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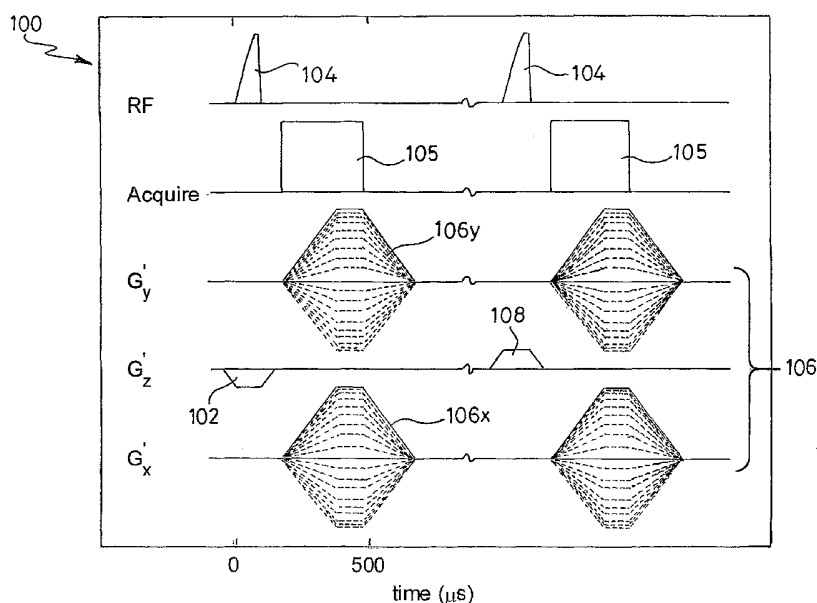
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(54) Title: PHOSPHORUS MAGNETIC RESONANCE IMAGING



(57) Abstract: Information relating to the distribution of phosphorus nuclei within an object, such as a bone, is obtained by applying to the object a magnetic field and also a series of RF electromagnetic pulses (104). After each pulse (104) magnetic field gradient pulses (106x, 106y) are applied to the object, and RF signals (105) emitted by the nuclei are acquired during a period when a magnetic field gradient pulse (106x, 106y) is rising to a maximum and remaining at a maximum value. The acquired signals are processed to obtain information relating to the distribution of phosphorus nuclei despite the very short spin-spin magnetic relaxation time (T_2) of phosphorus.



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PHOSPHOROUS MAGNETIC RESONANCE IMAGING

Field of the Invention

The present invention relates to magnetic resonance imaging and in particular to magnetic resonance imaging of the phosphorus content in bone.

Background to the Invention

It is often desirable to be able to obtain an image of a human bone whether for research purposes, diagnosis of disease or assessment of treatment of a disease. In particular it is of interest to be able to observe the density of a bone and the distribution of minerals within the bone and thus to determine bone mineral density which is a useful parameter in assessing the condition of a bone. In particular images of bones or measurements of bone mineral density are useful in diagnosing or monitoring diseases that affect the appearance or density of bone material such as osteoporosis, osteomalacia, renal osteodystrophy, osteogenesis imperfecta, fibrous dysplasia, rickets, osteosarcoma, thalassemia and sickle cell disease, osteomyelitis.

It is known to use X-rays to observe bone and common techniques include Computerised Tomography, shadowgraphs and dual X-ray densitometry. These techniques are particularly sensitive to the calcium content of bones. The X-rays used in these techniques are however an ionising radiation which is associated with damage to health.

Another important component of bone is phosphorus. The nucleus of phosphorus 31 has a non-zero nuclear spin magnetic moment and is thus capable of being imaged by Magnetic Resonance Imaging (MRI), which provides a method of imaging bodily structures without using ionising radiation.

MRI is capable of being applied to imaging the spatial distribution of nuclei with non-zero nuclear spin moments. Under the influence of a static magnetic field, the nuclear spin

magnetisation vector will align with and precess around the magnetic field vector at a frequency dependant upon the particular nuclei and the applied field known as the Larmor frequency. Application of a suitable radio frequency (RF) electromagnetic pulse at the Larmor frequency has the effect of flipping the magnetisation vector by an angle dependant upon the length of the RF pulse. After the pulse, the nucleus emits an RF signal as the magnetisation vector relaxes to its equilibrium position.

Typically magnetic field gradients in one or more directions are applied to a subject to be imaged. These vary the frequency and or phase of the signal emitted by nuclei located at different parts of the subject and thus, by analysing the frequency and phase of the received signal, spatial information about the distribution of nuclei within the subject can be obtained. The various RF pulses and magnetic field gradients applied to the subject are referred to as a pulse sequence. In most cases an initial RF pulse is applied to a subject followed by a sequence of field gradients intended to vary the frequency and phase of the emitted signals (in some techniques further RF pulses may additionally be used).

After completion of the pulse sequence, signals are acquired from the nuclei, the time delay between the flipping of the magnetisation vector and the acquisition of signals from the nuclei is known as the echo time TE. The signals acquired from the nuclei decline in intensity with time so signals acquired with longer TE are typically of lower intensity. The rate of decay is dependant upon two factors T_1 (the spin-lattice magnetic relaxation time) and T_2 (the spin-spin magnetic relaxation time). T_2 is dependant upon the chemical environment of the nuclei. Particular pulse sequences are optimised to obtain data from particular nuclei in a particular chemical environment.

The sequence is repeated many times with the magnitude and or duration of the field gradient pulses being varied stepwise between a minimum and maximum value. The effect of the whole sequence of pulses is to sample a series of lines in reciprocal or K-space, building up a reciprocal image of the distribution of nuclei. The reciprocal image is then Fourier transformed to provide a real image.

In order to achieve this a typical clinical MRI scanner has a main field coil for applying a magnetic field to an object within and three subsidiary coils for applying field gradients to the object. There is also provided either a single transmit-receive coil or separate transmitting and receiving coils for applying RF pulses to the subject and detecting the resultant RF signals. The RF coil or coils are typically optimised to image a particular object such as a subject's arm or leg.

Most existing clinical MRI techniques are optimised for imaging the spatial distribution of ^1H nuclei (protons) in soft tissue and use TE of 1-150ms. These techniques image fat and water surrounding bone successfully but leave bone displayed as voids in the image. The chemical environment within a bone results in phosphorus in bone having a very short T_2 ($\sim 180 \mu\text{s}$) in such situations, the T_2 effects dominate the signal decay, the intensity of which decays proportionally to $\exp(-TE/T_2)$. To obtain images it is necessary to be able to image with a very short TE, ideally as close to $0\mu\text{s}$ as possible. Current clinical systems are sensitive to TE of 1ms-150ms and phosphorus in bone is invisible at these time scales. In order to obtain information on the phosphorus content of bone non standard MRI pulse sequences must be used, in particular some limited success has been achieved using 'solid state' pulse sequences.

Solid state pulse sequences rely on applying a constant field gradient to an object for sufficient time to allow the gradient to stabilise before applying an RF pulse to the object. Signals may then be acquired from the object within a very short time interval from the end of the RF pulse. This technique however suffers from a number of drawbacks. It is necessary to use ultra short high power RF pulses typically of 1-10 μs duration. Pulses of this type require extremely large amplifiers which are very expensive to build and use. Additionally, the power deposited by an RF pulse in tissue is inversely proportional to the length of the pulse and hence ultra short pulses cause problems with Specific Absorption Rate (SAR) limits. Furthermore solid state techniques can only be applied to systems with a single transmit and receive RF coil otherwise much of the signal would have decayed during the finite time interval required to switch between coils. This reduces the improved signal to noise ratio that can be obtained by using dedicated transmit and receive coils.

Solid state methods have an additional drawback in that they may only be applied to operating in a three dimensional acquisition mode over the whole of the effective volume of the coil. This is because the system relies on an RF pulse being applied with a constant field gradient which means a slice selecting field gradient pulse cannot be applied concurrently with the RF pulse before applying further field gradients. Thus they cannot be used to image a two dimensional slice within the object which means that useful imaging takes significantly longer as far more information needs to be gathered.

It is therefore an object of the present invention to provide an improved technique for imaging phosphorus in bone by magnetic resonance imaging.

Summary of the Invention

According to a first aspect of the present invention there is provided a method of obtaining information relating to the distribution of phosphorus nuclei within an object comprising the steps of:

applying a magnetic field to the object;

applying an RF electromagnetic pulse to the object, the RF pulse flipping the magnetization vector of the phosphorus nuclei through a desired angle;

subsequently applying a magnetic field gradient to the object, the field gradient rising to a desired value, remaining at the desired value for a particular time period then declining;

acquiring RF signals emitted by the nuclei in response to the RF pulse and the applied magnetic field gradient, the RF signals being acquired in the interval between the beginning of the magnetic field gradient rise and the end of the magnetic field gradient decline; and

processing the acquired signals in order to obtain information about the distribution of phosphorus nuclei within the object.

According to a second aspect of the present invention there is provided a magnetic resonance imaging apparatus having a means for applying a magnetic field to an object, means for applying a magnetic field gradient to the object, means for transmitting an RF

signal to the object and means for receiving an RF signal from the object, and control means adapted to apply a pulse sequence to the object and to acquire and to process signals according to the method of the first aspect of the present invention.

Using the above method and apparatus images of the distribution of phosphorus nuclei in bone can be obtained despite the very short T_2 of phosphorus nuclei in bone and the consequent rapid decay of signals from the phosphorus nuclei. In particular this allows images showing variations in bone mineral density to be obtained, as well as allowing localised bone mineral density to be determined.

Signal acquisition preferably commences as soon as possible after the completion of the RF pulse. Most preferably signal acquisition commences 70 μ s or less after the completion of the RF pulse. Preferably signal acquisition ends before the magnetic field gradient starts to decline. The acquired signal is preferably digitised using a sampling rate of between 1 μ s and 64 μ s per point, preferably 2-8 μ s per point and most preferably 4 μ s per point.

The maximum value of the applied field gradient is preferably between 10mT/m and 200mT/m with a particularly preferred maximum value being 40mT/m. The time taken for the gradient to rise to its maximum value, the ramp time, is preferably approximately 220 μ s but faster or slower ramp times may be used if desired. The optimum ramp time is a trade off between the danger of faster ramp times causing nerve stimulation and slower ramp times increasing the blurring present in the image. It may however be safe to implement faster ramp times if the field gradient is confined to a small area only.

The frequency of the RF pulse is chosen to be that resonant with the Larmor frequency of phosphorus at the particular steady field applied to the object. In a typical example a field of 1.494T is applied to the object to be imaged and an RF pulse of frequency 25.4MHz is used.

The RF pulse length is preferably in the range 100 μ s – 1ms and is most preferably 200 μ s. Short pulses such as this avoid effects due to saturation and relaxation during the RF pulse

and the relatively low power RF pulses required to use this technique mean that problems due to absorption of the energy of the signal by a subject do not arise. For instance these pulses are typically 50-100 times longer than the pulses used in solid state methods and hence the pulses have a peak power level of 2500-1000 times lower than those used in solid state methods which results in 50-100 times less heat being absorbed by the object. The RF pulse is preferably optimised to flip the magnetisation vector of the phosphorus nuclei through an angle of between 1 and 90 degrees, the angle most preferably being 12 degrees.

In certain circumstances it may be necessary to apply further RF or magnetic field gradient pulses in order to calibrate or otherwise compensate for external influences or prior applications of pulse sequences to the object.

Preferably the means for applying a magnetic field to an object is a coil and most preferably there are additionally provided three coils each being adapted to apply a magnetic field gradient in a particular direction. Most preferably the three gradient coils are adapted to apply field gradients in mutually orthogonal directions.

Preferably the means for transmitting and receiving RF signals are coils and most preferably there are separate coils for transmitting and receiving signals.

Preferably a programmable computer is used to control the application of magnetic field gradients and RF pulses to the object to be imaged. Most preferably a programmable computer is provided for processing the signals acquired from the object. Particularly preferably the same programmable computer is used to control the application of magnetic field gradients and RF pulses to the object and to process the signals acquired from the object.

Preferably in order to obtain an image, the above sequence of RF and magnetic field gradient pulses is repeated a number of times, with magnetic field gradient pulses of varied magnitude and or direction. The repeated sequence may be adapted to image the whole or

a selected part of an object. In particular the whole of an object contained within the means for applying magnetic fields, field gradients and RF signals may be imaged or a single selected slice of the object may be imaged. If a single slice is selected to be imaged, it may be imaged in two or three dimensions. If the whole of the object is to be imaged it may be imaged in three dimensions only.

If a three dimensional image of the object or a selected slice of the object is to be obtained, then the above magnetic field gradient pulse is preferably a composite field gradient comprising three substantially mutually orthogonal components. If a two dimensional image of a selected slice of the object is to be obtained preferably the field gradient is parallel to the plane of the selected slice and is preferably a composite field gradient comprising two substantially mutually orthogonal components each being parallel to the plane of the selected slice.

In both cases the pulse sequence is then preferably repeated with the magnitude of each component of the pulse being varied stepwise in turn between a maximum positive value and a maximum negative value. The repetition of the sequence with magnetic field gradients in a variety of different directions corresponds to sampling along a series of radial lines in reciprocal or K-space, the orientation of the lines in K-space corresponding to the direction of the field gradients.

The time between repetitions TR is preferably in the range 50ms to 32s. The T_1 (the spin-lattice magnetic relaxation time) of phosphorus in bone is approximately 10s so long TR times are beneficial to yield the largest signals but do significantly increase imaging time. A particularly preferred TR for optimising signal strength in limited time is 300ms.

To obtain a two dimensional image of a selected slice of the object, two dimensions of K-space must be sampled, the pulse sequence is thus repeated with a series of different magnetic field gradients, the directions of which all lie parallel to the plane of the slice. In K-space this corresponds to sampling along a series of lines radiating from the origin, confined to a single plane. Preferably there is approximately equal angular separation

between successive magnetic field gradient directions (and hence successive sampling lines in K-space). Preferably the number of different gradient vectors applied to the object to be imaged is in the range 32 – 512 and is most preferably 128.

To obtain a three dimensional image of the object or a selected slice of the object, three dimensions of K-space must be sampled. In this case the pulse sequence is thus repeated with a series of different magnetic field gradient directions, successive field gradient directions preferably having substantially equal angular separation, the magnetic field gradients not being confined to directions parallel to a selected slice. This corresponds to a series of samples along radial lines in K-space, the lines extending in all three dimensions from the origin and having substantially equal angular separation therebetween. If K-space is to be sampled in three dimensions to a similar density as for the two dimensional image described above, obviously many more magnetic field gradients must be applied to the object.

In both the two dimensional and three dimensional imaging embodiments the points sampled in K-space are regridded onto a rectilinear grid to compensate for acquiring of signals during the rising portion of the field gradient pulses. The regridding provides a reciprocal image of the object. The reciprocal image may then be Fourier transformed to provide an image of the selected slice.

Preferably the regridding method is interpolation onto a grid and then division by the Fourier transform of the interpolation kernel. Preferably the data is filtered before Fourier transformation, most preferably using a second order Butterworth filter. Preferably the cut-off frequency is between 16 and 128, however 48 or 64 are particularly preferable as cut off frequencies (the cut-off frequencies of the filter being defined in terms of sample points).

The field of view is preferably set to be larger than the object to be imaged and typically is in the range 5-40cm. The sampling rate is preferably slowed if a smaller field of view is

being imaged so as to increase the signal to noise ratio for each point without unduly lengthening the time taken to acquire an image.

Preferably for embodiments wherein a selected slice of the object is to be imaged in either two or three dimensions the method further comprises applying a slice selecting magnetic field gradient pulse, for selecting the particular slice of the object which is to be imaged. If desired many separate slices may be imaged to build up an image of the phosphorus distribution in the object as a whole. Typically the slice selecting gradient is applied in a direction orthogonal to two of the field gradient components, resulting in a slice to which those two field gradient components are parallel. It is however possible to select a slice at any desired orientation by generating a suitable slice selecting pulse. It is also possible that given suitable hardware two (or more) separate slices of the object may be imaged simultaneously, the two or more slices of course need not necessarily be parallel to one another.

Preferably the slice selecting pulse comprises a substantially linearly increasing field gradient rising to a desired maximum value and staying substantially constant for a particular time period before decreasing substantially linearly. Preferably the RF pulse is applied substantially simultaneously with the period of time for which the slice selecting magnetic field gradient pulse is constant.

When applied, the slice selecting gradient pulse is preferably used to select a single slice of thickness 2-200mm and most preferably used to select a slice of thickness 20-60mm. The thickness of slice appropriate for successful imaging depends on the material to be imaged, Trabecular bone for example contains less phosphorus than cortical bone and thus thicker slices are required to image regions of Trabecular bone with a similar signal to noise ratio as can be obtained in a thinner slice for cortical bone.

Most preferably if a slice selecting gradient pulse is used in the imaging sequence, signals acquired from each stepwise variation of the field gradients are averaged together with signals acquired using a reversed slice selecting gradient pulse. The effect of averaging the

signals acquired using a reversed slice selecting gradient is to remove artefacts in the signal caused by individual excitations. The number of repetitions averaged together to create the final image is a trade off between the time required to repeat the sequence and the accuracy of the final image. In use the number of repetitions may vary between two and two hundred and fifty six but typically the sequence is repeated eight times, four times with a slice selecting gradient in one direction and four times with a reversed slice selecting gradient. As the pulse sequence is repeated with a reversed slice selection gradient, average values for each point in K-space are obtained and are then processed as described above to obtain an image.

Preferably the slice selecting gradient is applied in a direction parallel to one of the field gradient components if a three dimensional image of a slice is desired and preferably in a direction orthogonal to the plane of the slice. Most preferably the above technique is used to obtain two dimensional images of a slice, in which case a slice selecting gradient is applied in a first direction and the field gradient is comprised of two components orthogonal to the slice selecting gradient, the stepwise variation and repetition with a reversed slice selecting gradient being carried out as described above.

Preferably the object to be imaged comprises a bone and most preferably comprises a human or animal bone.

The above method and apparatus may be applied to determining T_1 and T_2 for the phosphorus content in a bone or in a selected slice of bone, either to provide an indication of the condition of the bone or otherwise. Preferably this may be achieved by further processing the acquired signals in order to obtain information about the T_1 and T_2 of phosphorus nuclei within the object.

Preferably T_2 is determined by repeating the method of the first aspect of the invention a number of times using different time intervals between the completion of the RF pulse and the start of the acquisition of signals. T_2 can then be determined by fitting the intensity of signal acquired to an exponential decay. Alternatively T_2 may be determined by applying a

number of RF pulses of different durations and or magnitudes to the object to be imaged to either suppress or preferentially excite components with long T_2 and thus act as a T_2 weighting mechanism.

Preferably T_1 is determined by repeating the method of the first aspect of the present invention with a variety of different magnetisation vector flip angles and a variety of different repetition times TR. The resultant signal intensity is a function of the flip angle, TR, T_1 and T_2 and thus T_1 can be determined if T_2 is known or T_1 can be determined by approximating the factors dependant on T_2 . Alternatively additional preparatory RF pulses may be applied to the object to remove effects due to transverse components of magnetisation, and this removes some of the T_2 dependant factors from the signal intensity function.

In alternative embodiments the above methods can be used to perform a bone mineral density scan. This can be achieved by repeating the method of the first aspect of the invention with a repetition time TR of greater than five times T_1 . The intensity of the subsequently acquired images is then proportional to the density of phosphorus in the bone except for an exponential decay factor due to T_2 effects. It is also possible to acquire signals using TR of less than five times T_1 and calculate the phosphorus density therefrom by performing an appropriate corrective calculation.

According to a third aspect of the present invention there is provided a method of diagnosing a bone disease by utilising the method of the first aspect of the present invention to image the phosphorus content of a bone.

Preferably the above method of diagnosis may include also imaging using other MRI pulse sequences and comparing the results obtained using each different pulse sequence. Most preferably the additional imaging sequences include a dark bone proton scan using standard clinical methods and or an ultra short TE proton scan.

Preferably the above method of diagnosis may also include obtaining a bone mineral density scan.

Preferably the above method of diagnosis may include measuring the T_1 and T_2 of the phosphorus content of a bone, in order to obtain an indication as to the health of the bone.

Preferably the above method of diagnosis may also include manipulation of the magnetisation state of protons in bone using RF pulses and then observing the transfer of magnetisation from the protons to the phosphorus nuclei.

A combination of the above methods of diagnosis allows detection of a wide variety of diseases in patients which affect the condition, appearance or mineral density of their bones. In particular such diseases include osteoporosis, osteomalacia, renal osteodystrophy, osteogenesis imperfecta, fibrous dysplasia, rickets, osteosarcoma, thalassemia and sickle cell disease, osteomyelitis.

Brief description of the drawings

In order that the present invention be more clearly understood one embodiment is described further herein with reference to the accompanying drawings in which:

Figure 1 is a schematic diagram of an MRI scanner;

Figure 2 is a block diagram, showing the connection between the components of the MRI scanner of Figure 1;

Figure 3 shows a pulse sequence for obtaining a two dimensional image of a slice of an object using the MRI scanner of Figure 1 ;

Figure 4 shows a pulse sequence for obtaining a three dimensional image of a slice of an object using the MRI scanner of Figure 1; and

Figure 5 shows another pulse sequence for obtaining a three dimensional image of an object using the MRI scanner of Figure 1.

Detailed Description

Referring to Figures 1 and 2, an MRI scanner 2 is in use to obtain an image of a leg bone 6 of a person 4. The scanner 2 comprises a main field magnet 8 for applying an overall magnetic field to any object placed within, gradient field coils 10 for applying a desired magnetic field gradient to an object placed within, RF coils 12 for transmitting and receiving RF signals from an object placed within the main coil 8 and a control unit 14 for controlling the field and RF coils and processing signals received by the RF coils 12. The main field coil 8 is typically a solenoid and is operative to generate a steady field along its axis, defined as the z direction. When in use the field is typically around 1.5T.

Three gradient field coils are provided 10x, 10y and 10z each being operative to provide a linear magnetic field gradient in a particular direction. Coil 10z is operative to provide a field gradient in the z direction, 10y in the y direction and 10x in the x direction. The x, y and z directions are substantially mutually orthogonal.

A single RF coil 12 is shown in Figure 1 and the invention may be implemented using a single RF coil but typically two coils are used, a transmit coil 12t and a receive coil 12r. It is well known in the field of MRI scanner design to optimise these coils 12t, 12r for receiving signals from a particular object at a particular frequency. In the case where signals are to be received from the limb of a person the receive RF coil 12r is usually adapted to fit closely around the limb.

In order to obtain an image of an object using the above equipment, a magnetic field is applied to the object and subsequently a sequence of magnetic field gradient and RF pulses are then applied to the object. The control unit 14, a programmable computer, is adapted to control the power supply to the coils 8-12 in order to generate the desired magnetic fields, magnetic field gradients and RF signals. In response to the above signals the object emits signals which are received by RF coil 12r and subsequently processed by the control unit 14 to produce an image. In order to facilitate the processing by digital processes an analogue to digital converter (not shown) is provided to convert the analogue signals received by coil 12r to digital signals.

The present invention relates to imaging the phosphorus content of bone and one suitable pulse sequence 100 for carrying this out is shown in Figure 3. This pulse sequence is operative to generate a two dimensional image of the spatial distribution of phosphorus within a slice of an object. In the case of Figure 1, it is operative to image a slice of the person's leg bone 6.

A particular slice to be imaged is selected using slice selecting field gradient pulse 102 and RF pulse 104. Slice selecting pulse 102 generates a magnetic field gradient in the z direction. The magnetic field gradient rises substantially linearly to a value, remains substantially constant for a time and then declines substantially linearly to zero, and RF pulse 104 is generated concurrently with the period of time that slice selecting pulse 102 remains constant. The variation in magnetic field along the z direction means that the Larmor frequency of the phosphorus nuclei, which is dependant on the local field, also varies along the z axis. The RF pulse 104 is chosen to have a frequency equal to the Larmor frequency of phosphorus nuclei located at a predetermined position along the z axis. The RF pulse 104 is thus effective to flip the magnetisation vectors of phosphorus nuclei in a slice of the object being imaged extending perpendicular to the z axis at the predetermined position along the z axis through a particular angle, and leave the magnetisation vectors of phosphorus nuclei outside the slice substantially unaffected. Slice selection pulses are well known in the art and may be adapted to select slices with different orientations if desired. Additionally it is known to select two separated slices by using an RF pulse 102 comprising two different frequencies, thus allowing more than one slice to be imaged at a time.

The shape and duration of the RF pulse 104 are such that they cause the magnetisation vectors in the selected slice to flip through a desired angle. Suitable RF pulses for achieving flips as above are well known in the art. In the present example, the pulse 104 is around 200 μ s in duration and flips the magnetisation vectors through approximately 12 degrees.

After the slice selecting pulse 102 has ended, imaging magnetic field gradient pulses 106x, 106y are generated. The pulses 106x, 106y rise substantially linearly to a value, remain substantially constant for a time and then decline substantially linearly to zero. The rise time for the pulses 106x, 106y is around 220 μ s and normally the maximum field gradient would be around 40mT/m. Larger maximum field gradients or shorter rise times can cause nerve stimulation in the person being imaged and are thus not generally used.

Concurrently with the rising and constant portions of the imaging pulses 106x, 106y, the control means 14 acquires digitised signals 105 from RF coil 12r, the signals being emitted by the magnetisation vectors of the phosphorus nuclei in the selected slice flipping back to their equilibrium positions. The signals are acquired with a sampling rate of between 1 and 16 μ s per point, typically 4 μ s per point although slower sampling of around 32 or 64 μ s per point may be useful for some applications. Faster sampling rates result in less signal decay during signal acquisition and thus minimal signal loss. However faster sampling rates also result in more noise in the sampled signal. For most applications there is thus a trade off between image detail and reduced signal to noise ratio. These rates are much faster than typical clinical scanner systems which image at around 50 μ s per point.

After the end of the imaging pulses 106x, 106y, the sequence is repeated with a reversed slice selecting gradient 108. The signals acquired are then averaged to remove artefacts generated during slice selection. The sequence is typically repeated 4 times with each slice selecting gradient pulse 102, 108. A time of 300ms is allowed between repetitions to allow the nuclear magnetisation to recover.

The imaging pulses 106x, 106y effectively subject the phosphorus nuclei in the selected slice to a field gradient in the same plane as the slice. The frequency and phase of the RF signals emitted by the phosphorus nuclei thus depend on their position in the slice. The above sequence is repeated using imaging pulses 106x, 106y at least one of which rises to a different constant value. The constant values of the pulses 106x, 106y are varied stepwise between a maximum positive and a maximum negative value and further averaged signals are obtained. In this manner signals are obtained from the slice when it is subjected

to gradients of substantially similar magnitude but a variety of different directions, each different direction lying within the plane of the selected slice. When the imaging pulses $106x$, $106y$ have been varied stepwise through their full range of values a plot of the directions of the various field gradients would resemble the spokes of a wheel.

A typical image might be obtained using anywhere between 32 and 512 gradient directions, the more different directions are used the better the quality of the image obtained but the longer the time required to obtain it. Good quality images can be obtained in a reasonable time using 128 gradient directions.

The signals acquired with different gradient directions correspond to points along a number of different radial lines emanating from the origin in K-space. The averaged signal points for each gradient direction are plotted on a corresponding radial line in K-space.

Subsequently the points are regridded onto a rectilinear grid to form a reciprocal image of the distribution of phosphorus nuclei within the slice. The regridding process compensates for the acquisition of some samples during the field gradient rise time. Regridding is achieved by interpolation onto a grid and then division by the Fourier transform of the interpolation kernel. If this method of regridding is used, the image may require further processing to remove artefacts due to the interpolation kernel. A real image may then be obtained by Fourier transforming the reciprocal image.

In order to improve the image, the data is filtered using a second order Butterworth filter to give the optimum trade off between signal to noise ratio and image resolution. For optimum imaging the Butterworth filter operates with a cut-off frequency of 48 or 64, the frequencies being defined in terms of sample points.

Figure 3 shows in schematic form the required acquisitions steps needed to create a two-dimensional image using the described technique. The gradient axes shown in this figure are not necessarily the same axis as the physical gradient axes and there may be arbitrary rotations between the two axes to allow the orientation of the imaged slice to be varied.

The initial RF excitation pulse is applied with a slice selection gradient, the frequency and bandwidth of the RF pulse and the strength of the slice selection gradient can be modified so as to move the selected slice and to vary the thickness of this slice.

The readout gradients for any particular step are chosen so that the integral of the gradient (106x and 106y) will allow us to sample (acquisition axis) a radial line in K-space, and that each step will acquire a single radial line at a slightly different angle. Consequently the peak gradient strength for each step will equal $G(\text{Max}) \sin(\alpha)$ in the G_x' direction, and $G(\text{Max}) \cos(\alpha)$ in the G_y' direction, with α varying in steps between 0 and 360° , the sequence of these acquisitions is flexible.

The second half of this pulse sequence diagram demonstrates the acquisition component for the complementary slice information that is required by the "half-slice" method. As can be seen the slice selection gradient is reversed, and by adding the two acquisitions with reversed slice selection gradients the resulting slice profile is improved. Once again this second half needs to be executed for each step incrementing α as above. α can be incremented as the inner variable in the loop, or the slice selection direction is varied most quickly, or some hybrid approach could be applied.

Referring now to Figure 4, a modified pulse sequence is shown for obtaining a three dimensional image of a selected slice. As for the sequence in Figure 3, a slice selecting field gradient pulse 102 and an RF pulse 104 are applied to the object to be imaged. This causes the magnetisation vectors of the phosphorus nuclei in the selected slice to be flipped through a desired angle. After the slice selecting pulse 102 and the RF pulse 104 have been applied an imaging magnetic field gradient pulse 106, is applied the pulse 106 rising substantially linearly to a value, remaining substantially constant for a time and then declining substantially linearly to zero. The imaging pulse 106 in this sequence has three components 106x, 106y, & 106z, each being gradients in substantially mutually orthogonal directions. Signals 105 are acquired as the imaging pulse 106 rises to a constant value and whilst it remains at a constant value.

As in the pulse sequence of Figure 3, the sequence is repeated with a reversed slice selection gradient and the acquired signals are averaged to remove slice selection artefacts from the data. The sequence is then repeated with the various components of the imaging field gradient pulse 106x, 106y, 106z being varied stepwise between a maximum positive and a maximum negative value. Signals from the selected slice thus vary in frequency and phase dependant on their location within the slice. Unlike the sequence of Figure 3 however the imaging gradient pulses are not confined to orientations within the plane of the slice so information relating to the variation in spatial distribution of phosphorus nuclei across the thickness of the slice can be obtained. Imaging using this sequence however takes significantly longer than imaging using the pulse sequence of Figure 3 as in order to sample the slice fully field gradients not lying parallel to the plane of the slice must be sampled.

In K-space this pulse sequence is equivalent to the data obtained using different imaging gradients and corresponds to a series of points along lines projecting radially from the origin in three dimensions. Regridding and Fourier transformation of the reciprocal image is carried out as described above to provide a three dimensional image of the spatial distribution of phosphorus nuclei within the slice.

As described in relation to the pulse sequence of Figure 3, slices imaged need not be confined to those lying in the xy plane and multiple slices may be imaged at one time.

Figure 4 shows a slab selected three-dimensional acquisition. In this case the half-pulse excitation approach is used (using RF pulses 104, and slice selection gradients 102) as before which enables a slab (thick slice) of data to be acquired in an arbitrary orientation. The three-dimensional acquisition is accomplished by scanning through K-space from the centre outwards. To sample the K-space fully we need to acquire a number of different K-space directions which is accomplished by playing out different combinations of readout gradients (106 x,y,z).

A further alternative imaging sequence is shown in Figure 5. This pulse sequence omits the slice selecting field gradient pulse 102 and thus results in a three dimensional image of the spatial distribution of all the phosphorus nuclei within the region of sensitivity of the MRI scanner to RF signals, typically limited by the region of sensitivity of the receive RF coil 12r. As the slice selecting gradient pulse is omitted it is not necessary to average signals acquired with reversed slice selecting pulses but it is still good practice to average together data acquired at different times using the same imaging gradient pulse 106, to improve the signal to noise ratio of the data.

Figure 5 shows a non-selected three-dimensional acquisition. In this case no slice selection is used, and the data are localised by the finite extent of the reception and/or transmission B1 profiles of the RF coils. Once again the K-space is sampled from the centre outwards, and different combinations of gradient strengths are used to sample a volume of K-space.

The above are illustrative pulse sequences. In operation it is likely that to achieve the best results variations in the magnitude and/or the timing and/or the frequency of some or all of the pulses described above may be implemented. Additionally or alternatively pre-pulses whether RF or magnetic field gradient or both may be applied to the object to be imaged to correct for ambient fields, coil inhomogeneity or other systematic errors. Typically such pre-pulses will be comprised of RF pulses alone or RF pulses in combination with magnetic field gradient pulses. Furthermore, additional post-acquisition signal processing may be required to improve the final image. Such adjustments and variations in the pulse sequences to optimise performance would be considered immaterial differences by one skilled in the art.

When imaging phosphorus in bone it is useful to measure T_1 (the spin-lattice magnetic relaxation time) and T_2 (the spin-spin magnetic relaxation time) of the phosphorus in bone. These parameters can give useful indications as to the condition of the bone.

A number of methods are appropriate for determining T_2 : a first is to use one of the pulse sequences described above to acquire several images of the same sample using identical

parameters, except for the delay between excitation and signal acquisition. In such cases the signal intensity decays exponentially with increased time delay, the time constant of the exponential decay being T_2 . Thus by plotting signal intensity against delay time, T_2 can be determined.

Alternatively T_2 can be determined by applying RF pulses 102 of different durations (and or magnitudes) as preparation pulses. The effect of these pulses is to suppress the signal from long T_2 components within the imaged volume, which (if appropriate RF pulses 102 are chosen) can then be used as a T_2 weighting mechanism. As a further alternative T_2 can be determined by applying RF pulses 102 of different durations (and or magnitudes) as excitation pulses. The effect of these RF pulses 102 is to excite the signal preferentially from long T_2 components within the imaged volume, which (if appropriate pulses and appropriate repetition times are used) can then be used as a T_2 weighting mechanism.

There are also a number of methods of determining T_1 . One such method is to acquire a succession of images using one of the pulse sequences described above but varying the flip angle ϕ of the magnetisation vectors or the time TR between repetitions. In these circumstances the signal intensity S, ignoring the exponential decay due to T_2 effects is proportional to $\sin\alpha(1 - \exp(-TR/T_1))/(1 - \cos\beta\exp(-TR/T_1))$ wherein α and β are both functions of T_2 . For an ideally short RF pulse, β and α in the above expression equal ϕ , this is however not generally the case. Given knowledge of the RF pulse and the T_2 of the sample, α and β can be determined for any ϕ and thus T_1 can be determined from fitting signal intensity to the above expression. Fitting signal intensity to the above expression can also be used to determine the density of phosphorus within the imaged volume.

Alternatively T_1 can be determined by applying additional RF pulses 102 to the object to be imaged prior to acquisition of RF signals (with or without additional magnetic field gradients). This removes effects due to transverse components of magnetisation from the signal. Thus the signal intensity, ignoring the exponential decay due to T_2 effects, is proportional to $\sin\alpha(1 - \exp(-TR/T_1))$ and thus T_1 can be determined from fitting signal intensity to this expression.

In addition to the previously mentioned method, if T_1 and T_2 are known phosphorus density can be determined by using a TR which is more than five times as long as T_1 . In such cases, the signal intensity is directly proportional to the density of phosphorus in the imaged volume of the object. It is also possible to use a TR of less than five times T_1 and calculate the phosphorus density using an appropriate correction.

A further possible application of these fast TE imaging pulse sequences is to manipulate the magnetisation of protons using RF pulses and then observe the transfer of magnetisation from the protons to phosphorus. This will provide information about the interaction of phosphorus with protons (predominantly part of the water content of the bone) within the bone.

Images such as provided by the above pulse sequences may be used for research, teaching, diagnosis, assessment of treatment or any other purpose requiring information as to the spatial distribution of phosphorus nuclei in a bone or the mineral density of a bone. It may be helpful to combine images of phosphorus distribution in bones with traditional dark bone proton imaging and an ultra short TE proton scan. Furthermore, measuring variation in the T_1 or T_2 of the phosphorus content in a bone or examining the bone mineral density within a bone provides a useful indication as to the condition of a bone.

The above methods provide a useful means of diagnosing or monitoring a number of conditions which cause variation in the density or other properties of bone such as osteoporosis, osteomalacia, renal osteodystrophy, osteogenesis imperfecta, fibrous dysplasia, rickets, osteosarcoma, thalassemia and sickle cell disease, osteomyelitis.

It is of course to be understood that the invention is not to be restricted to the details of the above embodiment which is described by way of example only. The invention is further described in the article by Robson *et al*, (2004 Magnetic Resonance in Medicine 51, p888-892), the content of which is incorporated herein by reference.

Claims

1. A method of obtaining information relating to the distribution of phosphorus nuclei within an object, the method comprising the steps of:

applying a magnetic field to the object;

applying an RF electromagnetic pulse to the object, the RF pulse flipping the magnetization vector of the phosphorus nuclei through a desired angle;

subsequently applying a magnetic field gradient to the object, the field gradient rising to a desired value, remaining at the desired value for a particular time period then declining;

acquiring RF signals emitted by the nuclei in response to the RF pulse and the applied magnetic field gradient, the RF signals being acquired in the interval between the beginning of the magnetic field gradient rise and the end of the magnetic field gradient decline; and

processing the acquired signals in order to obtain information about the distribution of phosphorus nuclei within the object.

2. A method according to claim 1, wherein signal acquisition commences 70 μ s or less after the completion of the RF pulse.
3. A method according to claim 1 or 2, wherein signal acquisition ends before the magnetic field gradient starts to decline.
4. A method according to any of the preceding claims, wherein the acquired signal is digitised using a sampling rate of between 1 μ s and 64 μ s per point, preferably 2-8 μ s per point and most preferably 4 μ s per point.
5. A method according to any of the preceding claims, wherein the maximum value of the applied field gradient is between 10mT/m and 200mT/m with a particularly preferred maximum value being 40mT/m.

6. A method according to any of the preceding claims, wherein the time taken for the gradient to rise to its maximum value, the ramp time, is substantially $220\mu\text{s}$.
7. A method according to any of the preceding claims, wherein the frequency of the RF pulse is chosen to be that resonant with the Larmor frequency of phosphorus at the particular steady field applied to the object.
8. A method according to any of the preceding claims, wherein the RF pulse length is in the range $100\mu\text{s}$ - 1ms and is most preferably $200\mu\text{s}$.
9. A method according to any of the preceding claims, wherein the RF pulse is optimised to flip the magnetisation vector of the phosphorus nuclei through an angle of between 1 and 90° , the angle most preferably being 12° .
10. A method according to any of the preceding claims, wherein a programmable computer is used to control the application of magnetic field gradients and RF pulses to the object to be imaged, the programmable computer processing the signals acquired from the object and being used to control the application of magnetic field gradients and RF pulses to the object and to process the signals acquired from the object.
11. A method according to any of the preceding claims, wherein a sequence of RF and magnetic field gradient pulses is repeated a number of times, with magnetic field gradient pulses of varied magnitude and/or direction.
12. A method according to claim 11, wherein if a three-dimensional image of the object or a selected slice of the object is to be obtained, the magnetic field gradient pulse is a composite field gradient comprising three substantially mutually orthogonal components.

13. A method according to claim 11, wherein if a two-dimensional image of a selected slice of the object is to be obtained the field gradient is parallel to the plane of the selected slice and is a composite field gradient comprising two substantially mutually orthogonal components each being parallel to the plane of the selected slice.
14. A method according to claim 12 or 13, wherein the pulse sequence is repeated with the magnitude of each component of the pulse being varied stepwise in turn between a maximum positive value and a maximum negative value, the repetition of the sequence with magnetic field gradients in a variety of different directions corresponding to sampling along a series of radial lines in reciprocal or K-space, the orientation of the lines in K-space corresponding to the direction of the field gradients.
15. A method according to claim 14, wherein the time TR between pulse repetitions is in the range 50ms to 32s.
16. A method according to claim 14 or 15, wherein to obtain a two dimensional image of a selected slice of the object, two dimensions of K-space are sampled, the pulse sequence being repeated with a series of different magnetic field gradients, the directions of which all lie parallel to the plane of the slice, this corresponding in K-space to sampling along a series of lines radiating from the origin, confined to a single plane.
17. A method according to claim 16, wherein there is equal angular separation between successive magnetic field gradient directions and hence successive sampling lines in K-space.
18. A method according to claim 17, wherein the number of different gradient vectors applied to the object to be imaged is in the range 32-512 and is most preferably 128.

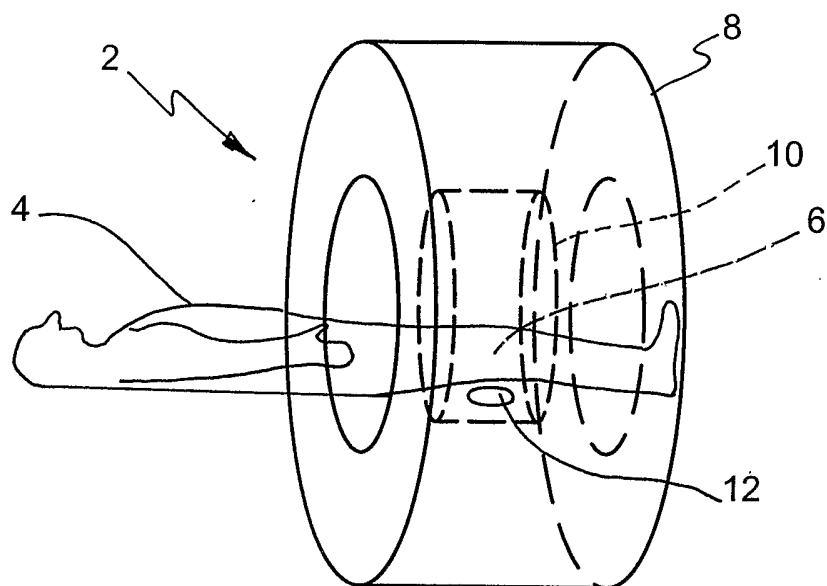
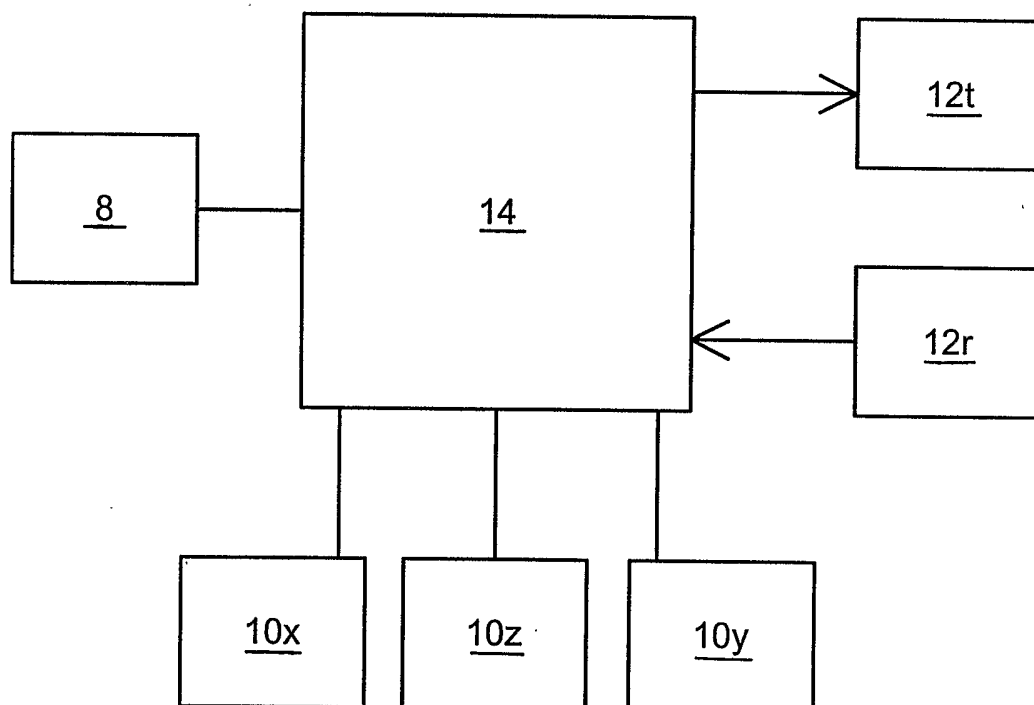
19. A method according to claim 14 or 15, wherein to obtain a three dimensional image of the object or a selected slice of the object, three dimensions of K-space are sampled, the pulse sequence being repeated with a series of different magnetic field gradient directions.
20. A method according to claim 19, wherein successive field gradient directions have substantially equal angular separation, the magnetic field gradients not being confined to directions parallel to a selected slice, this corresponding to a series of samples along radial lines in K-space, the lines extending in all three dimensions from the origin and having substantially equal angular separation therebetween.
21. A method according to any of claims 14 to 20, wherein the points sampled in K-space are regridded onto a rectilinear grid to compensate for acquiring of signals during the rising portion of the field gradient pulses, the regridding providing a reciprocal image of the object, after which the reciprocal image is Fourier transformed to provide an image of the selected slice.
22. A method according to claim 21, wherein the regridding is interpolation onto a grid and then division by the Fourier transform of the interpolation kernel.
23. A method according to any of the preceding claims, wherein the method further comprises applying a slice selecting magnetic field gradient pulse, for selecting the particular slice of the object which is to be imaged.
24. A method according to claim 23, wherein the slice selecting pulse comprises a substantially linearly increasing field gradient rising to a desired maximum value and staying substantially constant for a particular time period before decreasing substantially linearly.

25. A method according to claim 24, wherein the RF pulse is applied substantially simultaneously with the period of time for which the slice selecting magnetic field gradient pulse is constant.
26. A method according to claim 23, 24 or 25, wherein the slice selecting gradient pulse is used to select a single slice of thickness 2-200mm and most preferably used to select a slice of thickness 20-60mm.
27. A method according to any of claims 23 to 26, wherein signals acquired from each stepwise variation of the field gradients are averaged together with signals acquired using a reversed slice selecting gradient pulse.
28. A method according to any of claims 23 to 27, wherein the slice selecting gradient is applied in a direction parallel to one of the field gradient components if a three dimensional image of a slice is desired and preferably in a direction orthogonal to the plane of the slice.
29. A method according to any of claims 23 to 27, wherein to obtain two dimensional images of a slice, a slice selecting gradient is applied in a first direction and the field gradient is comprised of two components orthogonal to the slice selecting gradient.
30. A method according to any of the preceding claims, wherein the object to be imaged comprises a bone and most preferably comprises a human or animal bone.
31. A method according to claim 30, wherein the method is applied to determining T_1 and T_2 for the phosphorus content in a bone or in a selected slice of bone.
32. A method according to claim 31, wherein T_2 is determined by repeating the method of claim 1 a number of times using different time intervals between the completion of the RF pulse and the start of the acquisition of signals, T_2 then being determined by fitting the intensity of signal acquired to an exponential decay.

33. A method according to claim 31, wherein T_2 is determined by applying a number of RF pulses of different durations and or magnitudes to the object to be imaged to either suppress or preferentially excite components with long T_2 and thus act as a T_2 weighting mechanism.
34. A method according to claim 31, wherein T_1 is determined by repeating the method of claim 1 with a variety of different magnetisation vector flip angles and a variety of different repetition times TR.
35. A method of diagnosing or monitoring a bone disease by utilising the method of any of claims 1 to 34 to image the phosphorus content of a bone.
36. A method according to claim 35, comprising diagnosis or monitoring of a condition selected from the group consisting of: osteoporosis; osteomalacia; renal osteodystrophy; osteogenesis imperfecta; fibrous dysplasia; rickets; osteosarcoma; thalassemia and sickle cell disease; and osteomyelitis.
37. Magnetic resonance imaging apparatus having a means for applying a magnetic field to an object, means for applying a magnetic field gradient to the object, means for transmitting an RF signal to the object and means for receiving an RF signal from the object, and control means adapted to apply a pulse sequence to the object and to acquire and to process signals according to the method of any of the preceding claims.
38. Apparatus according to claim 37, wherein the means for applying a magnetic field to an object are constituted by three coils adapted to apply field gradients in mutually orthogonal directions.

39. Apparatus according to claim 37 and 38, wherein the means for transmitting and receiving RF signals are coils, there being separate coils for transmitting and receiving signals.

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*Fig. 1**Fig. 2*

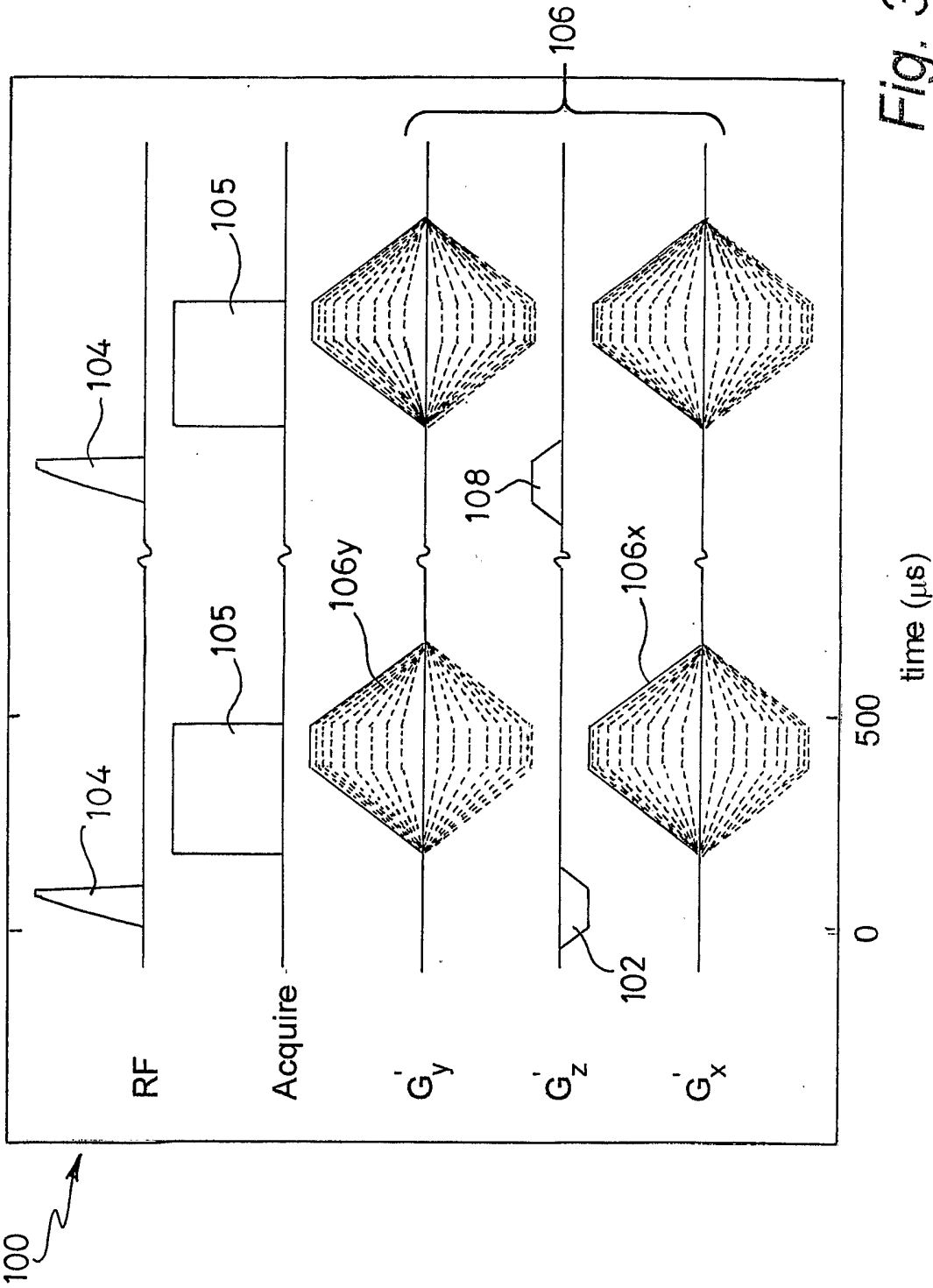


Fig. 3

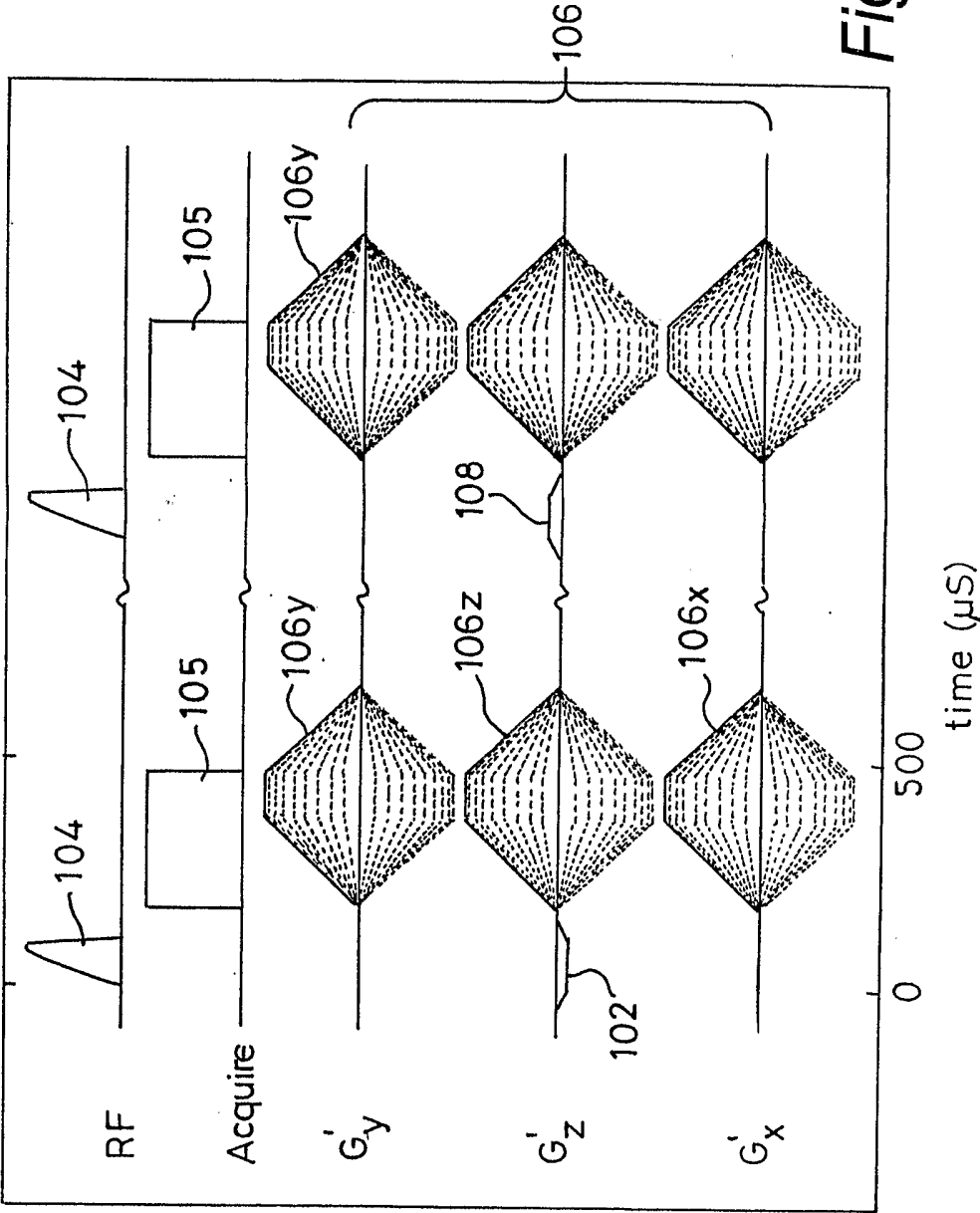


Fig. 4

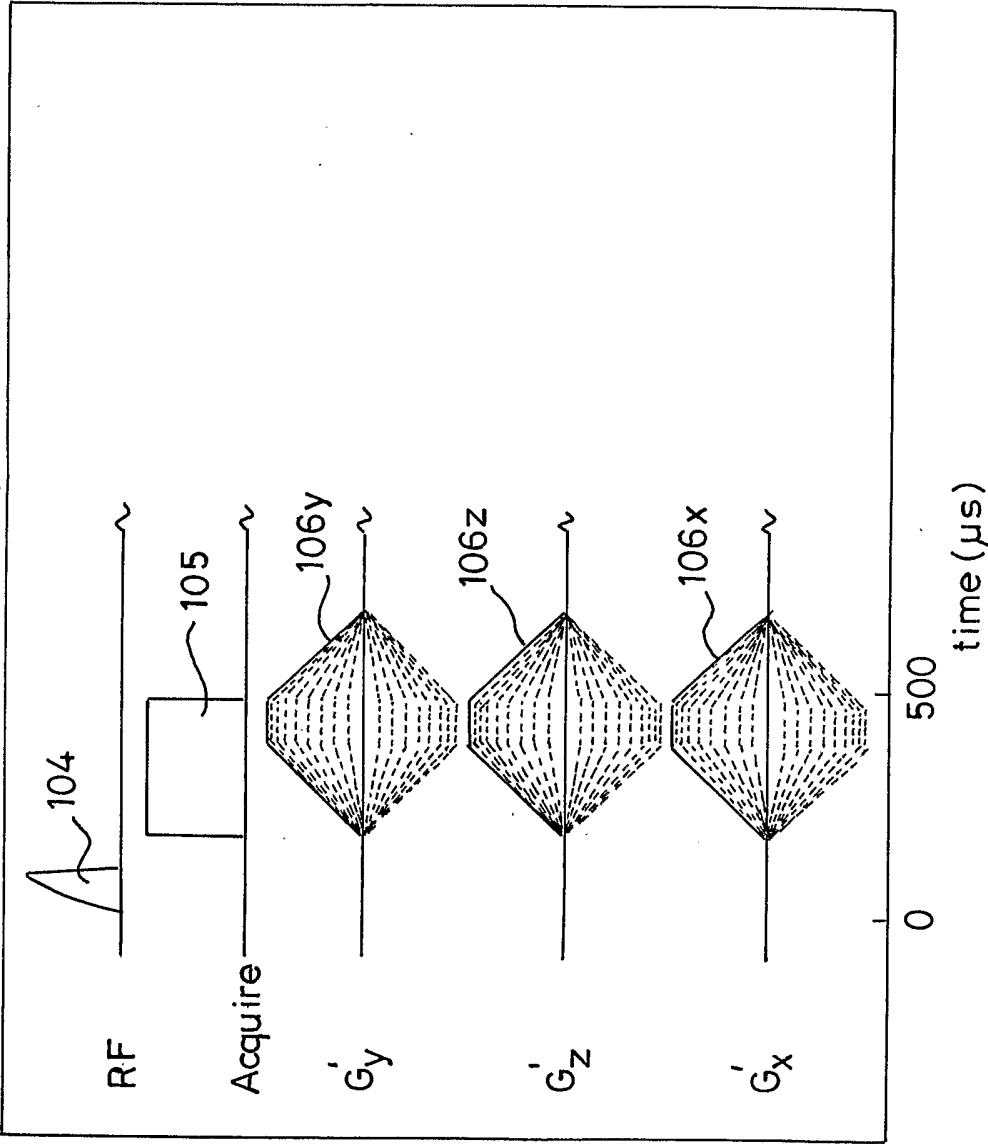


Fig. 5

INTERNATIONAL SEARCH REPORT

International Application No
/GB2004/001717

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01R33/54

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 G01R

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, MEDLINE, INSPEC, EMBASE, BIOSIS, COMPENDEX, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WU Y ET AL: "Multinuclear solid-state three-dimensional MRI of bone and synthetic calcium phosphates." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA. 16 FEB 1999, vol. 96, no. 4, 16 February 1999 (1999-02-16), pages 1574-1578, XP002288081 ISSN: 0027-8424 the whole document ----- -/-	1-39

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents:

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P document published prior to the international filing date but later than the priority date claimed

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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

13 July 2004

Date of mailing of the international search report

28/07/2004

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INTERNATIONAL SEARCH REPORT

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/GB2004/001717

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BERGIN C J ET AL: "Lung parenchyma: projection reconstruction MR imaging." RADIOLOGY. JUN 1991, vol. 179, no. 3, June 1991 (1991-06), pages 777-781, XP009033519 ISSN: 0033-8419 the whole document	1-39
A	MOORE J R ET AL: "Solid state phosphorus-31 magnetic resonance imaging of bone mineral" MAGNETIC RESONANCE IN MEDICINE, vol. 33, no. 3, March 1995 (1995-03), pages 293-299, XP002288115 USA ISSN: 0740-3194 the whole document	1-39
T	ROBSON MATTHEW D ET AL: "Human imaging of phosphorus in cortical and trabecular bone in vivo." MAGNETIC RESONANCE IN MEDICINE : OFFICIAL JOURNAL OF THE SOCIETY OF MAGNETIC RESONANCE IN MEDICINE / SOCIETY OF MAGNETIC RESONANCE IN MEDICINE. MAY 2004, vol. 51, no. 5, May 2004 (2004-05), pages 888-892, XP002288082 ISSN: 0740-3194 the whole document	1-39
A	GOLD G E ET AL: "MR spectroscopic imaging of collagen: tendons and knee menisci." MAGNETIC RESONANCE IN MEDICINE : OFFICIAL JOURNAL OF THE SOCIETY OF MAGNETIC RESONANCE IN MEDICINE / SOCIETY OF MAGNETIC RESONANCE IN MEDICINE. NOV 1995, vol. 34, no. 5, November 1995 (1995-11), pages 647-654, XP002288083 ISSN: 0740-3194 chapter "MATERIALS AND METHODS"	1