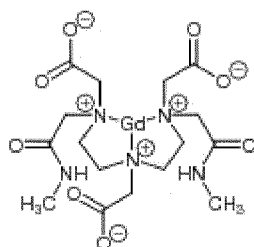


Gadopentetate

- 12 -

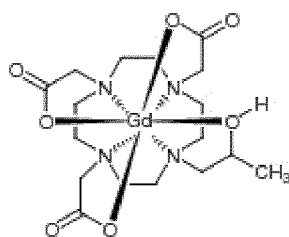


Gadoteric acid

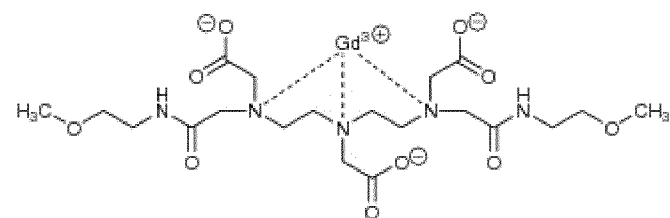


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Gadodiamide



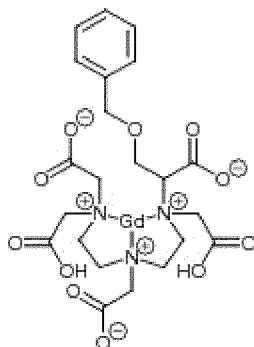
Gadoteridol



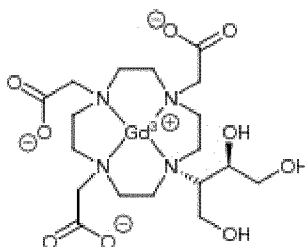
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Gadoversetamide

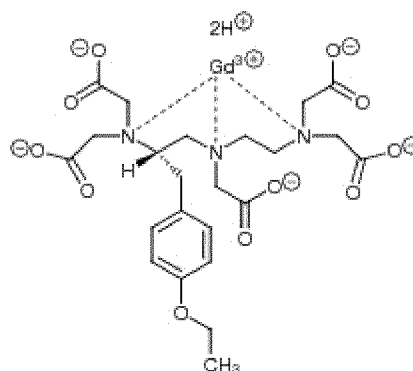
- 13 -



Gadobinate



Gadobutrol



Gadoxetinic acid

5

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Particular metal chelates useful according to the invention thus, for example, include compounds described in US7,767,196 (University of Hong Kong), US7,745,590 (University of Utah), US7,368,099 (Kyushu University), US4,647,447 (Schering), US4,957,939 (Schering), US4,963,344 (Schering), US 5,021,236 (Schering), US5,098,692 (Schering), US5, 277,895 (Schering), US5,316,756 (Schering), US5,334,371 (Schering), US5,362,475 (Schering), US5,403,572 (Schering), US5,419,894 (Schering), US5,560,903 (Schering), US5,595,725

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(Schering), US4,916,246 (Bracco), US4,980,502 (Bracco), US5,132,409 (Bracco), US5,182,370 (Bracco), US5,474,756 (Bracco), US5,674,470 (Bracco), US5,846,519 (Bracco) and US5,958,373 (Nycomed Salutar).

5 Gases

Insofar as gases are concerned, particular mention should be made of those agents already proposed in the literature for use as ultrasound contrast agents and to some extent for use as gastrointestinal X-ray contrast agents. Examples of such materials include many compounds with low toxicity, low solubility in blood and compounds may be selected which distribute preferentially within the body, e.g. which congregate at particular tissues, organs or tissue abnormalities or which are essentially confined to the circulatory system and act as blood pool agents.

Examples of gases suited for use according to the present invention include in air, sulfurhexafluoride and perfluorocarbons; for use within the vascular system gases with low solubility in blood are the most preferred gases. Perfluorocarbons such as perfluoropropane and perfluorobutane are particularly preferred.

The even most preferred gases for intravascular administration are sulfurhexafluoride, perfluoropropane and perfluorobutane, with perfluoropropane and perfluorobutane being particularly preferred. Perfluoropropane is the most preferred gas.

The most preferred agents gases for intravascular administration are preferably encapsulated into surfactants, phospholipids, carbohydrates, albumin or synthetic or semisynthetic polymer materials.

The even most preferred gas-based products according to the present invention are products like SonoVue, Sonazoid, Optison and Levovist.

Encapsulated gas-based compositions useful according to the invention thus, for example, include compounds described in US 6,221,337 (Nycomed), US6,274,120 (Nycomed), US5,674,468 (Nycomed), US5,670,135 (Nycomed), US5,648,062 (Nycomed), US5,637,289 (Nycomed), US5,618,514 (Nycomed), US5,614,169

(Nycomed), US5,569,449 (Nycomed), US5,567,412 (Nycomed), US5,558,856 (Nycomed), US5,558,857 (Nycomed), US5,536,490 (Nycomed), US5,529,766 (Nycomed), US6,217,850 (Nycomed), US6,177,061 (Nycomed), US6,165,442 (Nycomed), US6,110,444 (Nycomed), US6,106,806 (Nycomed), US6,054,118 (Nycomed), US5,928,626 (Nycomed), US7,083,778 (Bracco), US7,033,574 (Bracco), US6,613,306 (Bracco), US6,200,548 (Bracco), US6,187,288 (Bracco), US6,183,725 (Bracco), US6,139,818 (Bracco), US6,136,293 (Bracco), US5,846,518 (Bracco), US6,110,443 (Bracco), US5,840,275 (Bracco), US5,830,435 (Bracco), US5,827,504 (Bracco), US5,711,933 (Bracco), US5,686,060 (Bracco), US5,658,551 (Bracco), US5,643,553 (Bracco), US5,597,549 (Bracco), US5,587,199 (Bracco), US5,567,414 (Bracco), US5,556,610 (Bracco), US5,531,980 (Bracco), US5,445,813 (Bracco), US5,413,774 (Bracco), US5,380,519 (Bracco), US6,264,959 (Schering), US5,425,366 (Schering), US6,146,657 (ImaRx), US6,315,981 (ImaRx), US6,479,034 (Bristol-Myers Squibb), US6,528,039 (Bristol-Myers Squibb), US6,548,047 (Bristol-Myers Squibb), US6,551,576 (Bristol-Myers Squibb), US6,680,047 (Amersham Health), US6,7,16,412 (ImaRx), US6,998,107 (Bristol-Myers Squibb), US5,141,738 (Schering), US5,352,436 (Drexel University), US5,536,490 (Nycomed), US5,573,751 (Sonus), US5,585,112 (ImaRx), US5,614,169 (Nycomed), US5,656,211 (ImaRx), US6,045,777 (Acuphore), US7,374,745 (Mallinckrodt) and US7,892,522 (GE Healthcare).

Magnetic Iron Oxide

Insofar as magnetic iron oxides are concerned, particular mention should be made of those agents already proposed in the literature for use as MRI contrast agents. Examples of such materials include any particulate ferromagnetic or superparamagnetic material which distribute preferentially within the body, e.g. which congregate at particular tissues, organs or tissue abnormalities or which are essentially confined to the circulatory system and act as blood pool agents.

Examples of magnetic iron oxides suited for use according to the present invention include any particulate iron oxide like magnetite (Fe₃O₄) or gamma-iron(III)oxide.

Both the particle size and the size of the iron oxide crystals might vary over a large range from a few nanometers to micrometers. The iron oxide material might be encapsulated or coated with various organic materials like for example natural polymers, synthetic polymers, proteins, carbohydrates, polyethyleneglycols and other materials.

The even most preferred magnetic iron oxide-based products according to the present invention are products like Endorem (Feridex), Resovist, Sinerem, Combidex and Cliavist.

Iron oxide based compositions useful according to the invention thus, for example, include compounds described in US6,123,920 (Nycomed), US5,545,395 (Bracco), US7,807,137 (University of Puerto Rico), US4,452,773 (Advanced Magnetix), US4,770,183 (Advanced Magnetix), US4,827,945 (Advanced Magnetix), US5,102,652 (Advanced Magnetix), US5,160,726 (Advanced Magnetix), US5,262,176 (Advanced Magnetix), US5,204,457 (Meito Sangyo), US6,165,378 (Meito Sangyo), US7,871,597 (AMAG) and US7,892,520 (Hong Kong University).

Inorganic salts

Insofar as inorganic salts are concerned, particular mention should be made of those agents already proposed in the literature for use as X-ray contrast agents. Examples of such materials include any particulate insoluble material like for example barium sulphate. Inorganic salts are preferably administered directly into the gastrointestinal system by oral administration or by use of an enema

Barium salts are particularly preferred inorganic salts, with barium sulphate being the most preferred.

One further aspect of the present invention relates to use of liposome markers or as contrast agent in radar-based medical imaging. Liposomes are for example described in US6,217,849 (Bracco), US5,980,937 (Bracco), US5,702,722 (Bracco), US5,676,928 (Nycomed), US7,588,751 (Konica Minolta) and US7,785,568 (Marval Biosciences).

- 17 -

One further aspect of the present invention relates to use of targeted markers or as contrast agent in radar-based medical imaging. Targeted markers and contrast agents are for example described in US6,051,207 (Nycomed), US6,264,917 (Nycomed), US5,414,114 (Bracco), US6,139,819 (ImaRx), US6,261,537 (Nycomed), US6,261,537 (Nycomed), US6,331,289 (Nycomed), US6,521,211 (Bristol-Myers Squibb), US7,182,934 (GE Healthcare) and US7,413,727 (GE Healthcare).

Particularly preferred contrast agents have a Fresnel reflection coefficient of at least 0.15, more preferably at least 0.20, at frequencies of between 0.5 and 20 GHz (e.g. 5 GHz) with reference to healthy human blood as measured using a Agilent Network Analyzer N5245A at concentrations of 300 mg/ml.

By "healthy human blood" is meant blood that has recently been taken from a healthy human adult in which all blood markers such as platelet count, ion levels etc are within what would generally be deemed to be normal levels by a physician.

Particulate contrast agents for parenteral administration should preferably have particle sizes of no more than 1.5 micrometer, especially 1.0 micrometer or less.

Enteral administration of markers and contrast agents for radar based medical diagnosis including radar based medical imaging will preferably be by oral administration of the marker or contrast agent or by administration of the marker or contrast agent using an enema.

Parenteral administration of contrast agents according to the invention will generally be by injection or infusion, especially into the cardiovascular system. However the markers or contrast media may also be administered into body cavities having external voidance ducts, e.g. by catheter into the bladder, uterus etc.

The dosages of markers and contrast agents for radar-based medical diagnosis used according to the invention will vary over a broad range depending on a variety of factors such as administration route, the pharmacodynamic properties of the contrast agent (the more widely distributing the agent is the larger the dose may be), the chemical and physical nature of the contrast agent, and the frequency of

the electrical current applied in the impedance measurement.

Typically however agents will be administered in concentrations of 1 micromol/l to 1 mol/l, preferably 0.01 to 0.8 mmol/l and dosages will lie in the range 0.002 to 20 mmol/kg bodyweight, generally 0.005 to 10 mmol/kg. The overall dosage will generally be 1 to 200 ml when administered into the cardiovascular system or 5 ml to 1.5 litres of marker or contrast agent when administered into a body cavity having an external voidance duct, e.g. by oral or rectal administration.

- 10 The markers and contrast agents according to the present invention may be used for a wide range of clinical indications with appropriate selection of the contrast agent (for its pharmacodynamic properties) and of the administration route. Thus non-absorbable markers and contrast agents for radar-based medical diagnosis are particularly useful in the gastrointestinal tract, for diagnosis of abnormalities therein
- 15 or as markers of the gastrointestinal system. Such agents may also be used for dynamic studies, for example of gastric emptying. In studies of the gastrointestinal tract, it may be advisable to use a pH control agent such as cimetidine to suppress naturally occurring pH variations which might otherwise reduce imaging accuracy.
- 20 Some of the marker and contrast agents are absorbable from the gastrointestinal tract and may be taken up by the liver and excreted into the bile. Such agents can thus be used for imaging the hepatobiliary system and for liver function studies even following oral rather than parenteral administration.
- 25 The clinical indications for parenteral markers for contrast agents include CNS examination, perfusion studies, blood pool imaging, examination of body cavities, of the pelvic region and of the kidneys, hepatobiliary studies and studies of liver and kidney function, tumour imaging, and diagnosis of infarcts, especially in the heart.
- 30 As a further alternative means of improving radar-based diagnosis, also within the scope of the invention, contrast may be enhanced by administration of a physiologically active agent which serves to modify body fluid distribution, e.g. a diuretic, thereby causing image modification in body areas where body fluid is increased or decreased.

- 19 -

Preferred methods and uses described above utilise the preferred contrast agents mentioned herein.

Where the invention relates to a method of diagnosis or use in diagnosis, preferred
5 diseases are those diseases mentioned herein, such as diseases selected from abnormalities in the gastrointestinal tract, cancer and tumours such as for example breast cancer, lung cancer, liver cancer, metastasis, brain cancer and colorectal cancer; and infarcts or other cardiovascular diseases or cardiovascular events such
10 as in the heart infarcts. The invention will now be illustrated further by means of the following non-limiting Examples:

Example 1

15 **Iodinated marker and contrast agent for radar-based diagnosis including imaging**

A solution of iohexol (Omnipaque) (300 mg /ml, 50 ml) is administered intravenously to a patient. The patient undergoes a radar-based diagnosis of the
20 heart and the kidneys.

Example 2

25 **Gas-based marker and contrast agent for radar-based diagnosis including imaging**

A suspension of encapsulated perfluoropropane (Optison) (0.19 mg/ml, 3 ml) is administered intravenously to a patient. The patient undergoes a radar-based
30 diagnosis of the cardiovascular system.

35

Example 3**Metal chelate marker and contrast agent for radar-based diagnosis including imaging**

5

GdDTPA bis-meglumine salt (Magnevist) (0.5 mmol/ml), 16 ml) is administered intravenously to a patient. The patient undergoes a radar-based diagnosis of the heart, brain and the renal system.

10 **Example 4****Magnetic iron oxide-based marker and contrast agent for radar-based diagnosis including imaging**

15 Magnetic iron oxide particles (Resovist) (0.25 mmol/ml, 10 ml) is administered intravenously to a patient. The patient undergoes a radar-based diagnosis of the cardiovascular system.

Example 5

20

Inorganic salt marker and contrast agent for radar-based diagnosis including imaging

25 Barium sulphate (Mixobar) (1 gram/ml, 400 ml) is administered as an enema to a patient. The patient undergoes a radar-based diagnosis of abdomen.

Example 630 **Measurement of permittivity (medical radar contrast parameter) of various undiluted contrast agents and distilled water.**

One important contrast parameter in medical radar imaging is the permittivity. The permittivity is a measure of how the electrical field is affected by or affects the medium.

- 21 -

The permittivity in various contrast agents was determined using Agilent Network Analyzer N5245A with Agilent 5070E dielectric probe kit.(Agilent Technologies, USA).

The contrast agents were the following:

- 5 Particulate x-ray contrast agent: Barium sulfate suspension: 40% w/v (30% v/v) (Tagitol-V (E-Z-EM, Canada)).

Ionic iodinated X-ray contrast agent: 270 mg I/ml (diatrizoate sodium 100 mg/ml and diatrizoate meglumine 600 mg/ml, Gastrografin (Bayer Schering Pharma, Germany))

- 10 Non-ionic iodinated X-ray contrast agent : 350 mgI/ml (iohexol.(Omnipaque. GE Healthcare, USA))

Paramagnetic gadolinium based chelate: 334mg/ml (gadobenic acid (Multihance, Bracco, Italy))

- 15 The permittivity data on undiluted contrast agents and distilled water with reference values on whole blood are shown in Figure 1 and Figure 2

Example 7

Measurement of conductivity (medical radar contrast parameter) of various undiluted contrast agents and distilled water.

20

One important contrast parameter in medical radar imaging is the conductivity. The conductivity in various contrast agents was determined using Agilent Network Analyzer N5245A with Agilent (5070E dielectric probe kit.(Agilent Technologies, USA).

- 25 The contrast agents are described in Example 6.

The conductivity data on undiluted contrast agents and distilled water with reference values on whole blood are shown in Figure 3 and Figure 4.

30

35

Example 8**Measurement of permittivity (medical radar contrast parameter) of diluted Multihance.**

5

The permittivity in diluted Multihance was determined using Agilent Network Analyzer N5245A with Agilent (5070E dielectric probe kit.(Agilent Technologies, USA).

The permittivity data on diluted Multihance are shown in Figure 4 and Figure 6.

10

Example 9**Measurement of conductivity (medical radar contrast parameter) of diluted Multihance.**

15

The conductivity of diluted Multihance was determined using Agilent Network Analyzer N5245A with Agilent (5070E dielectric probe kit.(Agilent Technologies, USA).

The conductivity data on diluted Multihance are shown in Figure 7 and Figure 8.

20

Example 10**Measurement of permittivity (medical radar contrast parameter) of diluted Gastrografin.**

25

The permittivity in diluted Gastrografin was determined using Agilent Network Analyzer N5245A with Agilent (5070E dielectric probe kit.(Agilent Technologies, USA).

The permittivity data on diluted Gastrografin are shown in Figure 9 and Figure 10.

Example 11

30

Measurement of conductivity (medical radar contrast parameter) of diluted Gastrografin.

35

The conductivity of diluted Gastrografin was determined using Agilent Network Analyzer N5245A with Agilent (5070E dielectric probe kit.(Agilent Technologies, USA).

The conductivity data on diluted Gastrografin are shown in Figure 11 and Figure 12.

Example 12

Measurement of permittivity (medical radar contrast parameter) of diluted 5 Omnipaque.

The permittivity in diluted Omnipaque was determined using Agilent Network Analyzer N5245A with Agilent (5070E dielectric probe kit.(Agilent Technologies, USA).

10 The permittivity data on diluted Omnipaque are shown in Figure 13 and Figure 14.

Example 13

Measurement of conductivity (medical radar contrast parameter) of diluted 15 Omnipaque.

The conductivity of diluted Omnipaque was determined using Agilent Network Analyzer N5245A with Agilent (5070E dielectric probe kit.(Agilent Technologies, USA).

The conductivity data on diluted Omnipaque are shown in Figure 15 and Figure 16.

20

Example 14

Calculation of Fresnel reflection coefficient for undiluted contrast agent 25 versus blood

The Fresnel reflection coefficient versus blood is calculated and shown in Figure 17 and Figure 18.

Omnipaque (iohexol) shows a surprisingly high Fresnel reflection coefficient.

Example 15

Calculation of Fresnel reflection coefficient for undiluted contrast agent 30 versus muscle

The Fresnel reflection coefficient versus muscle is calculated and shown in Figure 19 and Figure 20.

35 1. Omnipaque (iohexol) shows a surprisingly high Fresnel reflection coefficient.

Claims

1. A method of imaging a sample comprising a radar marker or radar contrast agent, said method comprising:
 - 5 generating a radar-based signal or image of at least part of said sample, said marker or contrast agent being capable on dissolution or dispersion in water of yielding a fluid having an impact on the radar radiation signal in the sample.
2. The method as claimed in claim 1 wherein said marker or contrast agent is
10 selected from organic iodinated agents, metal chelates, gas, magnetic iron oxide particles or inorganic salts.
3. The method as claimed in claim 1 wherein said contrast agent comprises organic iodinated agents.
4. The method as claimed in claim 3, wherein said organic iodinated agent is
15 non-ionic.
5. The method as claim in claim 4, wherein said organic iodinated agent is selected from the group consisting of iohexol, iopamidol, iopentol, iodixanol, ioforminol, ioxaglate, ioxilan, iopromide, iotrolan, ioversol and iothalamate.
6. The method as claimed in claim 1 wherein said contrast agent comprises
20 metal chelates.
7. The method as claimed in claim 6, wherein said metal chelates are selected from the group consisting of gadolinium chelates, dysprosium chelates, iron chelates and manganese chelates.
8. The method as claimed in claim 1 wherein said contrast agent comprises
25 gas.
9. The method as claimed in claim 8, wherein the gas is selected from the group consisting of air, sulfurhexafluoride and perfluorocarbons, preferably perfluoropropane and perfluorobutane.
10. The method as claimed in claim 1 wherein said contrast agent comprises
30 magnetic iron oxide.
11. The method as claimed in claim 1 wherein said contrast agent comprises an inorganic salt, preferably a barium salt such as barium sulphate.
12. The method of any preceding claim, wherein the sample is a human or non-human animal subject.

13. The method of any preceding claim, further comprising the step of administering the radar marker or radar contrast agent to said sample.
14. The method of claim 13, wherein the marker or contrast agent is dissolved or dispersed in a physiologically tolerable liquid carrier medium.
- 5 15. The method of any of claims 12-14, wherein the marker or contrast agent is administered parenterally to the human or non-human animal subject, preferably by injection or infusion.
16. The method of any of claims 12-14, wherein the marker or contrast agent is administered enterally to the human or non-human animal subject, preferably by oral administration or using an enema.
- 10 17. The method of any preceding claim, wherein the step of generating a radar based signal or image of at least part of said sample comprises
- a. subjecting the sample to radar radiation;
 - b. detecting the radar radiation that has interacted with the sample; and
 - 15 c. processing the detected radar radiation to generate an image of the sample.
18. The method of any of claims 12-17, further comprising using the image of the sample to diagnose a disease in the human or non-human animal subject.
19. Use of a radar contrast agent as defined in any of claims 2-11 for medical
- 20 diagnosis based on radar technology.
20. A contrast agent as defined in any of claims 2-11 for use in medical diagnosis based on radar technology.
21. The method, use or contrast agent of any of claims 18-20, wherein the diagnosis is of abnormalities in the gastrointestinal tract; cancer and tumours
- 25 such as for example breast cancer, lung cancer, prostate cancer, stomach cancer, liver cancer, metastasis, brain cancer and colorectal cancer; or infarcts or other cardiovascular diseases or cardiovascular events such as in the heart infarcts.
22. Use of a radar contrast agent as defined in any of claims 2-11 in medical
- 30 imaging based on radar radiation.
23. An imaging apparatus comprising
- a radar contrast agent;
 - one or more antennas capable of emitting radar radiation to a defined volume and receiving radar radiation that has passed through that volume; and

- 26 -

a computer processor for processing the signals received by the one or more antennas to form an image of the defined volume.

24. The apparatus of claim 23, wherein the radar contrast agent is as defined in any of claims 2-11.

5 25. The apparatus of claim 23 or claim 24, wherein the defined volume is sized to accommodate a human body.

26. The apparatus of any of claims 23-25 further comprising a means for administering the radar contrast agent to a human or non-human animal, preferably a syringe, catheter or enema kit.

Permittivity non diluted agents

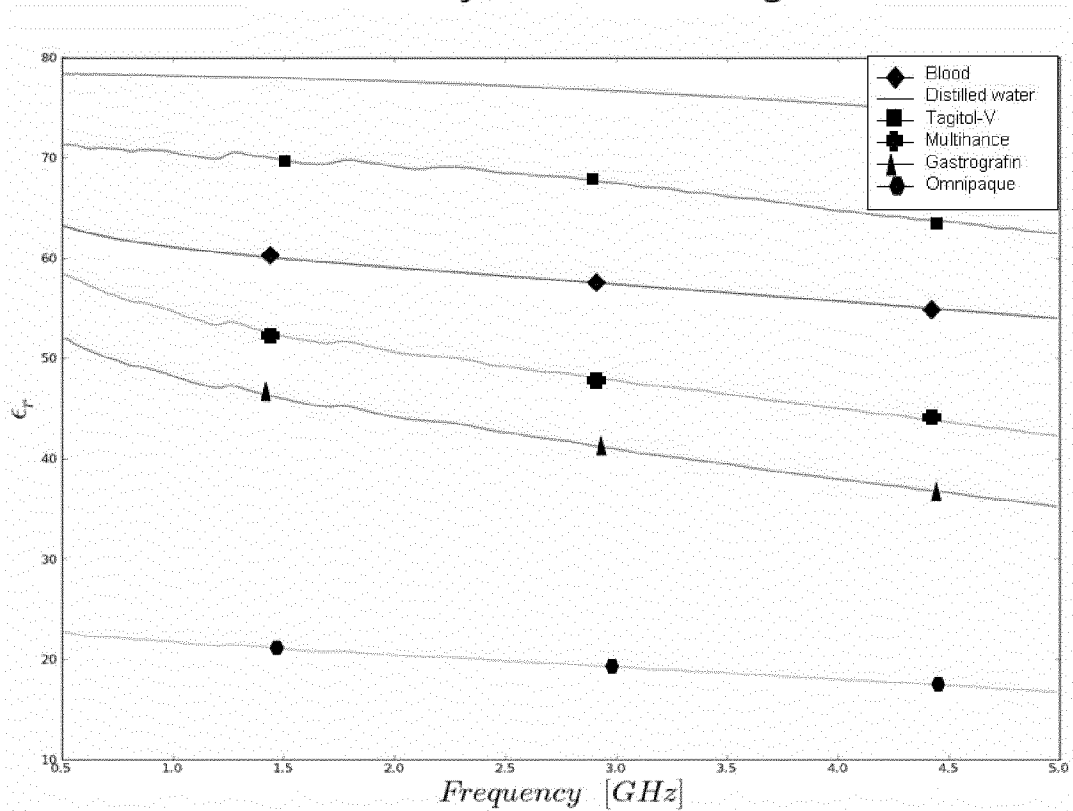


Figure 1

Permittivity non diluted agents

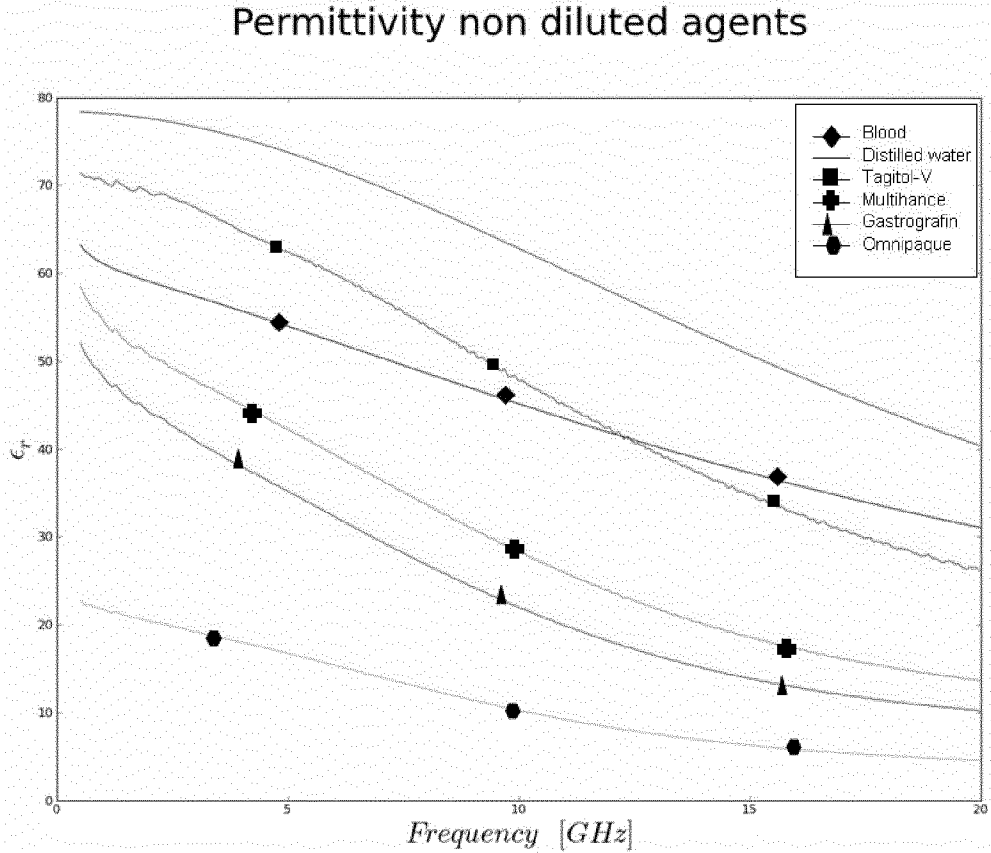


Figure 2

Conductivity non diluted agents

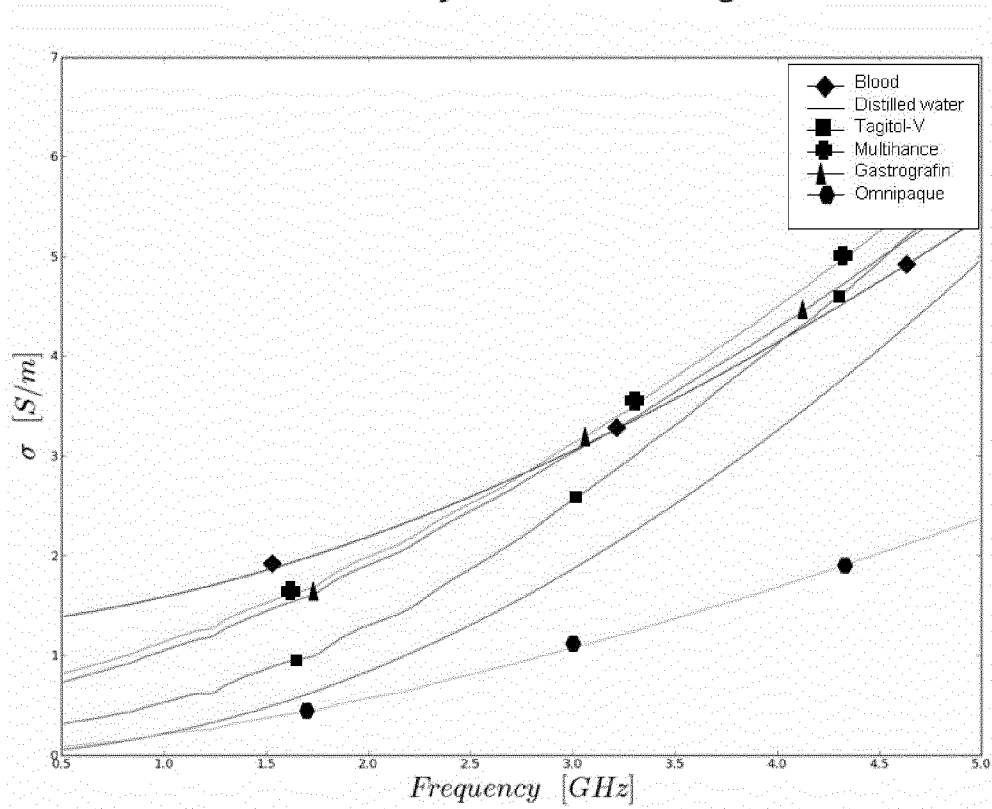


Figure 3

Conductivity non diluted agents

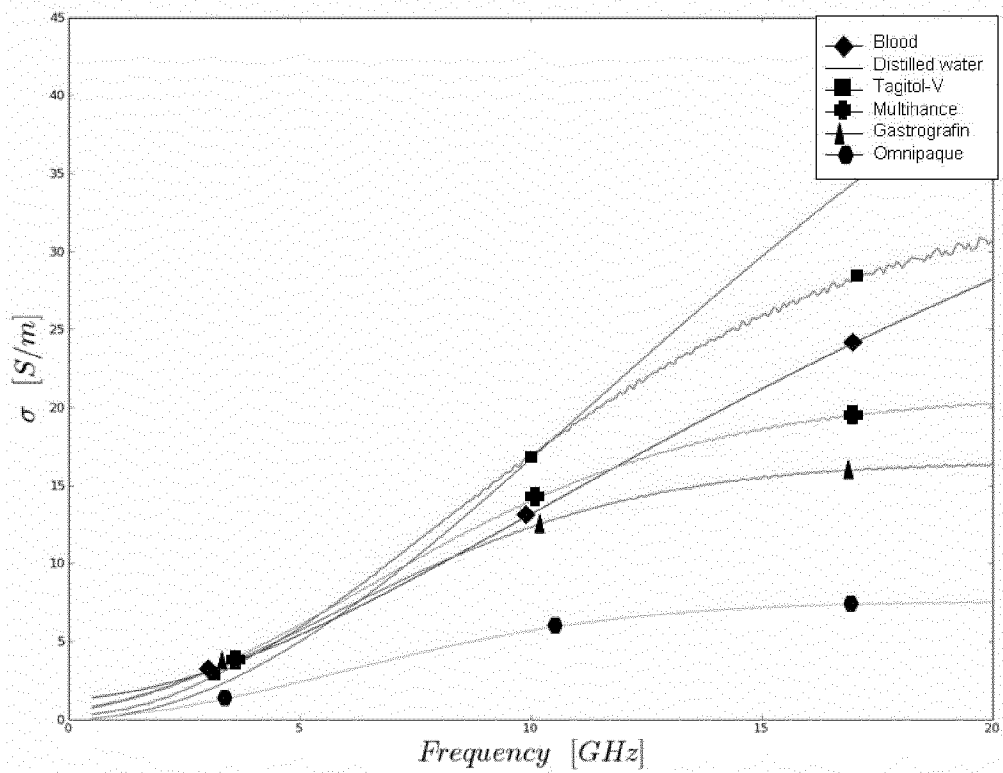


Figure 4

Permittivity Multihance

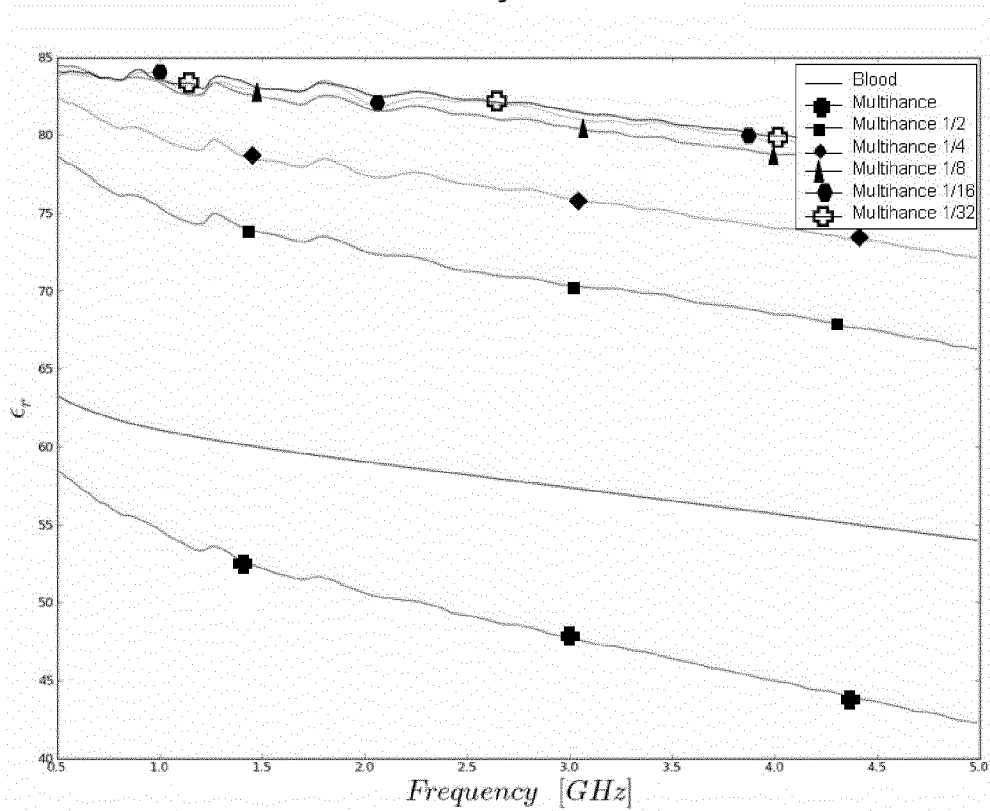


Figure 5

Permittivity Multihance

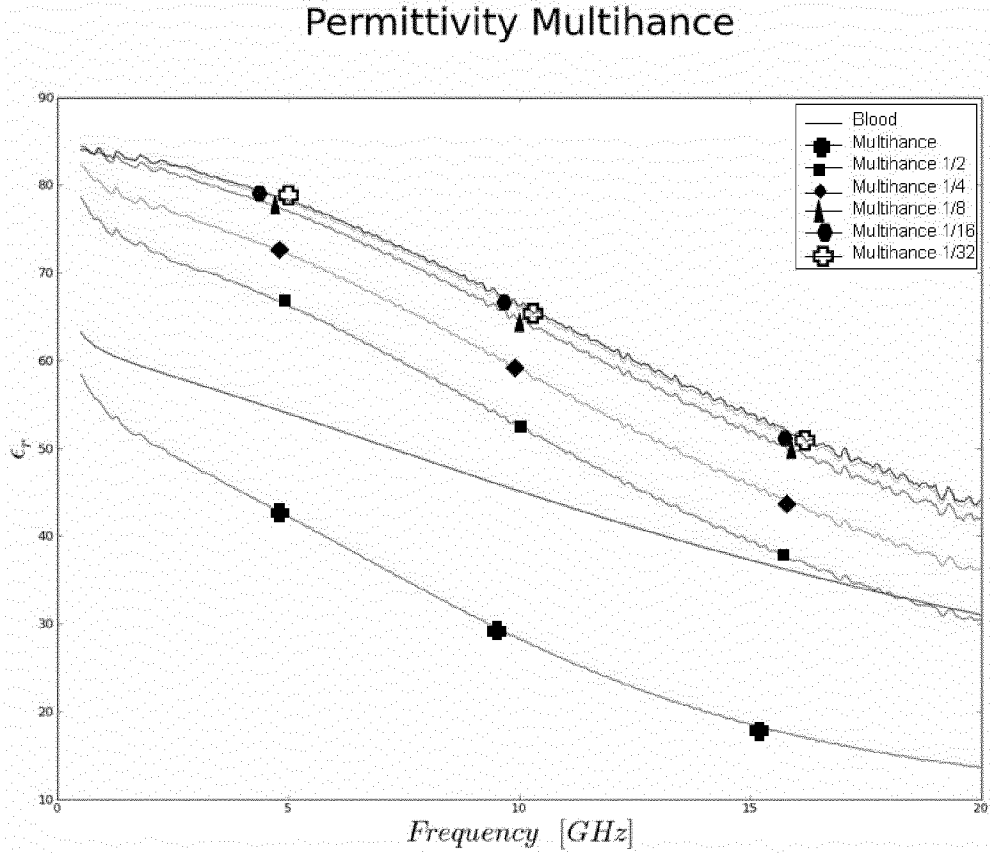


Figure 6

Conductivity Multihance

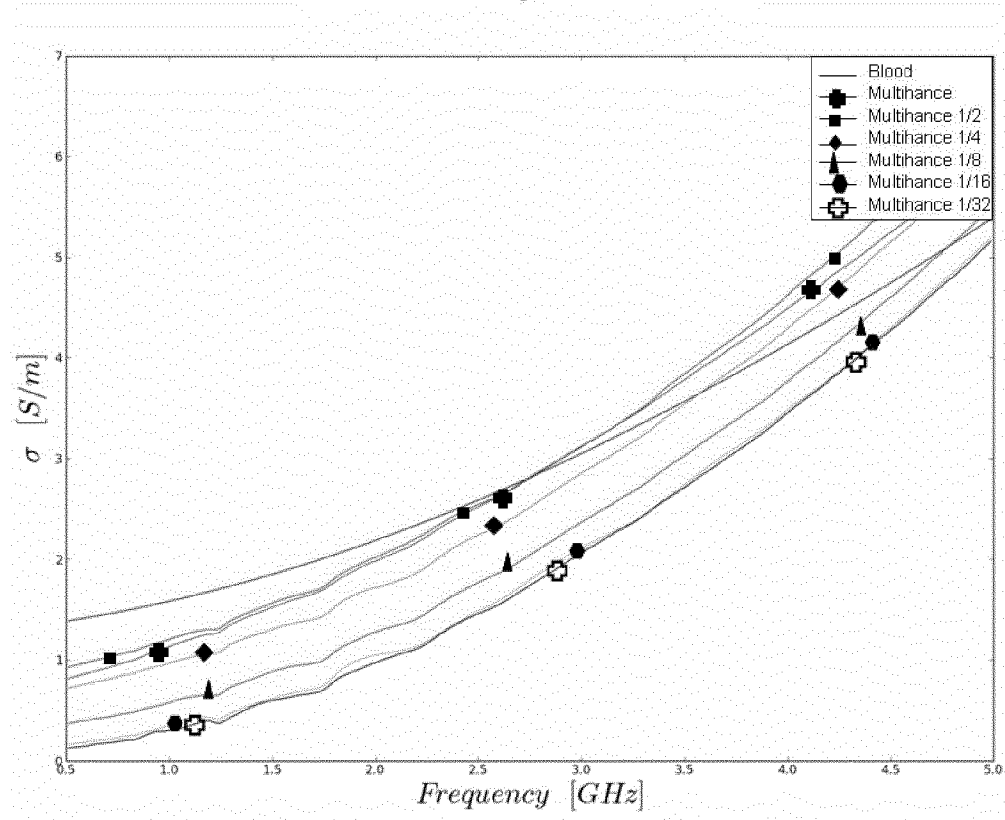


Figure 7

Conductivity Multihance

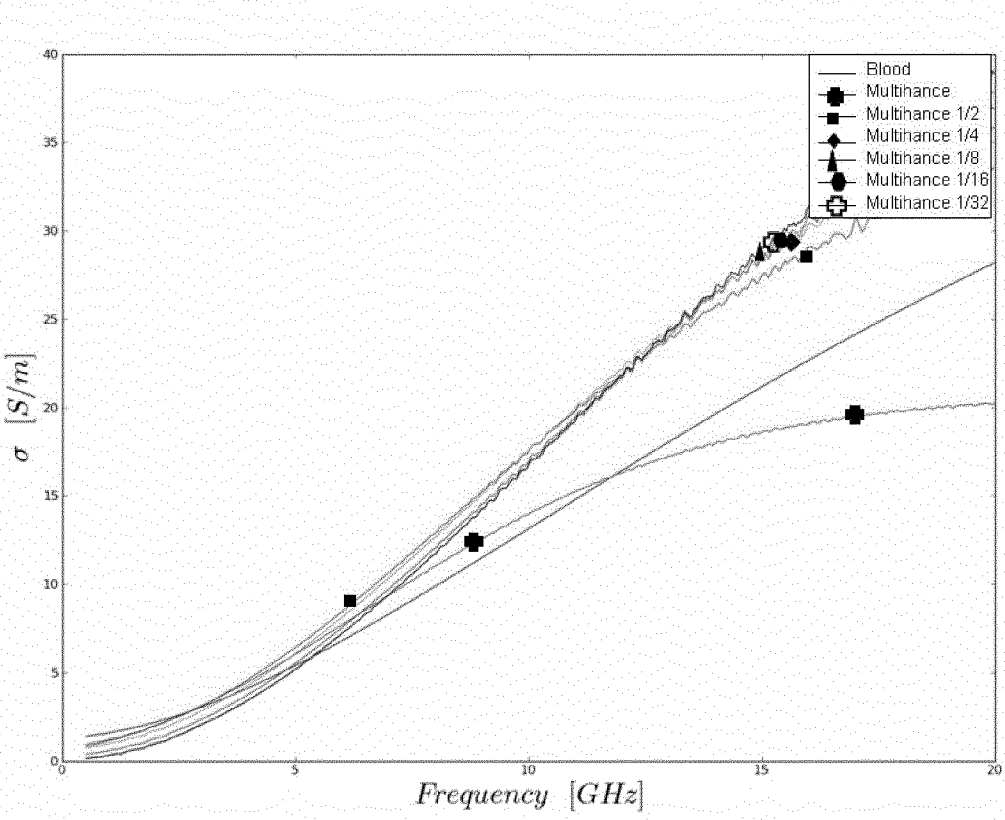


Figure 8

Permittivity Gastrografin

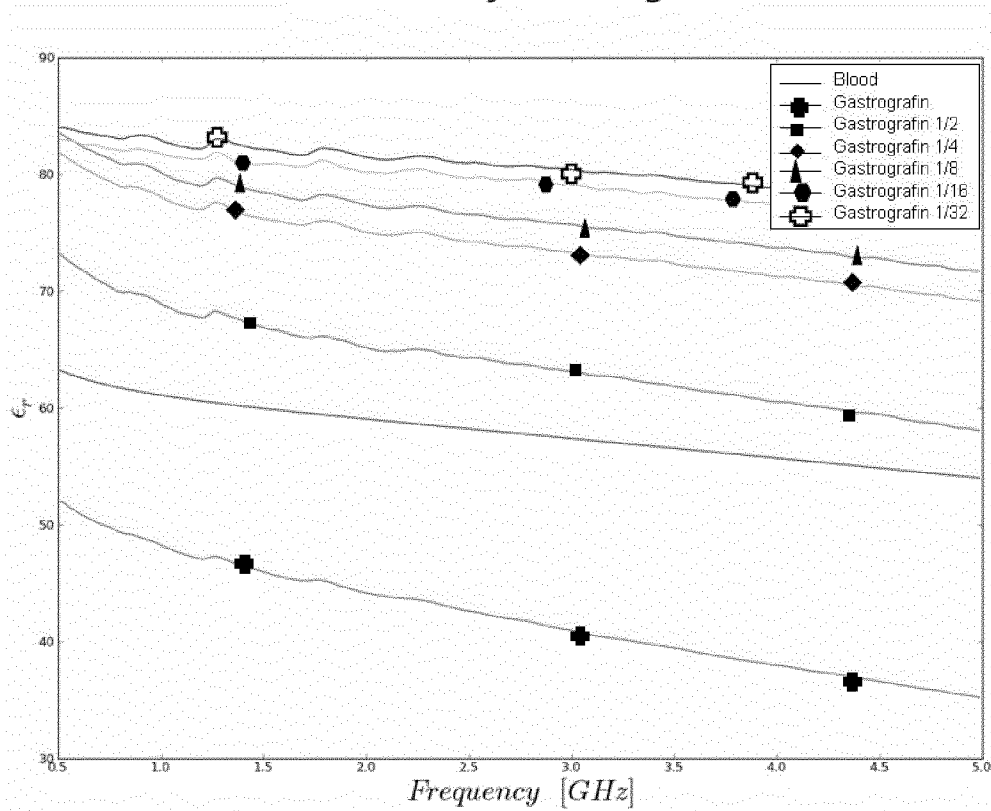


Figure 9

Permittivity Gastrografin

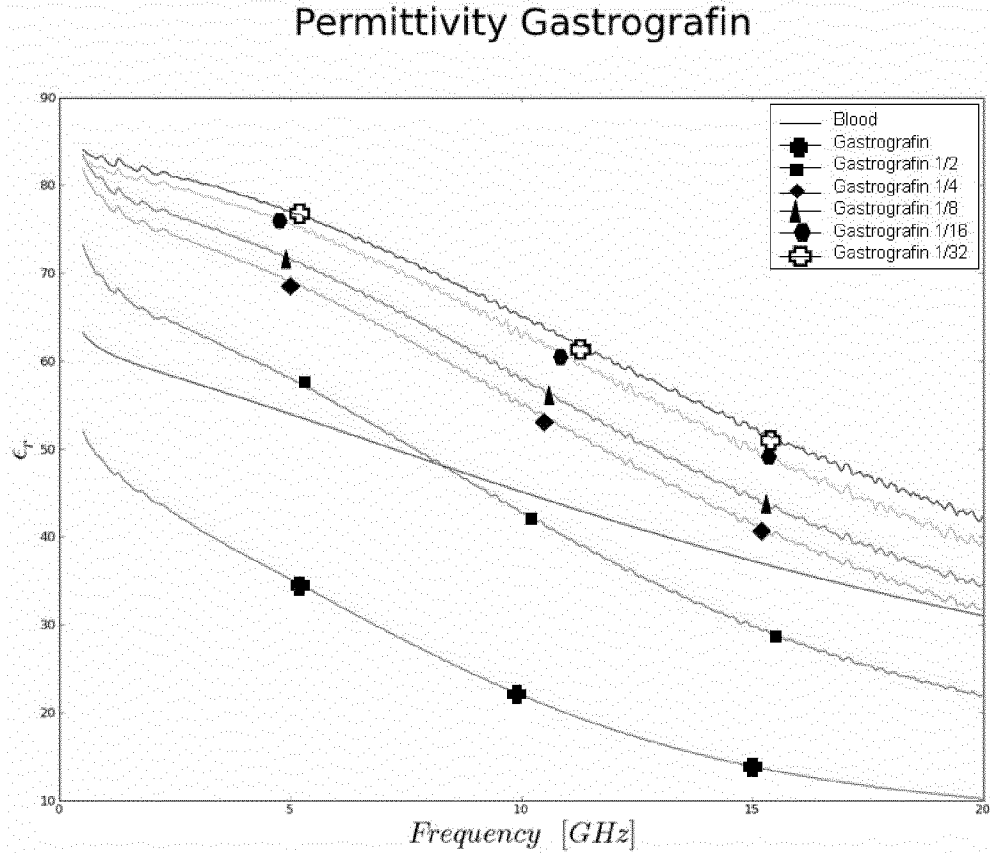


Figure 10

Conductivity Gastrografen

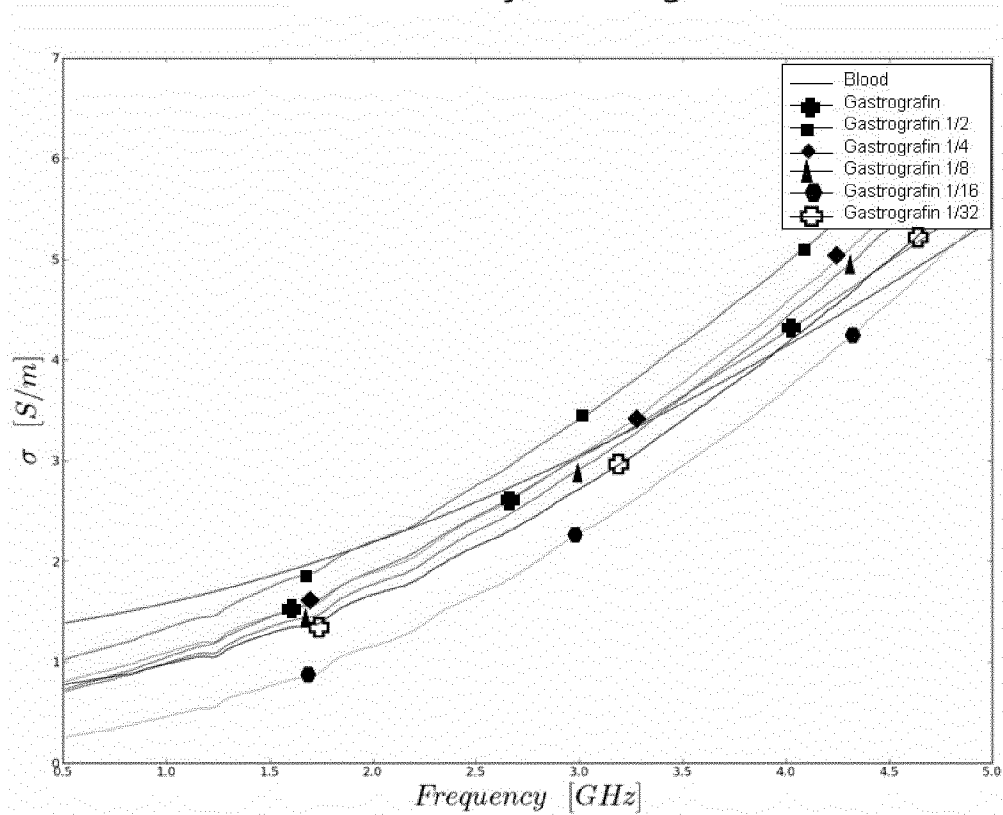


Figure 11

Conductivity Gastrografen

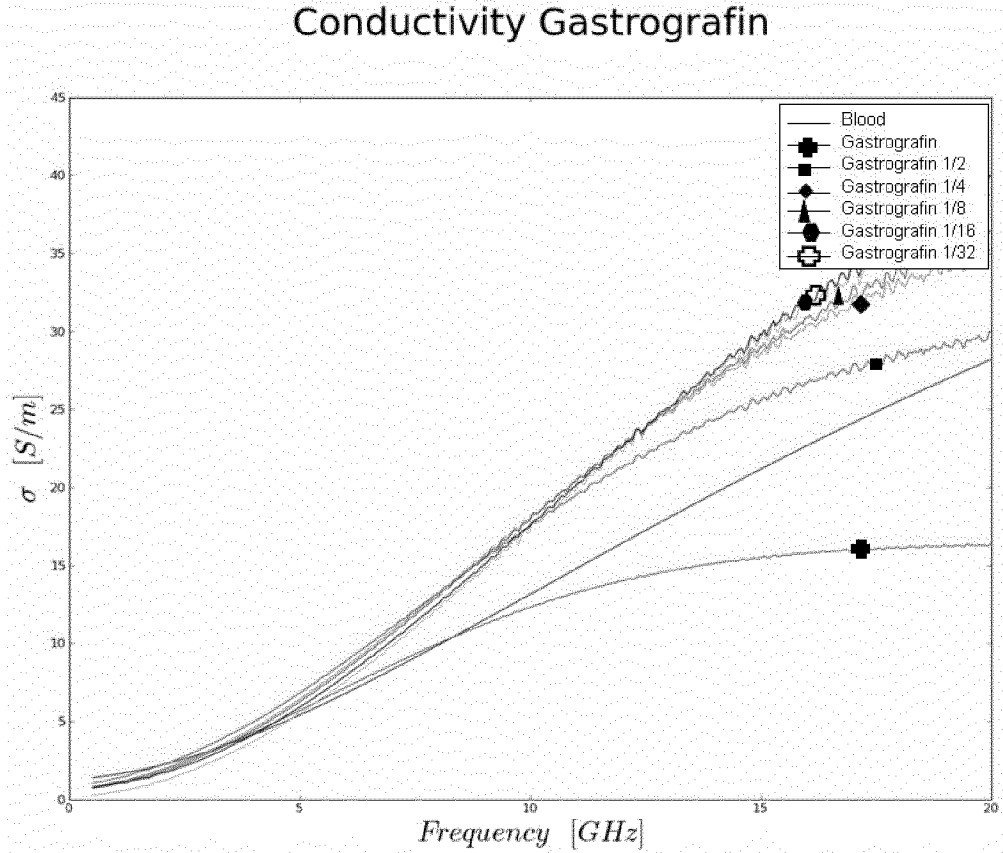


Figure 12

Permittivity Omnipaques

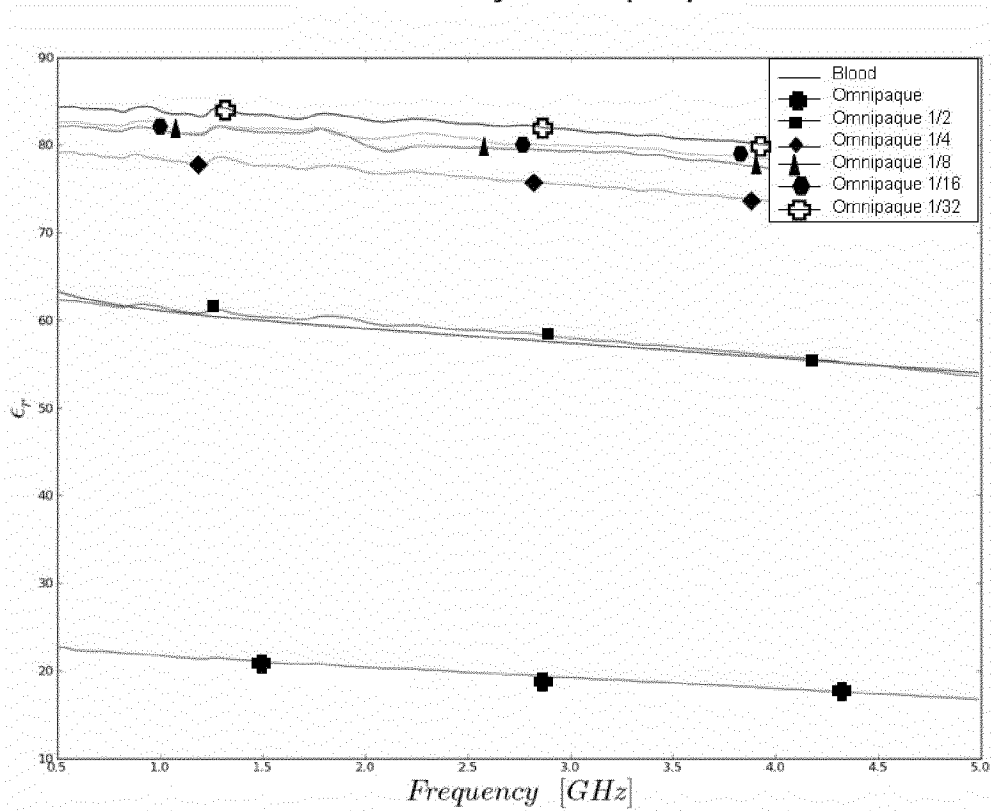


Figure 13

Permittivity Omnipaques

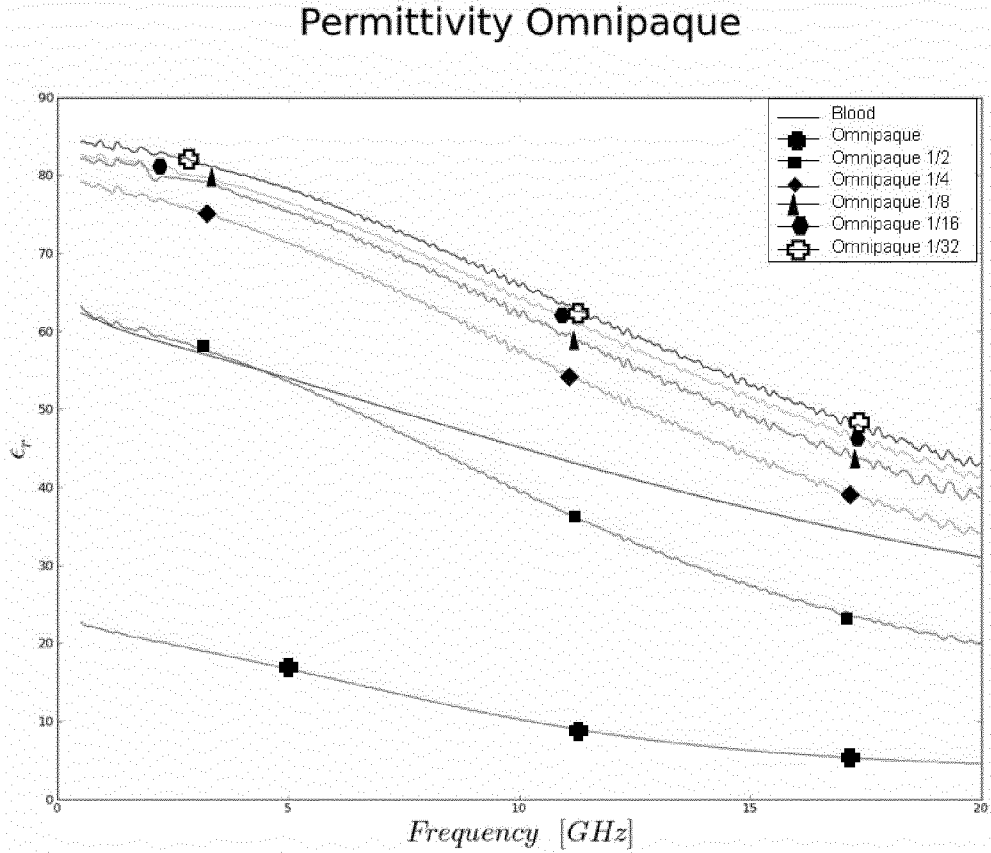


Figure 14

Conductivity Omnipaque

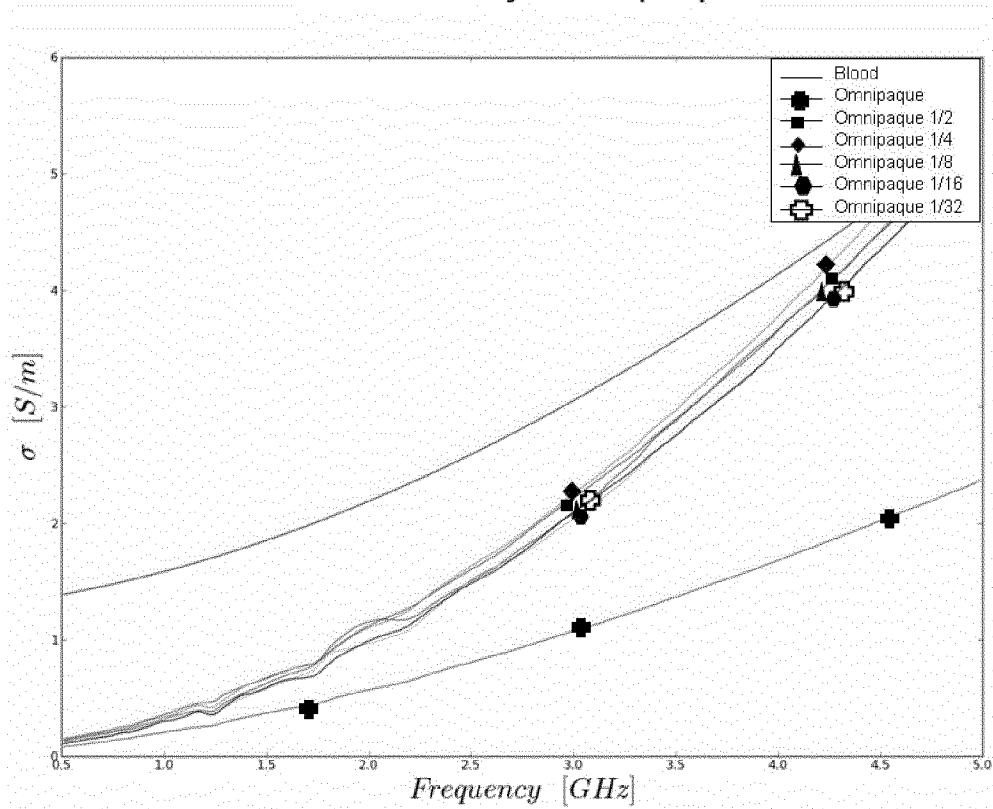


Figure 15

Conductivity Omnipaque

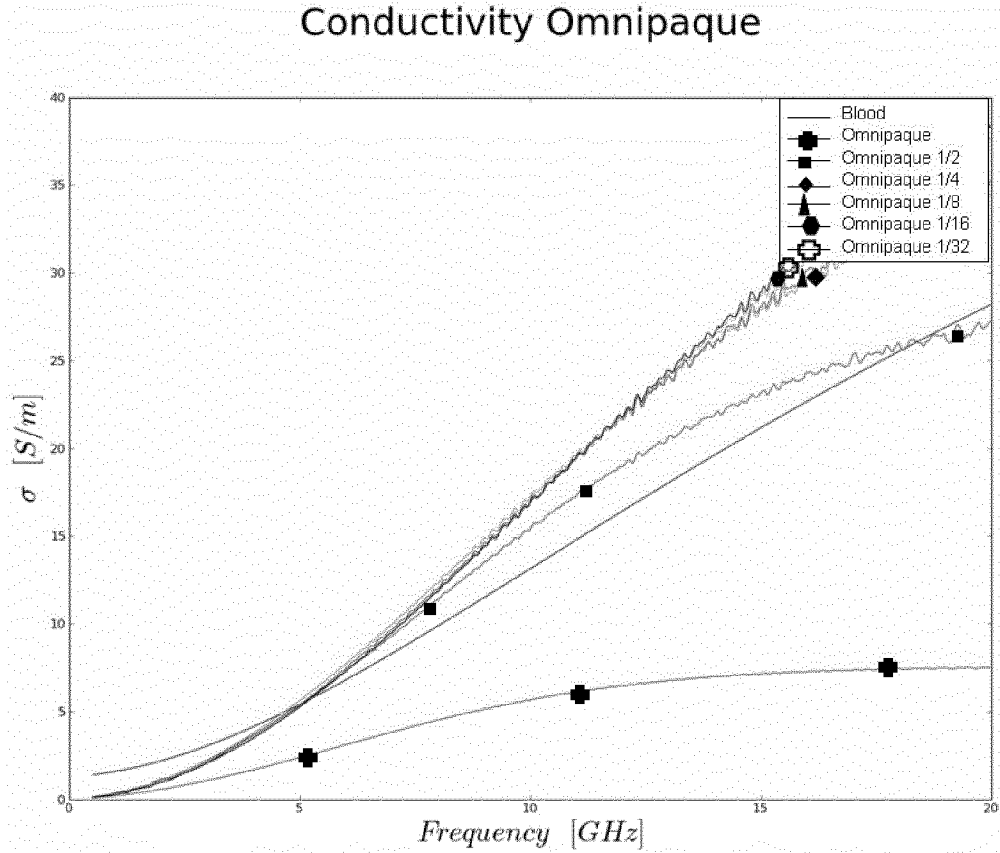


Figure 16

Fresnel reflection coefficient contrast agents - blood

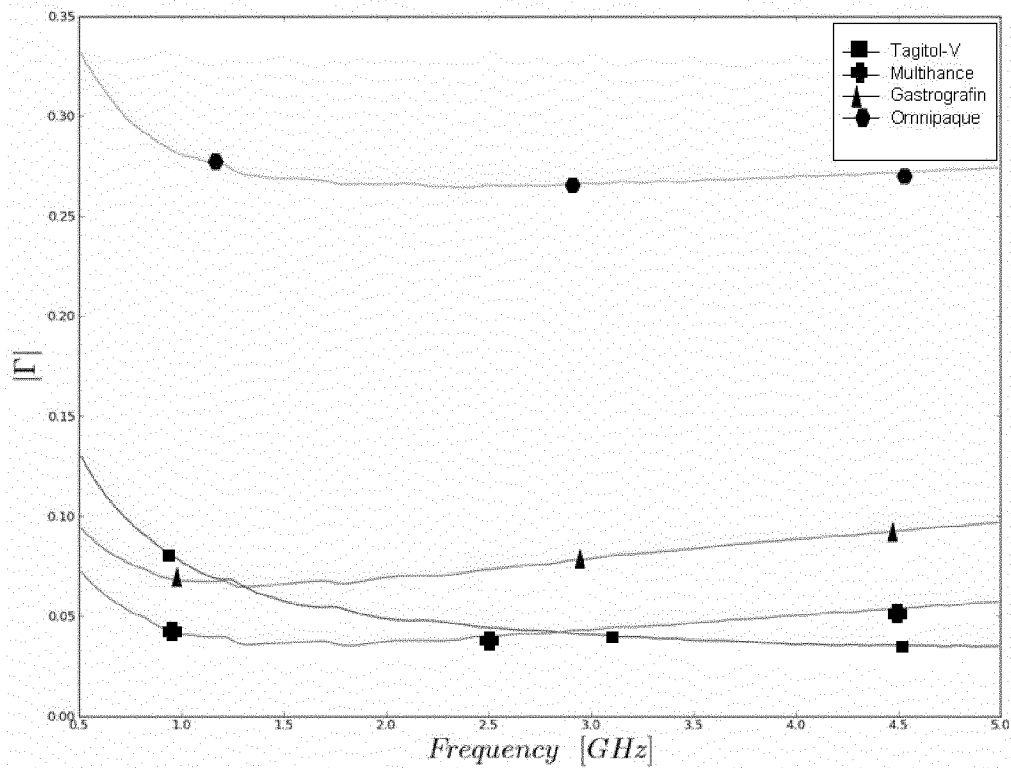


Figure 17

Fresnel reflection coefficient contrast agents - blood

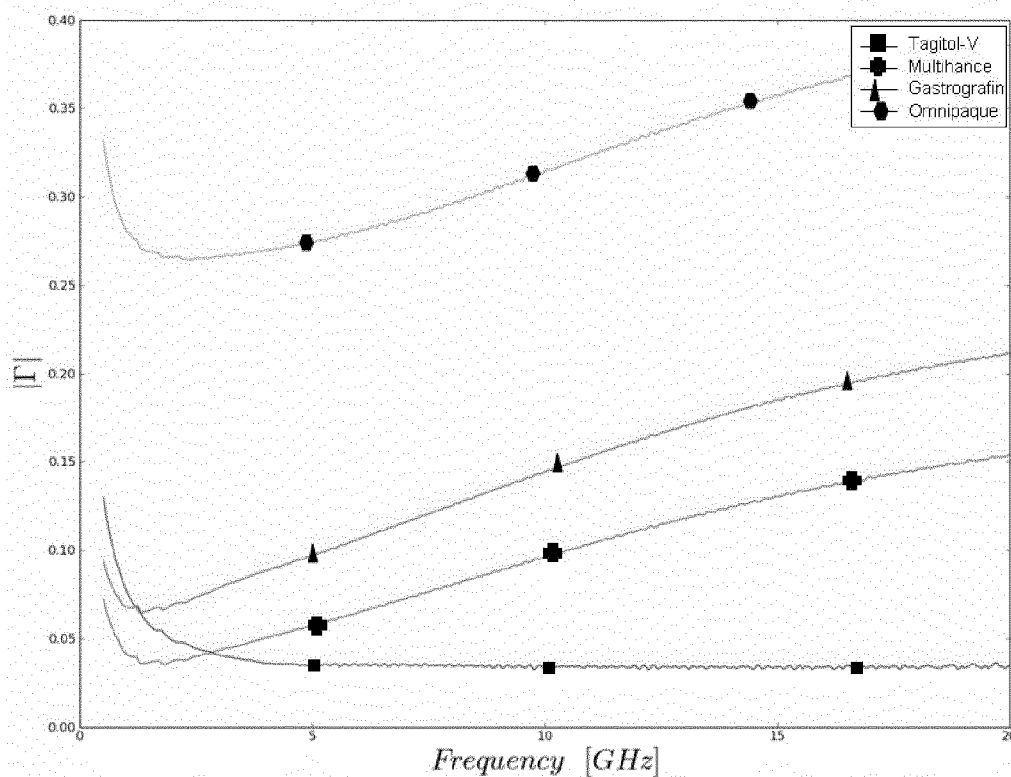


Figure 18

Fresnel reflection coefficient contrast agents - muscle

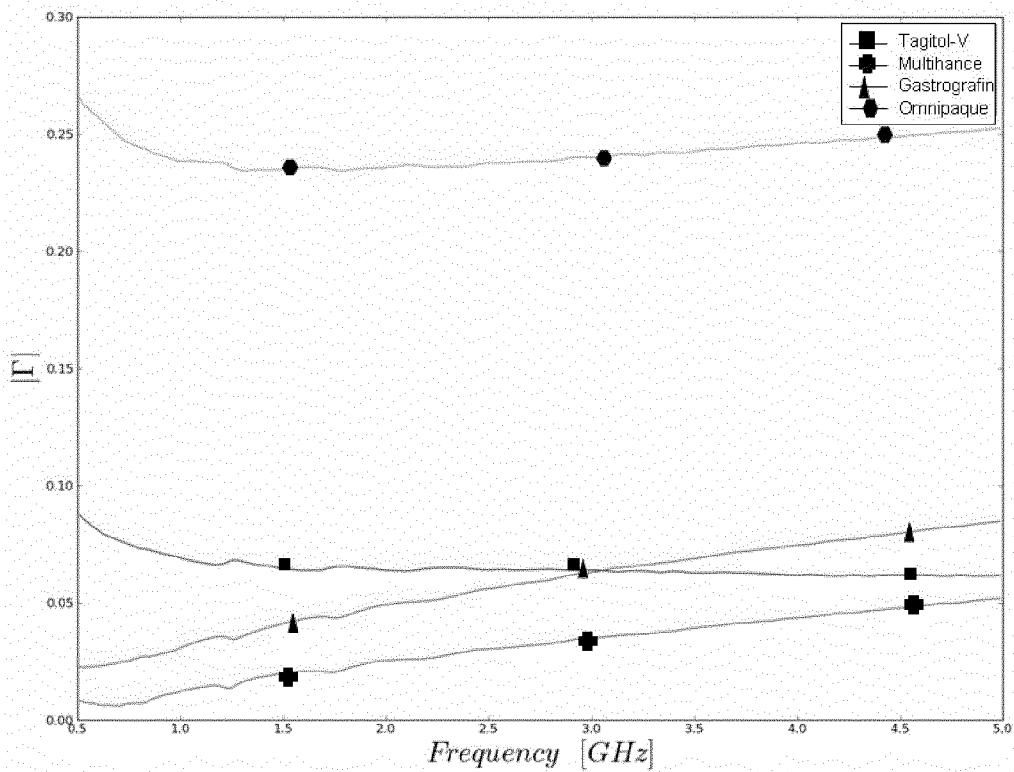


Figure 19

Fresnel reflection coefficient contrast agents - muscle

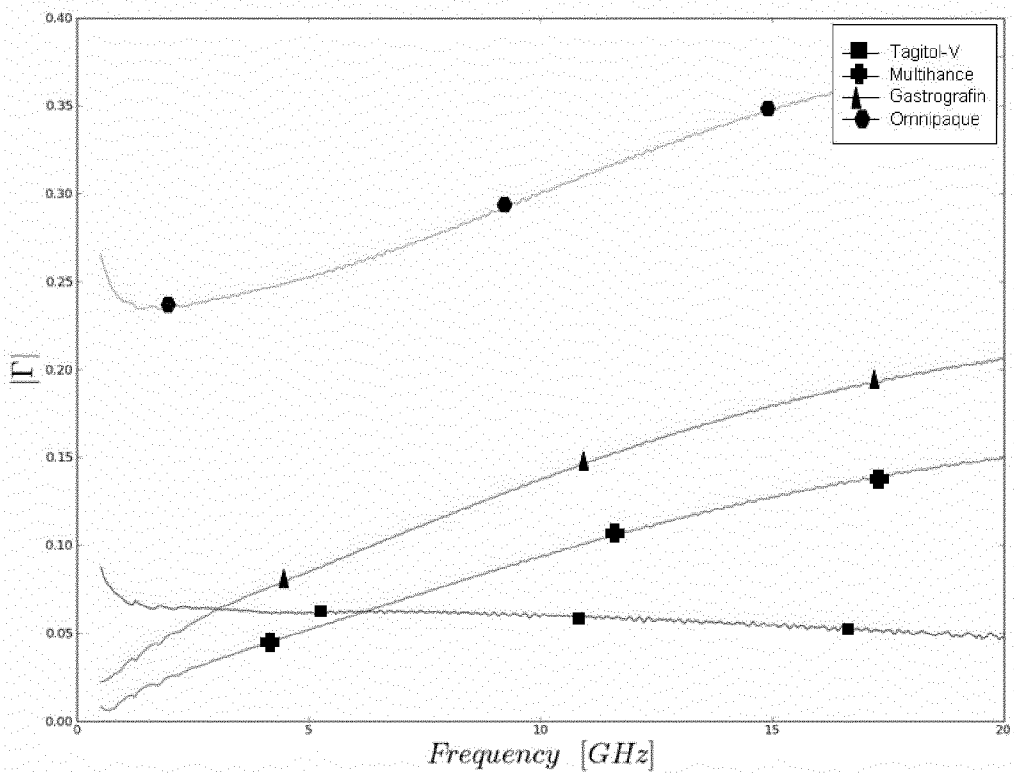


Figure 20