Diffusion Tensor Imaging Lawrence R. Frank, Ph.D.

CENTER FOR SCIENTIFIC COMPUTATION IN IMAGING AND UCSD CENTER FOR FMRI UNIVERSITY OF CALIFORNIA, SAN DIEGO



University of California SanDiego



Center For Scientific Computation in Imaging

csci.ucsd.edu



MACROSCOPIC INFORMATION FROM MICROSCOPIC MEASUREMENTS



tissue paper

newspaper

diffusing ink in paper

WHAT IS DIFFUSION AND WHY DO WE CARE ABOUT IT?

Self-diffusion is the thermally driven random motions of molecules that occurs in the absence of a concentration gradient

The self-diffusion of water is ongoing in the human body and its characteristics depend on the local tissue architecture and physiology

Therefore the ability to measure self-diffusion offers the possibility of non-invasively measuring tissue structure and physiology

INFERRING THE MICROSCOPIC FROM THE MACROSCOPIC



Meinschildesikulaistantipusukusih tiles Ipoloeiofles Publiky ingtted inteventitiki beforfatziket kaisebe bielders hadovogap kigbs..."

http://www.youtube.com/eYeFractal

CONVECTION VS DIFFUSION A CAUTIONARY NOTE

The large scale swirling of the dust particles is primarily due to air currents (convection) but the *much* smaller scale jittery movements are diffusion

Convection

A BRIEF HISTORY OF DIFFUSION MEASUREMENT



Jan Ingenhousz (1730 – 1799) Dutch botanist and physiologist Described the "irregular movements" of coal dust on the surface of alcohol

A BRIEF HISTORY OF DIFFUSION MEASUREMENT

"Brownian Motion"



Experiment: Repeat pollen experiment using tiny shards of window glass Robert Brown (1773 – 1858) Result: Same British botanist and surgeon Conclusion: Not anve Theoryhttp?//www.microscopy-uk.org.uk

EINSTEIN'S THEORY OF BROWNIAN MOTION

Einstein's Theory

Part 1: Equation describing motion of a Brownian particle

Part 2: Relate diffusion to experimentally measurable quantities



Albert Einstein (1879 – 1955) German patent clerk and physicist

The particle density $\rho(x,t)$ at a position x at time t obeys



change with time

diffusion coefficient

change with space

The Diffusion Equation

The solution to the Diffusion Equation for particles initially at location X0

$$\rho(x,t) = \frac{1}{\sqrt{4\pi Dt}} e^{-(x-x_0)^2/4Dt}$$

This is a Gaussian (or Normal) distribution with mean position

 $\bar{x} = x_0$

and variance in the position

$$\sigma_x^2 = \overline{(x - x_0)^2} = 2Dt$$

What does this mean?

 $\bar{x} = x_0$

implies that, on *average*, the particles do not move from their initial position

 $\sigma_x^2 = 2Dt$

implies that the *variance* of a Brownian particle's position is proportional to the diffusion coefficient *D* and time *t*

Einstein argued that the *displacement* of a Brownian particle is thus the RMS distance

$$\Delta x = \sqrt{(x - x_0)^2} = \sqrt{2Dt}$$

and thus *not* linearly proportional to time (like flow), but to the *square root of time*

> Diffusion in Brain Tissue: $D \approx 1 \ \mu^2/ms = (0.001 \ mm^2/s)$ For t=100 msec, $\Delta x \approx 14 \ \mu$

GAUSSIAN DIFFUSION



$$P(x|x_{o},\tau) = \frac{1}{\sqrt{4\pi D\tau}} e^{-\frac{(x-x_{o})^{2}}{(4\pi D\tau)^{2}}}$$



DIFFUSION VS FLOW

 $\tau = 100 \, ms$

Diffusion

Flow

 $D \approx 10^{-3} mm^2/s$

 $v \approx 1 \, mm/s$

 $\Delta x \approx 14 \,\mu m$



The diffusion coefficient is

$$D = \frac{\alpha}{\eta r}$$

where



gas constant Avogadro's number

Diffusion coefficient goes up with temperature and down with viscosity and particle radius

It's sensitive to the local environment!

MODELING DIFFUSION: RANDOM WALK

MRI is all about mapping the locations of molecules ...

... we need a way to model the spatial locations of Brownian molecules as a function of time

MODELING DIFFUSION: RANDOM WALK



$\tau = \text{constant}$

MODELING DIFFUSION: RANDOM WALK



$\tau = \text{constant}$

MODELING DIFFUSION: RANDOM WALK The distribution of particles after a time τ



ISOTROPIC DIFFUSION IN 2D





 $\Delta x \approx \left(\frac{1}{1000}\right)$ a typical imaging voxel dimension

PROBABILITY CONTOURS (ISOTROPIC DIFFUSION)



ANISOTROPIC DIFFUSION IN 2D



Restricted diffusion

ANISOTROPIC DIFFUSION IN 2D

 $P(\boldsymbol{r}|\boldsymbol{r}_0,\tau) \sim N(\boldsymbol{r}_0,\boldsymbol{\Sigma})$



DIFFUSION ANISOTROPY IN NEURAL TISSUES



DIFFUSION ANISOTROPY IN 3D



probability contours in 3D

THE SENSITIVITY OF MRI TO DIFFUSION

We've described the spatial and Temporal characteristics of the Molecules.

WHAT IS THE INFLUENCE OF THIS ON THE MRI SIGNAL?

THE BIPOLAR GRADIENT PULSE (GRADIENT ECHO)



THE BIPOLAR GRADIENT PULSE (SPIN ECHO)





ECHO-PLANAR IMAGING

Preparation

Acquisition





KEY FACT

Only diffusion along the direction of the applied gradient has an effect

EARLY NMR MEASUREMENTS OF DIFFUSION

PHYSICAL REVIEW

VOLUME 80, NUMBER 4

NOVEMBER 15, 1950

Spin Echoes*†

E. L. HAHN[‡] Physics Department, University of Illinois, Urbana, Illinois (Received May 22, 1950)

Intense radiofrequency power in the form of pulses is applied to an ensemble of spins in a liquid placed in a large static magnetic field H_0 . The frequency of the pulsed r-f power satisfies the condition for nuclear magnetic resonance, and the pulses last for times which are short compared with the time in which the nutating macroscopic magnetic moment of the entire spin ensemble can decay. After removal of the pulses a non-equilibrium configuration of isochromatic macroscopic moments remains in which the moment vectors precess freely. Each moment vector has a magnitude at a given precession frequency which is determined by the distribution of Larmor frequencies imposed upon the ensemble by inhomogeneities in H_0 . At times determined by pulse sequences applied in the past the constructive interference of these moment vectors gives rise to observable spontaneous nuclear induction signals. The properties and underlying principles of these spin echo signals are discussed with use of the Bloch theory. Relaxation times are measured directly and accurately from the measurement of echo amplitudes. An analysis includes the effect on relaxation measurements of the self-diffusion of liquid molecules which contain resonant nuclei. Preliminary studies are made of several effects associated with spin echoes, including the observed shifts in magnetic resonance frequency of spins due to magnetic shielding of nuclei contained in molecules.

Since there is an

established gradient of the magnetic field over the volume of the sample, a molecule whose nuclear moment has been flipped initially in a field H_0 , may, in the course of time 2τ , drift by Brownian motion into a randomly differing field H_0 . Therefore, as τ is increased, a lesser number of moments participate in the generation of in-phase nuclear radio-frequency signals.



signal = Sum over all spins



DIFFUSION PHASE IN A BIPOLAR PULSE


THE DIFFUSION WEIGHTED SIGNAL

Signal and Distribution are Fourier Transform pairs

 $\mathfrak{s}(\boldsymbol{q},\tau) = \int P(\bar{\boldsymbol{r}},\tau) e^{-i\boldsymbol{q}\cdot\bar{\boldsymbol{r}}} d\bar{\boldsymbol{r}}$ $P(\bar{\boldsymbol{r}},\tau) = \int \mathfrak{s}(\boldsymbol{q},\tau) e^{i\boldsymbol{q}\cdot\bar{\boldsymbol{r}}} dq$

So, in principal, you can measure $P(r,\tau)$ by collecting data throughout q-space, just like imaging. In practice, *very* time consuming

THE ESTIMATION PROBLEM FOR GAUSSIAN DIFFUSION



The signal from Gaussian Diffusion

$$s(b) = s(0)e^{-bD} + \eta(b)$$



THE B-VALUE



 \boldsymbol{n}

little time interval:

total attenuation $A_{\tau} = \begin{bmatrix} A_i & \text{where } A_i = e^{-k^2 D dt} \end{bmatrix}$

i=1 $A_{\tau} = \prod e^{-k^2 D \, dt} = e^{-D \sum_{i=1}^{n} k^2 \, dt} = e^{-D \int k^2 \, dt}$ i=1 $dt \rightarrow \epsilon$ b $A_{\tau} = e^{-D \int k^2 dt}$



 $b = g^2 \delta^2 \left(\underbrace{\Delta + \frac{21}{33}}_{33} \right)$



 $\int k^2 dt = g^2 \int_0^{\delta} t^2 dt + g^2 \delta^2 \int_0^{\Delta} dt + g^2 \int_0^{\delta} t^2 dt$

 $b = g^2 \frac{\delta^3}{2} + g^2 \delta^2 \Delta + g^2 \frac{\delta^3}{2}$

What gradients are doing to k-space

 $G_y(t)$

 $G_x(t)$

 $\boldsymbol{k} \cdot \boldsymbol{x} = k_x x + k_y y = \gamma G_x t x + \gamma G_y t y$

y



t

t

DIRECTIONAL DIFFUSION ENCODING



ANISOTROPIC DIFFUSION IN 2D

 $P(\boldsymbol{r}|\boldsymbol{r}_0,\tau) \sim N(\boldsymbol{r}_0,\boldsymbol{\Sigma})$



MEASURING THE DIFFUSION TENSOR





$\tilde{D} = \hat{r}^t D \hat{r} = D_x \cos^2 \theta + D_y \sin^2 \theta$

projection of an ellipsoid! not like projection of a vector

MEASURING THE DIFFUSION TENSOR



 $S(b,\theta) = S(0)e^{-bD(\theta)} + \mathbf{k}$ $D(\theta) = \lambda_x \cos^2 \theta + \lambda_y \sin^2 \theta$

THE SHAPE OF DIFFUSION



0 002 -0.002 _0.001 0.001 0.002 -0.002 $D_{app}(\theta) = -\frac{1}{b} \log\left(\frac{S_b}{S_0}\right)$



THE ESTIMATION OF DIFFUSION

eigenvectors

eigenvalues



ANISOTROPIC GAUSSIAN DIFFUSION



1. The relative dimensions of the contours tells us about local structure

2. The orientation of the eigenvectors is related to the orientation of the structure

ANISOTROPIC DIFFUSION IN 2D

Impermeable barriers (a 2D tube)

_ x∟ 15 –15

 $\tau = 1 ms$

au = 10 ms

 $\tau = 100 \, ms$

Restricted diffusion

10

Anisotropy induced by local geometry
Sensitivity to geometry depends upon diffusion time *τ* While the *D* of the liquid may be a constant, there is an *apparent diffusion coefficient* (ADC) that varies with direction

THE 3D GAUSSIAN DISTRIBUTION:

$P(\boldsymbol{r}|\boldsymbol{r}_0,\tau) \sim N(\boldsymbol{r}_0,\boldsymbol{\Sigma})$



THE DIFFUSION TENSOR

The three eigenvectors of **D**

 $\{\vec{e}_1,\vec{e}_2,\vec{e}_3\}$

are the three unique directions along which the molecular displacements are uncorrelated

The three eigenvalues of **D**

 $\{D_x, D_y, D_z\}$

are the principle diffusivities



If the tube is not aligned with the coordinate system of the measurements, the diffusion along the measurement axes appears correlated

THE 2D GAUSSIAN DISTRIBUTION:



GENERALLY FIBERS ARE NOT ALIGNED ALONG MAGNET COORDINATES!

laboratory coordinate system



same orientation as laboratory coordinate system



rotated relative to laboratory coordinate system

THE 3D GAUSSIAN DISTRIBUTION:

$P(\boldsymbol{r}|\boldsymbol{r}_0,\tau) \sim N(\boldsymbol{r}_0,\boldsymbol{\Sigma})$



THE 3D GAUSSIAN DISTRIBUTION:

$P(\boldsymbol{r}|\boldsymbol{r}_0,\tau) \sim N(\boldsymbol{r}_0,\boldsymbol{\Sigma})$



TENSOR ROTATIONS



A baseballus aphorball isieligssondaenandfloeisentation

WHAT WE WANT



$D = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix} \text{ rotation } D = \begin{pmatrix} D_x & 0 \\ 0 & D_y & 0 \\ 0 & 0 & D_z \end{pmatrix}$

This is what eigenvector routines do!

THE ESTIMATION OF DIFFUSION

CAUTION

$$S(b,\hat{r}) = S(0)e^{-bD(\hat{r})} + \eta$$



Not additive noise anymore!

EXTENSION TO IMAGING (FINALLY!)

THE BIPOLAR GRADIENT PULSE (SPIN ECHO)



Preparation

Acquisition



Because the diffusion weighting does not interfere with the stationary tissue signal, we can "insert" it into a standard imaging procedure







voxel signal from multiple images at different directions





reconstruct **D** (diffusion ellipsoid)

WHY DOES DTI WORK AT ALL?





DIFFUSION ELLIPSOID





diffusion ellipsoids

AVERAGE DIFFUSION IN A VOXEL

Three eigenvalues of D are the three principle mean-squared displacements along its three principal directions

$$D = \begin{pmatrix} \lambda_x & 0 & 0 \\ 0 & \lambda_y & 0 \\ 0 & 0 & \lambda_z \end{pmatrix}$$

 $\langle D \rangle = (\lambda_1 + \lambda_2 + \lambda_3)/3 = \langle \lambda \rangle$ = Tr(D)

Tr = Trace = sum of diagonal elements

AVERAGE DIFFUSION IN A VOXEL











DIFFUSION ANISOTROPY IN A VOXEL

One measure of diffusion anisotropy is the variance of the eigenvalues, normalized to the mean-squared eigenvalue

anisotropy
$$\propto \frac{(\lambda_x - \overline{\lambda})^2 + (\lambda_y - \overline{\lambda})^2 + (\lambda_z - \overline{\lambda})^2}{\overline{\lambda}^2}$$

Fractional Anisotropy



DIFFUSION ANISOTROPY IN A VOXEL











FA
DIFFUSION ANISOTROPY









THE USES OF ANISOTROPY: CARDIAC MECHANICS



FROM LOCAL (VOXEL) ANISOTROPY TO EXTENDED SPATIALLY COHERENT ANISOTROPY: TRACTOGRAPHY

Local Anisotropy

voxel

Local/Global Coherence





 $D_{\parallel} pprox 3D_{\perp}$ $(1.2\mu^2/ms) \qquad (0.4\mu^2/ms)$

STREAMLINES

Anisotropy



Flow vector field



low

(principal eigenvector)

WHAT WE EXPECT OF DIFFUSION IMAGING

Some information about the microscopic structure



For voxels with aligned fibers (as in the corpus callosum)... ...the primary diffusion direction should be oriented in the same direction as the fiber.

Supraspinatus DTI



WARD GROUP

Supraspinatus DTI



Supraspinatus Tractography @60 directions



A. RODRIGUES-SOTO, WARD GROUP



WHAT IS THE NEURAL STRUCTURE OF ELASMOBRANCHS?



SPINAL CORD INJURY (RAT MODEL AT 7T)

Posterior median septum Posterior intermediate septum spinal cord white matter spinal cord white matter dorsal ramus ventral ramus dorsal ramus ventral ramus But what's happening here?

fissure

Jacob Koffler, Ph.D. Mark H. Tuszynski, M.D., Ph.D. Center for Neural Repair University of California, San Diego

HOW MUCH INFORMATION CAN WE EXTRACT?

Scie

UFO AND PARANORMAL NEWS FROM AROUND THE WORLD

Mars monolith Photographed On Mars



Submitted by Dirk Vander Ploeg on Mon, 04/16/2012 - 09:02

Dirk Vander Ploeg is the publisher of UFODigest.com and other paranormal and UFO related websites. He is the author of the non-fiction book "Quest for MIddle-earth" and is currently writing a new book. He has worked in marketing for the Toronto Star and the <u>Hamilton</u> Spectator and as a publisher and writer for <u>travel</u> related and other magazines.

By: Natalia Wolchover

Published: 04/11/2012 05:50 PM EDT on Lifes Little Mysteries

reasc very

Acco



ersity, the uction is

ck

WHAT'S THE PROBLEM?



BUT WE KNOW NEURAL TISSUES AREN'T THAT SIMPLE



Rat WM electron microscopic image Courtesy, M. Ellisman, UCSD

FAILURE OF THE STANDARD MODEL

A simple partial-volume model

Two crossing fibers

resulting distributions

AMBIGUITIES IN THE STANDARD MODEL isotropic crossed fibers 90°



 $D(\theta)$

 $D(\theta)$

θ

FAILURE OF THE STANDARD MODEL

Distribution of spins

Estimated D



THE MAJOR PROBLEM: HETEROGENEOUS VOXELS

Anisotropy

high



low

TRACTOGRAPHY PROBLEM



FAILURE OF THE STANDARD MODEL

Not only angular issues, but b-value dependencies as well!



 $\frac{S(b)}{S(0)} = fe^{-bD_1} + (1 - f)e^{-bD_2}$
simple two diffusion coefficient model

HIGH ANGULAR RESOLUTION DTI (HARDI) b = 0, 500, 1000, 1500



signal

 $D_{app}(heta)$

-0.5

Structure of lobes relative to fiber orientation is "non-intuitive"!

TRACTOGRAPHY PROBLEM, REVISITED



HIGH ANGULAR RESOLUTION DTI (HARDI)



Standard DTI



HETEROGENEOUS VOXELS AND HIGH ANGULAR RESOLUTION SAMPLING





a voxel with crossing fiber bundles and random spherical cells...

signal from 162 directions

THE FUTURE

IEEE TRANSACTIONS ON MEDICAL IMAGING, VOL. XX, NO. X, APRIL 2014

Simultaneous Multi-Scale Diffusion Estimation and Tractography Guided by Entropy Spectrum Pathways

Vitaly L. Galinsky and Lawrence R. Frank





DWI ESP





ESP vs RSI







DWI ESP



ESP full brain tractography



CONCLUSION

Diffusion MRI has a unique sensitivity to tissue architecture and physiology

...and diffusion sensitivity is relatively easy to incorporate into standard sequences

However ...

Data artifact correction non-trivial
Analysis is complicated
Interpretation is difficult

But it's really cool!

THE END