Abstracts
Workshop on Diffusion MRI and Stochastic Geometry

Michiel Cottaar, Oxford University

Modelling the brain's cortical connectivity

Introduction: Distant brain regions communicate through axons travelling through the brain's white matter. Because water diffuses more easily along than perpendicular to these axons, we can use diffusion MRI to estimate the orientation of these axons. The goal of tractography is to find streamlines that connect these fibre orientation estimates in order to reconstruct the major bundles of axons running through the white matter and estimate the connectivity between brain regions.

Problem statement: Most of the higher-order processing of the brain takes place in the convoluted cortical surface, which is full of hills (called gyri) and valleys (called sulci) (Figure 1A). Unfortunately, while we know true connectivity is spread across the full cortical surface, tractography streamlines are strongly biased to terminate at the gyral crowns (Figure 1B), which is referred to as the gyral bias. This gyral bias is caused, because axons tend to bend sharply when transitioning from the white matter into the sulcal fundi or gyral walls (Figure 1A) and this sharp transition is missed in the low-resolution diffusion MRI data ([1]).

Method/Results: We start by showing that cortical geometry is a strong predictor of fibre orientations below the surface ([2]), which suggests taking this cortical geometry into account might improve tractography in these regions. We propose a new model for tractography close to the cortex, where the streamlines are not each modelled individually, but they are all modelled simultaneously as streamlines through a divergence-free vector field **F**. This model allows us to constrain both streamline density (i.e., constant density across the cortical surface) and streamline orientation (i.e., align with the fibre orientation estimates from diffusion MRI). The resulting streamline configurations in the gyral white matter matches the expected configuration based on post-mortem microscopic analysis (Figure 1C). As validation we show that this new algorithm shows better agreement with functional MRI, in that regions that are physically connected tend to be in sync with each other (Figure 1D).

Discussion: Tractography algorithms that move beyond modelling a single streamline at a time can by putting constraints on the fibre density and their relative configuration more accurately model the fibre configurations where there are strong geometric constraints, such as close to the cortex. We show that this improves the connectivity estimated in the sulci.

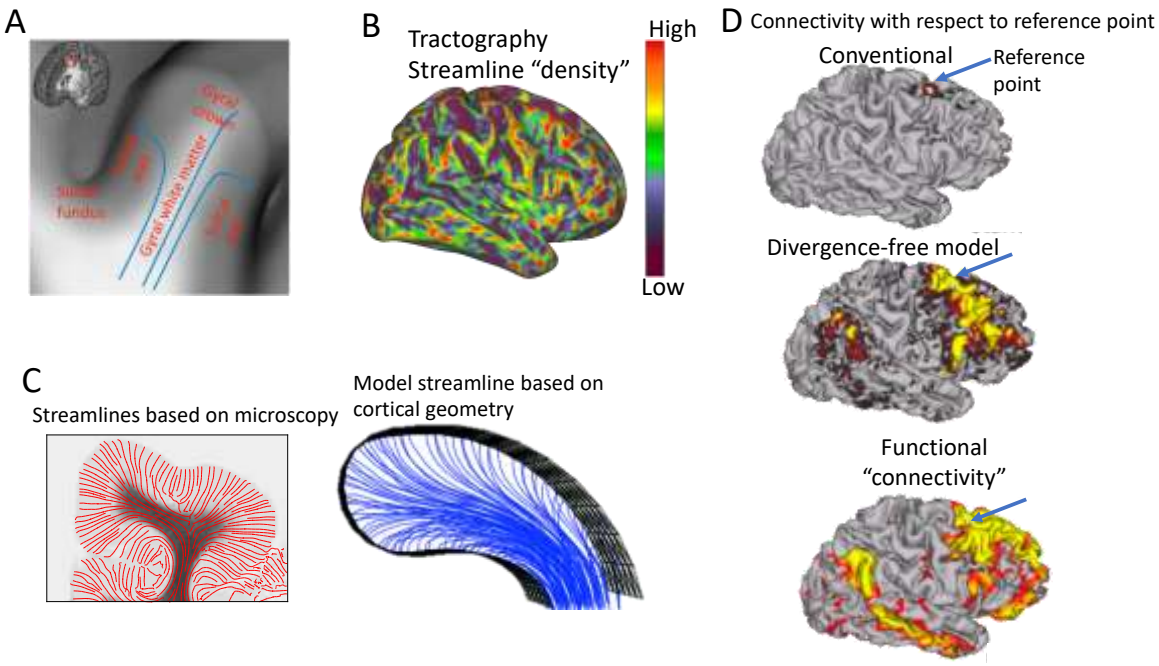

Figure 1.

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Tim Dyrby, Hvidovre Hospital

From structural brain connectivity to microstructural analysis: tomorrow's challenges of diffusion MRI?

Diffusion MRI enables non-invasive multiscale imaging from mapping the brain connectivity using tractography to microstructural analysis of anatomy in health and disease. Often the same acquisition setup (i.e. a standard pulse-gradient-spin-echo (PGESE) sequence including one to three shells) is used for both type of analysis. Prior to the analysis one or more models are fitted to the acquisition data. In tractography multi-fibre models are today widely used, and for microstructural analysis of patient groups the diffusion tensor model is widely used. It is known that tractography is challenged by many false-positives, and studies have a tendency to conclude that a better acquisition e.g. higher *b*-values, angular resolution, or image resolution might improve the sensitivity/specificity balance? Similarly, it is known that indices from the widely used diffusion tensor model intermingle microstructure anisotropy and fiber dispersion effects hence biasing microstructural estimates, which is rarely discussed.

In this lecture, I will discuss if scanning parameters actually are the limiting factor in structural connectivity analysis. Also, I will discuss the differences in diffusion tensor analysis if accounting for fiber dispersion effects. The questions arise what do we learn from these studies to define tomorrow's challenges?

Luc Florack, Eindhoven University of Technology
A new paradigm for geodesic tractography

Joint work with Rick Sengers, Stephan Meesters, Lars Smolders and Andrea Fuster

Clinical tractography is a challenging problem in diffusion weighted imaging (DWI), still hampered by persistent validation issues. Geodesic tractography, based on a shortest path principle, is conceptually appealing, but has not produced convincing results so far. A major weakness is its rigidity with respect to candidate tracts it is capable of producing given a pair of endpoints, showing a tendency to produce false positives (such as shortcuts) and false negatives (e.g. if a shortcut supplants the correct solution). We propose a new geodesic paradigm that appears to overcome these problems, making it amenable for semi-automatic clinical use. To this end we couple the DWI data to a *family* of metrics, governed by control parameters. These control parameters account for the ill-posed nature of tractography, and encapsulate unknown microstructural factors that have an impact on diffusion. In practice these may allow for edits by an expert through manual selection among multiple tract suggestions, or for bringing in a priori statistical knowledge. I consider a fully automatic, evidence-driven procedure to determine optimal controls and corresponding tentative tracts. The approach is deterministic, based on variational principles, but the control parameters provide anchor points for a stochastic perspective as well.

This work is part of the research programme `Diffusion MRI Tractography with Uncertainty Propagation for the Neurosurgical Workflow' with project number 16338, (partly) financed by the Netherlands Organisation for Scientific Research (NWO).

Denis S. Grebenkov, Ecole Polytechnique, Palaiseau
Accessing surface-to-volume ratio of an anisotropic medium by diffusion NMR with general gradient encoding

Joint work with Nicolas Moutal and Ivan I. Maximov

Since the seminal paper by Mitra *et al.* ([1]), diffusion MR has been widely used in order to estimate surface-to-volume ratios. Relying on the asymptotic short-time expansion for the heat kernels ([2,3]), we generalize Mitra's formula for arbitrary diffusion encoding waveforms, including recently developed *q*-space trajectory encoding sequences ([4]). We show that surface-to-volume ratio can be significantly misestimated, using the original Mitra's formula without

taking into account the applied gradient profile ([5]). In order to obtain more accurate estimations in anisotropic samples, we introduce a new isotropy condition on diffusion gradient waveforms and propose an efficient and robust optimization algorithm to design such waveforms with prescribed features [6].

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Ute Hahn, Aarhus University

Simulation based testing for stochastic geometry models

Joint work with Mari Myllymäki, Tomáš Mrkvička and Pavel Grabarnik

How can we test if a given stochastic geometry model is appropriate for observed complex spatial data? Or, in the case that data come in groups, how can we test if there are differences?

In both cases, one can generate "artificial" data from the null hypothesis, either by simulating from the assumed model, or by permutation. For univariate data, e.g. numbers, simulation based testing is well established and straightforward. To use these methods in the complex stochastic geometry, one would have to summarize the available information into one single number, such as the total fibre length per unit volume. This would mean a quite substantial loss of information.

After a general introduction to simulation based testing, I will discuss approaches that use functional summaries instead of a single number, in particular the global envelope test. This test can be extended to take various geometric aspects into account.

Matt G. Hall, University College London
Monte-Carlo simulation in diffusion MRI

Monte-Carlo simulation is now a well-established technique in diffusion MRI. The aim of the approach is to provide synthetic diffusion-weighted data from a known acquisition and tissue ground-truth. Monte-Carlo methods have underpinned a generation of analysis methods and models for diffusion MR data to be tested and (to some extent) validated. This talk describes Monte-Carlo simulation in diffusion MRI, including its historical development and implementation. It also lifts the lid a little on some of the inner mysteries which seldom see the light of day. The aim is to show how to do it well, what the important ingredients are, and some common pitfalls to avoid. This talk will be part review, part technical journey, and part thoughts on future directions.

Kristian Bjørn Hessellund, Aalborg University
Statistical analysis of multivariate point patterns using a case-control approach

The aim is to propose new methods for analysis of multivariate point patterns (MPP) that are observed in a heterogeneous environment. For instance, examples of such MPPs could be the locations of street crimes in a city, where the different types of point patterns correspond to different types of street crimes. Clearly, the street crimes must be non-stationary due to the geography of the city and the variation of crimes from one street to another, hence the intensity function of each street crime is complex. Therefore, the task to model the intensities is rather difficult. To accommodate this issue we adapt terminology and methodology from spatial case-control studies (See Diggle *et al.* (2017) for an overview). In this approach we assume that each type of crime shares a common unobserved and possibly complex factor. However, if we consider the street crimes as "cases" relative to some "control" pattern, this enable us to estimate some first order parameters along with an exploratory function, called the cross-pair correlation function, non-parametrically without specifying the complex factor. Thereby, we can analyze how the street crimes relate to some demographic covariates and we can study the pairwise dependence structure between the street crimes non-parametrically.

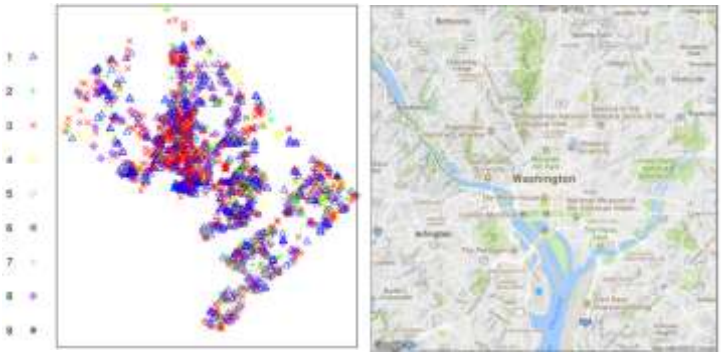

Figure 1. The left figure shows locations of the nine different street crimes (*n*=2614) commited in Washington D.C. The right figure shows a map of Washington D.C.

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Louis Gammelgaard Jensen, Aarhus University

Cluster marked cluster point processes with applications in super resolution microscopy

Joint work with Ute Hahn

Cluster Marked Cluster point processes (CMCpps) are a class of clustered, marked point process models with a simple dependence structure between locations and marks. They allow for modelling of clustered data where each cluster may depend on information provided by the mark of a (latent) parent process. CMCpps hold potential for modelling of data from super resolution microscopy, where photo-blinking artifacts give rise to clusters of multiple appearances from the same molecule. These blinking artifacts complicate matters of counting proteins, and quantifying the degree of clustering between them. On my poster, I will present a set of new methods that may hold promise for direct estimation of blinking characteristics, such as the mean number of blinks per protein, the expected waiting time between blinks, and the cluster shape. A model-specific summary function is computed that is a good surrogate for the pair correlation function of the true protein locations, allowing for quantification of the degree of clustering or repulsiveness between individual proteins. This is still very much work in progress.

Markus Kiderlen, Aarhus University

Fibre processes in stochastic geometry

This is an overview talk on fibre processes. I will start with the classical setting of stationary (homogeneous) collections of random fibres and their basic (first order) parameters: the *intensity*, describing the mean total fibre length per unit volume, and the *rose of directions*, which is the distribution of the unit tangent vector at a 'randomly' chosen fibre point. The problem to estimate these quantities from lower dimensional sections of the fibre process has got much attention and its solution will be outlined in the talk. We will also mention second order properties.

We will then turn to non-stationary fibre processes. In this case, the intensity and rose of directions are location dependent, the latter being a Markov kernel. Possible strategies for their estimation will be outlined.

Valerij G. Kiselev, University Medical Center Freiburg

Microstructure with diffusion: to see the invisible

Magnetic resonance imaging (MRI) has been mainly motivated by the demands of medicine to non-invasively image the interior of the human body in vivo. While the resolution of such images is about a millimeter, the fundamental scale of biology is three orders of magnitude finer (micrometers vs. millimeters). Imaging on this scale reveals individual cells with their complex shapes, mutual positions, orientations etc. Microstructural MRI ([1-3]) aims at bridging this gap by obtaining information from the cellular level while using the available resolution of MRI. It is a booming research area with an exponentially increasing number of publications ([3]). The main challenge is to understand which cellular properties are imprinted in the measured MRI signal after the massive averaging due to the coarse imaging resolution, a fundamental problem which has direct analogies to the relation between microscopic disorder and macroscopic transport measurements in condensed matter physics ([2,4-8]). The forerunner of this development is MRI sensitized to water self-diffusion in biological tissues. It is a gift of nature that the diffusion length of water molecules during the typical MRI signal acquisition is commensurate with the structure at the cellular level.

The aim of this talk is to sketch the main physical principles of accessing the tissue microstructure using diffusion ([1,2]) and transverse relaxation ([4-6]), and to connect them to the disorder averaging techniques adopted in describing transport phenomena in condensed matter physics ([6-8]). The versatile MRI methods will be classified using a roadmap (a q-t phase diagram) of diffusion MRI ([1,2]) to give a bird's eye view of this rapidly developing research field. Varying MRI acquisition parameters ([1,2,9,10]) enables observation of different regimes of non-Gaussian diffusion in which one can measure the ensemble-averaged diffusion propagator, access the microscopic geometry of water-confining compartments, get an idea about the structural organization of cells, and other biophysical tissue parameters.

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Hans Knutsson, Linköping University

Generating optimal sets of dMRI waveforms

The methodology outlined in this presentation is intended to provide a tool for the generation of sets of MRI diffusion encoding waveforms that are optimal given a certain distribution of tissue microstructure features. The methodology presented has five distinct components:

1. Defining the class of waveforms allowed, i.e. defining the measurement space. **2.** Specifying the expected distribution of microstructure features present in the targeted tissue. **3**. Learning the metric in the chosen measurement space. **4.** Designing a continuous parametric functional suitable for approximation of the estimated metric. **5.** Finding a distribution of a chosen number of waveforms that is optimal given the continuous metric.

The tissue is modeled as a collection of simple elliptical compartments with varying size and shape. Two waveform classes are tested: The classical Stejskal-Tanner waveform and an idealized Laun long-short waveform. The estimation of the metric is based on correlations between measurements obtained at given points in the measurement space using an information theoretical approach. An eight parameter metric functional is presented and used to approximate the measurement space metric. Optimal sets of waveforms are found using a simulated annealing inspired energy minimizing approach. The superior performance of the methodology is demonstrated for a number of different cases by means of simulations.

Hong-Hsi Lee, New York University School of Medicine

Exploring the effect of varying axonal shape on the diffusion time-dependence inside EM-reconstructed axons using 3-dimensional Monte Carlo simulations

Joint work with Els Fieremans and Dmitry S. Novikov

We focus on the intra-axonal diffusion MRI signal, where we study the interplay between the effect of confinement in the transverse direction (diffusion diffraction), and the restrictions in the longitudinal direction (e.g. axon beading). For the transverse direction, we show that coarse-graining of transverse axonal cross-sections due to the longitudinal motion results in a non-Gaussian transverse signal, whose cumulants acquire sensitivity to axonal diameter variations ([1-4]). Furthermore, for the longitudinal direction, we show that coarse-graining of caliber variations along axons leads to a specific power-law tail for the diffusion time-dependence,

indicating that the non-Gaussian diffusion along axons is restricted by short-range disorder ([5, 6]). We (i) validate our results using 3d Monte-Carlo (MC) simulations in artificially designed cylinders with periodic beads for the transverse direction, see Figure 1, and (ii) demonstrate the diffusion time-dependence in realistic microstructure of intra-axonal space (IAS) segmented from scanning electron microscopy (SEM) images of the mouse brain corpus callosum (CC) ([7]) for both directions (Figure 2).

In particular, for diffusion parallel to the fiber bundle, MC simulations in the realistic microstructure show that the diffusion along axons, either with or without orientation dispersion, is characterized by 1-dimensional short-range disorder and the ϑ = 1/2 dynamical exponent ([5, 6]). In the tortuosity limit, the bulk axial diffusivity of IAS highly correlates with the along-axon caliber variation, implying a potential biomarker to evaluate the mitochondria or neurite beadings.

In the transverse direction, our MC simulations show that axons with the same mean radius can have very different effective radius ([8]) measured by dMRI, depending on the strength of the caliber variation, or beading. In particular, the radial kurtosis (RK) contributed by IAS is non-negligible, RK ~ -0.2, and significantly different from the value -0.5 for a perfect cylinder. This is relevant for models ([9-13]) estimating axonal diameter using dMRI, especially for large axons (e.g. spinal cord), when strong gradients are applied, and for modeling IAS-specific metabolites. We note that in the long-time limit, the overall kurtosis transverse to aligned impermeable axons asymptotically depends on the relative volume fractions ([14,15]), not on the axonal radii; our results for diffusion transverse to axons are relevant in the intermediate-time regime.

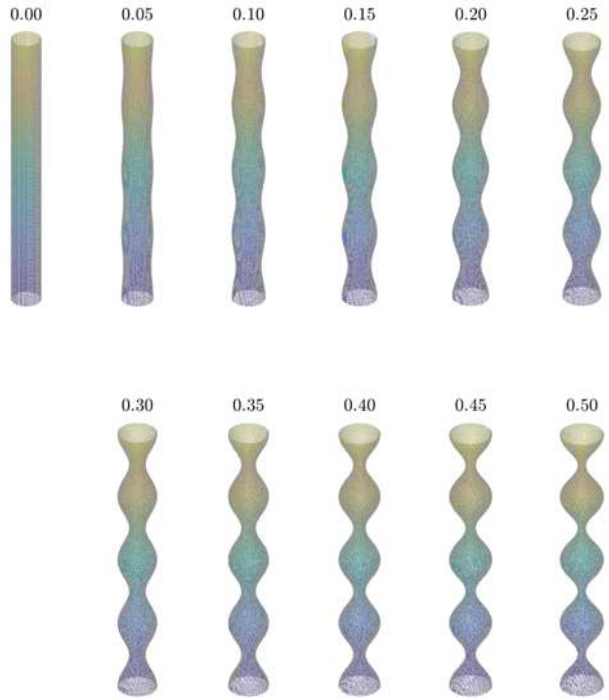

Figure 1. 3d geometries of cylinders with periodic beads. The coefficient of variation of the radii is labeled on top of each fiber.

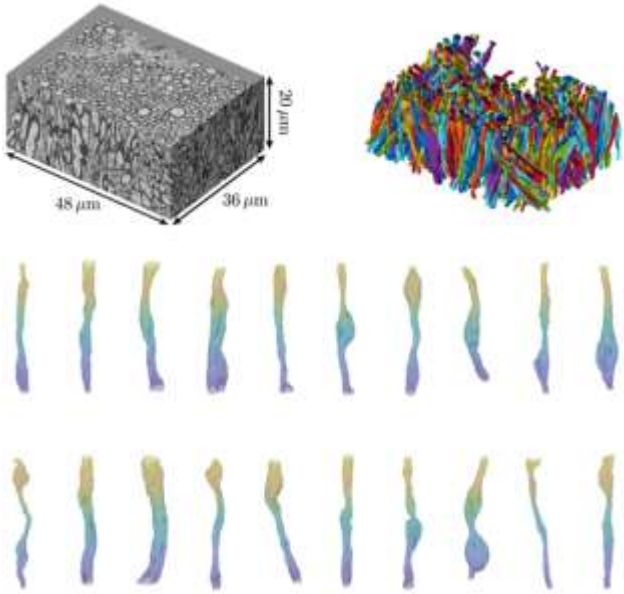

Figure 2. Realistic microstructure of the intra-axonal space reconstructed from 3d scanning electron microscopy images of mouse brain genu of corpus callosum.

Acknowledgements

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João P. de Almeida Martins, Lund University and Random Walk Imaging AB

Nonparametric Monte Carlo inversion of 6D diffusion-relaxation MRI data

Joint work with Paolo Mezzani and Daniel Topgaard

Diffusion MRI techniques are exquisitely sensitive to microstructural changes in the living human brain, but yield ambiguous results whenever the analyzed voxel comprises multiple tissue components with varying diffusion and relaxation properties. Inspired by multidimensional solid-state NMR literature ([1]), we devised a MRI protocol where sub-voxel heterogeneity is resolved with nonparametric 6D distributions of longitudinal (R_1) and transverse (R_2) relaxation rates, axial ($D_{||}$) and radial ($D_{\perp}$) diffusivities, and diffusion tensor orientation (θ,φ) ([2]). While the high-dimensionality of our approach allows the characterization of brain microstructure at an unprecedented level of resolution, it also complicates the inversion of the integral transform that relates the acquired signal and $P(R_1,R_2,D_{||}, D_{\perp}, \theta, \varphi)$. When using the analysis tools of traditional

relaxation-diffusion NMR methods ([3]) one is met with memory demands that are incompatible with the specifications of personal computers.

Here, we present a novel model-free inversion algorithm wherein our 12D correlation space is explored through a stochastic iterative approach. Following the works of Prange and Song ([4]), we avoid common regularization procedures and instead use a Monte Carlo approach to retrieve an ensemble of plausible distributions. By exploring the variability between solutions we derive error metrics and define confidence intervals. The feasibility and performance of our algorithm is demonstrated with both simulations and *in vivo* datasets.

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Amy R. McDowell, University College London

Time dependence and stability of diffusion tensor metrics in a hydrophilic, electrospun, water-perfused, hollow fibre phantom at 3T

Joint work with Matt G. Hall, Fenglei Zhou, Thorsten Feiweier, Geoff JM Parker and Chris A Clark

We have used a novel well-characterised hydrophilic phantom comprised of parallel hollow fibres with radii comparable to axons in healthy human white matter to assess the dependence of Diffusion Tensor Imaging metrics on diffusion time. We acquired 7 stimulated-echo (STEAM) diffusion acquisitions with pulse duration of 10ms and diffusion times (DL) between 55-300ms, each acquiring non-collinear 24 directions at *b*-values of 0, 800, 1000, 1200, 1400, 1800 and 2000 s/mm^2 on a 3T Siemens Prisma scanner using a 64-channel head coil. MD, FA, and principle eigenvectors were analysed in each voxel of interest. Angular dispersion of eigenvectors was calculated relative to the spherical mean of all directions. It was found that the mean MD decreases from 77.74 x 10-5mm^2/s at DL=55ms to 63.09 x 10-5mm^2/s at 300 ms and that mean FA increases from 0.720 at DL=55ms to 0.795 at DL=300ms. The differences between neighbouring values are not significant but the differences across the complete range are (MD: p<0.0001, FA: p=<0.0001). We observed a consistent trend in MD and FA as a function of diffusion time: a decrease in MD and an increase in FA. There was significant change in FA and MD across the range of diffusion times considered. This indicates that the diffusion tensor measured in this phantom is not completely stable with respect to diffusion time, and that diffusion time must be explicitly considered when comparing acquisitions between sites and scanners using phantoms of this kind.

Nicolas Moutal, Ecole Polytechnique, Palaiseau

Localization regime in an open medium

Joint work with F. B. Laun, K. Demberg, T. A. Kuder and D. Grebenkov

It has been known for over twenty years that diffusion MRI signals exhibit a peculiar behavior at high gradients in confined domains, in what is called the *localization regime*. Let us consider a PGSE sequence with diffusion time Δ and gradient strength g. If one denotes by l_s the typical size of the confining medium along the gradient direction, by $l_D = \sqrt{D\Delta}$ the diffusion length and by $l_g = \left(\frac{D}{\gamma g}\right)^{1/3}$ the 'gradient length', then the localization regime emerges if $l_g \ll l_D, l_s$. As one can interpret l_g as the typical distance travelled by diffusing nuclei before their phases begin to decorrelate from each other, the above conditions imply that the magnetization vanishes everywhere in the medium except near the points where the boundary of the medium is perpendicular to the gradient and thus completely prevents diffusion along the gradient direction. Moreover, the signal exhibits a stretched exponential behavior

$$\ln S \propto -\left(\frac{l_D}{l_g}\right)^2 \propto -g^{2/3}t\ .$$

In this work, we investigate, both experimentally and numerically, the emergence of the localization regime in an open medium, i.e. free space with obstacles. Experiments are conducted on Xenon gas diffusing outside an array of cylinders. Preliminary results show excellent agreement between experiments and simulations, see Figure 1 below.

The localization regime naturally emerges at high gradients and long encoding times, which are required to probe fine-scale microstructure in complex media. However, it has been ignored so far, and most theoretical works rely on the Gaussian phase approximation and phenomenological corrections. We believe that a better understanding of the signal formation at high gradients is required to extend the capability of modern diffusion MRI.

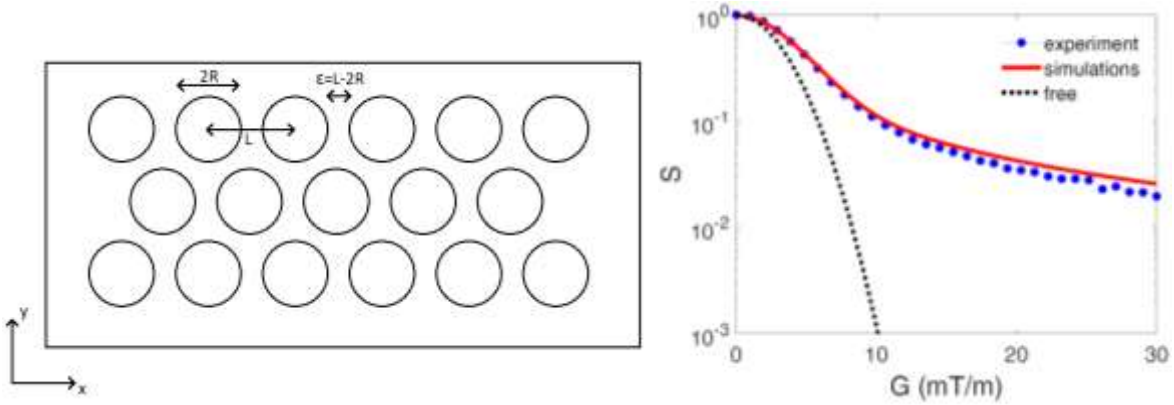

Figure 1. (left) Schematic representation of the setup (view from above). (right) Experimental signal (dots) and numerical simulation (full line) show very good agreement. The localization regime signal decays very slowly compared to the signal from free diffusion (dashed line), and significant deviations can be observed at gradients as small as 10mT/m.

Dmitry S. Novikov, New York University School of Medicine

Microstructure with diffusion: what do we see?

The fundamental scientific challenge, and an unmet clinical need of MRI, is to become sensitive and specific to tissue structural changes at the cellular level of micrometers, given its nominally coarse millimeter-level imaging resolution. This “super-resolution" can be only achieved indirectly, by virtue of biophysical modeling, which links diagnostic radiology with the modern physics methodology ([1,2]). Brownian motion of water molecules provides an essential length scale, the diffusion length, that can be experimentally controlled within the micrometer range, commensurate with cellular dimensions. This opens up a unique window for quantifying tissue properties in vivo using diffusion MRI.

The aim of this talk is to outline biophysical modeling of non-Gaussian water diffusion in different tissue types from the overarching perspective of coarse-graining over an increasing diffusion length scale, placing different tissues and MRI methodologies on the MRI roadmap (the q-t phase diagram) formulated in the previous talk ([1,2]). Moving along the temporal dimension, coarse-graining will be shown to enable the application of the ideas of universality, borrowed from condensed-matter and mesoscopic physics, to identify distinct structural universality classes in living tissues ([3]), and to connect them to the observed time-dependent diffusive dynamics measured with MRI in the brain ([3-5]) and body ([3,6]). Moving along the q-dimension, at long times, will lead us to the introduction of the so-called Standard Model ([2,7,8]) of diffusion in neuronal tissue represented by anisotropic Gaussian compartments, whose parameter estimation is nontrivial due to inherent degeneracies ([8]). The physics beyond the Standard Model will be considered in terms of time-dependent non-Gaussian corrections to the intra- and extra-cellular tissue compartments, as well as via the extension ([9]) of effective medium theory methodology ([2,3]) onto arbitrary q-space trajectories ([10]).

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Evren Özarslan, Linköping University

Influence of structural heterogeneity and curvilinear diffusion on MR diffusion measurements

Characterizing intravoxel heterogeneity of the tissue is one of the primary goals of quantitative diffusion-weighted MRI. Dispersion in the local structure, represented via tensor distributions, leads to the prediction that the signal decay could follow power-laws. Orientationally-averaging the diffusion-attenuated signal provides the signal response for a powdered version of the local structure, thus effectively introducing additional dispersion. I will review our contributions [1-3] over the years on the emergence of such signatures of heterogeneity, their measurement via traditional as well as general gradient waveforms, and the deviation from power-laws due to curvilinear diffusion.

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Anders Rønn-Nielsen, Copenhagen Business School

Lévy-based modelling: tail asymptotics and excursion sets

Joint work with Eva B. Vedel Jensen

A continuous, infinitely divisible *d*-dimensional random field given as an integral of a kernel function with respect to a Lévy basis with convolution equivalent Lévy measure is considered. For a large class of such random fields the asymptotic probability that the supremum of the field exceeds the level *x* is computed as *x* tends to infinity. A main result is that the asymptotic probability is equivalent to the right tail of the underlying Lévy measure. Furthermore, the asymptotic behaviour of the probability that an excursion set contains rotations of a given

geometrical objects of fixed size, e.g. a ball or a line, is studied. This probability is similarly asymptotically described by the right tail of the Lévy measure. Finally, an extension of the model to a situation, where the field is indexed by both time and space, is considered.

Matthias Schulte, University of Bern
Random geometric graphs

Random geometric graphs are an important model for spatial random graphs. They are constructed by taking the points of an underlying point process as vertices and by connecting two points by an edge whenever their distance does not exceed a given threshold. The first half of this talk will be a brief introduction to random geometric graphs and their properties. In the second half an application to goodness-of-fit tests will be discussed.

Thomas Schultz, University of Bonn
Diffusion MRI tractography: methods, challenges, applications

Observing the preferred directions of water self-diffusion with magnetic resonance imaging allows us to infer the local orientation of neural fiber bundles in the brain. Tractography integrates them into longer-range curves that are collectively referred to as a tractogram, and that reflect the trajectories of major white matter tracts. The first part of this talk will introduce some of the fundamental approaches that have been taken when developing algorithms for tractography. In particular, it will clarify the difference between local and global, as well as deterministic and probabilistic tractography. It will also address practical considerations (effects of data quality, choice of algorithms, seeding and filtering) and comment on the interpretation of results, uses, and limitations.

The second part will focus on recent related developments from my own group. They include the use of positive definite fourth-order tensors and their low-rank approximations in tractography, joint parametrization and bag-of-feature representations of tractograms as a basis of group studies and predictive modeling, as well as contributions to an ongoing scientific debate on whether crossing white matter pathways are organized in parallel sheets.

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Evgeny Spodarev, Ulm University

Nonparametric statistics for infinitely divisible random fields

First, we give some basics on stationary random fields. We then introduce stationary infinitely divisible moving average random fields via their spectral representation and discuss recent methods for the nonparametric estimation of the kernel function as well as of the Lévy density for these fields. In particular, we are interested in heavy tailed random fields and their statistical inference where the standard correlation theory does not work. We show consistency and give error bounds for our estimates. Some inverse problems in statistics of random fields are touched upon as well.

Anne Marie Svane, Aalborg University

Estimation of geometric functionals in image analysis

Joint work wth Daniel Hug and Markus Kiderlen

This poster contains a review of some of the challenges that arise when estimating boundary properties of a digitized object. The problem occurs for instance in microscopy when surface area and other Minkowski functionals are used to quantify the geometry of an object under study and only a pixel/voxel image is available. The natural high-speed algorithms based on local pixel configurations in most situations lead to a bias even in high resolution. Instead, we propose a new class of algorithms based on Steiner type formulas.

Chantal Tax, Cardiff University

Investigating the geometrical structure of brain fibre pathways with diffusion MRI

Joint work with Tom Dela Haije, Carl-Fredrik Westin, Andrea Fuster, Max A. Viergever, Luc Florack and Alexander Leemans

Diffusion MRI tractography can give an estimate of fibre trajectories by virtually reconstructing pathways based on the main directions of diffusion. These virtual reconstructions have been used to infer geometrical information on brain-pathways, such as curvature and torsion [1] and dispersion [2]. Recently, tractography has been used to investigate the presence of geometric ‘sheet-structures’: compositions of two sets of tracts that locally cross each other on the same

surface [3]. The existence of such structures could have significant impact on models of structural and functional brain connectivity, embryogenesis, and development. They could for example play an important role in axonal path-finding during embryogenesis by guiding growing fibres [3,4]. However, later work suggested that the observed grid pattern is most likely an artefact, attributed to the limitations of diffusion MRI and tractography [5]. Moreover, the lack of a clear exposition of the relevant mathematical concepts may have contributed to this ongoing debate.

This talk will focus on our efforts to develop quantitative methods to infer a sheet-probability-index (SPI) from directional data, indicating the likelihood of local sheet-structures [6,7]. Specifically, we present a definition of sheet structure in terms of integral curves of vector fields, and discuss the relevant measure used to assess its presence, i.e. the Lie bracket. The Frobenius theorem subsequently formalizes the necessary and sufficient condition for the sheet-structure to exist. We compare two implementations to compute the Lie bracket from noisy vector fields, and show results on human and animal diffusion MRI data.

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Christoph Thäle, Ruhr-Universität Bochum

Introduction to stochastic geometry

Stochastic geometry provides the mathematical framework for the description and analysis of random sets. In this „crash course“, we will present the most fundamental aspects of this theory. We concentrate on random sets, random measures and point processes. Also the most fundamental models like the Boolean model or the Voronoi tessellation are introduced.

Daniel Topgaard, Lund University
Multidimensional diffusion MRI

Diffusion MRI is an excellent method for detecting subtle microscopic changes of the living human brain, but often fails to assign the experimental observations to specific structural properties such as cell density, size, shape, or orientation. When attempting to solve this problem, we have chosen to disregard essentially all previous work in the field of diffusion MRI, and instead translate data acquisition and processing schemes from multidimensional solid-state NMR spectroscopy [1,2]. Key elements of our approach are *q*-vector trajectories and correlations between isotropic and directional diffusion encoding. By approximating the water displacement probability as a sum of anisotropic Gaussians, the voxel composition can be reported as a diffusion tensor distribution where each component of the distribution is related to a distinct tissue environment. Our new methods yield estimates of the complete diffusion tensor distribution or well-defined statistical properties thereof, such as the mean and variance of isotropic diffusivities, mean-square anisotropy, and orientational order parameter, which derive from analogous parameters in solid-state NMR and can be related to the structural properties of the tissue. This presentation will give an overview of the new methods, including basic physical principles, pulse sequences, and data processing, as well as examples of applications in healthy and diseased brain.

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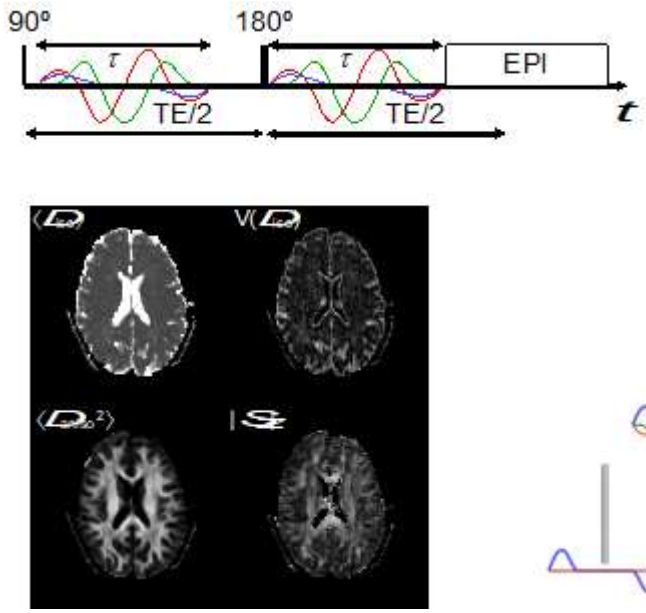

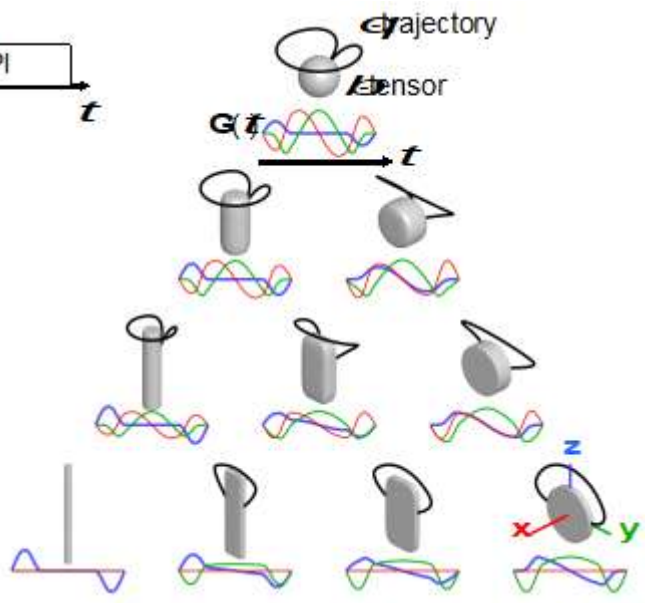

J.-Donald Tournier, King's College London

Diffusion MRI in practice

Diffusion MRI is now widely used for a number of investigations, all related to this technique's unique ability to probe tissue microstructure based on the mobility of (typically) water molecules undergoing thermally-driven self-diffusion. The displacement of these molecules is an inherently stochastic process, influenced by the presence of barriers and other cellular structures on the scale of micrometers (the typical root-mean-square displacement of these molecules over the ~50ms timescale of diffusion MRI experiments). There are two primary areas of application for diffusion MRI: microstructure imaging, and tractography.

The aim of microstructure imaging is typically to infer or estimate microstructural characteristics of the tissue that may be of interest for clinical or scientific investigations. In brain white matter, this can include attempts to estimate the typical axon diameter or the axon diameter distribution, estimate axonal volume fractions, or the intrinsic diffusivity of water within the axonal compartment. In brain grey matter, this can include investigations into dendritic arborisation or neurite orientation distribution (although this type of work is still in its early days). Ideally, microstructural features would be independent of the *meso*-structure (i.e. the larger-scale arrangement of the tissue within each imaging voxel), most prominently the voxel-wise distribution of fibre orientations, or fibre orientation density function (fODF).

The aim of tractography is to provide a reconstruction of the white matter pathways of the brain. This can be used to delineate major eloquent white matter tracts, for example with the aim of planning surgical intervention to minimise the risk of irreversible damage and loss of function (currently this is the only established clinical application of tractography). It can also be used to provide estimate of the 'connectivity' between the end points of white matter pathways, providing the basis for the emerging field of *connectomics*. A crucial prerequisite for tractography is a robust method for estimating the fODF: this is the information that most (but not all) tractography algorithms rely on.

Hence, most practical applications of diffusion MRI to date rely on the ability to cleanly separate microstructure from mesostructure. In the ideal case, it would be possible to estimate both of these aspects simultaneously. This however is a particularly poorly conditioned problem. Instead, most viable techniques currently available rely on simplifying assumptions. For instance, most (if not all) fODF estimators assume that the microstructural features of the tissue are known and constant over the brain (leading to the use of a canonical response function or *kernel* in e.g. spherical deconvolution approaches). This is justified on the basis that biologically plausible variations in microstructure will have a relatively small impact on the kernel, to the extent that errors introduced by any attempt to introduce flexibility in the microstructure parameters will outweigh biases inherent in holding these parameters fixed. Conversely, microstructure imaging methods either restrict themselves to regions assumed to contain a homogeneous, well-behaved

fODF (i.e. a single, known fibre orientation, e.g. the corpus callosum); or make use of rotationally invariant features of the signal to factor out the effect of the fODF.

There is hence scope for approaches that can approximate the statistical properties of the relevant features of the tissue, and more importantly their impact on the diffusion MRI signal, and to identify any relationships, invariants, or other approximations that can be used to simplify the models, and hence develop new methods with sufficient numerical stability for routine use in a practical setting.

Rasmus Waagepetersen, Aalborg University

A brief introduction to spatial point processes

A spatial point process is a random collection of points on some space like the real line, *d*-dimensional Euclidean space $\mathbb{R}^d$ or perhaps on subsets of $\mathbb{R}^d$ like surfaces or curves. We will review basic concepts like the intensity function, the pair correlation function and the *K*-function that characterize the first and second order moments of a spatial point process. We further discuss some specific models for spatial point processes like Poisson, Cox and Gibbs point processes. We finally discuss how random configurations of random objects can be modelled in terms of marked spatial point processes.

Carl-Fredrik Westin, Harvard Medical School