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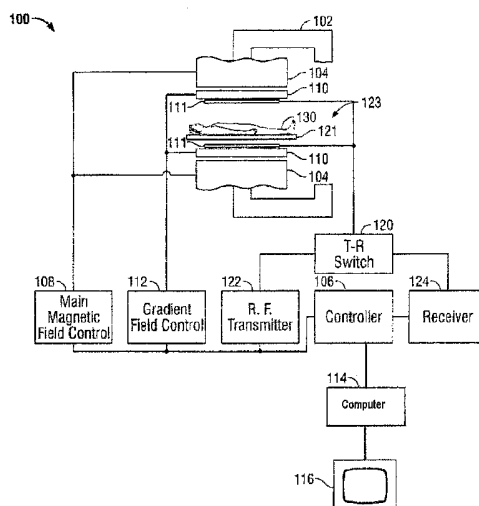
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(54) Title: VARIABLE DIFFUSION-TIME MAGNETIC RESONANCE-BASED SYSTEM AND METHOD



(57) Abstract: A computer-implemented diffusion magnetic resonance (diffusion-MR) method analyzes biological tissue by detecting diffusion in tissue (130). A disordered media model for modeling scaling laws of diffusion in the tissue (130) is provided, where the geometry of the tissue is modeled as disordered media. MR diffusion data is collected from the tissue (130) using an MR system (100). The MR diffusion data can be acquired from the tissue (130) at an arrayed plurality of different diffusion times and diffusion gradient strengths. At least one scaling law parameter relating to the tissue (130) is calculated using a computer or processor (114) by applying the model to the MR diffusion data. The calculated scaling laws can be used to create new contrast mechanisms in MR imaging that can detect changes in tissue microstructure and improve the sensitivity and specificity of MR studies for clinical patients.

VARIABLE DIFFUSION-TIME MAGNETIC RESONANCE-BASED SYSTEM AND METHOD

FIELD OF THE INVENTION

[0001] The invention relates to nuclear magnetic resonance (NMR) and, more particularly, to a method and system for measuring the scaling characteristics of molecular diffusion and for generating images related thereto.

BACKGROUND OF THE INVENTION

[0002] NMR spectroscopy is a well-established technique that has been used to infer information regarding chemical and structural environments. Localized NMR spectroscopy is a technique where a NMR signal is detected from a single volume in space. Magnetic resonance (MR) imaging (MRI) is a method that enables the assignment of different NMR signal values to different locations in space.

[0003] Using MRI it is possible to distinguish regions of biological tissue with different local environments based on the differences in their MR characteristics leading to "contrast" in MR images. Different MR-based parameters may yield different contrast mechanisms hence different information regarding the local environment. Commonly used MR parameters are the proton density, longitudinal relaxation time (T_1), and transverse relaxation time (T_2). It is also possible to create contrast based on the motion, such as flow and diffusion, of molecules within tissue.

[0004] Diffusion magnetic resonance spectroscopy, localized magnetic resonance spectroscopy, and magnetic resonance imaging (diffusion MRI) are based on measuring the diffusion of molecules in biological tissues. Following an ischemic injury (or "stroke"), energy failure in brain cells decreases the function of cellular membrane pumps that maintain

normal ion gradients (e.g. Na^+/K^+ ATPase). Because water passively follows ion gradients, this change leads to changes in water compartmentation that affect water diffusion behavior in the ischemic tissue. The resultant areas of restricted diffusion are detectable by diffusion weighted methods including diffusion weighted magnetic resonance (MR) methods. This finding is identifiable much earlier after a stroke than findings relying on CT or conventional MRI, making diffusion-weighted imaging (DWI) a very useful method for the early detection of stroke. Diffusion MRI has become a useful, frequently-employed clinical imaging modality for the noninvasive detection of disease in human patients, such as for acute detection of ischemic stroke.

[0005] Diffusion MRI is also a tool to study connections in a variety of tissue, including brain tissue. In an isotropic medium, such as inside a container of water, water molecules naturally move according to random Brownian motion. In biological tissues, however, the diffusion is very often anisotropic. For example a molecule inside the axon of a neuron has a low probability to cross a myelin membrane. Therefore the molecule will move principally along the axis of the neural fiber. Conversely if it is observed that molecules locally diffuse principally in one direction it can be assumed that this corresponds to a set of fibers. Identifying fibers on diffusion MRI is called tractography.

[0006] Diffusion weighted MR measurements can be performed in a controllable way by the introduction of a pair of magnetic field gradients to the common MR pulse sequences. When these diffusion gradients are embedded in a spin-echo based method, the technique is called pulsed gradient spin echo (PGSE) (See E. O. Stejskal, and J. E. Tanner, J. Chem. Phys., 42, 288, (1965)). More generally, when the diffusion gradients are employed in pulse sequences including spin echo based ones and others, such as stimulated echo based methods, the technique is called the pulsed field gradient (PFG) method.

[0007] PFG based methods provide an experimental tool to investigate the dependence of the MR signal on the diffusion sensitizing gradient strength (G), diffusion gradient pulse duration (δ) and time between the application of the two pulses (Δ). The sensitivity of the MR measurements to variations in these parameters has been used to infer structural information from the observed sample. One way to characterize the diffusional process from PFG based methods is to calculate diffusivity (or diffusion coefficient), which is related to the mobility of the diffusing molecules.

[0008] Q-space NMR is a spectroscopy and imaging modality that enables the measurement of displacement probabilities noninvasively. Using this approach, the signal is observed at a plurality of q values, where q is a quantity proportional to δ , and G . The Fourier transform of the resulting array of signal values gives the average displacement probabilities (also called average propagators) of the molecules in space. When a one-dimensional Fourier transform is taken, the projection of the average probability density onto the axis defined by the gradient direction is obtained.

[0009] In most studies involving diffusion weighted MR the time parameter Δ , that is related to the time over which diffusion is observed, is held constant. The diffusion time dependence of MR-based parameters have been observed in porous media in the short diffusion time regime (see M. D. Hürlimann, L. M. Schwartz, P. N. Sen, Phys. Rev. B, 51:14936-14940, 1995), (L.L. Latour, P. P. Mitra, R. L. Kleinberg, C. H. Sotak, J. Magn. Reson. A, 101:342-346, 1993). These studies generated quantities such as surface-to-volume ratio from the short diffusion time behavior of the MR signal. These studies lack any consideration regarding the scaling behavior of the diffusional process.

[0010] Although available diffusion MRI contrast mechanisms generally provide sensitive detection of acute brain injury and other neuropathologies, they are often unable to distinguish particular disease processes that need to be treated differently, such as a tumor

from edema. What is needed is new MRI diffusion contrast mechanisms that provide better specificity for particular disease processes and thus, improve the utility of diffusion MRI systems for evaluating clinical patients.

SUMMARY OF THE INVENTION

[0011] An object of the present invention is to quantify different scalar measures, namely walk dimension and spectral dimension that characterize the diffusional scaling behavior of MR signal in time. A further object of the present invention is to provide new MR imaging and spectroscopy modalities that use information contained in the diffusion time dependence of diffusion weighted MR signals.

[0012] A method and system for measuring the scaling laws for diffusion of spin-labeled nuclei is described herein. A pulse sequence is applied using an NMR spectrometer or imager to a sample within the NMR apparatus for generating NMR signals from which the scaling laws of diffusion can be calculated. The MR diffusion data is preferably acquired from the tissue at an arrayed plurality of different diffusion times and diffusion gradient strengths. A computer-implemented diffusion magnetic resonance (diffusion- MR) method analyzes biological tissue by detecting diffusion in the tissue. A disordered media model for modeling scaling laws of diffusion in the tissue is provided.

[0013] Details regarding a suitable disordered media model can be found in various papers regarding random motion within disordered systems which have been theoretically studied in the field of physics. It has been shown that disordered structures can be regarded as random fractals where diffusion in these structures can be anomalous (D. Ben Avraham, S. Havlin, Diffusion and Reactions in Fractals and Disordered Systems, Cambridge University Press, 2000, pp. 312, ISBN 0-521-62278-6). Surprisingly, the model disclosed by D. Ben Avraham et al. has been successfully used by the inventors with the claimed invention. MR

observation of this theory has also been performed on simple controlled systems such as percolation clusters (A. Klemm, R. Metzler, and R. Kimmich. *Phys Rev E*, 65(2): 021112, 2002). In this work, the authors quantify the scaling laws of diffusion in percolation clusters through NMR experiments. Neither D. Ben Avraham et al. nor A. Klemm et al. disclose or suggest applying their disordered media model to biological tissues or using it as part of a diagnostic tool.

[0014] A characterization of anomalous diffusion in a variety of tissue samples have been suggested by quantifying the asymptotic behavior of the signal attenuation as the diffusion sensitizing gradients get large (M. Köpf, C. Corinth, O. Haferkamp, and T. F. Nonnenmacher. *Biophys J*, 70: 2950–2958, 1996) (M. Köpf, R. Metzler, O. Haferkamp, and T. F. Nonnenmacher. *Fractals in Biology and Medicine*, Vol. 2, Birkhäuser). This way, the authors calculate the fractal dimension. However, the authors felt that this kind of an approach is not clinically feasible because of the very high gradient strengths required.

[0015] Calculated MR characteristics are preferably visualized on double logarithmic plots where diffusion time (or a function of the diffusion time) is displayed on one axis. At least one quantity describing the scaling behavior is calculated using the computer by applying the MR diffusion data to the model. The quantities that describe the scaling behavior of diffusion may be related to the microstructure of the medium. Spatial images of these quantities describing the scaling behavior of the underlying diffusion can be produced and can be related to other structural characteristics within each voxel. Diffusion data obtained using measurements performed—at different diffusion times—are plotted, including the option of a single curve, such that at least one of the axes correspond to quantities that are calculated through the incorporation of at least one scaling parameter obtained. Measurement of the diffusion scaling laws may also be employed in calibrating the NMR apparatus itself.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] There are shown in the drawings embodiments which are presently preferred, it being understood, however, that the invention can be embodied in other forms without departing from the spirit or essential attributes thereof.

[0017] Figure 1 shows a block diagram of an exemplary system, including an MR device and a computer, that can be used in performing methods of the present invention.

[0018] Figure 2 shows the entire diffusion-weighted spectroscopy data set in the form of a scanned image obtained from an excised human brain tissue with glioblastoma multiforme tumor. A histogram equalization procedure and interpolation was performed for display purposes.

[0019] Figure 3 shows scanned diffusion weighted scanned images from an excised rat hippocampus with varying q-value and diffusion time. The first 6 time points were included in the horizontal axis, where every other image from the first 14 q-values are included in the vertical axis.

[0020] Figure 4(a)-(d) shows various fits used in the estimation of the walk dimension (d_w). Panel a demonstrates the variation of the mean square displacements along the gradient direction with increasing diffusion times. Panel b shows direct fits of a model to the signal attenuation values (given by the signal values divided by the signal at $q=0$) when the q-value is kept constant. In panel c, the dependence of the radial mean square displacements on diffusion time are shown. Panel d shows the constant signal attenuation curves in the low-q regime overlaid on an image formed from signal attenuation values. Panels a, b and d show results from spectroscopy experiments whereas to produce panel c, the imaging data set obtained from an excised rat hippocampus was used. The regions-of-interest (ROIs) specified on a slice of this scanned image is shown in the inset of panel c.

[0021] Figure 5 shows the dependence of the return-to-origin-probabilities on diffusion time observed in spectroscopy (panel a) as well as imaging (panel b) data sets. These fits were used in the estimation of d_s .

[0022] Figure 6 shows the diffusion time dependence of the probability density for the particles to undergo no net displacement along the z-axis. These fits were used in the estimation of d_s' .

[0023] Figure 7 shows the signal attenuation values obtained from the spectroscopy experiment performed on the human gray-matter sample and a model function fitted to extrapolate these signal values.

[0024] Figure 8 shows scanned images depicting the scaling exponents d_w, d_s and apparent fractal dimension d_f from a slice of the imaging data set obtained from the excised rat hippocampus calculated on a voxel-by-voxel basis.

[0025] Figure 9 shows the average water displacement probability density functions with varying diffusion times (panel a) computed from the normal gray matter sample. The same data points were plotted in a different way in panel b, incorporating the scaling behavior characterized by the exponents d_w, d_s' and d_f' . Panel c shows the same data points when another scaling that employs only the exponent d_w was used. The probabilities shown in this figure are obtained through a one dimensional Fourier transform.

[0026] Figure 10 shows the average probability density values obtained using a Fourier sine transform that yields the probability densities in three dimensional space. The collapse of the curves of panel a as demonstrated in panel b was obtained using the scaling exponents d_w, d_s and d_f . The signal values were taken from an ROI in the imaging data set.

DETAILED DESCRIPTION OF THE INVENTION

[0027] In one embodiment of the invention a computer-implemented diffusion magnetic resonance (diffusion-MR) method analyzes biological tissue by detecting diffusion in the tissue. A disordered media model for modeling scaling laws of diffusion in the tissue is provided, where a geometry of the tissue is modeled as disordered medium and a diffusion process inside the disordered media is modeled as anomalous. MR diffusion data is collected from the tissue using an MR device. At least one scaling parameter relating to the tissue is estimated using the computer by applying the MR diffusion data to the model. The MR diffusion data is preferably acquired from the tissue with an arrayed plurality of different diffusion times and diffusion gradient strengths.

[0028] The MR diffusion data can be collected using magnetic resonance spectroscopy, localized magnetic resonance spectroscopy, or magnetic resonance imaging (MRI). Data signals associated with different ones of the plurality of diffusion times correspond to different length scales for the diffusional process in the tissue being imaged.

[0029] The scaling law parameter(s) can be calculated using a variety of methods. For example, methods include q-space analysis (including functional fits, estimation of derivatives or computation of integrals), direct parameterization of raw signal acquisition, or fractional differential equations.

[0030] Definitions: Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by a person having ordinary skilled in the art to which this invention belongs. As used herein, the following terms have the meanings ascribed to them unless specified otherwise.

[0031] As used herein, the terms "computer" and "processor" are used in their broadest general contexts and incorporate all such devices. The methods of the invention can be practiced using any computer/processor and in conjunction with any known software or

methodology. For example, a computer/processor can be a conventional general-purpose digital computer, e.g., a personal "workstation" computer, including conventional elements such as microprocessor and data transfer bus. The computer/processor can further include any form of memory elements, such as dynamic random access memory, flash memory or the like, or mass storage such as magnetic disc optional storage.

[0032] As used herein, the term magnetic resonance (MR) device incorporates all devices capable of magnetic resonance spectroscopy, MR imaging or equivalents. The methods of the invention can be practiced using any such device, or variation of an MRI device or equivalent, or in conjunction with any known MRI methodology. In magnetic resonance methods and apparatus a static magnetic field is applied to a tissue or a body under investigation in order to define an equilibrium axis of magnetic alignment in a region of interest. A radio frequency field is then applied to that region in order to excite magnetic resonance in the region. When spatial information is desired, carefully designed sequences of magnetic field gradients are applied that make localized MR spectroscopy and MR imaging possible. The resulting signals are detected by radio-frequency coils placed adjacent the tissue or area of the body of interest.

[0033] Figure 1 is a block diagram of an exemplary system that may be useful in performing methods according to the present invention. The system includes a typical MR device 100 which includes an associated computer 114. As shown, the MR device 100 includes an electromagnet 102, pole pieces 104, a controller 106, a main magnetic field control 108, a gradient coil sub-system 110, a gradient field control 112, a transmit-receive (T-R) switch 120, a radio frequency (RF) transmitter 122, a receiver 124 and an array of detectors 111. In order to image tissue 130, whether in vivo, ex vivo, cultured, or post mortem, the tissue is placed in an opening 123 between the pole pieces 104 on a suitable support 121. The computer 114 of MR device 100 is connected to display device 116. The

display device 116 may be used to view images generated using the inventive method and system. As noted above, and as will be recognized by one skilled in the art, this figure is illustrative of but one MR device useful in the present invention and many varieties may be utilized without deviating from the spirit and scope of the invention.

[0034] The methods of the invention include diffusion-weighted magnetic resonance signal measurement. Briefly, this approach is based on the measurement of Brownian motion of molecules and the capability of nuclear magnetic resonance to quantify diffusional movement of molecules. Diffusion-weighted imaging (DWI) is a method that combines diffusion measurement with MRI. This technique can characterize diffusion properties of spin labeled molecules at each picture element (pixel or voxel) of an image. Properties of the diffusion of spin labeled molecules are related to the chemical and geometrical environments.

Consequently, diffusion imaging can be used to infer information regarding the tissue microstructure (e.g., cellular membranes and large macromolecules) that restrict or hinder the water molecular motion.

[0035] By looking at the time evolution of diffusional characteristics in biological tissue at multiple length scales, it has been discovered that the tissue can be modeled as disordered media and diffusion within disordered media may be anomalous. This new finding provides previously undiscovered information about tissue that can be used to generate data and images from the data have a new contrast based on different mathematical parameters, such as the walk, spectral and apparent fractal dimensions. Further, it has been found that the scaling laws of diffusion in biological tissue can be successfully modeled if tissue is assumed to have a random fractal structure. Based on this finding, it is possible to estimate additional parameters for generating image contrast. These new contrast-mechanisms should provide additional information about tissue microstructure that can improve the clinical specificity

and clinical utility of diffusion MRI for characterizing disease in human patients. As noted above, the method can be practiced *in vitro*, *in vivo*, or *ex vivo*.

[0036] MR system 100 including an MR magnet 102 and its controller 106, including operation software, is configured to collect MR signals from the tissue 130 at a plurality of different diffusion gradients and diffusion times. Such MR signals can be used to characterize anomalous diffusion and the scaling laws of diffusion within particular organs or tissues of human or animal subjects. The computer 114 may contain software that can acquire, organize, analyze and parameterize diffusion using a disordered media model applied to biological tissue.

[0037] The system can be embodied as a magnetic resonance imaging or spectroscopy device 100 and a computer 114 containing software for acquiring, organizing, analyzing and parameterizing diffusion using a disordered media model applied to biological tissue. Applied to diffusion MRI, although current diffusion MRI contrast mechanisms (e.g. diffusivity or anisotropy) can provide sensitive detection of acute brain injury and other neuropathologies, they are often unable to distinguish particular disease processes that need to be treated differently (e.g. tumor from edema). A system according to the invention can provide several new MRI diffusion contrast mechanisms that will provide better specificity for particular disease processes. Thus, the invention can improve the utility of diffusion MRI for evaluating clinical patients.

[0038] By detecting changes in diffusion in a tissue over a plurality of diffusion times and diffusion gradients, the invention provides previously unattainable contrast for detecting changes in the microstructure of those cells and tissues or organs. The methods of the invention also provide methods for monitoring changes in the physiology or the health of a collection of cells or a tissue. These methods can be particularly useful for monitoring the effectiveness of a treatment (e.g. chemotherapy) or a healing process. Contrast-mechanisms

based on this invention should provide additional information about tissue microstructure that may improve the clinical specificity and clinical utility of diffusion MRI for characterizing disease in human patients.

[0039] The invention can be applied to any biological tissue in human, animal or plant subjects (e.g. nervous, cardiac or muscle tissue from rats, mice or humans). The data may be acquired from tissue that is in vivo, ex vivo, in vitro, cultured or post mortem tissue. This application also can be used for simulated tissue or artificial tissue models, such as red blood cell ghosts, tissue slices or cell cultures (with cells originally acquired from biological tissue).

[0040] The invention can also be used to distinguish healthy from pathologically injured tissue. Pathological tissue includes, but is not limited to, cancerous, ischemic, traumatized, chronically-injured or degenerative tissue. This application can also be used to study genetically-altered tissue. This application also can be used to recognize or characterize the similarity of diffusion in tissue substitutes or replacements (such as stem cells, organ transplants or tissue created by 3-D scaffolds) to diffusion in normal, healthy tissue.

[0041] The invention can also be used to calibrate the MR apparatus itself. This is done by measuring the scaling laws of diffusion in simple systems such as free water. In this case, the diffusion process should be normal. Thus, acquisition of a series of diffusion weighted data from such a sample can give accurate information about the accuracy of the gradient timings.

ESTIMATION OF THE WALK DIMENSION

[0042] The walk (or path or trail) dimension, d_w , is defined by the relationship

$$\langle r^2 \rangle \propto t^{2/d_w}, \quad (1)$$

where $\langle r^2 \rangle$ is the mean square displacement (MSD) for the diffusing particles and t is the diffusion time. When $d_w=2$, the diffusion process is considered normal. Otherwise, the

diffusion is anomalous. When $d_w > 2$, the process is called subdiffusion, where as the case $d_w < 2$ corresponds to superdiffusion. The exponent d_w can be measured using magnetic resonance (MR) methods since it is possible to relate the diffusion related MR signal attenuation to the MSD and the MR pulse sequences provide the flexibility to change the diffusion time, for example by adjusting the separation time between the two diffusion gradient pulses. The separation time between the diffusion gradients will be denoted by Δ . The diffusion gradient and diffusion pulse separation are other controllable parameters of the experiment and will be denoted by $\mathbf{G}$ and δ respectively. The magnitude of the gradient vector $\mathbf{G}$ will be denoted by G ($G = |\mathbf{G}|$). The product of $\mathbf{G}$ and δ is related to a particularly useful quantity $\mathbf{q}$ through the relationship $\mathbf{q} = \gamma \delta \mathbf{G} / 2\pi$. Similarly, the magnitude of $\mathbf{q}$ will be denoted by q .

[0043] The ensemble average particle displacement probability density will be denoted by $\bar{P}(\mathbf{r}, \Delta)$, which indicates the probability of particles to move a distance $\mathbf{r}$ in time Δ . This function is related to the MR signal attenuation $E(\mathbf{q}, \Delta)$ through the Fourier transform

$$\bar{P}(\mathbf{r}, \Delta) = \int E(\mathbf{q}, \Delta) e^{-2\pi i \mathbf{q} \cdot \mathbf{r}} d\mathbf{q}. \quad (2)$$

The magnitude of $\mathbf{r}$ will be denoted by r . In isotropic space, the radial moments of the above probability density function are given by

$$\langle r^m \rangle = 4\pi \int_0^\infty \bar{P}(r, \Delta) r^{2+m} dr \quad (3)$$

The MSD is related to the MR signal attenuation through the relationship

$$\langle r^2 \rangle = -\frac{3}{2\pi^2} \lim_{q \rightarrow 0} \frac{\partial \log E(q, \Delta)}{\partial q^2} = 6D(\Delta)\Delta, \quad (4)$$

where $D(\Delta)$ is the diffusion coefficient. Therefore, MSD, can be estimated from the derivative of the logarithm of the signal attenuation at $q=0$. Then using Eq. 1, one may plot the estimated MSD as a function of Δ . On a double logarithmic plane, the data points are

expected to lie on a straight line. The d_w value is expected to be twice the reciprocal of the slope of the line fitted to the data points on the double logarithmic plot.

[0044] The experiment may be performed such that the direction of the diffusion gradients is kept constant, but its magnitude is varied. If the z -axis is defined to be along the direction of the gradient direction, then a projected probability density function can be obtained from the MR signal attenuations through the relationship

$$\overline{P}_1(z, \Delta) = \int E(q, \Delta) e^{-2\pi i q z} dq. \quad (5)$$

In isotropic space, the following relationship between the three dimensional probability and its projection on to the z -axis holds:

$$\overline{P}_1(z, \Delta) = 2\pi \int_z^\infty \overline{P}(r, \Delta) r dr. \quad (6)$$

The moments of this projected probability density function are given by

$$\langle z^m \rangle = \int_{-\infty}^{\infty} \overline{P}_1(z, \Delta) z^m dz. \quad (7)$$

These moments are related to the radial moments of the three dimensional probability density via

$$\langle r^m \rangle = (m+1) \langle z^m \rangle. \quad (8)$$

Therefore,

$$\langle z^2 \rangle = -\frac{1}{2\pi^2} \lim_{q \rightarrow 0} \frac{\partial \log E(q, \Delta)}{\partial q^2} = 2D(\Delta)\Delta. \quad (9)$$

Hence, d_w is also twice the reciprocal of the slope of the line fitted to the data points on the double logarithmic $\langle z^2 \rangle$ vs. Δ plot.

[0045] An alternative to d_w estimation is fitting a model function directly to the data. This approach may make it possible to incorporate the effects of finite pulse duration in the estimation.

[0046] The entire data obtained from an MR spectroscopy experiment or the entire data in a single voxel of an MR image can be visualized on a Δ - q plane. For small values of q , a quadratic dependence of the logarithm of the MR signal attenuation on q is expected. The contours of the data overlaid on a double logarithmic Δ - q plane are expected to be linear when q values are small and are described by the expression

$$\log q = C - \frac{1}{d_w} \log \Delta, \quad (10)$$

where C is a constant. Therefore, the reciprocal of the slopes of the constant signal curves near the Δ -axis are expected to yield d_w .

ESTIMATION OF THE SPECTRAL DIMENSION

[0047] Another scaling exponent that characterizes the scaling behavior of the density of states function for the Laplacian operator in fractal environments is called the spectral (fracton) dimension, which will be denoted by d_s . In the case of diffusion, the return-to-origin probability (RTOP) values obey a power-law given by $\bar{P}(0, t) \propto t^{-d_s/2}$. The exponent d_s can be measured using magnetic resonance (MR) methods since it is possible to relate the MR signal attenuation due to diffusion to the RTOP values. Setting $r=0$ in Eq. 2 yields

$$\bar{P}(0, \Delta) = \int E(\mathbf{q}, \Delta) d\mathbf{q}. \quad (11)$$

In isotropic space, this relation takes the form

$$\bar{P}(0, \Delta) = 4\pi \int_0^\infty E(q, \Delta) q^2 dq. \quad (12)$$

Therefore, a double logarithmic plot of the RTOP values estimated using this integral as a function of diffusion time should yield a line whose slope will be negative of the half of the spectral dimension.

ESTIMATION OF THE EFFECTIVE SPECTRAL DIMENSION

[0048] When the scaling behavior of the projected probability density function $\bar{P}_1(z, \Delta)$ is of interest, it is possible to define an effective spectral dimension d_s' that will characterize the scaling behavior of this function at $z=0$, which yields the integral of the three-dimensional probability values over the entire xy-plane. It is possible to estimate $\bar{P}_1(0, \Delta)$ using the expression

$$\bar{P}_1(0, \Delta) = \int E(q, \Delta) dq \propto \Delta^{-d_s'/2}. \quad (13)$$

Therefore, a double logarithmic plot of the $\bar{P}_1(0, \Delta)$ values estimated using this integral as a function of diffusion time should yield a line whose slope will be negative of the half of the effective spectral dimension.

[0049] The quality of estimation of the integrals in Eqs. 12 and 13 can be improved by various methods like extrapolating the signal values.

ESTIMATION OF THE APPARENT FRACTAL DIMENSION

[0050] In fractal spaces, the fractal dimension (d_f) characterizes the scaling of the mass density of the fractal with changing length scales. The fractal dimension is related to the walk and spectral dimensions through the expression

$$d_f = \frac{d_w d_s}{2}. \quad (14)$$

Therefore, since the estimations of the walk and spectral dimensions are feasible using MR techniques, it is possible to estimate the fractal dimension using this relationship.

[0051] When the scaling characteristics of the projected probability density function is of interest, an apparent effective fractal dimension can be defined using the expression

$$d_f' = \frac{d_w d_s'}{2}. \quad (15)$$

Therefore, the apparent effective fractal dimension can be estimated from the MR signal attenuation values.

AVERAGE DISPLACEMENT PROBABILITY FUNCTIONS AND THEIR COLLAPSE

[0052] The three dimensional average displacement probability density function, $\bar{P}(\mathbf{r}, \Delta)$, for each diffusion time point of the MR experiment can be estimated using Eq. 2. A scheme such as Fast Fourier Transform (FFT) can be employed in the implementation of this transform. When the diffusion gradients are applied along one direction, and the space is isotropic, it is possible to estimate the same probability values using a one dimensional Fourier sine transform:

$$\bar{P}(r, \Delta) = \frac{2}{r} \int_0^{\infty} E(q, \Delta) \sin(2\pi q r) q \, dq. \quad (16)$$

This transform can be computed using various methods such as taking the imaginary part of a Fourier transform.

[0053] The scaling arguments used in the estimations of the scaling exponents imply that a reasonable form of the average probability density function is given by

$$\bar{P}(r, \Delta) \propto \frac{r^{d_f-3}}{\Delta^{d_s/2}} \Phi\left(\frac{r}{\Delta^{1/d_w}}\right), \quad (17)$$

where the argument of the function Φ is necessary for the scaling relation in Eq. 1, the numerator r^{d_f-3} is related to the scaling of the mass of the fractal and the denominator $\Delta^{d_s/2}$ ensures that the probability is normalized. The form of the probability as given in Eq. 17 requires that a plot of $r^{d_f-3} / (\bar{P}(r, \Delta) \Delta^{d_s/2})$ vs. $r / \Delta^{1/d_w}$ should yield the same curves for the

estimated average three dimensional probability density functions corresponding to different diffusion time values.

AVERAGE PROJECTED DISPLACEMENT PROBABILITY FUNCTIONS AND THEIR COLLAPSE

[0054] The one dimensional projection of the three dimensional average displacement probability function on to the axis defined by the gradient direction, $\bar{P}_1(z, \Delta)$, for each diffusion time point of the MR experiment, can be estimated using Eq. 5. A scheme such as Fast Fourier Transform (FFT) can be employed in the implementation of this transform.

[0055] The scaling arguments used in the estimations of the scaling exponents d_w , d_s' and d_f' imply that a reasonable form of the average projected probability density function is given by

$$\bar{P}_1(z, \Delta) \propto \frac{z^{d_f'-1}}{\Delta^{d_s'/2}} \Psi\left(\frac{z}{\Delta^{1/d_w}}\right). \quad (18)$$

Therefore, plots of $\bar{P}_1(z, \Delta) \Delta^{d_s'/2} / z^{d_f'-1}$ functions for different diffusion times vs. $z / \Delta^{1/d_w}$ values should yield the same curves.

[0056] If the form of the three-dimensional displacement probability density function given in Eq. 17 is assumed, then Eq. 6 implies that the form of the projected displacement probability density should be given by:

$$\bar{P}_1(z, \Delta) \propto \frac{1}{\Delta^{1/d_w}} \Psi\left(\frac{z}{\Delta^{1/d_w}}\right), \quad (19)$$

which is a special case of Eq. 18. If Eq. 19 holds, then plots of $\bar{P}_1(z, \Delta) \Delta^{1/d_w}$ vs $z / \Delta^{1/d_w}$ for different diffusion times should coincide.

EXAMPLES

[0057] The following Example section is provided to illustrate, but not to limit the claimed invention.

Spectroscopy Experiments on Excised Human Normal and Tumorous Gray Matter

Samples

[0058] In order to investigate the scaling behavior of the diffusional processes in neural tissue, MR q-space spectroscopy measurements were performed on excised human gray matter tissue samples. One of the samples was a human cerebral cortex tissue from a normal person. The second sample was a tumorous human brain tissue where the type of the tumor was glioblastoma multiforme (or grade-4 astrocytoma). The experiments were performed using a 14.1T Bruker Avance spectrometer. A diffusion-weighted stimulated echo pulse sequence was used. The data from these samples were acquired with TR/TE values of 4s/11ms. The stimulated echo was sampled at 2048 points. A total of 129 q-values were used for each diffusion time. Gradients were applied along all three orthogonal directions simultaneously yielding gradient strengths of up to 4892.5 mT/m. The q-space resolution was $2\mu\text{m}$. The gradient duration (δ) was 2.4ms, and we repeated the q-space measurements 12 times varying the gradient pulse separation (Δ) between 12 and 613ms on a logarithmic scale. Figure 2 shows the entire data set in the form of a scanned image from the tumorous sample. The grayscale intensity in this figure is obtained by applying a histogram equalization procedure and interpolation to the original signal values. In the parameter estimations however, the original signal values.

Imaging Experiments on Excised Rat Hippocampi

[0059] In order to test the performance of the model on MR imaging data obtained from neural tissue, a series of diffusion-weighted MR images were acquired from three excised rat hippocampi with varying diffusion gradient strengths and diffusion times. Prior to imaging, rats were perfusion-fixed with 4% paraformaldehyde in phosphate buffered saline (PBS) (pH 7.4, 300 mOsm/kg). The hippocampi were dissected medially from each hemisphere and immersed in fresh fixative for 8-10 days, then washed overnight in PBS prior to imaging.

Samples were imaged with a 5-mm birdcage coil inside a 600-MHz narrow-bore spectrometer.

[0060] The imaging protocol used a pulsed gradient stimulated-echo pulse sequence with the following parameters: TR=1000ms, TE=12.6ms, resolution=(78×78×500) μm , matrix size=(64×64×3), diffusion gradient pulse length (δ)=2ms. Images were acquired with 33 different diffusion gradient strengths increasing from 0 to 2935mT/m in steps of 91.75mT/m. This created a q-space resolution of 4 μm . This q-space acquisition scheme was repeated for 10 values of diffusion pulse separation (Δ) ranging from 12 to 300 ms on a logarithmic scale. The number of averages were increased from 4 to 15 for increasing diffusion time values in order to produce images with comparable signal-to-noise ratios at different diffusion times. The experiments were performed at 37°C. At this temperature, the probed distance measure as given by $\sqrt{D_0\Delta}$ varied between 6.2 μm to 31 μm . In order to prevent the bias that can be introduced by biological processes that may occur during the course of the experiment, such as autolysis, the ordering of experiments with different Δ values was random. These q-space images for the first 6 time points (left to right) and selected gradient strengths are shown in the form of a scanned image in Fig. 3.

Results

[0061] The diffusion-weighted spectra and images were analyzed to estimate the scaling laws that characterize the diffusion time dependence of the MR signal. For the estimation, theoretical work developed to model the diffusional processes occurring in disordered media and fractal structures was used as described above.

[0062] The estimated scaling exponents obtained from the q-space spectroscopy data are tabulated in Table 1. The estimation of the walk dimension was performed using 6 different schemes. In the constant-q method, the MSD values for particle displacements along the z

direction were computed by discretizing the derivative in Eq. 9. One of the two points used in the estimation of the derivative was the signal value at $q=0$, whereas the second point was obtained from a fixed q -value of 3.905mm^{-1} . In the constant- b method, the b -values (where $b = 4\pi^2 q^2 \Delta$) were kept constant, and the MSD values were estimated similarly from a two point difference of the logarithm of the signal attenuation values as shown in Eq. 9. In the constant- E method, Eq. 10 was fitted to 12 contours of the signal attenuation values in the low- q region. The mean value of the 12 estimations of the walk dimension was reported. The integration method estimated the MSD values by computing the integral given in Eq. 7 with $m=2$ using a five-point Newton-Cotes formula. In the integration with extrapolation method, the signal values were extrapolated by fitting the function

$$E(q, \Delta) = f_1 e^{-uq^2} + f_2 e^{-(vq^2)^\alpha} + f_3 (1 + wq^2)^{-\eta} \quad (20)$$

to the data points and subsequently integrated using the same scheme. Finally a model for the signal attenuation values given in (J. Karger, H.Pfeifer, G.Vojta, Phys Rev A 37 (11) 1988, p.4514-4517) was fitted directly to the signal attenuation values at a q -value of 3.905mm^{-1} .

TABLE 1

	Estimation method	gray matter	tumor
d_w	constant- q	2.371 ± 0.014	2.189 ± 0.029
d_w	constant- b	2.353 ± 0.013	2.188 ± 0.031
d_w	constant- E	2.376 ± 0.285	2.217 ± 0.369
d_w	integration	2.374 ± 0.014	2.183 ± 0.031
d_w	integration with extrapolation	2.394 ± 0.015	2.195 ± 0.028
d_w	model fit	2.353	2.183
d_s	integration	3.166 ± 0.210	1.909 ± 0.091
d_s	integration with extrapolation	3.408 ± 0.283	2.140 ± 0.144

d_s'	integration	0.991 ± 0.008	1.018 ± 0.009
d_s'	Integration with extrapolation	1.018 ± 0.010	1.105 ± 0.012

[0063] For the estimations of d_s and d_s' , the integrals given in Eqs. 12 and 13 were computed using the five point Newton-Cotes formula yielding RTOP and $\bar{P}_1(0, \Delta)$ values respectively. Linear fitting on double logarithmic plots was performed on these probability values to estimate the desired exponents d_s and d_s' . The computations were repeated on extrapolated data where the extrapolation employed Eq. 20 as before.

[0064] Scaling exponents were computed also from the imaging data. Several ROIs on the hippocampi slices were selected, and the scaling behaviors of $P(r=0)$ and $\langle r^2 \rangle$ were characterized using the same techniques. The inset of the plot in Figure 4c is a scanned image showing four (4) such ROIs specified on the hippocampus image. These ROIs correspond to free water (region A), subiculum (region B), the border between granular cell layer and molecular layer (region C) and stratum radiatum from the CA1 region (region D).

[0065] Figure 4(a)-(d) shows the fits obtained when estimating the walk dimension using various techniques. Figure 4(a) shows the fits obtained when the MSD values were computed from projected displacements. Figure 4(c) shows the same from radial displacements. Figure 4(b) shows the fits obtained when a relationship derived in (J. Karger, H. Pfeifer, G. Vojta, Phys Rev A 37 (11) 1988, p.4514-4517) was fitted directly to the data. Figure 4d shows the constant signal attenuation contours overlaid on the entire spectroscopy data set from the tumorous sample. Panels a, b and d in Figure 4 are from the spectroscopy data whereas Figure 4(c) is a scanned image from the imaging data.

[0066] Figure 5 shows the fits used in the estimation of the spectral dimension. Panel a depicts the data from spectroscopy data whereas panel b shows the same for ROIs specified on imaging data.

[0067] Figure 6 shows the average probability density for the particles to undergo no net displacement along the z-axis. The fitted lines were used in the estimations of the effective spectral dimension for the spectroscopy data.

[0068] Figure 7 shows the original spectroscopy data points (in symbols) from the tumor sample and the functional fits (continuous lines) obtained by fitting Eq. 20 to the data. These functional fits were used merely to extrapolate the data outside the range of q-values used in the experiments.

[0069] In Figure 8, scanned images generated by voxel-by-voxel estimations of the scaling exponents on a slice of one of the hippocampus images are shown. The variations of the estimated parameters may be due to structural differences between different regions.

[0070] The water displacement probability density functions computed by taking the one dimensional Fourier transform of the signal values from the normal human gray matter sample are plotted in Fig. 9a. The scaling relations consistent with the form of the probability density function as given in Eq. 18 are used in producing Figure 9b where the scaling exponents d_w , d_s and d_f were used. Another form of scaling relations were used in Figure 9c that used only the exponent d_w . The collapse of the data points onto a single curve demonstrates that these scaling relations successfully characterized the diffusion time dependence of the computed average probabilities.

[0071] A one-dimensional Fourier sine transform was employed to generate the plots provided in Figure 10(a) which is the three dimensional Fourier transform in isotropic space. The curves show the average probability densities in three dimensional space. The spreading of the probabilities and the decay of the peak are clearly seen in this logarithmic plot. In

addition, it was investigated whether the calculated scaling exponents are sufficient to characterize the diffusion process across different time scales. In Figure 10(b), the same data points

were plotted in a different way, where the values of the quantity $r^{d_f-d} / [P(r, \Delta) \Delta^{d_s/2}]$ are shown as a function of $r / \Delta^{1/d_w}$. In this plot all data points from different diffusion times appear to fall on to the same curve. This ‘collapse’ of the displacement probabilities onto a single curve indicates that there is a universal scaling law associated with the observed diffusion which is characterized by the computed scaling laws.

MR DATA ACQUISITION

[0072] Options for MR data acquisition are not limited to the imaging or spectroscopy experiments outlined for the case of excised rat hippocampi and human tissues described above. For example, localized spectroscopy, and related methods can also be employed.

[0073] MR data needed for the derivation of scaling laws can be obtained from diffusion-weighted acquisitions with a plurality of q-values (which can be obtained by changing the gradient strength and/or diffusion pulse length) and a plurality of diffusion times (which can be obtained by changing the diffusion pulse separations and/or diffusion pulse lengths). A particular sampling scheme of the q-space or time axis is not required and many different alternatives could be employed to characterize the scaling behavior of the observed diffusion process in accordance with the present invention. For example d_w can be estimated by sampling only two points on the q-axis for each diffusion time.

[0074] The pulse sequence used can be selected from one of many possibilities such as those utilizing spin echoes, stimulated echoes, gradient echoes, or free induction decays. Also fast imaging techniques such as echo planar imaging can be employed in accordance with the present invention. Data need not be acquired using a pulsed field gradient (PFG) based

technique. Other options, such as constant field gradient experiments and those that are acquired in the fringe field of the MR magnet can also be used in accordance with the present invention.

[0075] The process of computing displacement probabilities for diffusion in tissue involves the evaluation of a transform of the observed signal attenuations. As mentioned previously, the reconstruction scheme described above involved a Fourier sine transform. However, whenever the number of samples of the function in the spectral domain is small and the spectral window is limited, the discrete transform can generate quantities that do not generally yield accurate approximations to the true analytical transform. In order to prevent this from happening, in the analysis described for the experiments on excised rat hippocampi, a Rigaut-type asymptotic fractal expression was fitted to the signal attenuations. Although the numerical fits were quite accurate, other numerical techniques (such as spline interpolations) can be employed that could also provide accurate estimates of the displacement probabilities and scaling laws computed from them. The calculated function from the fitting of the data to the Rigaut-type asymptotic fractal formula was more densely sampled over a wider window along the q -axis. Next, the Fourier- sine transform of the samples of the function $qE(q, \Delta)$ was evaluated by taking the imaginary part of a discrete Fourier transform that was implemented using the Fast Fourier Transform (FFT) algorithm. The resulting function is $rP(r, \Delta)$, so the probabilities are evaluated by dividing the result of the transform by the distance r .

[0076] The estimation of the displacement probabilities can be accomplished in alternate ways that would also lead to accurate estimations of the scaling laws. For data that samples the three-dimensional q -space, a three-dimensional Fourier transform can be evaluated. Another alternative for data sampled along one direction in q -space is that, instead of the Fourier sine transform, one-dimensional conventional Fourier transform can be evaluated as shown on the spectroscopy data sets. In this case the result is the probabilities defined in the

three-dimensional space projected on to the axis specified by the diffusion gradient direction. Next, one can either estimate the probabilities on three-dimensional space by differentiating the result from one-dimensional transform, or one can directly estimate the scaling laws from the one-dimensional transform. All these different alternatives may also be used to derive the scaling laws associated with the observed diffusional processes in accordance with the present invention.

[0077] Scaling laws can be obtained through different techniques. For example, RTOP can be evaluated by integrating the q-space data over the entire q-space without evaluating any transform. Similarly, the MR signal attenuations can be fitted to a function that contains the MSD values as a dependent parameter without the need to evaluate a transform. Then the scaling laws can be obtained in a similar fashion as outlined. Yet another approach is to estimate the scaling laws directly from the MR signal attenuations using analytical solutions of fractional differential equations that are capable of describing the desired scaling behavior. All these different approaches yield estimations of the scaling laws in accordance with the present invention.

[0078] Scalar measures describing the scaling behavior of the observed diffusional processes are not restricted to d_w , d_s , d_s' , d_f and d_f' . Other measures such as those describing the scaling behavior of higher order moments ($\langle r^4 \rangle$, $\langle r^6 \rangle$, etc. and $\langle z^4 \rangle$, $\langle z^6 \rangle$, etc.) can be evaluated in accordance with the invention.

[0079] This invention can be embodied in other forms without departing from the spirit or essential attributes thereof and, accordingly, reference should be had to the following claims rather than the foregoing specification as indicating the scope of the invention.

CLAIMS

We claim:

1. A computer-implemented diffusion magnetic resonance (diffusion-MR) method for analyzing biological tissue by detecting diffusion in tissue, comprising the steps of:

providing a disordered media model for modeling scaling laws of diffusion in said tissue, wherein a geometry of said tissue is modeled as disordered media and a diffusion process inside said disordered media is modeled as anomalous;

collecting MR diffusion data from said tissue, and

calculating using a computer or processor at least one scaling law parameter relating to said tissue by applying said MR diffusion data to said model.
2. The method of claim 1, wherein said MR diffusion data is acquired from said tissue at an arrayed plurality of different diffusion times and diffusion gradient strengths.
3. The method of claim 1, wherein said MR diffusion data is collected in said collecting step using magnetic resonance imaging, magnetic resonance spectroscopy or localized magnetic resonance spectroscopy.
4. The method of claim 1, wherein said scaling law parameter is calculated using q-space analysis, direct parameterization of raw signal acquisition, or fractional differential equations.

5. The method of claim 1, wherein said scaling law parameter comprises at least one selected from the group consisting of walk dimension, spectral dimension, apparent fractal dimension, effective spectral dimension, and effective apparent fractal dimension.

6. The method of claim 2, further comprising the step of imaging said tissue from said MR data collected at said plurality of diffusion times using said computer or processor, wherein different ones of said plurality of said diffusion times correspond to different length scales for diffusion in said tissue.

7. The method of claim 1, wherein said MR diffusion data is collected from tissue that is in vivo, ex vivo, in vitro, cultured or post mortem, simulated, artificial tissue models, tissue slices or cell cultures.

8. The method of claim 1, wherein said MR diffusion data is used to distinguish healthy from pathological tissue, study genetically-altered tissues, tissue substitutes and replacements.

9. The method of claim 1, wherein said scaling laws of diffusion is used to calibrate an MR apparatus used for implementing said method.

10. A diffusion MR-based system for analyzing diffusion in biological tissue, comprising:

a MR device, wherein said MR device projects a sequence of magnetic field gradient pulses and radiofrequency pulses into a tissue sample and collects MR diffusion data from said tissue, said MR device collecting said MR data from said tissue at a plurality of different diffusion times and diffusion gradient strengths, wherein different ones of said plurality of diffusion times correspond to different length scales in said tissue, and

a computer or processor associated with said MRI device, said computer or processor for analyzing said diffusion data collected by said MR device and applying said diffusion data to a disordered media model for modeling scaling laws of diffusion in said tissue, wherein a geometry of said tissue is modeled as disordered media and the diffusion process inside said disordered media is modeled as anomalous, said computer calculating at least one scaling law parameter relating to said tissue by applying said MR diffusion data to said model.

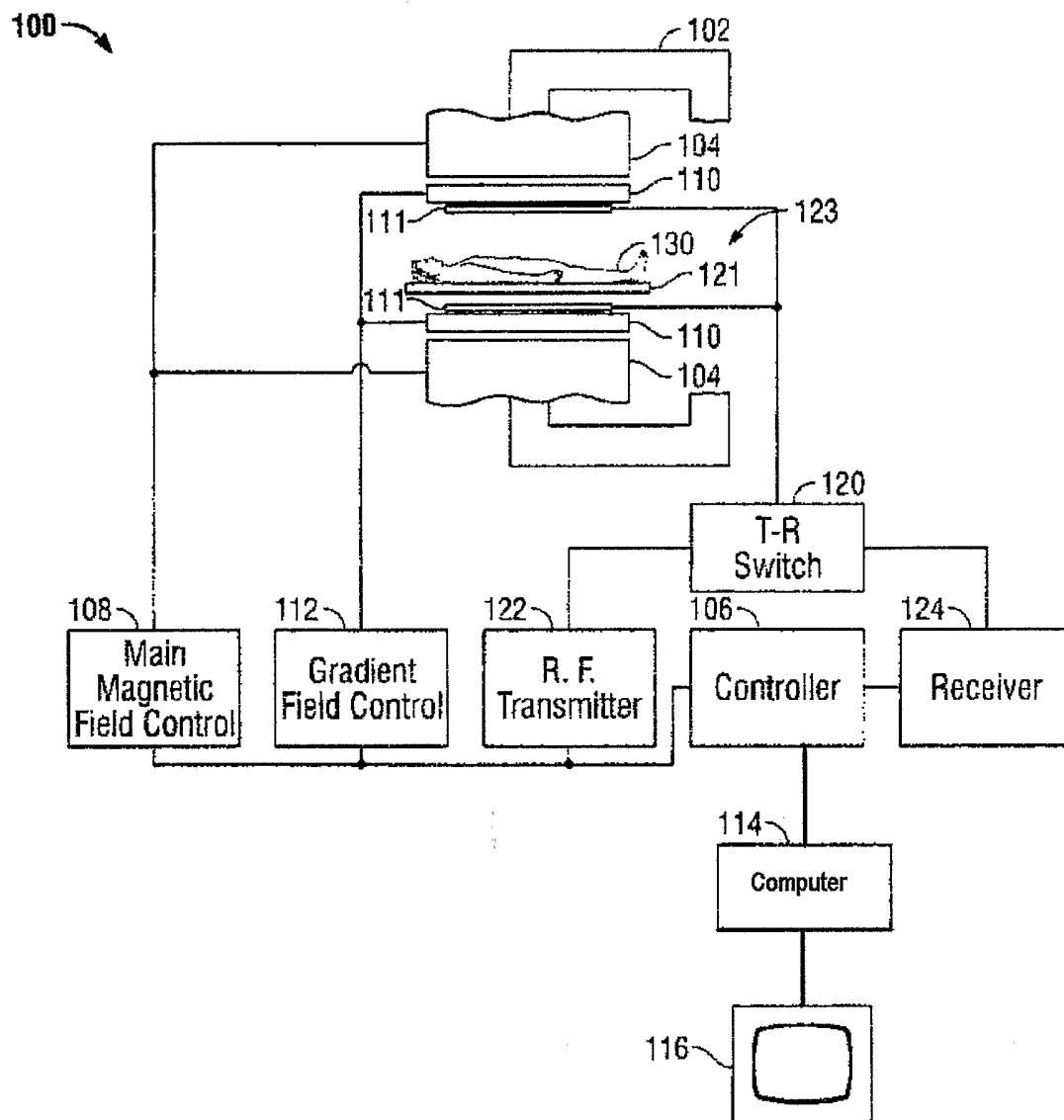


FIG. 1

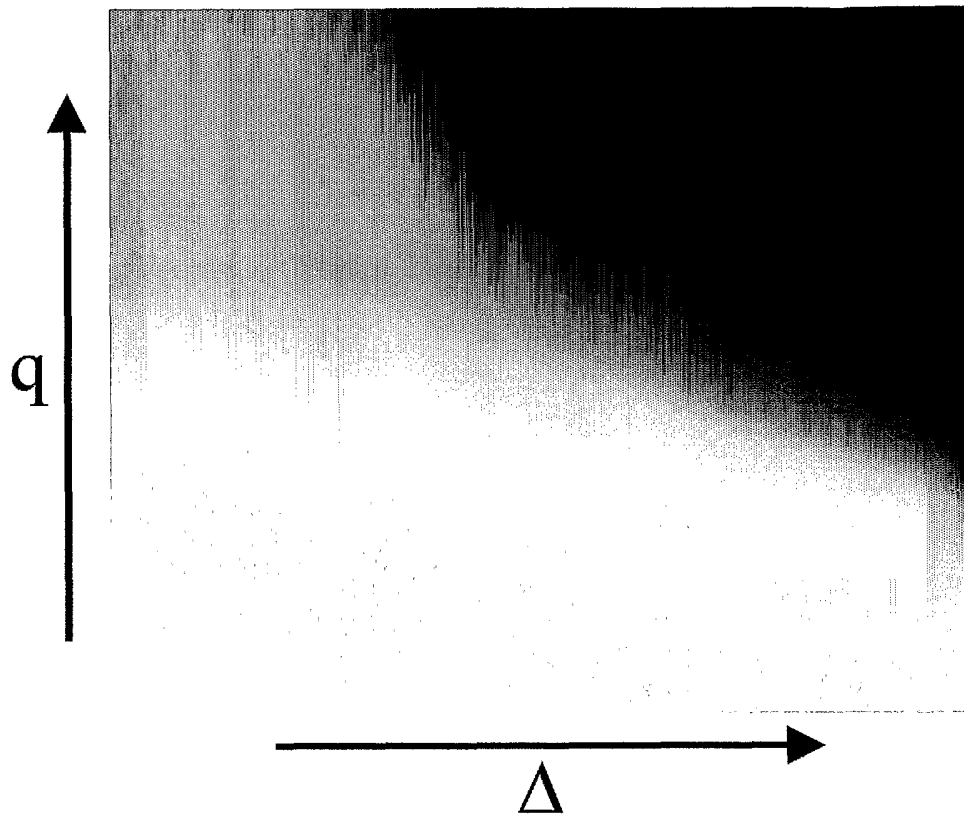


FIG. 2

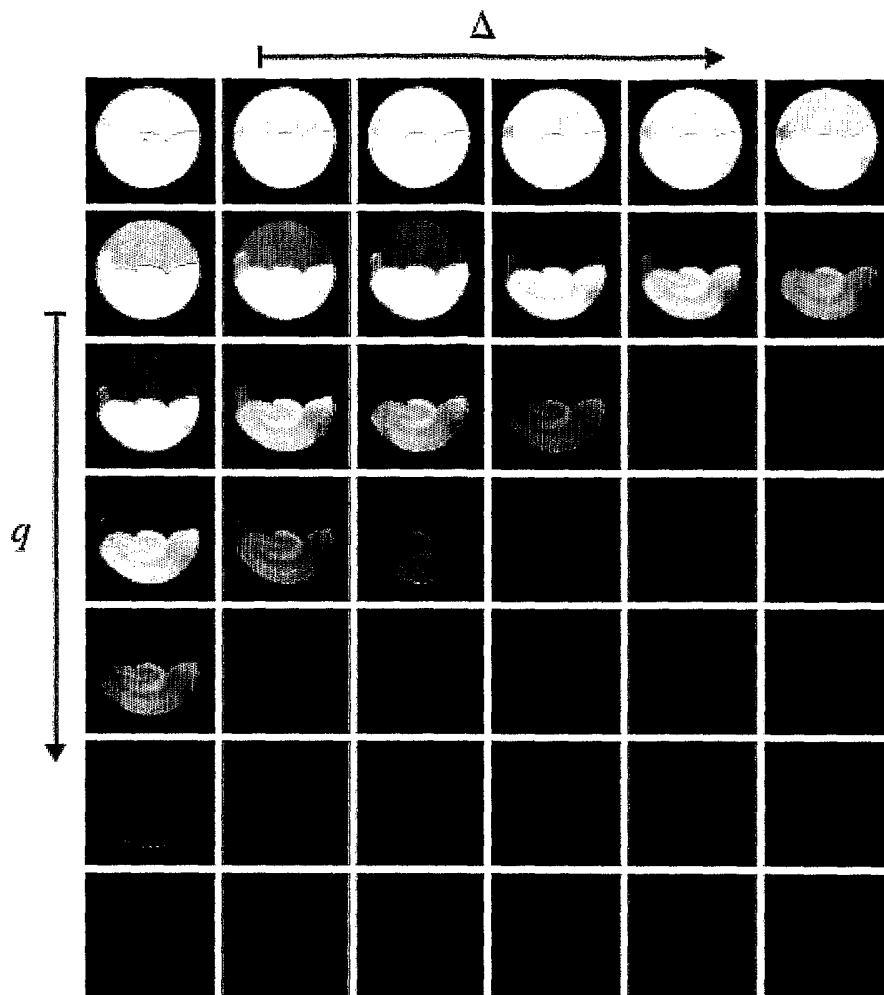


FIG. 3

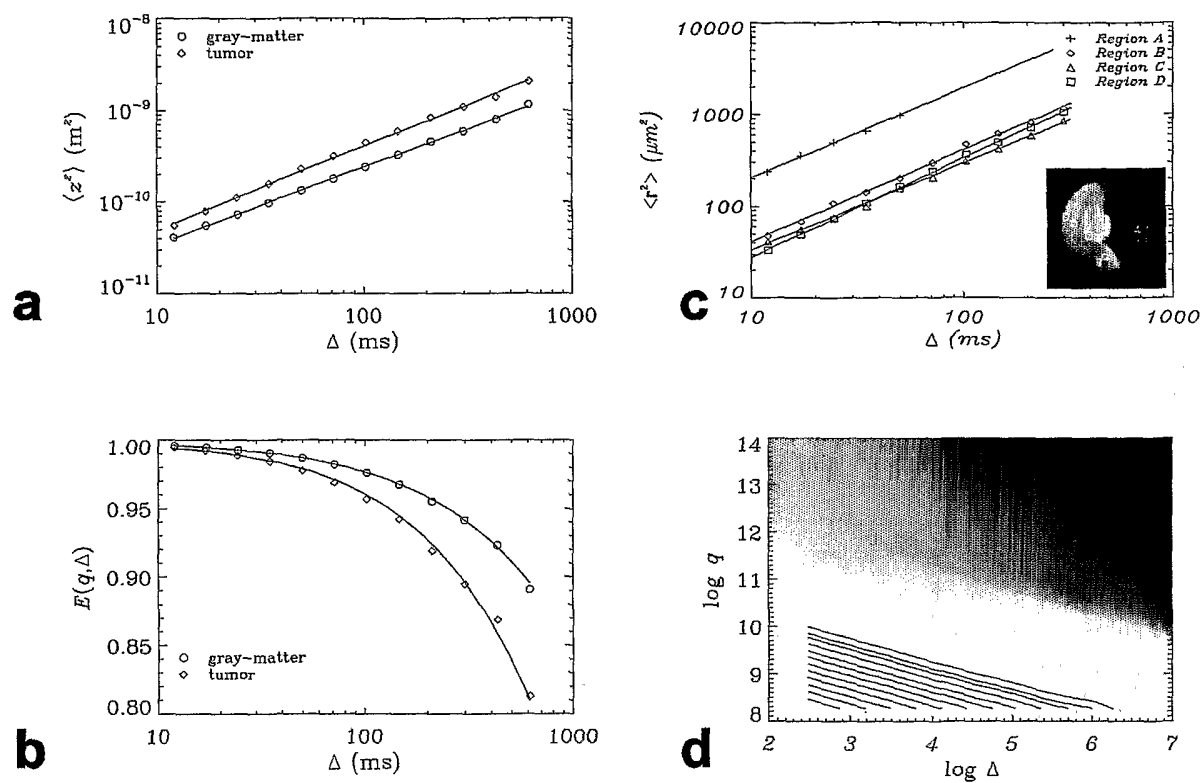


FIG. 4

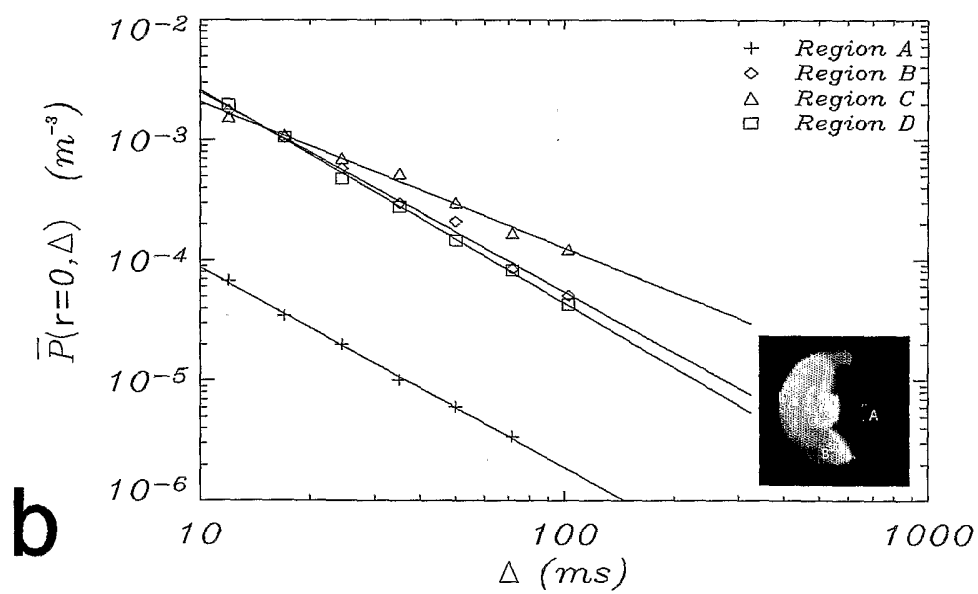
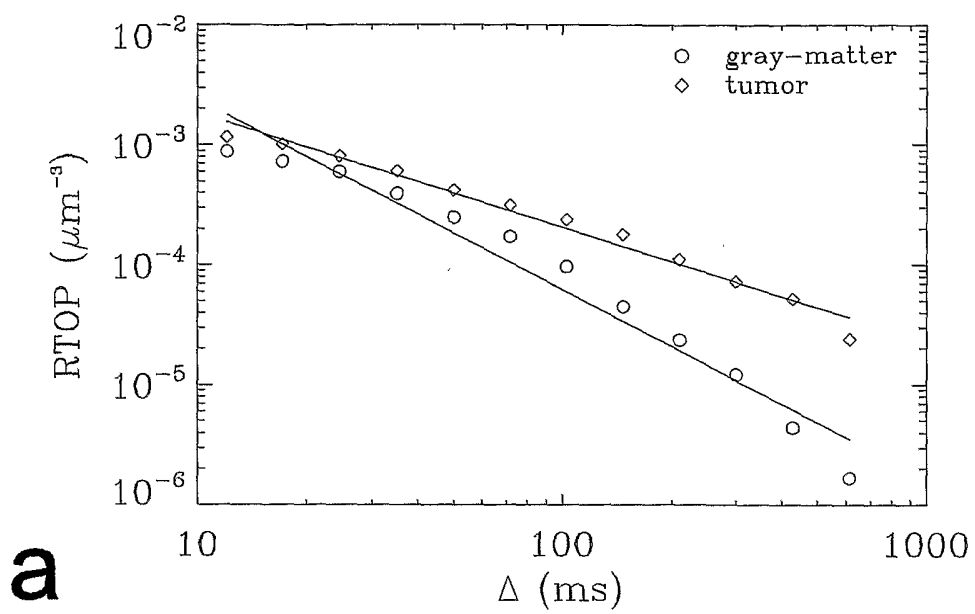


FIG. 5

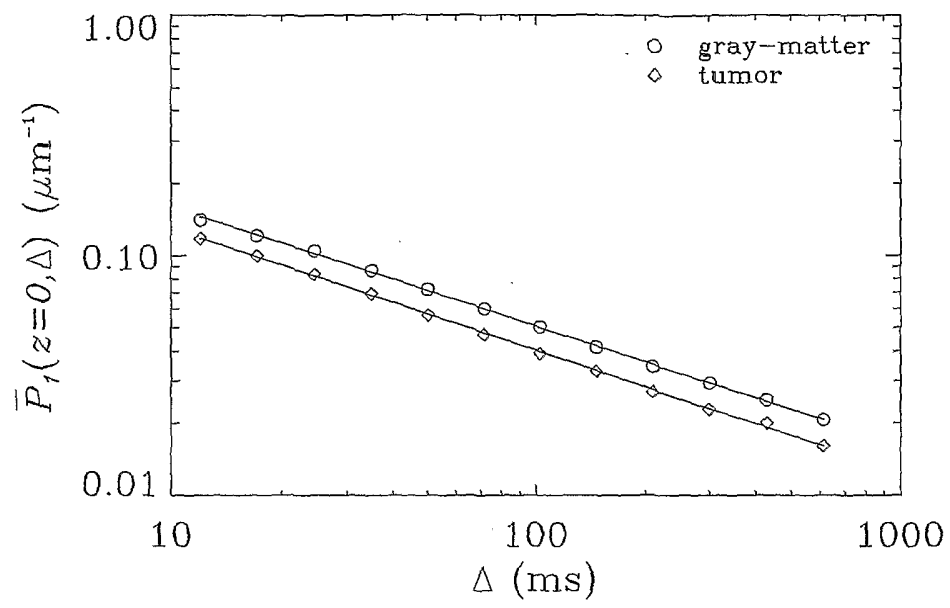


FIG. 6

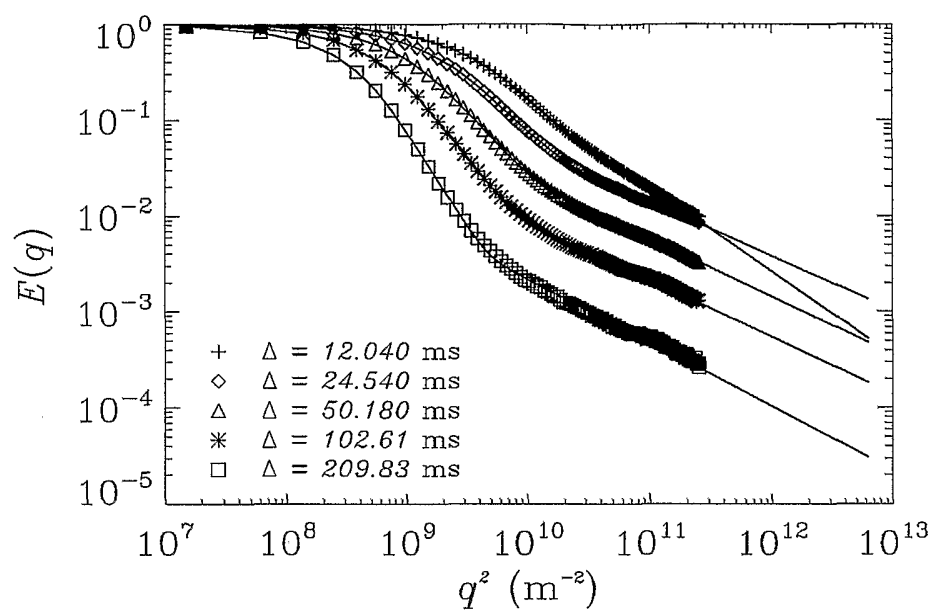


FIG. 7

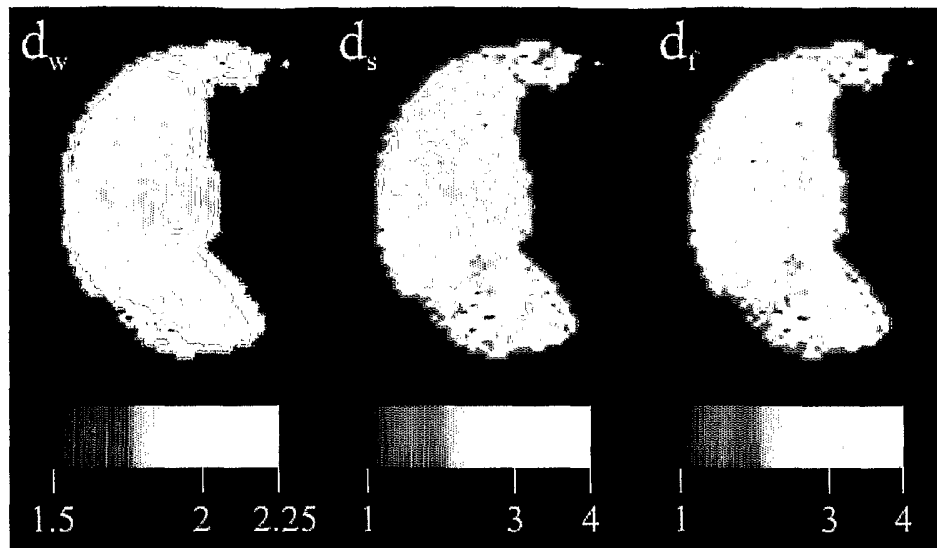


FIG. 8

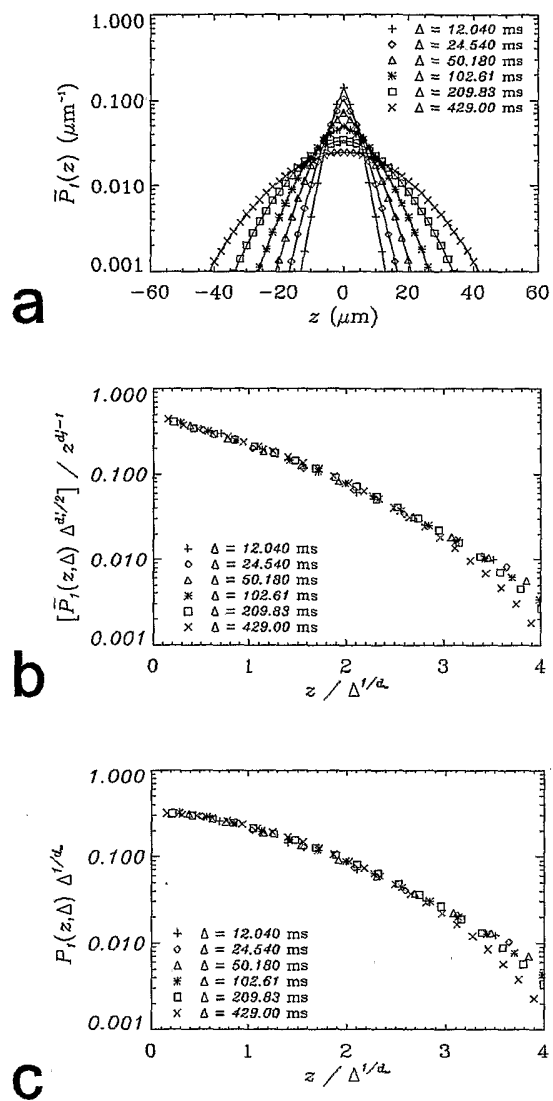


FIG. 9

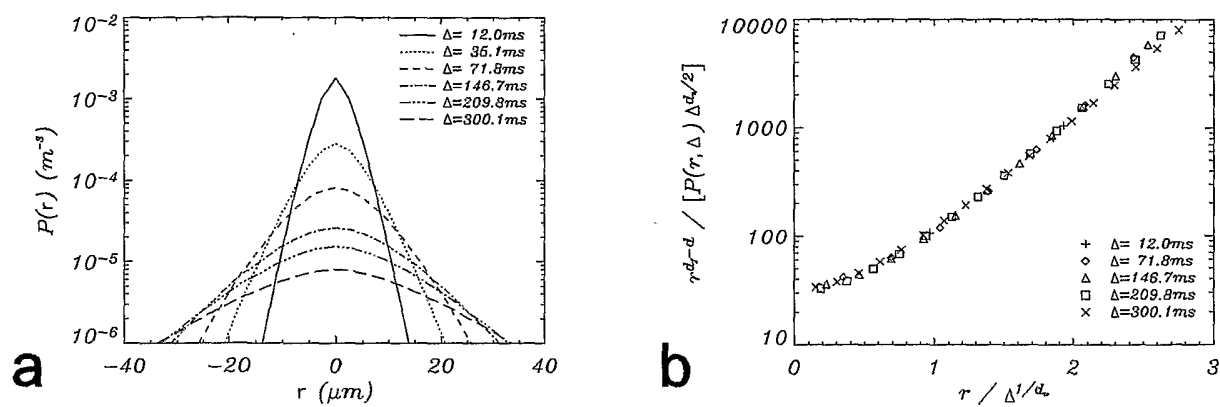


FIG. 10