Annual Report 2010


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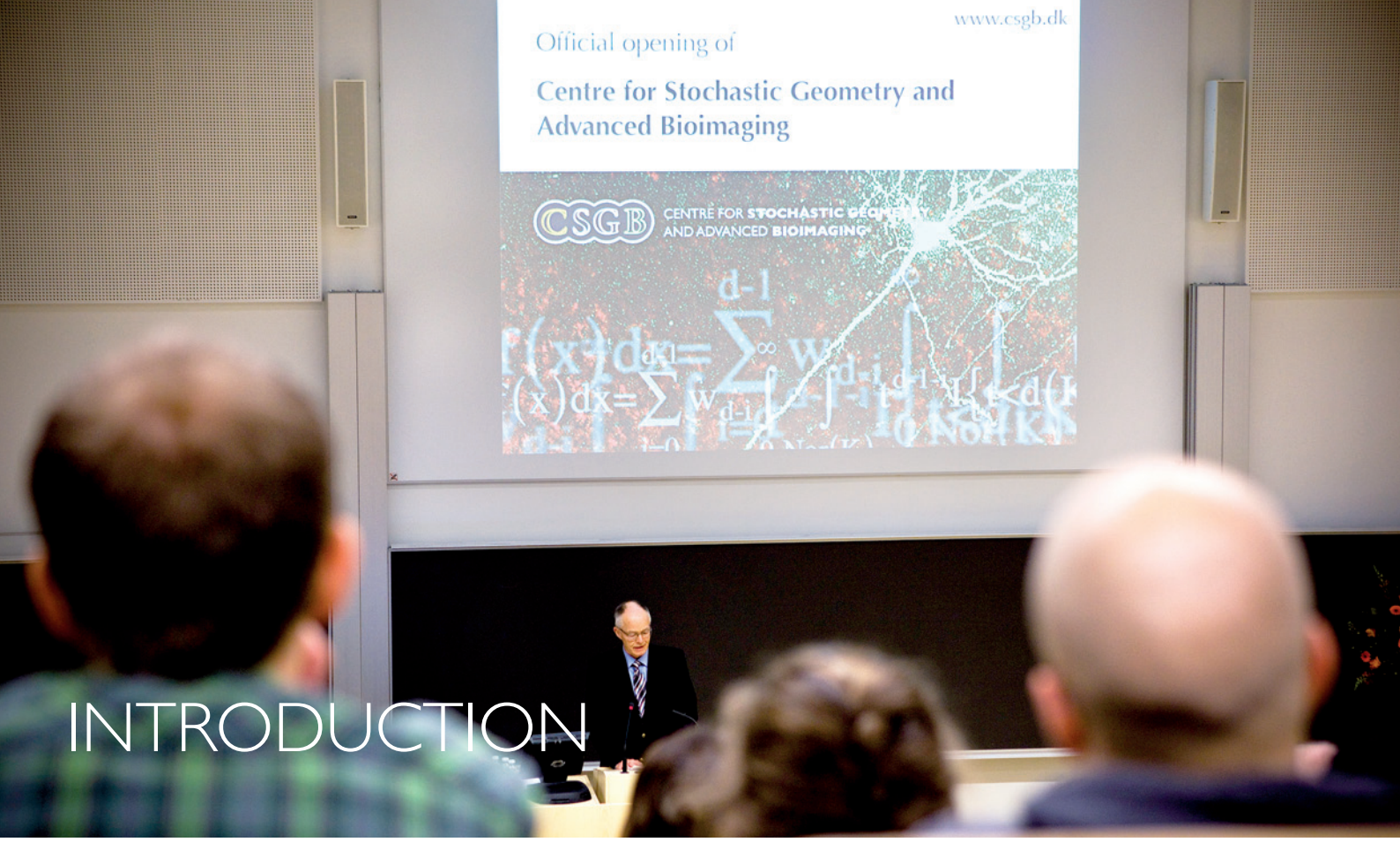
CSGB CENTRE FOR **STOCHASTIC GEOMETRY** AND ADVANCED **BIOIMAGING**

Annual Report 2010



INTRODUCTION

From the official opening of CSGB 2 November 2010. Chairman of the Villum Foundation Lars E. Kann-Rasmussen motivates the establishment of the new VKR Centre of Excellence - CSGB.

CSGB CENTRE FOR **STOCHASTIC GEOMETRY** AND ADVANCED **BIOIMAGING**

Officiel Opening of Centre for Stochastic Geometry and Advanced Bioimaging

The establishment of the new VKR Centre of Excellence, Centre for Stochastic Geometry and Advanced Bioimaging (CSGB), was marked by an official opening 2 November 2010.

At the official programme, Lars E. Kann-Rasmussen (chairman of the Villum Foundation) emphasized the importance and also the uniqueness of this ambitious project. After a short break, the leaders of the participating research groups presented their work and explained how to contribute to this big project. The ceremonial event was completed by four musicians from Aarhus Symphony Orchestra with beautiful music by Haydn.

In 2010, the Villum Foundation donated 25 mill DKK to the new **VKR Centre of Excellence**, Centre for Stochastic Geometry and Advanced Bioimaging (CSGB). The main aim of CSGB is, through a concentrated interdisciplinary collaboration between four Danish research groups, to develop a new generation of stochastic geometry methods of analyzing advanced bioimaging data. A particular focus is on the analysis of molecular microscopy data.

CSGB is an inter-institutional collaboration between the Universities of Aarhus, Aalborg and Copenhagen. Within CSGB, an interdisciplinary network of groups with backgrounds in computer science, stochastic geometry and spatial statistics as well as structural, molecular and cell biology has been formed with the aim of advancing methodologies needed to exploit the potential offered by novel microscopy and other bioimaging techniques.

The new advanced experiments that give access to the molecular level, including **laser scanning** and

From the official opening of CSGB 2 November 2010. In front (from left to right): Erik Meineche Schmidt (dean of Faculty of Science, Aarhus University), Lars E. Kann-Rasmussen (chairman of the Villum Foundation), Lauritz Holm-Nielsen (rector of Aarhus University) and Peter Landrock (member of the board of the Villum Foundation).

cryo-electron microscopy (cryo-EM), require the development of new computer-based mathematical and statistical methods of analysis. In particular, cryo-EM has experienced several successes in recent years with many publications in *Nature* and *Science*, but is now facing a number of barriers that can only be broken in collaboration with mathematicians, statisticians and computer scientists.

Stochastic geometry, a research field at the borderline between mathematics and statistics, has been developed with the purpose of describing geometric structures with random shape fluctuations. Stochastic geometry is expected to play a very decisive role in the development of future methods of analyzing **advanced microscopy** and other types of **bioimaging** data.

With this background CSGB has been established. The mission of the Centre is:

- to develop a new generation of stochastic geometry methods with the ultimate purpose of establishing a mathematical and statistical fundament for computer based analysis of advanced bioimaging data

- to contribute to the education of the next generation of international researchers in this important discipline at the borderline between mathematics, statistics, computer science and bioscience

- to develop the Centre into a leading international player within frontier research and research training in stochastic geometry and its applications in advanced bioimaging

With this annual report, we want to inform our colleagues, potential research students, the Danish funding partner and the Universities of Aarhus, Aalborg and Copenhagen about the organization, research and other centre activities that took place in the first year of CSGB.

March 2011
Eva B. Vedel Jensen

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ORGANIZATION AND STAFF

CSGB SCIENTIFIC STAFF

PROFESSORS

- Eva B. Vedel Jensen (EBVJ)
- Christian Igel (CI)
- Jens Ledet Jensen (JLJ)
- Jesper Møller (JM)
- Mads Nielsen (MN)
- Jens R. Nyengaard (JRN)
- Rasmus P. Waagepetersen (RPW)

ASSOCIATE PROFESSORS

- Johnnie B. Andersen (JBA)
- Kasper Klitgaard Berthelsen (KKB)
- Karl-Anton Dorph-Petersen (KADP)
- Ute Hahn (UH)
- Asger Hobolth (AH)
- Markus Kiderlen (MK)
- François Lauze (FL)
- Kim Stenstrup Pedersen (KSP)
- Andrew du Plessis (AP)
- Jakob G. Rasmussen (JGR)
- Jon Sporring (JS)

ASSISTANT PROFESSORS

- Monika Golas (MG)
- Merete Raarup (MR)
- Björn Sander (BS)

POSTDOCS

- Sune Darkner (SD)
- Aasa Feragen (AF)
- Jürgen Kampf (JS)
- Ege Rubak (ER)

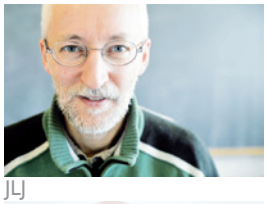
PH.D. STUDENTS

- Camilla Mondrup Andreassen (CMA)
- Sabrina Tang Christensen (STC)
- Mohammad Ghorbani (MG)
- Linda V. Hansen (LVH)
- Katrine Hommelhof (KH)
- Jai Rai (JR)
- Allan Rasmusson (AR)
- Stefan Sommer (SS)
- Ólöf Thorisdottir (OT)

PROFESSORS


EBVJ


CI


JLJ


JM


MN


JRN


RPW

ASSOCIATE PROFESSORS


JBA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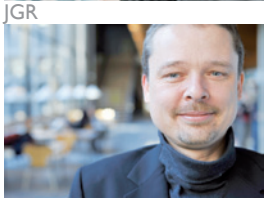
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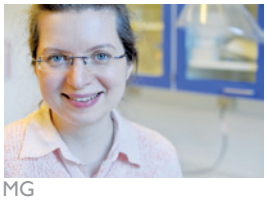
ORGANIZATION AND STAFF

ASSISTANT PROFESSORS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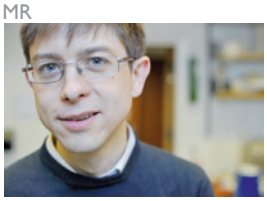
MR


BS

POSTDOCS


SD


AF


ER

PH.D. STUDENTS


CMA


STC


LVH


KH


AR


SS


OT

CSGB ADMINISTRATIVE STAFF AND ADVISORY BOARD

CSGB is directed by Eva B. Vedel Jensen (EBVJ) with Jens R. Nyengaard (JRN) as codirector. EBVJ has earlier been coordinator of the interdisciplinary **Marie Curie** training site **Advanced Medical Imaging and Spatial Statistics** (MISS) in 2002-2006 (16 foreign Ph.D. students). In the period 2004-2007, EBVJ received a major postdoc grant from the Carlsberg Foundation (3 postdoc positions, each of 3 years duration). JRN is in charge of the experimental group at CSGB, working in light and electron microscopy, including advanced fluorescence and cryo-EM microscopy.

Administrative staff

- **Lars Madsen**, it support
- **Daniela Mayer**, design
- **Annette Møller Petersen**, finances
- **Oddbjørg Wethelund**, secretary

Advisory board

- **Professor Håvard Rue**, Norwegian University of Science and Technology, Trondheim, Norway
- **Professor Dietrich Stoyan**, Institute of Statistics, TU Bergakademie Freiberg, Germany
- **Professor Hans Hebert**, School of Technology and Health at the KTH Royal Institute of Technology, Stockholm, Sweden
- **Professor Steven W. Zucker,** Department of Computer Science and Electrical Engineering, Yale University, USA

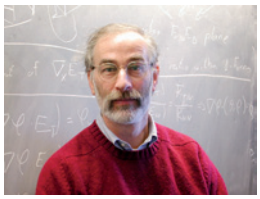
Håvard Rue is Professor in Statistics at the Department of Mathematical Sciences, Norwegian University of Science and Technology. His research interest includes

Bayesian computing and spatial statistics, which is summarized through the R-INLA package, see *www.r-inla.org*. He has been an associate editor of *JRSS Series B, Scandinavian Journal of Statistics, Statistic Surveys, Annals of Statistics* and *Environmetrics*. His main research interest is Gaussian Markov random fields (GMRF) models, and with Professor Leonhard Held he has written a monograph on the subject published by Chapman & Hall. GMRFs are also a main ingredient in his 2009 discussion paper for *JRSS Series B*, co-authored with S. Martino and N. Chopin.

Dietrich Stoyan is Professor Emeritus in Applied Stochastics at Bergakademie Freiberg, Germany. He has also served as Rector of the Academy (1991-1997). Dietrich Stoyan is the grand-old-man of stochastic geometry. He has contributed to a number of areas of stochastic geometry, most prominently in the area of statistics for point processes. Together with Professors Joseph Mecke and Wilfrid Kendall, Dietrich Stoyan published in 1987 the monograph *Stochastic Geometry and Its Applications*. Its second edition (1995) is currently the most cited book on stochastic geometry, and with good reason.

Hans Hebert is Professor in Biotechnology at School of Technology and Health at the KTH Royal Institute of Technology, Stockholm, Sweden. Hans Hebert has earlier held a professorship in cryo electron microscopy at Lund University (2001-2004). In the period 1995-2000, Hans Hebert had a research position at the Swedish Natural Science Research Council. The research focus of Hans Hebert is membrane related processes in living organisms. These processes are dependent on the interplay between the barrier function of the lipids and the mechanisms of membrane proteins. An overall aim is to characterize such processes under close to native conditions. Another focus is the determination of structures of large macromolecular complexes in their unconstrained, physiological states.

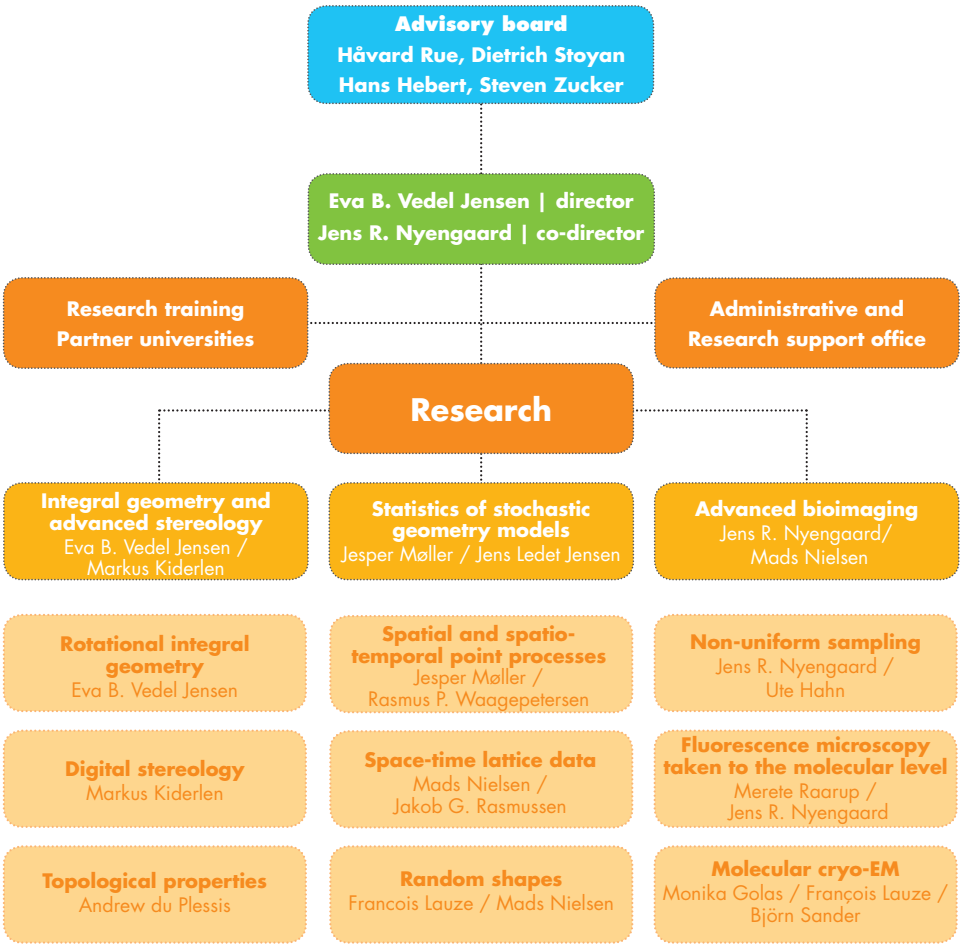
Steven W. Zucker is the David and Lucile Packard Professor of Computer Science and Electrical Engineering



at Yale University. Before moving to Yale in 1996, he was Professor of Electrical Engineering at McGill University, Director of the Program in Artificial Intelligence and Robotics of the Canadian Institute for Advanced Research, and the Co-Director of the Computer Vision and Robotics Laboratory in the McGill Research Center for Intelligent Machines. He was elected a Fellow of the Canadian Institute for Advanced Research, a Fellow of the IEEE, and (by)Fellow of Churchill College, Cambridge. The group of Steven Zucker is aiming at developing an abstract theory of computational vision. Based on differential geometry, it leads to methods of curve detection, shading, texture analysis and generic shape analysis.

OVERVIEW OF ORGANIZATION

CSGB is organized along three streams of research, coordinated by senior scientists of the Centre. Each stream contains three innovative research projects; the principal investigators(s) of each research project is (are) indicated in the diagram below.



Biomedical group

THE FOUR PARTICIPATING RESEARCH GROUPS

Stochastic geometry group

Spatial statistics group

Image group

CSGB joins the following internationally recognized research groups:

- **Stochastic geometry group**, Department of Mathematical Sciences, Aarhus University – led by Professor Eva B. Vedel Jensen

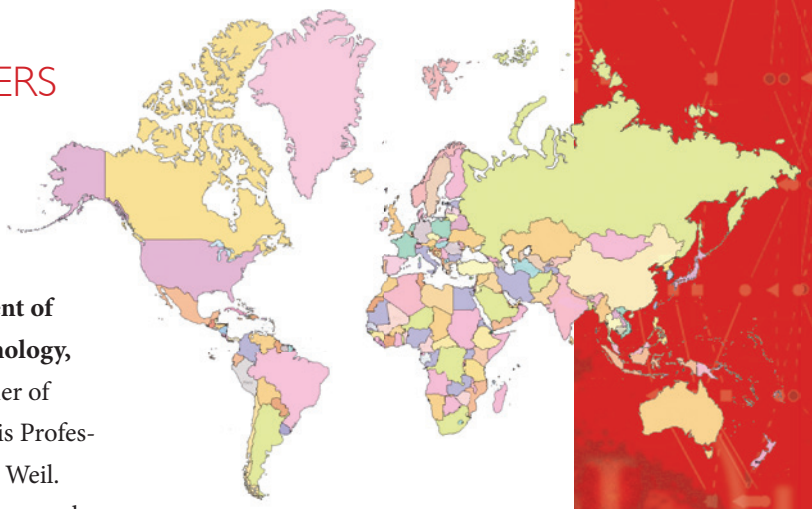
- **Biomedical group, Clinical Institute and Department of Anatomy,** Aarhus University – led by Professor Jens R. Nyengaard

- **Spatial statistics group, Department of Mathematical Sciences**, Aalborg University – led by Professor Jesper Møller

- **Image group, Department of Computer Science**, University of Copenhagen – led by Professor Mads Nielsen

The two Aarhus University groups have had a fruitful collaboration for many years and have in 2007-2010 been supported by the Danish Council for Strategic Research. The stochastic geometry group and the spatial statistics group have in recent years only collaborated informally but this collaboration has now been intensified by the creation of CSGB. The image group contributes with its expertise in image processing, computer simulation, grid computing and visualization. These competences are crucial when analyzing complex microscopy images such as those obtained by cryo-EM.

INTERNATIONAL PARTNERS



The stochastic geometry group, Department of Mathematics, Karlsruhe Institute of Technology, is an important international research partner of CSGB. The senior researchers of this group is Professors Günter Last, Daniel Hug and Wolfgang Weil. The Karlsruhe group is very strong in basic research in stochastic geometry. The group takes active part in the CSGB research stream entitled **Integral geometry and advanced stereology**. Very recently, the Karlsruhe group obtained substantial support from the Deutsche Forschungsgemeinschaft (DFG) and is now a DFG Research Unit. CSGB is the international research partner in this Research Unit.

Professor Adrian Baddeley, CSIRO, Perth, will be the first Crofton Professor at CSGB. These adjunct/guest professorships have been created with the purpose of attracting very strong researchers from abroad to CSGB. Adrian Baddeley is internationally recognized for his research in spatial statistics, especially within the theory and analysis of spatial point processes, but he has also developed very innovative methods in stereology (vertical sections, highly cited). In addition, he has contributed to stochastic geometry and image analysis for decades. His competences are therefore very centrally placed within CSGB. By now, he has intensive research collaboration with three of the four participating research groups at CSGB.

The biomedical group is collaborating closely with **Professor John Bertram**, Department of Anatomy and Developmental Biology, Monash University, Australia. Professor Bertram is currently the Chair of the Healthy Start to Life Research Initiative at his Faculty, which supports and enhances research on embryonic, fetal and postnatal development, and the consequences of suboptimal development for adult health. He is also the Chair of the Executive Committee of the Renal Regeneration Consortium developing new cell-based and factor-based therapies for patients with end stage renal disease. Stereology has been a major tool throughout John Bertram's research.

Daniel Hug

Günter Last

Wolfgang Weil

Adrian Baddeley

THE STOCHASTIC GEOMETRY GROUP (AU-MATH)

Ute Hahn Research Associate Professor
Point processes are the fundamental building blocks of many models in stochastic geometry. Such processes are used to model point patterns observed in biomedical microscopy images. Very often, the task is to decide whether two observed point patterns can be regarded as realizations from the same point process model.

In 2010, Ute Hahn has developed an ingenious non-parametric method of testing whether this hypothesis is true. A paper has been submitted to the prestigious *Journal of the American Statistical Association*. It is expected that it is possible to extend the test such that it can be used for distinguishing different models for inhomogeneous point patterns. Due to the generous donation from the Villum Foundation, it has been possible to employ Ute Hahn as CSGB researcher for a four year period.

The stochastic geometry group at Department of Mathematical Sciences, Aarhus University, has been built by Eva B. Vedel Jensen. The group is recognized worldwide for its groundbreaking research in mathematical stereology. The local stereological methods developed by the group are now used as central tools in an unusually wide range of disciplines, including medicine, biology and materials science. The group has been able to cover the full spectrum from very advanced mathematical research to practical applications within all these disciplines.

The group comprises at present two full professors and four associate professors with unique competences within stereology, stochastic geometry, topology, singularity theory and statistical inference for high dimensional data.

THE SPATIAL STATISTICS GROUP (AAU)

The spatial statistics group, Department of Mathematical Sciences, Aalborg University, is the leading research group worldwide within spatio-temporal point process modelling and simulation methods based on MCMC (Markov Chain Monte Carlo simulation). The group is directed by Jesper Møller who in 2008 was selected by 'Essential Science Indicators' as 'Rising Star' due to his highly cited papers in leading international mathematical journals.

The spatial statistics group at Aalborg University comprises two full professors, two younger associate professors and a postdoc with cutting edge competences within inhomogeneous point processes, spatio-temporal point processes, generalized mixed models, MCMC and perfect simulation. The group collaborates intensively with internationally leading researchers within these active research areas.

Rasmus Waagepetersen full Professor in Mathematical Statistics

On 10 June 2010, Rasmus Waagepetersen gave his inaugural lecture ***Cox process analysis of clustered point patterns*** as full professor at Department of Mathematical Sciences, Aalborg University.

Rasmus Waagepetersen is member of the spatial statistics group from Department of Mathematical Sciences, Aalborg University. This group is the leading research group worldwide within spatio-temporal point process modelling and simulation based on MCMC (Markov Chain Monte Carlo simulation).

Within CSGB, the spatial statistics group participates in the project **Fluorescence microscopy taken to the molecular level**. One of the aims of this project is to develop stochastic geometry/point process models for bivariate configurations of proteins in cells. Signals from FRET (Fluorescence Resonance Energy Transfer) microscopy depend on the model considered and this has important implications for the estimation of the so-called K_d values.

THE BIOMEDICAL GROUP (AU-BIO)

Monika Golas is Young Researcher of the Year 2010

Dr. Monika Golas, 34, has been awarded the Ung Elit-eforskerpris 2010 from Det Frie Forskningsråd (DFF). DFF has thereby granted support for her research related to the structural understanding of protein complexes, which are involved in the regulation of gene expression and development of cancer. Concurrently with her degree in Human Biology, Monika Golas took a degree in Medicine and completed both educations with outstanding grades within the standard period of study. Alongside her degree in Medicine, she completed a doctorate in Biochemistry, which was granted "summa cum laude", in less than four years.

The biomedical group, Stereology and EM Research Laboratory and Department of Anatomy, Aarhus University, is directed by Jens R. Nyengaard who is a leader in quantitative microscopy and has well-established competence in cell and tissue processes for light, fluorescence and electron microscopy. Under the direction of Jens R. Nyengaard, the Laboratory has since 2001 published nearly 200 papers in international scientific journals on new quantitative principles and their application in biomedicine.

Five years ago, the Laboratory established a new group working with advanced fluorescence microscopy, using a 2-photon confocal microscope with membrane-bound neuroreceptors. Lately, the implementation of a new cryo-EM facility at Aarhus University has become possible because we have been able to recruit two excellent researchers, Monika Golas and Björn Sander, each with ten years experience from the prestigious Max Planck Institute for Biophysical Chemistry, Göttingen, Germany. Cryo-EM is the method of directly visualizing macromolecules.

THE IMAGE GROUP (KU)

The image group, Department of Computer Science, University of Copenhagen, is internationally leading within the central area of mathematical and statistical shape and image modelling and its applications in biomedical image analysis. The group has unique competences in stochastic shape modelling, application of stochastic partial differential equations in image enhancement and fitting of statistical image models and the interplay with differential geometry.

The group comprises two full professors and seven associate professors and publishes on a yearly basis more than 50 papers in leading international journals and proceedings volumes. Five of these senior researchers participate in CSGB. Under the direction of Mads Nielsen, the group has maintained an internationally unique combination of mathematical depth and application driven research in image analysis and pattern recognition. The primary application areas have until now been in cardiovascular disease, osteoporosis, osteoarthritis, breast cancer and smoker's lung disease.

Stefan Sommer among the 3% Selected for Oral Presentation

A paper on manifold valued statistics and the PGA method by Stefan Sommer together with members of the Image Group, University of Copenhagen, was among the 3% of total submissions selected for oral presentation at the European Conference on Computer Vision 2010. Stefan Sommer, 2nd year Ph.D. student, is MSc in mathematics with minor in computer science from University of Copenhagen in 2009.

The work being part of the **Random shapes** project presents new computational methods for non-linear statistics and evaluates the effect of curvature on different shape spaces. This approach of using methods from geometry and geometric analysis in modelling in computer science has been very fruitful and has since resulted in the development of a new model for registration of geometric objects, merging ideas from scale space and Lie group theory.

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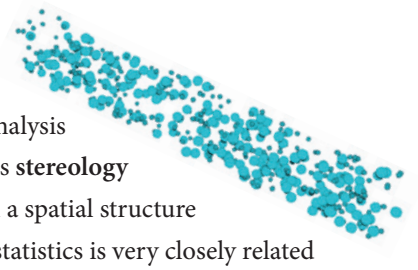
RESEARCH

BACKGROUND AND STATE OF THE ART



Stochastic geometry is concerned with modelling and analysis of random geometric structures. An important subfield is **stereology** by means of which valid information can be obtained on a spatial structure from sections through the structure. The field of spatial statistics is very closely related to stochastic geometry with definite overlaps between the two fields. **Spatial statistics** provides methods of statistical analysis of stochastic geometry models. The analysis often involves **computer simulation and visualization**.

Basic problems to attack in bioimaging

- we never observe directly what we want – instead we observe, for instance, sections and projections
- it is not enough just to look at the images – we need objective ways of describing the images
- bioimages may be extremely noisy – often we go to the limit for what is possible to observe

Neurobiology challenges spatial statistics

The cerebral cortex is structured both horizontally in six layers parallel to the brain surface as also vertically into columnar arrays that are visible on microscopical sections at least in parts of the brain. The vertical structures are believed to be built of small functional units, so called micro- or minicolumns, that measure about 30-80 micrometers in diameter and consist of roughly ten to a hundred neurons and accompanying glia cells. A loss of microcolumnar organization has been reported in brains with Alzheimer disease, and Autism has been associated with smaller microcolumn diameter.

Still, the proper way to detect and quantify microcolumns is subject to controversial discussion, and even their existence is questioned. Previous investigations are often based on two dimensional images of thin sections that fail to reflect fine vertical structures which do not run parallel to the section plane. With modern light microscopy equipment, it has become possible to register 3D coordinates of cells. Such data could help to clarify the hypotheses about existence or size of microcolumns. This requires the development of new, taylor-made statistical methods for the analysis of inhomogeneous 3D spatial point processes and appropriate models. The analysis is hampered by the fact that data collection is extremely time consuming and therefore usually restricted to very narrow windows, as shown in Figure 1. A CSGB team consisting of members of the Aalborg group and both Aarhus groups has just started to tackle this challenge.

Figure 1:
A thin slice of a section of the neocortex perpendicular to the brain surface, seen from above and sideways. 3D positions of neuron cells and glial cells are depicted as large and small spheres, respectively. Cortex layers are indicated by different colours. The dimensions of specimen are about 2600 µm x 150 µm x 80 µm. Data by courtesy of Dorte Pelvig, København.

One of the important contributions of stochastic geometry has been to supply a number of geometric functionals that describe global properties of a spatial structure. Classical functionals are the intrinsic volumes (volume, surface area, length, number, Euler characteristic and other curvature integrals). These functionals deliver first order information about the random geometric structures and have been used extensively in the stereological studies of biostructures at the light microscopic level.

There is now an increasing interest in going beyond this global analysis that leaves subtle changes in the spatial arrangement of the biostructure unnoticed. For example, in the stereological studies of the cerebral cortex of the human brain of subjects with dementia or schizophrenia, no major changes in total cell number have been found. Some postmortem studies of schizophrenia have, however, reported changes in the spatial arrangement of cells in specific cortical areas. There is therefore a need for developing methods by means of which more detailed non-global information about the structure can be obtained. Important examples relate to description of **anisotropy, inhomogeneity** and **relative positioning** of parts of a biostructure.

Local stereological methods, developed by CSGB researchers through the last 25 years, constitute now the mathematical and statistical fundament of the quantitative study of cell size at the light microscopy level. Since disease-caused changes in tissue may leave the size distribution of cells unaffected and instead affect shape or orientation distributions, there is a need to go beyond description of cells in terms of volume or surface area and in addition develop flexible local methods of describing cell orientation distribution, shape distribution, symmetry, etc.

During the last decades, **stochastic geometry** has provided a wealth of stochastic models. Most of these models have point processes as fundamental building blocks. Until now, stochastic geometry models have not had the influence in **bioimaging**, especially in **quantitative microscopy**, that they deserve. It is therefore necessary to explore the use of stochastic geometry models more extensively in microscopy and generally in bioimaging. In particular, the obvious potential of point process models in the analysis of spatial arrangements of cells has not yet been thoroughly investigated. This model class may also be used in noise reduction at the molecular microscopy level.

On the other hand, quantitative microscopy and bioimaging also challenge stochastic geometry. The intriguing mathematical and statistical questions arising from the study of the connection between objects in the real world and their digital representations are still not fully understood. The new advanced experiments within microscopy that give access to the molecular level, including laser scanning microscopy and cryo-EM, require the development of completely new stochastic geometry models for series of random fields. Especially cryo-EM has experienced several successes in recent years with many publications in *Nature* and *Science*, but is now facing a number of barriers concerning speed and optimization that can only be broken in collaboration with mathematicians, statisticians and computer scientists.



COLLABORATIVE PROJECTS

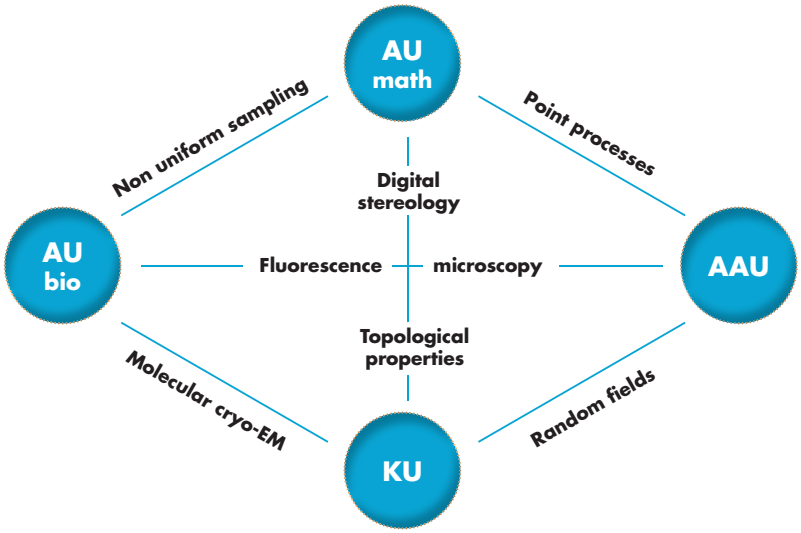
When developing the research plan of CSGB, it was realized that a number of the planned research projects needed the participation of at least two of the four research groups in CSGB, see the diagramme.

During 2010, it has been decided *to start five of the planned seven collaborative research projects*:

• The project **Non uniform sampling** has considerable applied interest in microscopy. At the moment, the principle has been put forward in the scientific literature and it has been shown that drastic reductions in estimator variances may be obtained by using non-uniform sampling compared to traditional systematic uniform sampling. If this technique is going to be widely used in microscopy, it is needed to fully develop the statistical inference for microscopy data obtained by this type of weighted sampling. A Ph.D. student, jointly supervised by AU-math and AU-bio, has been allocated to this project.

• **Molecular cryo-EM** represents an advanced technique to study 3D structures of many biological macromolecules. Projection images of frozen cellular particles are recorded in an electron microscope and afterwards three-dimensionally reconstructed with the help of computers. However, a special challenge encountered in this process is the very high level of noise as well as initially unknown projection parameters. In this respect, optimizations of the 3D reconstruction process can contribute to improvement of 3D structures determined by cryo-EM. A Ph.D. position has been allocated to the work with cryo-EM image data and the development and evaluation of 3D algorithms. The Ph.D. student will be supervised by Mads Nielsen from the image group at University of Copenhagen but will have regular visits to the cryo-EM group at Aarhus University.

• In the collaborative project between the AU-bio and AAU groups on **Fluorescence microscopy taken to the molecular level**, Ege Rubak has in 2010 been appointed as postdoc with main base at the AAU group but with weekly meetings with both AU groups. The aim of the fluorescence project is to develop advanced mathematical and statistical inference procedures for fluorescence microscopy data, primarily FRET (Fluorescence Resonance Energy Transfer) data. Such data can be characterized as multivariate random fields.



• The project on **Topological properties** has shown some interesting new directions in 2010. The KU group has considerable expertise in noise removal in bioimages with a complicated topological structure. It is planned to use this expertise in noise removal of diffusion tensor images. The critical issue is here to remove noise without destroying the topological structure of the images, including information about nerve fibre bundles that cross each other inside a voxel. In diffusion tensor imaging, a tensor (positive-definite quadratic form) is observed in each voxel and the eigenvector of the largest eigenvalue is used as a representative of the preferred direction of the nerve fibres in the voxel. This approach is not appropriate at voxels with crossing fibre bundles. Several other approaches are possible. In essence, the idea is to replace the tensor by a positive function on the sphere. A Ph.D. student has been allocated to this collaborative project between the KU and AU-math groups. The Ph.D. student will have main base at the KU group.

• The AU-math and AAU groups have a number of plans for joint projects within the subproject **Point processes**. This includes modelling the interaction between proteins binding at the surface of cells and the modelling of alignments in so-called minicolumns of neurons in the human brain cortex. A Ph.D. student has been allocated to this project with main base at the AAU group.




CSGB minisymposium on Recent Advances in Integral Geometry

On 14 October 2010, a minisymposium on *Recent Advances in Integral Geometry* was held at Department of Mathematical Sciences, Aarhus University. The main lecturers were Professor Daniel Hug, Karlsruhe Institute of Technology, and Professor Ximo Gual-Arnau, Universitat Jaume I, Spain.

ROTATIONAL INTEGRAL GEOMETRY

As an ambitious goal, CSGB intends to develop a theory of rotational integral geometry, dual to the theory of translative integral geometry (Schneider & Weil, 2008). This theory will combine Alesker's profound work (Alesker, 1999) on rotation invariant valuations, published in the prestigious *Annals of Mathematics*, with recent work done by CSGB researchers and colleagues (Jensen & Rataj, 2008; Gual-Arnau & Cruz-Orive, 2009; Gual-Arnau *et al.*, 2009).

In 2010, rotational integral geometry for intrinsic volumes has been fully developed, see Auneau-Cognacq (2010), Auneau & Jensen (2010) and Auneau *et al.* (2010). Especially, Auneau-Cognacq (2010) represents a breakthrough because here a new type of weighted intrinsic volumes, so-called **flagged intrinsic volumes**, is introduced for which a genuine rotational Crofton formula holds. These new flagged intrinsic volumes and their connection to flag measures will be further investigated in 2011 and onwards. The results have been obtained in close collaboration with Jan Rataj, Charles University, Prague.

Some first attempts to derive **rotational integral geometry formulae for tensor valuations** were also made in 2010 in collaboration with Professor Daniel Hug from the Karlsruhe stochastic geometry group and postdoc Johanna Ziegel, Heidelberg. Stereology for tensor-valued functionals has a totally different character than stereology for scalar-valued functionals and requires clever 3D sampling. These issues have been discussed with researchers from the AU-bio group. In 2011, it is planned to design concrete pilot experiments to evaluate the practicability of these 3D designs.

Rotational integral geometry of tensor valuations is expected to be the key tool in developing new local stereological methods of analyzing the distribution of cell orientation and shape.

The focus points at the minisymposium were tensor valuations and rotational geometric identities. The minisymposium has been followed up by a course on *Advanced Valuation Theory*, 14-18 March 2011, Aarhus, given by Professor Andreas Bernig, Goethe-Universität, Frankfurt.

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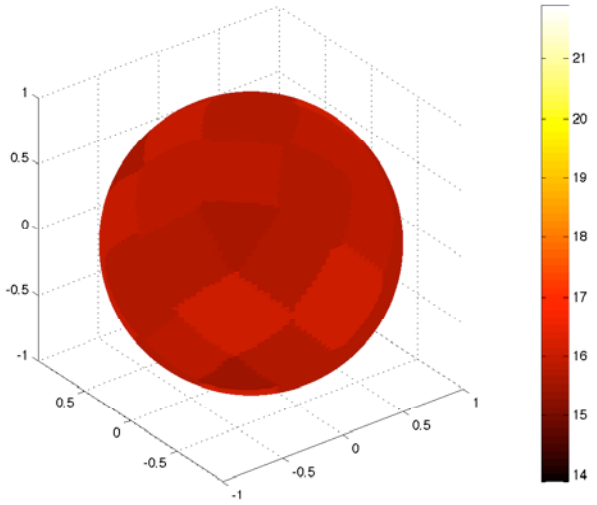

DIGITAL STEREOLOGY

This project, concerned with the estimation of geometric characteristics from discrete binary images of a structure, has made considerable progress in the first year of the CSGB.

The now-published work Ziegel & Kiderlen (2010a) on **surface area estimation** from local counts in voxel images, has been extended in Ziegel & Kiderlen (2010b) to a stereological setting: Configuration counts are now observed in a digitization of an isotropic randomized thin slice through a fixed reference point. We were able to define a surface area estimator based on this data, which is unbiased for simple shapes such as balls centered at the reference point. For general shapes the asymptotic expected relative worst case error was shown not to exceed 4.7%, and turned out to be considerably smaller in several simulation examples.

Binary configuration counts actually not only contain global information on the surface of an object, but also indicate the direction of a typical surface normal. This was used in Ziegel & Kiderlen (2010a) to estimate the **rose of normal directions** from binary data. In Figure 1 estimates of the roses of normal directions for an isotropic and a non-isotropic shape are shown - indicating the potential of such reconstructions to identify surface anisotropy.

The above defined digital estimators for surface area are based on a powerful asymptotic formula (Kiderlen & Rataj, 2006) for contact distributions with finite structuring elements. It generalizes the fact that the directional derivative of the set-covariogram of a convex set is proportional to its projection area in the given direction. Quite recently, it was shown in Galerne (2011) that a generalization of the latter result holds

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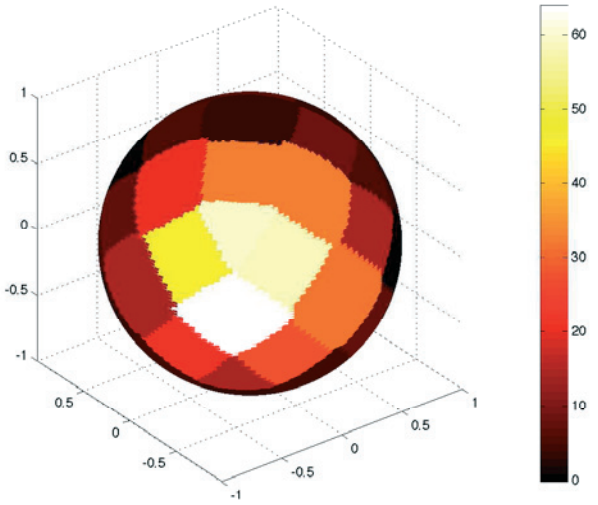


Figure 1: Surface area measure estimates of a unit sphere (left) and an oblate spheroid (right).

for a **very general class of sets**, namely so-called sets with bounded perimeter. First results in a working paper Kiderlen & Rataj (2011) by members of the CSGB group and Jan Rataj, Prague, indicate that this new combination of the theory of generalized functions and geometric reasoning allows to extend the asymptotic formula in Kiderlen & Rataj (2006) to this general set-class. This will allow to omit - in retrospective unnecessary and rather complicated - assumptions on the regularity of the digitized structure.

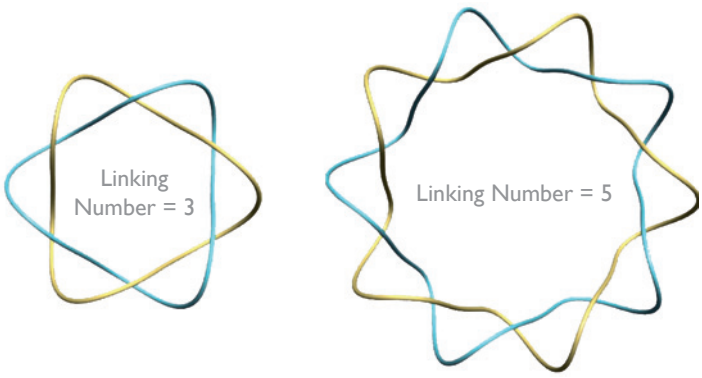
Concerning the estimation of other intrinsic volumes than volume or surface area, we have in 2010 focused on the evaluation of existing local digital algorithms for standard (random) set models like the stationary Boolean model in n-dimensional space. None of the known local digital algorithms leads to unbiased estimates of the specific intrinsic volumes of this model. An analysis of the bias requires a purely geometric Laurent expansion of **large parallel volumes** for finite sets in R^n. Such expansions will be provided in a forthcoming paper Kampf & Kiderlen (2011) by Jürgen Kampf, Germany, and members of the CSGB group, see also Kampf (2010). These results pave the way to an exhaustive analysis of the bias in the planar case (n=2), which is the next mid-term project. The exciting new feature of these results is that the bias is not only available asymptotically, but depends explicitly on the finite resolution of the digitization. The higher dimensional analogues (n>2) are in reach but will certainly require individual treatment of algorithms, depending on the underlying adjacency system.

In 2010, methods of evaluating the effect of variation of voxel size have also been developed (Ziegel *et al.*, 2010a, b). Both papers will appear in the prestigious journal *Biometrika*.

TOPOLOGY AND DIGITAL IMAGE ANALYSIS

Modern light, laser and electron microscopes, as well as scanners, yield digital pixel (two-dimensional) or voxel (three-dimensional) images; it is therefore crucial for the analysis of microscopy results that the interplay between objects in the real world and their digital representations be well understood.

Given an object in two or three dimensions with a **smooth boundary**, any digitalisation of **sufficiently high resolution** of the object preserves its topology; the required resolution is related to the curvature of the boundary. This has been known since 1982 in the two-dimensional case, but only since 2007 in the three-dimensional case. In as yet unpublished work, done in connection with CSGB, the result has been sharpened, to etablish an ambient isotropy between an object, again with smooth boundary, and any digitalisation of sufficiently high resolution; this ensures, for example, that knotting of the object is accurately reflected in the digitalisation.



It remains an open question to what extent the full differential-geometry structure of the object's boundary can be reconstructed from a digitalisation – so that, for example, curvature and surface area are well-approximated in a reconstruction. A promising approach to this question is to use **an ambient isotropy** connecting an inner and an outer digitalisation, and to seek a section of this minimising curvature and surface area.

For objects with **singular boundary** it is no longer necessarily true that a digitalisation no matter how fine the resolution, preserves the topology; and thus analysis of the

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object via digitalisation will require a family of possible reconstructions. Clearly it is important to be able to describe families of this kind; a natural approach is to describe the family in terms of which singularities are present on the boundaries of the reconstructed object.

This project is being worked on by Andrew du Plessis and Sabrina Tang Christensen, as well as Markus Kiderlen.

NEW TOPOLOGICAL SUMMARY CHARACTERISTICS FOR THE ANALYSIS OF RANDOM POINT PATTERNS

In Mecke & Stoyan (2005), it has been suggested to consider specific Minkowski functionals of the r-parallel set of a stationary point process in the plane. The geometric idea is that specific area, perimeter and Euler-Poincaré characteristic of the union of all disks with radius r centered at the points of the point process will reveal cluster- and hard-core tendencies when r varies.
Based on the observation that the specific Euler-Poincaré characteristic appears to have the strongest discriminative power, this CSGB project has focused on similar topological quantities related to r-parallel sets X_r of point processes X.

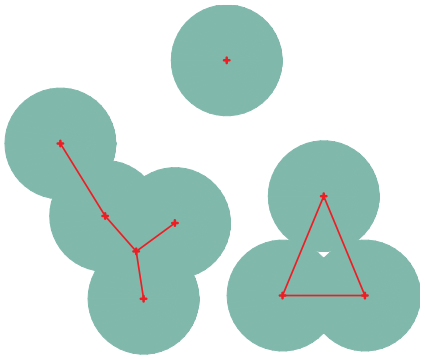


Figure 1:
Medial axis (red) of a union of 8 disks in R^2.

The topology of X_r is captured by its medial axis, see Figure 1, consisting of all points in X_r for which there are more than one closest point in the boundary of X_r. This set turns out to be a random planar graph, and the (specific) number of its vertices or edges may give valuable topological information. It is important for applications to describe the behavior of these new summary statistics in the case of established point process models. Kiderlen & du Plessis (2011), in preparation, discuss this issue when X is a stationary Poisson point process. In this case, a beautiful classic distribution result (Siegel & Holst, 1982) on the number of connected components of a Boolean model of arcs on the unit circle can be used to determine the new summary characteristics numerically; see Figure 2. This paper is scheduled for submission in mid-2011.

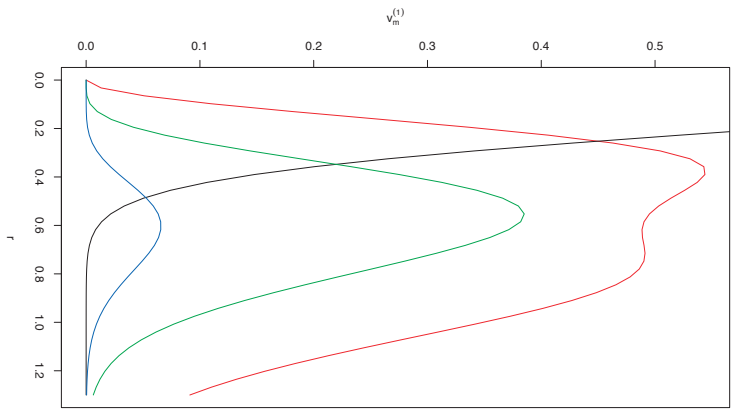


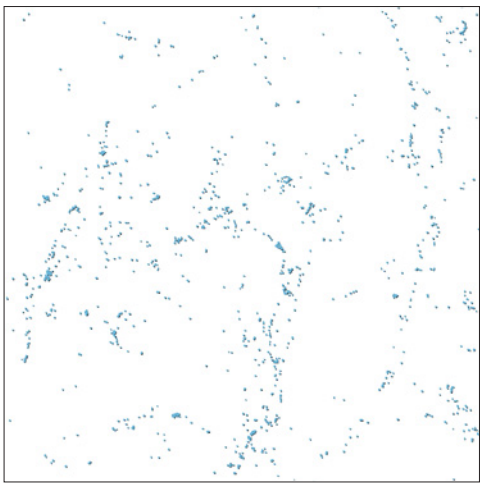
Figure 2:
The specific numbers of vertices of the medial axis of X_r as functions of r for a Poisson process X. The colours indicate the degree of the vertices: zero (black, isolated vertices), one (red, 'dead ends'), two (green, kinks) and three (blue, 'Y-crossings').

SPATIAL AND SPATIO-TEMPORAL POINT PROCESSES

During 2010, a number of advanced statistical inference procedures for spatial and spatio-temporal point processes have been developed. In Baddeley, Rubak & Møller (2010) **new tools for formal inference and informal model validation** in the analysis of spatial point pattern data are introduced. The score test is generalized to a 'pseudo-score' test derived from Besag's pseudolikelihood, and to a class of diagnostics based on point process residuals. The results lend theoretical support to the established practice of using functional summary statistics such as Ripley's K-function, when testing for complete spatial randomness; and they provide new tools such as the compensator of the K-function for testing other fitted models. The results also support localisation methods such as the scan statistic and smoothed residual plots. Software for computing the diagnostics is provided.

Most finite spatial point process models specified by a density are locally stable, implying that the Papangelou intensity is bounded by some integrable function β defined on the space for the points of the process. It is possible to superpose a locally stable spatial point process X with a complementary spatial point process Y to obtain a Poisson process $X \cup Y$ with intensity function β. Underlying this is a bivariate spatial birth-death process which converges towards the distribution of (X, Y). Møller & Berthelsen (2010) study the joint distribution of X and Y and their marginal and conditional distributions. In particular, they introduce a fast and easy simulation procedure for Y conditional on X. This may be used for **model checking**. Whether the superposition is actually such a Poisson process can easily be examined using well known results and fast simulation procedures for Poisson processes. Møller & Berthelsen (2010) illustrate this approach to model checking in the case of a Strauss process.

Møller & Rasmussen (2010) introduce a flexible spatial point process model for spatial **point patterns exhibiting linear structures**, without incorporating a latent line process. The model is given by an underlying sequential point process model, i.e. each new point is generated given the previous points. Møller & Rasmussen (2010) demonstrate the flexibility of the model for producing point patterns with linear structures, and propose to use the model as the likelihood in a Bayesian setting when analyzing a spatial point pattern exhibiting linear structures but where the exact mechanism responsible for the formations of lines is unknown.



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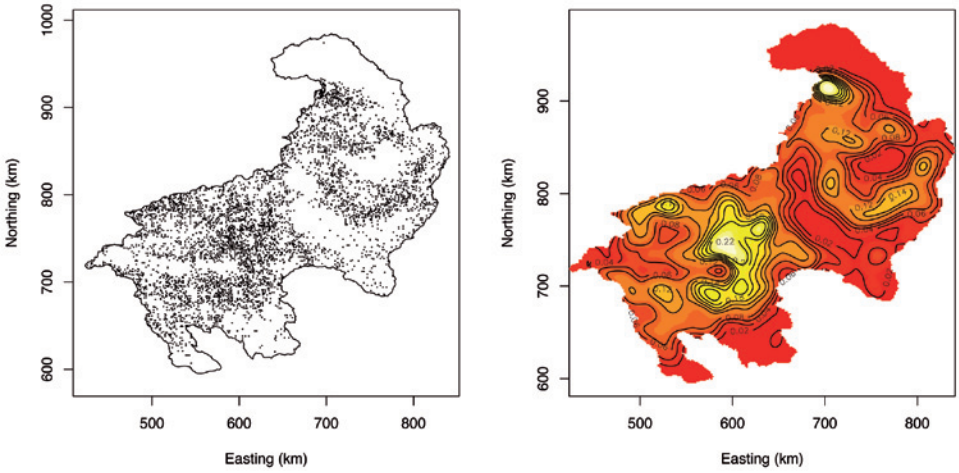


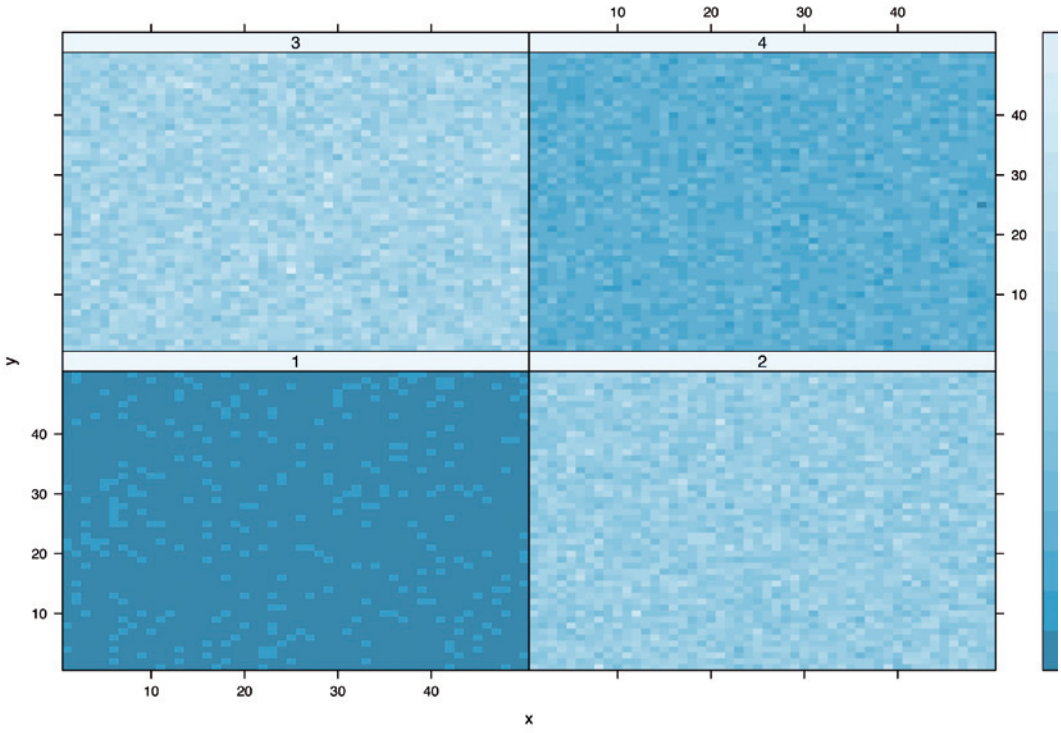
From Møller & Diaz-Avalos (2010). *Scandinavian Journal of Statistics* **37**, 2-25.

Statistical methodology for spatio-temporal point processes is in its infancy. Møller & Ghorbani (2010) consider **second-order analysis** based on pair correlation functions and *K*-functions for first general **inhomogeneous spatio-temporal point processes** and second inhomogeneous spatio-temporal Cox processes. Assuming spatio-temporal separability of the intensity function, they clarify different meanings of second-order spatio-temporal separability. One is second-order spatio-temporal independence and relates e.g. to log-Gaussian Cox processes with an additive covariance structure of the underlying spatio-temporal Gaussian process. Another concerns shot-noise Cox processes with a separable spatio-temporal covariance density. Møller & Ghorbani (2010) propose diagnostic procedures for checking hypotheses of second-order spatio-temporal separability.

The majority of statistical methods for the analysis of spatial point processes aim at characterizing the arrangement of points by summary statistics or at fitting parametric models to observed data. Literature on statistical tests for point processes almost exclusively concerns goodness of fit; to the best of our knowledge the only non-parametric tests have been proposed by Peter Diggle and coworkers (1991 and 2000) for the comparison of groups of independent replicates. According to a brief query on the web, about half of the more than hundred citations of these two papers concern analysis of mainly biomedical microscopy images. In many applications, however, observations consist of a single point pattern per group, and independent replications are not available. To fill this gap, a non-parametric studentized permutation test that allows the **comparison of two** (or more) **single, non replicated, point patterns** has been developed in Hahn (2010). This test will form the base of a test of model classes for inhomogeneous spatial point processes in a forthcoming paper by A.J. Baddeley, U. Hahn and E.B.Vedel Jensen.

Palm likelihood methods for statistical inference in spatial point processes are studied in Prokešová & Jensen (2010).

SPACE-TIME LATTICE DATA



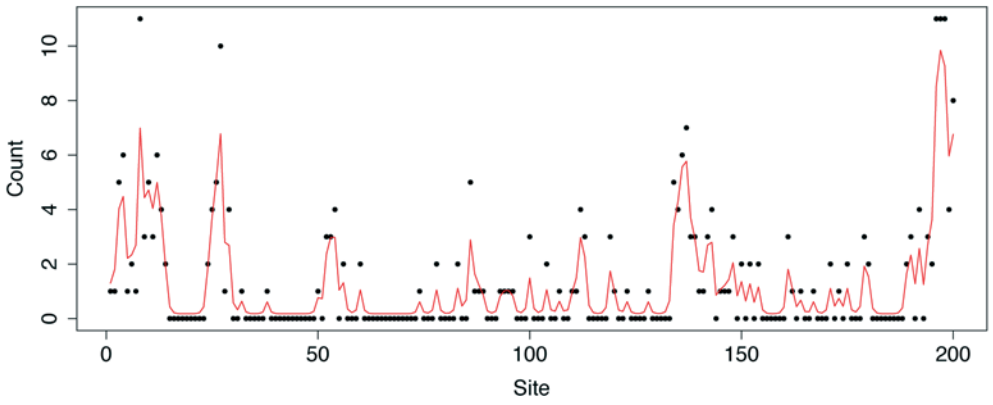
From Møller & Rubak (2010).

This CSGB project concerns statistical inference for space-time lattice data with emphasis on data generated in important bioimaging applications, where typically the sites of the lattice corresponds to pixels or voxels in a 2D or 3D digital image. To each site, one or several response variables may be associated, which are highly depending on the spatial neighbouring response variables observed at the same or previous time instances. The advanced bioimaging data may be binary (indicating e.g. the presence or absence of molecules), of counting type (e.g. indicating number of molecules), or continuous and possibly also multivariate (e.g. in FRET microscopy). In 2010, the focus has mainly been on modelling of binary data and counting data.

Rubak, Møller & McCullagh (2010) consider statistical inference procedures for a class of models for positively correlated count variables called **α-permanental random fields**. These random fields can be viewed as a family of multivariate negative binomial distributions. Their appealing probabilistic properties have earlier been studied in the literature, while this is the first statistical paper on α-permanental random fields. The focus is on maximum likelihood estimation, maximum quasi-likelihood estimation and on maximum composite likelihood estimation based on uni- and bivariate distributions. Furthermore, new results for α-permanents and for a bivariate

α-permanental random field are presented. In particular, the models and statistical inference procedures can be used for lattice processes in a spatial or spatio-temporal setting.

From Rubak, Møller & McCullagh (2010).



A probability model has been developed for a binary image lattice that is capable of modelling the appearance and shapes of calcifications in X-ray radiographs (Ganz *et al.*, 2010). The model can be characterized as a **generative shape model** for archipelago-like structures and has been constructed such that it facilitates sequential simulation. The generative model has been constructed by (1) learning a patch-based dictionary for possible shapes, (2) building up a time-homogeneous Markov model to model the neighbourhood correlations between the patches, and (3) automatic selection of the model complexity by the minimum description length principle. Our results show that a relatively simple model is able to generate structures visually similar to the training images. Furthermore, the model has been used as **shape prior** in the statistical segmentation of calcifications, where the area overlap with the ground truth shapes improved significantly compared to the case where the prior was not used.

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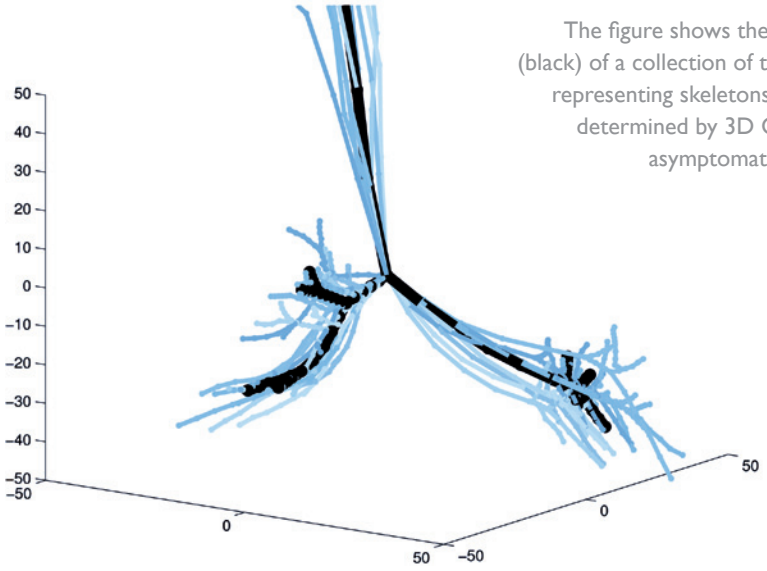
RANDOM SHAPES



The figure shows the mean tree (black) of a collection of trees (blue), representing skeletons of airways determined by 3D CT scans in asymptomatic smokers.

Various ways of defining shape are available. D.G. Kendall used labeled point sets (Kendall, 1984) where position (most often represented as the similarity group: translation, rotation, scale) is factored out. By such a representation, shapes become points in a complex projective space. An alternative, that has been adopted in the present project, is to represent shapes as (closed) curves in the plane or as surfaces in 3D space. In such a representation of shape, arbitrary reparameterizations of the curves/surfaces are factored out in addition to the similarities, as these are not geometrical.

To implement **statistical testing in shape spaces**, the space must be equipped with a suitable metric. Furthermore, due to the intrinsic curvature in most shape spaces, statistical tests must be translated to curved spaces.

In Kendall's shape space a metric may be inherited from the embedding space without conceptual problems. However, the reparametrization to be factored out for curves and surfaces makes the metric in the shape space degenerate if the inherited L2 metric from the embedding space is used (Michor & Mumford, 2006). This has been repaired in various technical fashions: Charpiat *et al.* (2005) has restricted the space of curves to curves of bounded curvature, Sundaramoorthi *et al.* (2007) has substituted the L2 norm by a Sobolev norm, Sommer *et al.* (2009) has discretized the curve into a finite number of equidistant points, and metrics induced by groups of diffeomorphisms have been studied in the LDDMM framework.

During 2010, we have concentrated on the two last approaches. The shape models of Sommer *et al.* (2009) have been extended to allow for freedom in the choice of embedding space metric resulting in **spline models for curves with equidistant control**

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points. The increased stability offered by this model is in particular useful when optimizing over the space of curves. The approach has been used for image segmentation (Tatu *et al.*, 2010). The distribution of a set of human vertebrae outlines has been studied with the PGA approach in Sommer *et al.* (2010a), and the study has resulted in **new computational methods for manifold valued statistics**.

Groups of diffeomorphisms act on geometric objects including curves and allow the study of curves to be lifted to the study of suitable spaces of diffeomorphisms. We have extended the LDDMM model, which introduces a metric on such spaces, to simultaneously include several regularization measures and, in particular, introduce a mechanism for **measuring warps at different scales**. The construction promises to introduce sparsity and allow statistics incorporating scale information as well as removing the need for scale selection when defining the regularizing measures (Sommer *et al.*, 2010b).

Finally, work on defining metrics on **tree-like geometric shapes** with varying topology has been initiated leading to first potential useful constructions (Feragen *et al.*, 2010a, b).

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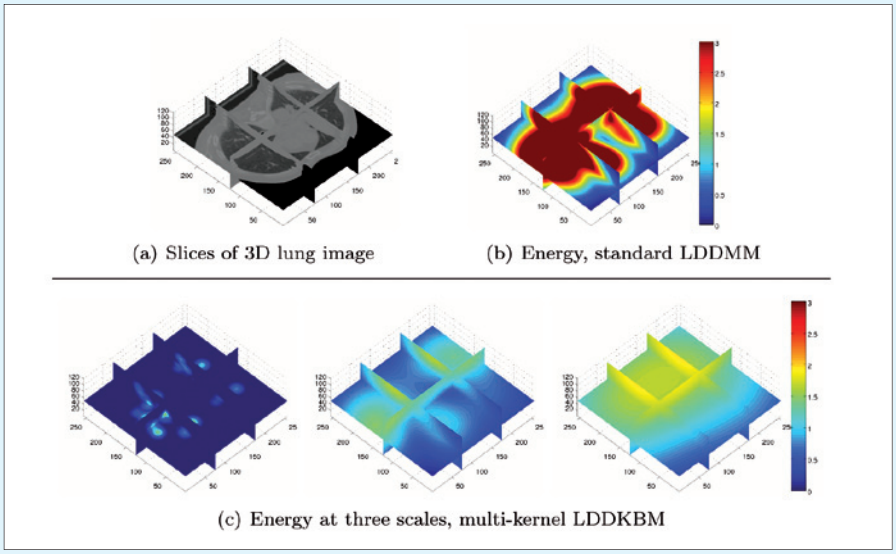

Slices of 3D lung image and energy needed to perform registration of inhale and exhale respiratory phases. Top row: 3D image of lung to be registered and energy for standard LDDMM diffeomorphic registration. Lower row: Energy at three scales with the developed multi-kernel LDDKBM method. Even for the best scale, standard LDDMM is not localized with high energy to account for the warp across scales, while LDDKBM use the appropriate scales localized and sparsely for the smallest scales.

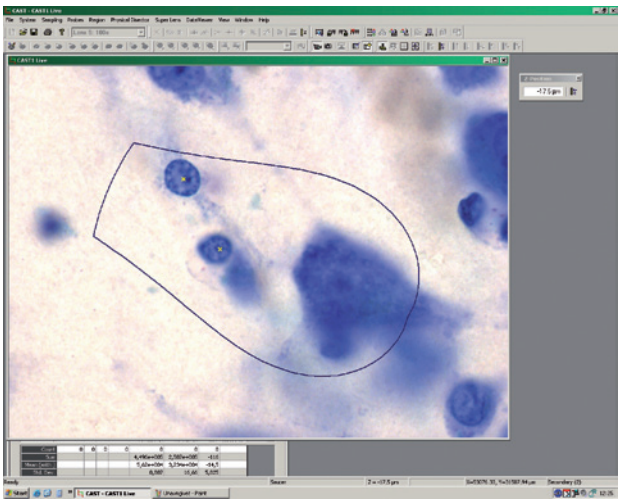

Figure 1:
The saucor probe on the live screen, the focal plane of the image is several µm below the central focal plane centred on the nucleolus of a large neuron (type *i* particle) of polygonal shape. Two glia cells (type *j* particles) have been recorded, marked with a cross.

NON-UNIFORM SAMPLING

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Hansen, L.V., Nyengaard, J.R., Andersen, J.B. and Jensen, E.B.V. (2010b): The semi-automatic nucleator. *CSGB Research Reports* **3**. To appear in *Journal of Microscopy*.

Stark, A.K., Gundersen, H.J.G., Gardi, J.E., Pakkenberg, B. & Hahn, U. (2010): The saucor, a new stereological tool for analysing the spatial distributions of cells, exemplified by human neocortical neurons and glial cells. *Journal of Microscopy*, in press.

Sterio, D.C. (1984): The unbiased estimation of number and sizes of arbitrary particles using the disector. *Journal of Microscopy* **134**, 127–136.

In 2010, **sampling with probability proportional to size** (pps sampling) in a spatial statistics frame work has been investigated closely. In Gardi *et al.* (2008), it was shown that considerable variance reductions may be obtained for specific particle systems by using pre-estimates, obtained from low resolution images, to direct the sampling. Hansen *et al.* (2010a) give theoretical support to this empirical finding. It still remains to fully develop the statistical inference for microscopy data obtained by this type of weighted sampling.

During 2010, a geometric sampling scheme was developed for estimating the **cross Palm intensity function** of spatial point processes. The Palm intensity function N_{Vij} is an unnormalized version of the (multitype) pair correlation function and describes the intensity of a stationary spatial point process as a function of the distance r to a typical point, see Figure 2. It characterizes the mutual spatial arrangement of points or particles, which is of interest in many applications, as e.g. in neuroscience: the intensity of glial cells in the brain changes with the distance to neurons, indicating a clustering of glia around neurons, whereas neurons themselves have a tendency towards mutual repulsion. Here, certain conditions as e.g. Alzheimer disease can imply changes in the Palm intensity function.

Modern computer assisted microscopy techniques, developed in the past 10 to 15 years, have made it possible to register three dimensional coordinates of cells or particles in thick sections of tissue. Still, only very few studies were carried out to estimate the Palm intensity or related second order statistics, since existing methods require cumbersome recording of all particle positions in large, thick brick shaped probes. In the paper (Stark *et al.*, 2010), we have introduced a local, non uniform sampling scheme for estimating N_{Vij}, which consists of two steps. First, type *i* particles (or points) are uniformly sampled within a thick isotropic (IUR) or vertical uniform

random (VUR) section, using e.g. a disector (Sterio, 1984). The second step locally estimates the intensity of type *j* particles as a function of the distance, by recording their coordinates in smaller windows with random orientation around every primary particle. The **shape of the counting windows** is designed such that a large portion of the volume close to the primary (type *i*) particle is examined and a smaller portion of the volume as the distance to the primary particle increases, see Figure 1.

The estimator for the Palm intensity function combines Horvitz-Thompson weights for both sampling steps. Up to now, we considered IUR and VUR thick sections for the first sampling step, and chose the orientation of the saucor window uniform random in the second step. However, we suspect that in the VUR case it might be better to use sine weighted directions for the saucor window. Future research will include derivation of the proper Horvitz-Thompson weights for sine weighted VUR saucor sampling, and aim at assessing the variance of the estimator, at least for the case of a multivariate Poisson point process, thus providing at least rough guidelines for stereological study design.

Finally, in Hansen *et al.* (2010b), we discuss non-uniform sampling in relation to local stereological estimation of particle volume. It was concluded that non-uniform positioning of lines inside a section will not generate a significant variance reduction, due to a considerable variation in the true particle volume.

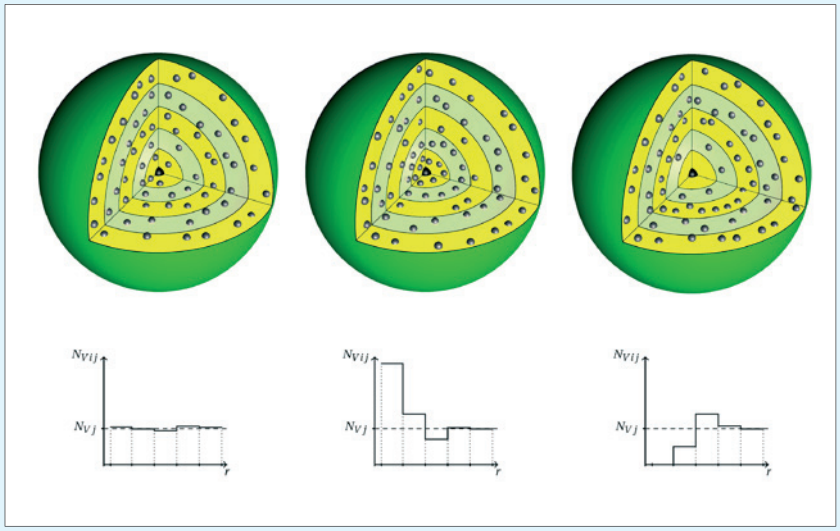
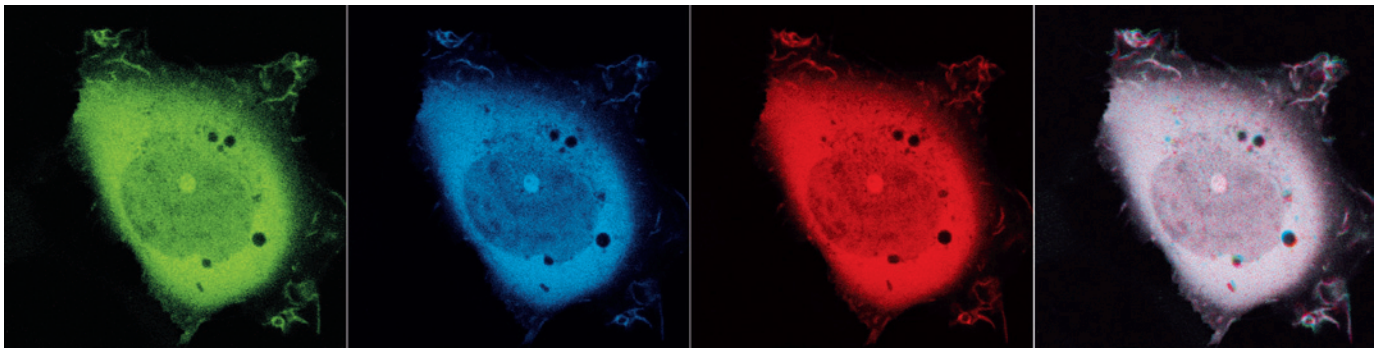
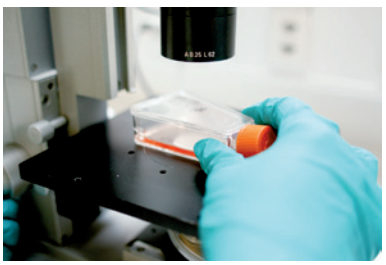


Figure 2: Spatial arrangement of particles with respect to other particles. The top row shows different possibilities of a type *i* particle (dark) with surrounding type *j* particles (light gray): complete spatial randomness (Poisson case, left panel), clustering of type *j* around type *i* particles (middle) and repulsion beween type *i* and type *j* particles (right). Spherical shells with different distance to the primary are shaded in different colours. The bottom row depicts the piecewise constant version of the cross Palm intensity N_{Vij} corresponding to these shells.

FLUORESCENCE MICROSCOPY TAKEN TO THE MOLECULAR LEVEL



Confocal images of Human Embryonic Kidney (HEK) cells expressing FKBP12 (FK506 Binding Protein 12) as well as the Frb domain of FRAP1 (FKBP12-Rapamycin Associated Protein).
FKBP12 and Frb have been linked to the fluorescent proteins Cerulean and Venus for methodological imaging studies of Fluorescence Resonance Energy Transfer (FRET). Both proteins are present throughout the cell, although to a less extent in the nucleus (the large circular area). FKBP12 and Frb interact in the presence of the immunosuppressant Rapamycin as signified by an increase in the fluorescence signal in the FRET channel image (as shown here).



In this project we wish to study **interactions between proteins** within a living cell by measuring inter-protein distances. However, the interaction distances are typically at the 1-10 nm scale and this resolution is impossible to achieve by traditional light (fluorescence) microscopy. As an alternative, Förster Resonance Energy Transfer (FRET) is a technique which allows indirect measurement of these short distances.

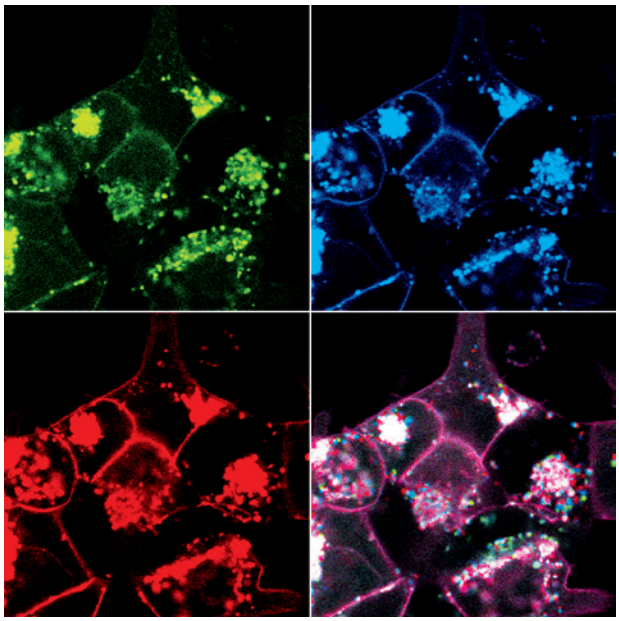
The raw FRET data consists of three noisy digital fluorescence images representing three different light intensities indirectly quantifying the concentration of each of the two proteins and the ratio of interacting proteins. The amount of interaction between the proteins can be described in terms of a chemical equilibrium parameter denoted K_d. This parameter depends non-linearly on the light intensities, and the main interest is to estimate this parameter. The non-linearity implies that the measurement noise enters in a complicated fashion in the analysis, and **it is important to model the noise correctly** to obtain reliable estimates and reliable statements about the precision of the estimates.

The paper Chen *et al.* (2007) presents a method for estimating K_d, based on averages of the measured intensities, which does not take into account the non-linear relations. Computer simulations indicate that this estimation procedure works well when the noise is sufficiently low whereas a high noise scenario results in biased estimation. As an alternative to this method, we have developed a probability model for this data which permits a full **Bayesian analysis** which takes the non-linearity into account. Another advantage of this new approach is that it is possible to work with the pixel-wise data rather than averages, making it possible to get reliable estimates of K_d based on fewer measurements. This possibility has not been thoroughly investigated yet, but it is a goal of the future research to obtain a more detailed understanding of how much the data material can be reduced.

At CSGB, FRET data is collected with a confocal microscope while the data of Chen *et al.* (2007) was collected with a widefield microscope. Due to the difference of microscope type our data is more noisy, and the method of Chen *et al.* (2007) cannot be applied to this data. To make a more detailed comparison, we have obtained access to the widefield data of Chen *et al.* (2007) and we are currently analysing this data.

Before analysing FRET data, there are several **preprocessing steps** which are commonly conducted including background correction, normalization of intensity values and extraction of the cells of interest from the images. We have developed image software to help automate major part of this process, and we will use this to investigate the significance of choosing different preprocessing techniques.

As part of the future research plans for the FRET project, we aim at developing **a model at the protein level** rather than at the pixel level. Specifically, we want to develop a point process model for the proteins and their interactions, which in turn induces a model at the pixel level where the data is observed. With this approach, the model for the pixel data is based on a model with a clear interpretation for the underlying protein interactions.

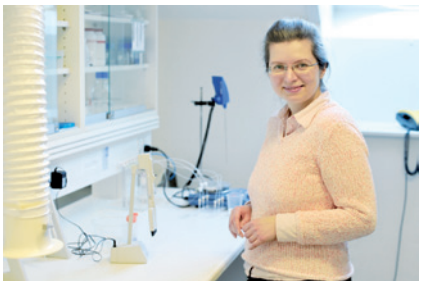


Confocal images of Human Embryonic Kidney (HEK) cells expressing the Sortilin and $p75^{NTR}$ neuronal membrane receptors. Sortilin $p75^{NTR}$ and Sortilin have been linked to the fluorescent proteins Cerulean and Venus for visualization and Fluorescence Resonance Energy Transfer (FRET) analysis. Both receptors are present in the cellular membrane (cell boundaries) as well as in the membranes of (high-intensity) intracellular vesicles.

References

Chen, H., Puhl, H.L. & Ikeda, S.R. (2007): Estimating protein-protein interaction affinity in living cells using quantitative Förster resonance energy transfer measurements. *Biomed. Opt.* **12**, 054011.

MOLECULAR CRYO-EM

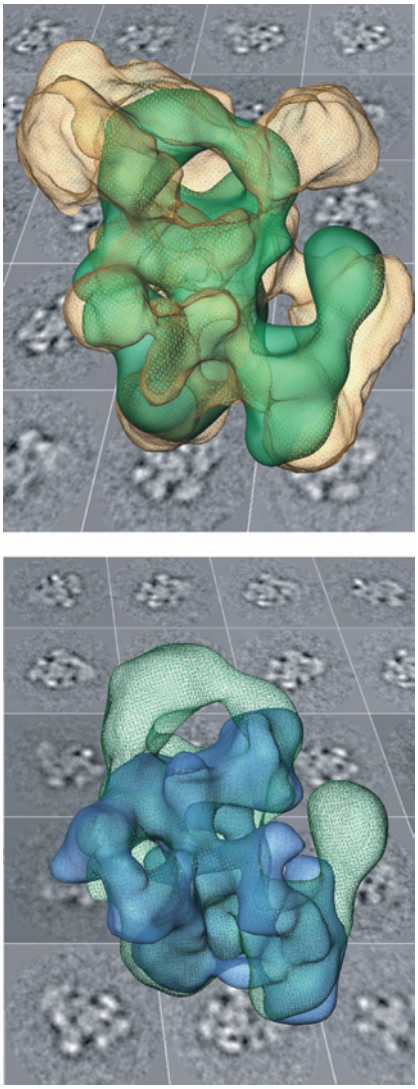




In cells, the genetic information is encoded on the DNA and copied into pre-messenger RNA (pre-mRNA) which serves as a blueprint for the synthesis of proteins. However, the pre-mRNA typically contains regions ("introns") that have to be cut out as they do not encode for building blocks of proteins, while the coding regions ("exons") have to be joined. In analogy to splicing of ropes, this process is called pre-mRNA splicing. Pre-mRNA splicing is catalyzed by the **spliceosome**, a highly dynamic and complex cellular machine comprising more than 150 components. By alternative combination and skipping of individual exons, alternative pre-mRNA splicing constitutes a major source of protein diversity and is particularly frequent in human. In accord with the importance of pre-mRNA splicing for the functions of cells, inborn or acquired impairment of pre-mRNA splicing can result in severe human disease such as some forms of blindness, neurodegeneration and cancer.

In order to decipher the molecular mechanism of the pre-mRNA splicing machinery, a detailed understanding of its structure is essential. In collaboration with scientists at the Max Planck Institute for Biophysical Chemistry, Germany, Monika Golas and Björn Sander from the biomedical group, Aarhus University, have now **uncovered the structural organization** of the catalytically active human spliceosome which is just a few millionth of a millimeter in size. To this end, Monika Golas and Björn Sander are using a cutting-edge technology called electron cryomicroscopy (cryo-EM) in combination with sophisticated imaging processing. By rapid freezing of the sample snapshots of the molecules in solution are obtained which are visualized in a special electron microscope operated at about -180°C. These cryogenic conditions help to preserve the sensitive biological material. Similar to computed tomography (CT) in medicine, images are taken in the electron cryomicroscope and combined into three-dimensional maps by high-performance computing.

The three-dimensional structure of the human spliceosome shows a unique architecture comprising a network of interconnected domains (see Figure 1). Through a series of experiments, the researchers located the catalytic center of the pre-mRNA splicing machinery in the central region of the assembly. These pioneering studies open now the way to describe alterations of the spliceosome in disease.

Figure 1:
Structural Organization of the Human Catalytically Active Spliceosome by Molecular Cryo-EM.



Shown is the 3D structure of the spliceosome (golden), its salt-stable core (green) and the post-spliceosomal 35S U5 snRNP (blue). Upon salt-treatment of the spliceosome, weakly interacting components dissociate from the spliceosome (golden domains that are not covered by the green volumes). Upon completion of the pre-mRNA splicing reaction, the post-spliceosome is disassembled leading to the release of the 35S U5 snRNP. This complex shares a substantial set of components with both, the native and the salt-treated spliceosome (green volume), but lacks other components. These lacking components are located in the green domains that are not covered by the 35S U5 snRNP densities (blue domains). In the background, typical electron microscopical views of the spliceosome are shown.

The most important future challenges are (1) to increase the resolution of cryo-EM by developing new statistical methods of identifying subpopulations of macromolecules and (2) find new efficient computational methods of three-dimensional reconstruction of macromolecular structures. Right now, (2) is taken up in a collaboration with the Image Group at the University of Copenhagen, using a likelihood-based set-up.

Insights into the Molecular Architecture of the Catalytically Active Pre-mRNA Splicing Machinery

In order to translate the genetic information into protein, pre-messenger RNA, a molecule serving as blueprint, has to be brought into shape by removing non-coding sequences. This process is accomplished by a highly dynamic and complex molecular machine called spliceosome, and alterations of this essential cellular process are associated with severe human disorders including neurodegeneration and cancer. Within an international network of researchers, Monika Golas and Björn Sander have uncovered the structural organization of the catalytically active human spliceosome. This pioneering work has now been published in *Molecular Cell*.

Original publication:
Golas MM*, Sander B*, Bessonov S, Grote M, Wolf E, Kastner B, Stark H, Lührmann R. 3D Cryo-EM Structure of an Active Step I Spliceosome and Localization of Its Catalytic Core. *Molecular Cell* **40**, 927-938 (Dec 22nd, 2010). DOI 10.1016/j.molcel.2010.11.023

http://www.cell.com/molecular-cell/abstract/S1097-2765%2810%2900889-0

* These authors contributed equally to this work.


hardcore1
hardcore2
cluster1
cluster2
cluster3
rejection rate
number of points
size: 0.5 × 0.5
size:

CENTRE ACTIVITIES

OVERVIEW OF PAST AND PLANNED INTERNATIONAL ACTIVITIES

CSGB researchers have organized or will take part in the organization of the following international activities.

International conferences and workshops

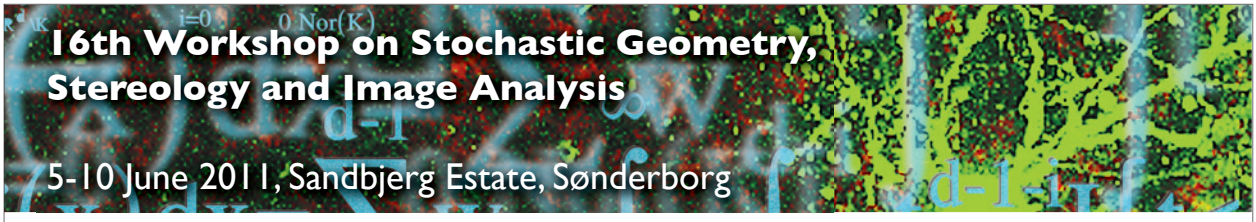
- *Stereology Workshop*, 23-27 August 2010, Bern
- *16th Workshop on Stochastic Geometry, Stereology and Image Analysis*, 5-10 June 2011, Sandbjerg
- *13th International Conference on Stereology*, 19-23 October 2011, Beijing

International minisymposia

- *Minisymposium on Singularity Theory in Computer Vision*, 28-30 June 2010, Aarhus. Main lecturer: Peter Giblin, Liverpool
- *Minisymposium on Recent Advances in Integral Geometry*, 14 October 2010, Aarhus. Main lecturers: Daniel Hug, Karlsruhe, and Ximo Gual-Arnau, Universitat Jaume I, Spain

International Ph.D. courses

- *Sparsity in Image and Signal Analysis*, 15-20 August 2010, Hólar, Iceland
- *Stereology Course*, 25-29 October 2010, Drew University, Los Angeles
- *Course on Advanced Valuation Theory*, 14-18 March 2011, Aarhus. Teacher: Andreas Bernig, Frankfurt.
- *Summer Camp on Analysis of Spatial Point Patterns,* 1-5 June 2011, Sandbjerg. Main teachers: Adrian Baddeley, Perth, and Yongtao Guan, Yale.
- *Summerschool on Graphs in Computer Graphics, Image and Signal Analysis*, 14-19 August 2011, Bornholm
- *Distributed Video Coding and Processing*, 22-28 August 2011, Copenhagen
- *Stereology Course*, 29 August-2 September 2011, Bern
- *Stereology Course*, 13-15 September 2011, Sandbjerg



Scope of the Workshop
This interdisciplinary workshop will bring together scientists from integral geometry, stereology, stochastic geometry, applied probability, spatial statistics and bioimaging. An important scope of the workshop is to promote the advance of stochastic geometry. The workshop will have longer talks by invited speakers and shorter contributed talks by the participants as well as a poster session.

Invited Speakers
Semyon Alesker (Tel Aviv), Adrian Baddeley (Perth), Yongtao Guan (Yale), Daniel Hug (Karlsruhe), Mathew Penrose (Bath), Ege Rubak (Aalborg), Håvard Rue (Trondheim), Gennady Samorodnitsky (Cornell), Johanna Ziegel (Melbourne)

Scientific Programme Committee
Eva B. Vedel Jensen (Aarhus), Günter Last (Karlsruhe), Jesper Møller (Aalborg)

Local Organizing Committee
Ute Hahn (Aarhus), Markus Kiderlen (Aarhus), Oddbjørg Wethelund (Aarhus)

www.csgb.dk

RESEARCH TRAINING

CSGB offers advanced training opportunities in the full range of its study areas, including international Ph.D. courses in spatial statistics, stochastic geometry, point processes, MCMC simulation, biomedical image analysis, high performance computing, quantitative microscopy, advanced fluorescence microscopy and cryo-EM.

Since the opening of CSGB 1 April 2010, seven international Ph.D. courses have taken place or are planned for the near future. These courses cover important areas in spatial statistics, stochastic geometry, biomedical image analysis and quantitative microscopy.

The Ph.D. students at CSGB are in addition offered participation in a wide range of workshops and conferences. Individual research and training plans are tailored for each Ph.D. student. Exchange of Ph.D. students between the research groups participating in CSGB is part of the training plan when relevant, especially exchange between theoretical and experimental groups at CSGB.

The donation from the Villum Foundation involves a total of four full Ph.D. stipends. Because of cofinancing from the three participating Danish universities, it has been possible to advertise a much larger number of Ph.D. stipends. The actual number of Ph.D. students at CSGB is in mid-2011 expected to be twelve. Four of these students will come from abroad. To maintain a high level of international recruitment of Ph.D. students, the close connections to a number of university departments abroad will also be used in the future.

During 2010, an Erasmus exchange programme (including both master students and teachers) was established between Department of Mathematical Sciences, Aarhus University, and Institut für Mathematik, Goethe-Universität, Frankfurt.

Ph.D. students at CSGB

The Ph.D. students at CSGB come from a number of different disciplines, mathematics, statistics, computer science and biology. In spring 2011, nine Ph.D. students are associated to CSGB:

- Camilla Mondrup Andreassen (mathematical statistics)
- Sabrina Tang Christensen (mathematics)
- Mohammad Ghorbani (mathematical statistics)
- Linda V. Hansen (mathematical statistics)
- Katrine Hommelhof (computer science)
- Jai Rai (biology)
- Allan Rasmusson (computer science)
- Stefan Sommer (mathematics and computer science)
- Ólöf Thorisdottir (mathematical statistics)

During summer 2011, it is planned to hire additional three Ph.D. students, one in each of the areas mathematical statistics, computer science and biology.

CSGB RESEARCH REPORTS 2010

CSGB has its own research report series that mainly publishes *mathematical and statistical manuscripts*. The major part of these manuscripts will later appear in international journals. The publication traditions are different in computer science and biology for which reason publications written by CSGB researchers from these fields will appear directly in international journals, proceedings, etc.

1. Auneau-Cognacq, J. (2010): A rotational Crofton formula for flagged intrinsic volumes of sets of positive reach. *CSGB Research Reports* **5**.

2. Auneau, J., Rataj, J. & Jensen, E.B.V. (2010): Closed form of the rotational Crofton formula. *CSGB Research Report* **2**. To appear in *Mathematische Nachrichten*.

3. Baddeley, A, Rubak, E. & Møller, J. (2010): Score, pseudo-score and residual diagnostics for goodness-of-fit of spatial point process models. *CSGB Research Report* **4**. Conditionally accepted by *Statistical Science*.

4. Bianchi, G., Gardner, R.J. & Kiderlen, M. (2010): Phase retrieval for characteristic functions of convex bodies and reconstruction for covariograms. *CSGB Research Report* **9**. Submitted.

5. Hahn, U. (2010): A studentized permutation test for the comparison of spatial point patterns. *CSGB Research Report* **12**. Conditionally accepted by *Journal of the American Statistical Association*.

6. Hansen, L.V., Nyengaard, J.R., Andersen, J.B. & Jensen, E.B.V. (2010): The semi-automatic nucleator. *CSGB Research Report* **3**. To appear in *Journal of Microscopy*.

7. Kampf, J. (2010): The parallel volume at large distances. *CSGB Research Report* **1**. Submitted.

8. Møller, J. & Berthelsen, K.K. (2010): Transforming spatial point processes into Poisson processes using random superposition. *CSGB Research Report* **7**. Submitted.

9. Møller, J. & Ghorbani, M. (2010): Second-order analysis of structured inhomogeneous spatio-temporal point processes. *CSGB Research Report* **10**. Submitted.

10. Møller, J. & Rasmussen, J.G. (2010): A sequential point process model and Bayesian inference for spatial point patterns with linear structures. *CSGB Research Report* **6**. Submitted.

11. Prokešová, M. & Jensen, E.B.V. (2010): Asymptotic Palm likelihood theory for stationary point processes. *CSGB Research Report* **11**. Submitted.

12. Rubak, E., Møller, J. & McCullagh, P. (2010): Statistical inference for a class of multivariate negative binomial distributions. *CSGB Research Report* **8**. Conditionally accepted by *Bernoulli*.

CSGB JOURNAL AND PROCEEDINGS PUBLICATIONS, BOOK CHAPTERS

1. Aukema, B. H., Zhu, J., Møller, J., Rasmussen, J.G. & Raffa, K.F. (2010): Predisposition to bark beetle attack by root herbivores and associated pathogens: Roles in forest decline, gap formation, and persistence of endemic bark beetle populations. *Forest Ecology and Management* **259**, 374 - 382.

2. Auneau, J. & Jensen, E.B.V. (2010): Expressing intrinsic volumes as rotational integrals. *Advances in Applied Mathematics* **45**, 1-11.

3. Boyce, R.W., Dorph-Petersen, K.-A., Lyck, L. & Gundersen, H.J.G. (2010): Design-based stereology: introduction to basic concepts and practical approaches for estimation of cell number. *Toxicol Pathol* **38**, 1011-1025.

4. Chen, C., Chernoff, K., Karemore, G.R., Lo, P.C.P., Nielsen, M. & Lauze, F.B. (2010): Classification in medical image analysis using adaptive metric K NN. In: *Proceedings of SPIE 2010*. USA. 9 pages.

5. Feragen, A., Lauze, F.B., Lo, P., de Bruijne, M. & Nielsen, M. (2010a): Geometries on spaces of treelike shapes. To appear in *Proceedings of ACCV* 2011.

6. Feragen, A., Lauze, F.B. & Nielsen, M. (2010b): Fundamental geodesic deformations in spaces of treelike shapes. *ICPR* 2010.

7. Golas, M.M.*, Sander, B.*, Bessonov, S., Grote, M., Wolf, E., Kastner, B., Stark, H. & Lührmann, R. (2010): 3D Cryo-EM structure of an active step I spliceosome and localization of its catalytic core. *Molecular Cell* **40**, 927-938 (Dec 22nd, 2010). DOI 10.1016/j.molcel.2010.11.023.

8. Greilich, S., Hahn, U., Kiderlen, M., Andersen, C.E. & Bassler, N. (2010): A novel track-structure based algorithm for solid-state detector efficiency in mixed particle fields. *Proceedings Radiation Measurements*, Krakow, Polen, 12 – 17 July 2009.

9. Hansen, L.V., Kiderlen, M. & Jensen, E.B.V. (2010): Image-based empirical importance sampling: an efficient way of estimating intensities. To appear in *Scandinavian Journal of Statistics*.

10. Hauberg, S., Sommer, S.H. & Pedersen, K.S. (2010): Gaussian-like spatial priors for articulated tracking. In: *Computer Vision –11th European Conference on Computer Vision, Crete, September 5-11, 2010. Proceedings, Part I*, eds.: K. Daniilidis; P. Maragos; N. Paragios. Springer Lecture Notes in Computer Science **6311**, p. 425-437.

11. Kamper, P., Bendix, K., Hamilton-Dutoit, S., Honoré, B., Nyengaard. J. & d'Amore, F. (2010): Tumor-infiltrating macrophages correlate with adverse

COLLABORATION WITH SURROUNDING CENTRES

CSGB collaborates with a number of other centres at Aarhus University

- Thiele Centre for Applied Mathematics in the Natural Sciences
- MindLab (UNIK initiative)
- Pumpkin
- Mind Centre

During 2010, especially the collaboration with MINDLab has been intense. The focus point has been Lévy based modelling of non-Gaussian random fields. These random fields turn out to be of importance in the analysis of neuroscience images where distinctive departures from Gaussianity are often observed. Lévy based random fields offer a valid method of analysis in cases where traditional methods of comparing small groups of subjects break down.

INTERNAL CSGB WORKSHOPS

The internal CSGB workshops are held twice a year. They are arranged alternatingly by the two Aarhus groups (the Stochastic Geometry and the Bioimedical groups), the Spatial Statistics group at Aalborg University and the Image Group at University of Copenhagen.

The aim of these internal workshops is to discuss the present status of the CSGB research projects by presentations by the members of CSGB and to plan the further progress of the research projects. Furthermore, new activities arranged by CSGB such as workshops, courses, establishment of new international contacts, etc. are also discussed at these internal workshops. An equally important aim of the internal workshops is to tighten the connections between the researchers associated to CSGB.

prognosis and Epstein-Barr virus status in classical Hodgkin lymphoma. *Haematologica* November 11.

12. Keller, S. H., Lauze, F. & Nielsen, M. (2010): Temporal super resolution using variational methods. In: *High Quality Visual Experience: Creation, Processing and Interactivity of High-Resolution and High-Dimensional Video Signals.* (Springer)

13. Kiderlen, M. (2010): Introduction to integral geometry and stereology. *Thiele Research Report*, Department of Mathematical Sciences, Aarhus University.

14. Lo, P., Sporring, J., Ashraf, H., Pedersen, J.H. & Bruijne, M. de (2010): Vessel-guided airway tree segmentation: a voxel classification approach. *Medical Image Analysis* **14**, 527-538.

15. Loog, M. & Lauze, F.B. (2010): The improbability of Harris interest points. *IEEE Transaction on Pattern Analysis and Machine Intelligence* **32**, 1141-1147.

16. Mühlfeld, C., Papadakis, T., Krasteva, G., Nyengaard, J.R., Hahn, U. & Kummer, W. (2010): An unbiased stereological method for efficiently quantifying the innervation of the heart and other organs based on total length estimations. *Journal of Applied Physiology* **108**, 1402-1409.

17. Mühlfeld, C., Weibel, E.R., Hahn, U., Kummer, W., Nyengaard, J.R. & Ochs, M. (2010): Is length an appropriate estimator to characterize pulmonary alveolar capillaries? A critical evaluation in the human lung. *Anatomical Record* **293**, 1270-1275.

18. Møller, J. (2010a): Inference. Chapter 9 in *New Perspectives in Stochastic Geometry*. Eds. W.S. Kendall and I. Molchanov. Oxford University Press, Oxford, 307 - 347.

19. Møller, J. (2010b): Parametric methods. Chapter 19 in *A Handbook of Spatial Statistics*. Eds. A.E. Gelfand, P. Diggle, M. Fuentes, and P. Guttorp. Chapman and Hall/CRC Press, 317 - 337.

20. Møller, J. & Diaz-Avalos, C. (2010): Structured spatio-temporal shot-noise Cox point process models, with a view to modelling forest fires. *Scandinavian Journal of Statistics* **37**, 2 - 25.

21. Møller, J. & Helisova, K. (2010): Likelihood inference for unions of interacting discs. *Scandinavian Journal of Statistics* **37**, 365 - 381.

22. Møller, J., Huber, M.L. & Wolpert, R.L. (2010): Perfect simulation and moment properties for the Matérn type III process. *Stochastic Processes and their Applications* **120**, 2142 - 2158.

23. Møller, J. & Rubak, E. (2010): A model for positively correlated count variables. *International Statistical Review* **78**, 65 – 80.

24. Møller, J. & Schoenberg, R.P. (2010): Thinning spatial point processes into Poisson processes. *Advances in Applied Probability* **42**, 347 - 358.

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FIRST INTERNAL WORKSHOP

The internal CSGB workshops are held twice a year. The first internal workshop was arranged by the Stochastic Geometry group and took place at Vingstedcentret 26 - 27 May 2010.

CSGB SEMINARS

5 May, 2010 | Joachim Ohser (Hochschule Darmstadt): **Permeability and percolation of porous media**

12 May, 2010 | Bryony Hill (University of Warwick): **Identifying fibres in spatial point patterns**

11 June, 2010 | Richard Gardner (Western Washington University): **Intersections of convex bodies**

17 June, 2010 | Jan Rataj (Charles University, Praha): **Surface area and curvatures by approximation with parallel set**

24 June, 2010 | Richard Gardner (Western Washington University): **Reconstruction from covariograms and the phase retrieval problem**

25 June, 2010 | Peter Giblin (University of Liverpool): **Views of illuminated surfaces**

28 June, 2010 | Peter Giblin (University of Liverpool): **Some applications of singularity theory to computer vision**

29 June, 2010 | Peter Giblin (University of Liverpool): **Functions, mappings and singularities I**

30 June, 2010 | Peter Giblin (University of Liverpool): **Functions, mappings and singularities II**

2 July, 2010 | Matt Brown (UCLA Department of Radiological Sciences): **Lung CT image analysis: determining which emphysema patients are good candidates for treatment**

2 July, 2010 | Cristian Lorenz (Philips Research Laboratory, Hamburg): **Pulmonary Motion Estimation and Modeling**

23 September, 2010 | Abdollah Jalilian (Shahid Beheshti University, Iran): **Residual analysis for inhomogeneous Neyman-Scott processes**

11 October, 2010 | Horst Bischof (Institute for Computer Graphics and Vision, Graz University of Technology): **Solving vision tasks with variational methods on GPUs**

11 October, 2010 | Joseph Reinhard (Department of Biomedical Engineering, University of Iowa): **Reproducibility of registration-based estimates of regional lung expansion**

1 November, 2010 | Julia Schnabel (Institute of Biomedical Engineering, University of Oxford): **Biomedical image analysis at Oxford**

1 November, 201 | Gary E. Christensen (Department of Elect & Comp Eng, University of Iowa): **Contemporary topics in medical image registration**

18 November, 2010 | Bryony Hill (University of Warwick): **Gradient fields, fibre processes and point patterns**

SECOND INTERNAL WORKSHOP



The internal CSGB workshops are held twice a year. The second internal workshop was arranged by the Image Group and took place at Axelborg, Copenhagen, 10-11 November 2010.

25 November, 2010 | Matthias Tuma (Bochum Universität): **Online multi-class SVMs and hydroacoustic signal classification**

25 November, 2010 | Asja Fischer (Bochum Universität): **Challenges in training restricted Boltzmann machines**

9 December, 2010 | Michaela Prokesova (Charles University, Praha): **Moment estimation for parametric spatial Cox process models**

9 December, 2010 | Jens Ledet Jensen (Aarhus University): **Asymptotics for hidden Markov models with covariates**

SANDBJERG CONFERENCE CENTRE

The Sandbjerg Estate serves as the main conference centre for Aarhus University. The estate is situated in an area of outstanding natural beauty about 7 km northwest of Sønderborg in the southern part of Jutland.

CSGB VISITORS

Jürgen Kampf (University of Karlsruhe, Germany), 1 April - 31 July, 2010

Joachim Ohser (Hochschule Darmstadt, Germany), 4-6 May, 2010

Bryony Hill (University of Warwick, United Kingdom), 9-16 May, 2010

Rirchard J. Gardner (Western Washington University, USA), 4-30 June, 2010

Jan Rataj (Charles University, Praha, Czech Republic), 14-19 June, 2010

Peter Giblin (University of Liverpool, United Kingdom), 25 June -3 July, 2010

Matt Brown (UCLA Department of Radiological Sciences, USA), 2 July, 2010

Christian Lorenz (Philips Research Laboratory, Hamburg, Germany), 2 July, 2010

Michaela Prokešová (Charles University, Czech Republic), 2-7 August, 2010

Abdollah Jalilian (Shahid Beheshti University, Iran), 1 September - 31 December, 2010

Horst Bischof (Institute for Computer Graphics and Vision, Austria), 11 October, 2010

Joseph Reinhard (University of Iowa, USA), 11 October, 2010

Daniel Hug (Karlsruhe Institute of Technology, Germany), 12-15 October, 2010

Ximo Gual-Arnau (Universitat Jaume I, Castello, Spain), 13-15 October, 2010

Gary E. Christensen (University of Iowa, USA), 1 November, 2010

Julia Schnabel (University of Oxford, United Kingdom), 1 November, 2010

Bryony Hill (University of Warwick, United Kingdom), 14-19 November, 2010

Asja Fischer (Bochum Universität, Germany), 25 November, 2010

Matthias Tuma (Bochum Universität, Germany), 25 November, 2010

Michaela Prokešová (Charles University, Czech Republic), 5-11 December, 2010

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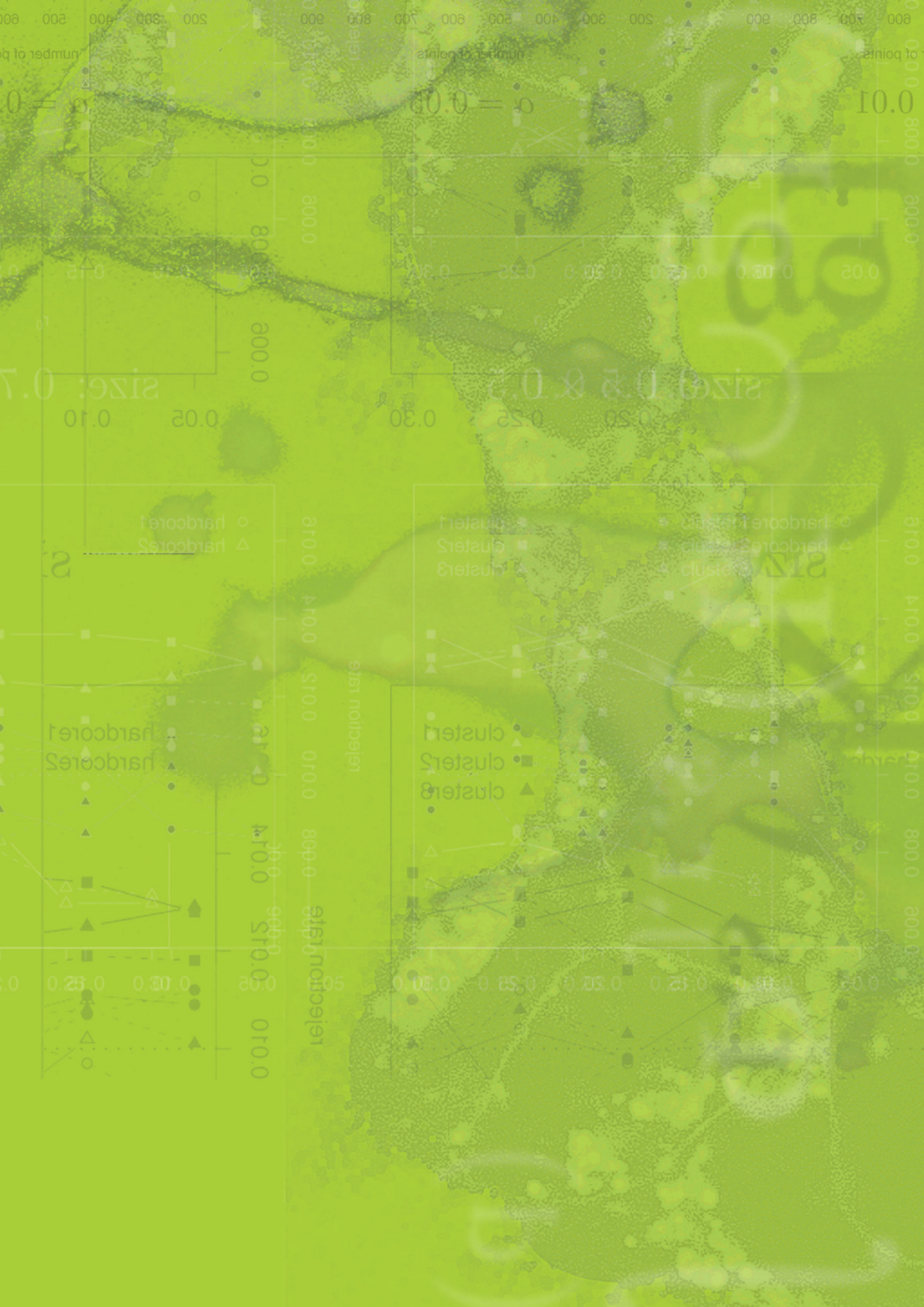

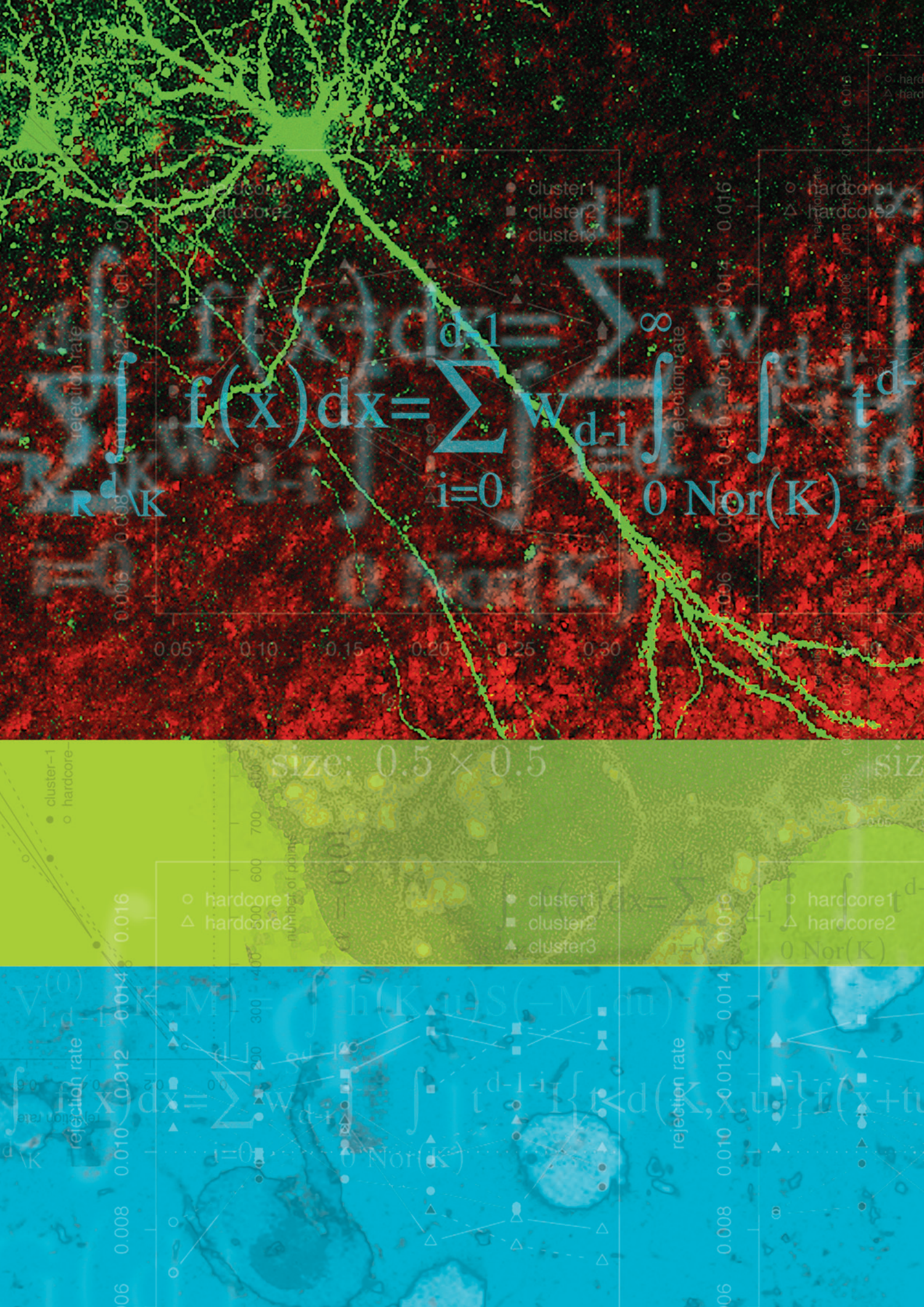
cluster1
cluster2
cluster3
hardcore1
hardcore2
rejection rate
number of points
size: 0.5 × 0.5