CSGB

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

Annual Report 2011


CSGB
CENTRE FOR STOCHASTIC GEOMETRY
AND ADVANCED BIOIMAGING
www.csgb.dk

Annual Report 2011

From the 16th Workshop on Stochastic Geometry, Stereology and Image Analysis that was held 5-10 June 2011 at the Sandbjerg Estate in the southern part of Jutland, Denmark. Group photo of participants in front of the manor. The workshop had approximately 70 participants from 17 different countries.

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

In 2010, the Villum Foundation donated 25 mill DKK to the **VKR Centre of Excellence**, Centre for Stochastic Geometry and Advanced Bioimaging (CSGB). The main aim of CSGB is to develop new mathematical, statistical and computational methods of analyzing advanced **bioimaging data**. An important tool is **stochastic geometry**. 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. Four research groups participate in CSGB: the **stochastic geometry group** (AU), the **biomedical group** (AU), the **spatial statistics group** (AAU) and the **image group** (KU).

The year of 2011 was a period of expansion for CSGB. Eleven new researchers started at CSGB during 2011, including seven new Ph.D. students, four of which came from abroad (pp. 10-11). The staff was now ready for initiating five of the planned collaborative projects where the mathematical, statistical and computational expertice available at CSGB is used in the development of new methods of analyzing advanced bioimaging data (pp. 18-21).

On the international scene, the scientific collaboration with the stochastic geometry groups in Karlsruhe and Erlangen was intensified. CSGB is the international research partner in the DFG Research Unit entitled **Geometry and Physics of Spatial Random Systems** that was formed in February 2011. During 2011, CSGB researchers met with the German research partners three times for scientific exchange.

In 2011, an Erasmus exchange programme was established with Department of Mathematics, Goethe-Universität, Frankfurt. Professor Andreas

From the Summer Camp on the Analysis of Spatial Point Patterns 1-5 June 2011 that was arranged prior to the 16th Workshop. The summer camp took also place at the Sandbjerg Estate. The photo shows the participants as well as the teachers that included Adrian Baddeley (left) from CSIRO, Perth.

Bernig, Frankfurt, gave a successful course on **Advanced Valuation Theory** in March 2011 for CSGB researchers and collaborators. These lectures opened a new world for us. In March 2012, I gave Erasmus lectures in Frankfurt on **Rotational Integral Geometry** (pp. 22-23).

Research-wise, 2011 was the year where we seriously started to work with integral geometry for tensors and obtained a genuine rotational Crofton formula for such quantities. Rotational integral geometry of Minkowski tensors is expected to be the key tool in developing new local stereological methods of analyzing the distribution of cell orientation and shape. During 2011, we also found that analysis of FRET (Förster Resonance Energy Transfer) microscopy data that allows indirect measurement of interaction distances between proteins in living cells is considerably more challenging than originally expected.

CSGB hosted in 2011 the international stochastic geometry workshop, **16th Workshop on Stochastic Geometry, Stereology and Image Analysis**, Sandbjerg, 5-10 June 2011. This workshop was a big success and very well attended with 70 participants, see the group photo on the opposite page and page 49. The upcoming big international event for CSGB in 2012 will be the **Workshop on Geometry and Statistics in Bioimaging: Manifolds and Stratified Spaces**, Sandbjerg, 8-12 October 2012 (p. 43). This workshop is arranged jointly by the stochastic geometry group, AU, and the image group, KU. Apart from CSGB, the workshop is supported by the international network activity programme under the Ministry of Science, Innovation and Higher Education.

March 2012
Eva B. Vedel Jensen

[9] BADDELEY, A. J. (1999). Spatial sampling and censoring. In *Stochastic Geometry* (*Toulouse*, 1996). *Monogr. Statist. Appl. Probab.* **80** 37–78. Chapman & Hall/CRC, Boca Raton, FL. MR1673114

[10] BADDELEY, A. J. and MØLLER, J. (1989). Nearest-neighbour Markov point processes and random sets. *Int. Stat. Rev.* **57** 89–121.

[11] BADDELEY, A. J. and VAN LIESHOUT, M. N. M. (1995). Area-interaction point processes. *Ann. Inst. Statist. Math.* **47** 601–619. MR1370279

[12] BARNARD, G. (1963). Discussion of "The spectral analysis of point processes" by M. S. Bartlett. *J. R. Stat. Soc. Ser. B Stat. Methodol.* **25** 294.

[13] BERMAN, M. (1986). Testing for spatial association between a point process and another stochastic process. *J. Roy. Statist. Soc. Ser. C* **35** 54–62.

... J. (1978). Some methods of statistical analysis for ... *Bull. Int. Statist. Inst.* **44** 77–92.

... (1983). Score tests for regression models. *J. Amer. ...* **78** 15 ... 61.

... GGLE, P. J. (1998). On estimating ... measure of a stationary spatial ... **40** 11–15. MR1628212

... IER, F. (2010). Residuals ... int. Avail-

... ance parame- ... *tist. Plann.*

... nostics

[30] GEORGII, H.-O. (1976). Canonical and grand canonical Gibbs states for continuum systems. *Comm. Math. Phys.* **48** 31–51. MR0411497

[31] GEYER, C. (1999). Likelihood inference for spatial point processes. In *Stochastic Geometry* (*Toulouse*, 1996). *Monogr. Statist. Appl. Probab.* **80** 79–140. Chapman & Hall/CRC, Boca Raton, FL. MR1673118

[32] HANISCH, K. H. (1984). Some remarks on estimators of the distribution function of nearest neighbour distance in stationary spatial point processes. *Math. Operationsforsch. Statist. Ser. Statist.* **15** 409–412. MR0756346

[33] HANSEN, B. E. (1996). Inference when a nuisance parameter is not identified under the null hypothesis. *Econometrica* **64** 413–430. MR1375740

[34] HEINRICH, L. (1988). Asymptotic behaviour of an empirical nearest-neighbour distance function for stationary Poisson cluster processes. *Math. Nachr.* **136** 131–148. MR0952468

[35] HEINRICH, L. (1988). Asymptotic Gaussianity of some estimators for reduced factorial moment measures and product densities of stationary Poisson cluster processes. *Statistics* **19** 87–106. MR0921628

[36] HOPE, A. C. A. (1968). A simplified Monte Carlo significance test procedure. *J. R. Stat. Soc. Ser. B Stat. Methodol.* **30** 582–598.

[37] HUANG, F. and OGATA, Y. (1999). Improvements of the maximum pseudo-likelihood estimators in various spatial statistical models. *J. Comput. Graph. Statist.* **8** 510–530.

[38] ILLIAN, J., PENTTINEN, A., STOYAN, H. and STOYAN, D. (2008). *Statistical Analysis and Modelling of Spatial Point Patterns*. Wiley, Chichester. MR2384630

[39] JENSEN, J. L. and MØLLER, J. (1991). Pseudolikelihood for exponential family models of spatial point processes. *Ann. Appl. Probab.* **1** 445–461. MR1111528

[40] JOLIVET, E. (1981). Central limit theorem and convergence of empirical processes for stationary point processes. In *Point Processes and Queuing Problems* (*Colloq., Keszthely*, 1978). ... *Soc. János Bolyai* **24** 117–161. North-Holland, ... 7406

... (1978). On conditional intensities of ... *Verw. Gebiete* **41** 205–220.

... clustering. *Biometrika* **65** 3..–3... MR04513..

... *Spatial* ... *Statist.* **134**. Springer.

... M. (2011). Poisson process Fock ... chaos expansion and covariance in- ... *Theory Related Fields* **150** 663–690.

... B. (1993). On the analysis of mortality events ... specified fixed point. *J. Roy. Statist. Soc. Ser. A* ... **56** 363–377.

[48] LOTWICK, H. W. and SILVERMAN, B. W. (1982). Methods for analysing spatial processes of several types of points. *J. Roy. Statist. Soc. Ser. B* **44** 406–413. MR0693241

ORGANIZATION AND STAFF

OVERVIEW OF ORGANIZATION

THE FOUR PARTICIPATING RESEARCH GROUPS

CSGB joins the following internationally recognized research groups: the stochastic geometry group (AU-math) at Department of Mathematics, AU, the biomedical group (AU-bio) at Clinical Institute and Department of Anatomy, AU, the spatial statistics group at Department of Mathematical Sciences, AAU, and the image group, Department of Computer Science, KU.

The two AU groups have collaborated for many years. The stochastic geometry group and the spatial statistics group have in recent years only collaborated informally but with the formation of CSGB the collaboration has been intensified. New synergies between the image group and the remaining research groups are developing because of the unique complementary competences of the image group.

The full CSGB scientific staff is presented on pages 52-53.

Spatial statistics group
Department of Mathematical Sciences
Aalborg University
led by Professor Jesper Møller

AAU

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

AU-BIO

Image group
Department of Computer Science
University of Copenhagen
led by Professor Mads Nielsen

KU

Stochastic geometry group
Department of Mathematics
Aarhus University
led by Professor Eva B. Vedel Jensen

AU-MATH

APPOINTMENTS 2011

INA TROLLE ANDERSEN (AU-BIO/MATH)

Ina Trolle Andersen started in August 2011 as a Ph.D. student. Her Ph.D. project concerns **Non-uniform sampling**. She is associated to AU-bio as well as AU-math. She has a bachelor degree in mathematical statistics from Department of Mathematics, AU. In summer 2010, she attended a 6 week summer school at Oxford University. This event made her decide to take up a research education.

JÉRÉMY AUNEAU-COGNACQ (AU-MATH)

Jérémy Auneau-Cognacq has been a postdoc at AU-math since May 2011. He is working in the CSGB project **Rotational integral geometry**. Jérémy has a Ph.D. degree in this topic from October 2010. His competences include integral geometry and geometric measure theory.

SAMI BRANDT (KU)

Sami Brandt was appointed as associate professor at KU September 2011. He is working in the CSGB team developing new algorithms for reconstruction of macromolecules from **Cryo-EM** data. He has a Doctor of Science degree in computer science from Helsinki University of Technology.

SABRINA TANG CHRISTENSEN (AU-MATH)

Sabrina Tang Christensen started in February 2011 at AU-math immediately after finished bachelor studies in a special Ph.D. stipend, co-financed by the Faculty of Science and Technology, AU. Sabrina is working in the CSGB project entitled **Topological properties**. Her bachelor thesis lies within topology.

MOHAMMAD GHORBANI (AAU)

Mohammad Ghorbani has a master degree in statistics from Tarbiat Modaress University, Iran. He initiated a Ph.D. study in September 2011 at AAU. He is working in the CSGB project **Spatial and spatio-temporal point processes.**

JAN-OTTO HOOGHOUDT (AAU)

Jan-Otto Hooghoudt has a master degree in applied physics from University of Twente, The Netherlands. From August 2011, he has worked as a Ph.D. student at AAU. Jan-Otto is associated to the CSGB project **Fluorescence microscopy taken to the molecular level**. The aim of the project is to use point process models in the inference of within cell protein interactions and spatial structure.

KATRINE HOMMELHOFF JENSEN (KU)

Katrine Hommelhoff Jensen has a master degree in computer science from University of Copenhagen, specialized in image analysis, machine learning and 3D computer graphics. Since May 2011, she has been a Ph.D. student at the image group, KU, working in the CSGB team developing new algorithms for reconstruction of macromolecules from **Cryo-EM** data.

JAY RAI (AU-BIO)

Jay Rai has two (!) master theses from Vrije Universiteit, Amsterdam, one in structural biology and one in molecular microbiology. Since October 2011, he has worked as a Ph.D. student at AU-bio. He is associated to the team working with **Cryo-EM**.

ALI HOSEINPOOR RAFATI (AU-BIO)

Ali Hoseinpoor Rafati has studied medicine at Tehran University of Medical Sciences. Since August 2011, Ali has worked as research assistant at AU-bio. He is part of the interdisciplinary team working with **Spatial and spatio-temporal point processes** for microcolumns of human cerebral cortex. The project is a collaboration between AU-bio and AAU. Ali has in 2011 been responsible for collecting a unique spatial data set.

FARZANEH SAFAVIMANESH (AAU)

Farzaneh Safavimanesh graduated from Department of Statistics, Shahid Beheshti University, Iran, with a thesis in point process theory. Since December 2011, she has been a Ph.D. student at AAU. She is part of the interdisciplinary team working with **Spatial and spatio-temporal point processes** for microcolumns of human cerebral cortex.

ANNE MARIE SVANE (AU-MATH)

Anne Marie Svane obtained her Ph.D. degree in autumn 2011 within the field of algebraic topology. Immediately after, she was hired at CSGB 1 November 2011 as postdoc at AU-math. Anne Marie is working in the CSGB project **Digital stereology**. Besides, she is a skilled runner.

NEWS FROM AU-MATH, AU-BIO, AAU, KU

(Photo: Jesper Rais, AU Communication)

Monika Golas

SAPERE AUDE GRANT FOR CSGB RESEARCHER

Monika Golas from the Department of Biomedicine, CSGB, AU, has been awarded 8.6 mill DKK from the career program Sapere Aude of the Danish Council for Independent Research (DFF) - a talent development program for the elite.

By combining her experience with molecular biology with advanced cryo-electron microscopical techniques, she purifies cellular complexes and images them in order to make 3D models of the macromolecular assemblies of the cell. Monika Golas has a double academic degree in human biology and medicine from the University of Marburg and University of Göttingen, Germany, and holds a Ph.D. in biochemistry. After finishing her postdoctoral position at the Max Planck Institute for Biophysical Chemistry in Göttingen, Germany, she was recruited to the Faculty of Health Sciences, AU. Together with Björn Sander, she is building a laboratory for molecular cryo-electron microscopy. In 2011, their laboratory has been expanded with an impressive long list of molecular analytical capabilities and the very advanced FEI Titan microscope has been installed at Aarhus University.

Monika Golas has published various manuscripts, amongst others in **Science, Nature, Cell** and **Molecular Cell**.

13TH INTERNATIONAL CONGRESS FOR STEREOLOGY, 19-23 OCTOBER 2011, BEIJING

At the International Conference for Stereology and Image Analysis held in Beijing 19-23 October 2011, CSGB was very well represented and was responsible for three of the seven invited lectures. Karl-Anton Dorph-Petersen and Markus Kiderlen held key-note lectures and Ólöf Thorisdottir and Allan Rasmusson won 1st and 2nd price, respectively, in the "Young Stereologist Competition".

Jens R. Nyengaard had at the end of 2011 served his full 4-year term as the President of the International Society for Stereology.

Above, Jens gives his presidental speech at the Beijing Congress.

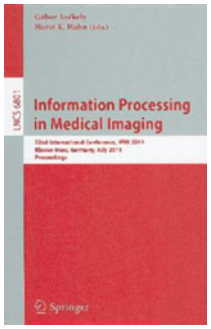
PAPER IN THE PRESTIGIOUS JOURNAL STATISTICAL SCIENCE

Together with Adrian Baddeley (Research Scientist at CSIRO Mathematical and Information Sciences, Perth), Ege Rubak and Jesper Møller (AAU) have written a more than 30 pages long paper entitled **Score, pseudo-score and residual diagnostics for goodness-of-fit of spatial point process models** which has been accepted for publication in the prestigious journal **Statistical Science**.

In the paper, they develop new diagnostic tools for the analysis of spatial point pattern data. The results lend theoretical support to the established practice of using functional summary statistics, when testing for complete spatial randomness; and they provide new tools for testing other fitted models. The results also support localization methods such as the scan statistic and smoothed residual plots. Software for computing the diagnostics is provided.

FOUR PAPERS AT IPMI 2011

The oldest and most prestigious conference in methodologies of medical image analysis called Information Processing in Medical Imaging (IPMI) had its 22nd biannual meeting in Kloster Irsee, Germany, July 3-8, 2011. The representation of the image group, not surpassed by any other group, was four papers including two oral presentations. Here, works on a continuous formulation of image matching for registration [Darkner], an optimal graph algorithm for segmentation of airway walls in lung CTs [Petersen], a methodology for analysis of geometric tree structures for classification of COPD [Sorensen], and a multi-scale bundle extension of the large deformation diffeomorphic metric mapping framework for registration [Sommer] were presented.



- [Darkner] Generalized Partial Volume: An Inferior Density Estimator to Parzen Windows for Normalized Mutual Information. Pages 436-447. LNCS 6801.
- [Petersen] Optimal Graph Based Segmentation Using Flow Lines with Application to Airway Wall Segmentation. Pages 49-60. LNCS 6801.
- [Sorensen] Dissimilarity-Based Classification of Anatomical Tree Structures. Pages 475-485. LNCS 6801.
- [Sommer] A Multi-scale Kernel Bundle for LDDMM: Towards Sparse Deformation Description across Space and Scales. Pages 624-635. LNCS 6801.


0.05
0.10
0.15

RESEARCH

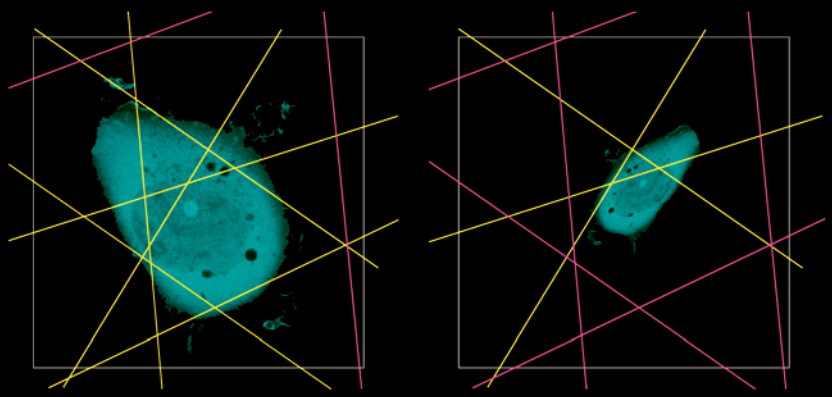


Figure 1:
In stochastic geometry, the fraction of random lines hitting an unknown spatial object is used to estimate the size of the object.

Figure 2:
In stochastic geometry, non-uniform sampling of fields of view (yellow quadrats) is used in cases where the biostructure under study is inhomogeneous in spatial distribution. An important increase in efficiency can be obtained.

THE ROLE OF STOCHASTIC GEOMETRY IN BIOIMAGING

Some of the most basic challenges of bioimaging can be summarized as follows

- **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

How does stochastic geometry contribute to the tackling of these challenges? The very name of the discipline indicates the issues taken up by stochastic geometers. Stochastic geometry is concerned with probabilities for random geometric events such as the probability that a random line hits a spatial object. It is useful to know such probabilities if the object is not directly observable. Imagine that you repeat the procedure of sending a random line through the region where the object is positioned and observe how many of these lines hit the object, see Figure 1. Since the **hitting probability** carries information about the size of the object, the fraction of lines you observe hitting the object can be used to estimate the **size** (area, volume, ...) of the object.

It is even possible to estimate the correct **number** of, for instance, cells in biological tissue using hitting probabilities, but the situation is here somewhat more complex. Imagine you want to estimate the number of a particular type of neurons in the human brain. Neurons seen in a section through the brain do not constitute a representative sample of the population under study. The reason is that the probability that a neuron is sectioned (hit by the section) depends on its size, the bigger the neuron the larger the probability of being sectioned. Using stochastic geometry the probability of being sectioned can be calculated and corrected for, so that a correct estimate of the number of neurons can be calculated.

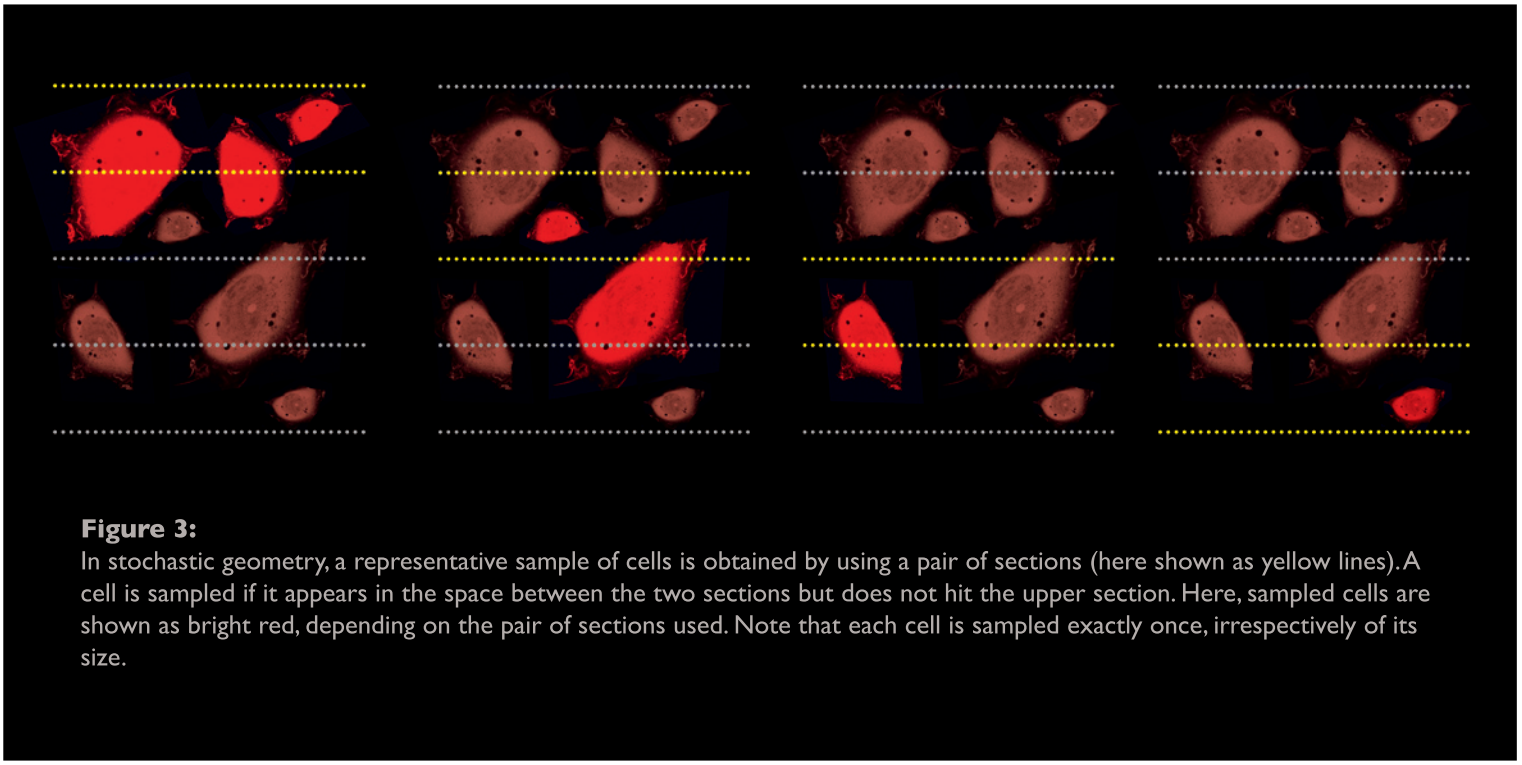


Figure 3:
In stochastic geometry, a representative sample of cells is obtained by using a pair of sections (here shown as yellow lines). A cell is sampled if it appears in the space between the two sections but does not hit the upper section. Here, sampled cells are shown as bright red, depending on the pair of sections used. Note that each cell is sampled exactly once, irrespectively of its size.

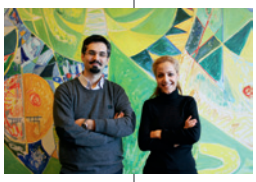
This correction depends, however, on assumptions concerning the shape of the neurons that may not be fulfilled. This is the reason why stochastic geometry has provided an alternative way of determining the number correctly, see Figure 3. It requires that the user is willing to compare the information on two parallel sections a small distance apart. The user will count the number of neurons seen in one section and not in the other. This number of neurons 'disappearing' between the two sections can be used to calculate a correct estimate of the total number of neurons. The CSGB project **Non-uniform sampling** is concerned with issues of this type, involving more complicated probes than line and planes such as virtual 3D probes, see also Figure 2.

Stochastic geometry also provides a wealth of stochastic models for random geometric structures. Typical examples are random point patterns and random tree-like structures. The statistical analysis of such models for random geometric structures is far from being trivial and is the object of study in the CSGB projects **Spatial and spatio-temporal point processes** and **Random shapes**.

As mentioned above, it is not enough just to look at the bioimages – we need objective ways of describing them. Traditionally, scalar quantities such as volume, surface area and number have been used here. In the CSGB project **Rotational integral geometry**, we work with more complicated quantities such as volume and surface tensors that are able to describe, for instance, changes in the spatial arrangement of neurons as well as changes in shape and orientation distributions. The fascinating mathematical and statistical questions relating to the connection between spatial objects in the 'real' world and their digital representation is studied in the CSGB projects **Digital stereology** and **Topological properties**.

Bioimages are very often extremely noisy and it is crucial to model the noise correctly in order to obtain correct estimates of model parameters. Non-Gaussian noise has been taken up in the CSGB project **Space-time lattice data**. Specific bioimaging projects relating to the molecular level are the CSGB projects **Fluorescence microscopy taken to the molecular level** and **Molecular cryo-EM**.

Intelligent Sampling



Point Processes
and
Protein Interactions

Modelling Microcolumns by Point Processes

COLLABORATIVE PROJECTS

MODELLING MICROCOLUMNS BY POINT PROCESSES

professor Jesper Møller (AAU)
associate professor Karl-Anton Dorph-Petersen (AU-bio)
associate professor Jakob G. Rasmussen (AAU)
research associate Ali Hoseinpoor Rafati (AU-bio)
Ph.D. student Farzaneh Safavimanesh (AAU)

The cerebral cortex is structured vertically into columnar arrays. The proper way to detect and quantify these **microcolumns** is subject to controversial discussion, and even their existence is questioned. Previous investigations are typically 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**. The analysis is hampered by the fact that data collection is extremely time consuming and therefore usually restricted to very narrow windows. A CSGB team consisting of members of the AAU and AU-bio groups has just started to tackle this challenge.

STOCHASTIC GEOMETRY GROUP - AARHUS UNIVERSITY

AU-MATH

INTELLIGENT SAMPLING

professor Jens R. Nyengaard (AU-bio)
research associate professor Ute Hahn (AU-math)
Ph.D. student Ina Trolle Andersen (AU-math/bio)

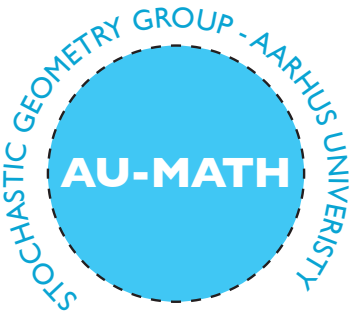
Intelligent sampling is an important issue when analyzing biostructures which are often **inhomogeneous** either in spatial distribution or orientation. Significant increase in precision can be obtained by using **non-uniform sampling**. An important issue is here to determine optimal, i.e. variance minimizing, sampling probabilities. In this CSGB project, it is planned to use a flexible modelling approach to determine such optimal sampling. The idea is to establish a **functional model relationship** between an auxiliary variable and the target variable (either parametrically or non-parametrically) and use this relationship to calculate optimal sampling probabilities. The approach could be characterized as model assisted probability sampling. Ph.D. student Ina Trolle Andersen, jointly supervised by AU-math and AU-bio, is working in this project.

POINT PROCESSES AND PROTEIN INTERACTIONS

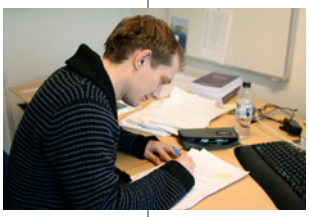
professor Rasmus Waagepetersen (AAU)
associate professor Kasper K. Berthelsen (AAU)
assistant professor Merete Raarup (AU-bio)
Ph.D. student Jan-Otto Hooghoudt (AAU)

To understand cellular processes, e.g. biogenesis and **protein-protein interactions**, it is important to know which specific cellular components (e.g. proteins) are distributed in close proximity of each other within a biological cell and within the cell membrane. The distribution of proteins in living cells and the interaction processes between proteins in living cells are until now not well understood. The interactions take place at the molecular level which can not be resolved directly by presently available microscopy techniques. However, **FRET microscopy** provides indirect information regarding proximity of proteins at an aggregated level, without explicitly resolving the molecule scales. In this project, we wish to develop **spatial point process models** for the protein distribution at the molecular level. Further, we want to develop inference methods to obtain estimates for protein concentrations in living cells as well as estimates for parameters that define the type and strength of **clustering**.

Reconstruction Algorithms in Cryo-EM



Fluorescence Microscopy taken to the Molecular Level



COLLABORATIVE PROJECTS

FLUORESCENCE MICROSCOPY TAKEN TO THE MOLECULAR LEVEL

professor Jens Ledet Jensen (AU-math)
assistant professor Merete Raarup (AU-bio)
postdoc Ege Rubak (AAU)

This collaborative project was started in 2010 with participation from three of the four research groups participating in CSGB, viz. the spatial statistics group (AAU), the biomedical group (AU-bio) and the stochastic geometry group (AU-math). The main aim of the project is to develop new statistical methods of analyzing pixel data from Förster resonance energy transfer (FRET) microscopy and use these methods to obtain information about protein interactions. **FRET data** consist of three noisy digital fluorescence images representing three different light intensities. These images indirectly quantify the concentration of each of the two proteins under study and the ratio of interacting proteins. FRET data may be very noisy and in such cases it is extremely important **to model the noise correctly** in order to obtain reliable estimates of interaction parameters. Statistically, FRET data may be characterized as a **three-dimensional random field**.

RECONSTRUCTION ALGORITHMS IN CRYO-EM

professor Mads Nielsen (KU)
associate professor Sami Brandt (KU)
associate professor François Lauze (KU)
associate professor Björn Sander (AU-bio)
Ph.D. student Katrine Hommelhoff Jensen (KU)

Single particle electron cryomicroscopy (cryo-EM) is a form of transmission electron microscopy (EM), aimed at determining three-dimensional (3D) structures of biological macromolecules from single-molecule EM images, which exhibit very **low signal-to-noise ratios**. The ability to image a given sample in a frozen hydrated state is an important strength, as it enables to capture natural snapshots of the particles in physiological aqueous solution. In 3D single particle reconstruction, randomly oriented copies of the macromolecular complex are available, each of which represents a certain viewing direction and eventually even a certain conformation, given that structural changes accompany changes of the functional state of the particle.

We focus on recovering the information underlying the noisy images as well as on the subsequent 3D reconstruction of these images. For these two purposes, we use **Bayesian statistical inversion** to optimally cope with the high amount of noise. For the image registration part, we investigate model-based methods. The Bayesian approach also allows the incorporation of **prior structural information** into the reconstruction problem for which we intend to develop efficient statistical algorithms. We are additionally investigating evaluation methods to assess the validity of the reconstructions.

IMAGE GROUP - COPENHAGEN UNIVERSITY
KU

$$\Phi^{j,t}_{k,r,s}(X) = \frac{1}{c_{d-j-1,p-j-1}} \int_{\mathcal{L}^d_p} \Phi^{j,d-p+t}_{k,r,s}(X \cap L_p) \mathrm{d}L^d_p$$

Figure 1: Rotational Croften Formula for Minkowski tensors.

ROTATIONAL INTEGRAL GEOMETRY

Johanna Ziegel

Jérémy Auneau-Cognacq

Rotational integral geometry is a subdiscipline of stochastic geometry, not more than 10-15 years old. This subfield provides rotational integral geometric identities which are the key tools in **local stereology**.

In 2011, the focus has been on derivation of rotational integral geometry formulae for **tensor valuations** (Alesker, 1999a, b; Hug *et al.*, 2008). In collaboration with postdoc Johanna Ziegel, Heidelberg, CSGB researchers have succeeded in developing a genuine **rotational Crofton formula** for integrated Minkowski tensors, see Figure 1. The result will be presented in a forthcoming paper (Auneau-Cognacq *et al.*, 2012). The new rotational formula contains a number of interesting special cases important for applications. In particular, using this formula, it is possible to estimate classical Minkowski volume and surface tensors of rank two from virtual isotropic sections passing through reference points. The formula also shows some new light on rotational integral geometry for intrinsic volumes. The two problems of (1) calculating rotational averages of intrinsic volumes on sections passing through a reference point and (2) expressing the intrinsic volumes of the spatial structure under study as a rotational average of suitably chosen measurements in the sections can thus be given a common formulation.

References

Alesker, S. (1999a): Continuous rotation invariant valuations on convex sets. *Ann. Math.* **149**, 977-1005.

Alesker, S. (1999b): Description of continuous isometry covariant valuations on convex sets. *Geom. Dedicata* **74**, 241-248.

Auneau-Cognacq, J., Ziegel, J. & Jensen, E.B.V. (2012): Rotational integral geometry of tensor valuations. *CSGB Research Reports* **12-02**. Submitted.

Hug, D., Schneider, R. & Schuster, R. (2008): Integral geometry of tensor valuations. *Adv. Appl. Math.* **41**, 482-509.

Kiderlen, M. & Jensen, E.B.V. (2012): On uniqueness of rotational integrals. In preparation.

Rasmusson, A., Hahn, U., Larsen, J. O., Gundersen, H.J.G., Jensen, E.B.V. and Nyengaard, J.R. (2011): The spatial rotator. *CSGB Research Reports* **11-06**. Submitted.

During 2011, the AU-math and AU-bio groups have discussed how to use the new rotational Crofton formula for Minkowski tensors in **stereology for tensor valued functionals**. Concrete pilot experiments with the 3D virtual probe called the spatial rotator, see Rasmusson *et al.* (2011), show that this 3D design is appropriate for tensor estimation as well, but there are issues of overprojection in thick microscopy sections that need to be solved before the new methods can be implemented on real tissue.

In 2011, CSGB researchers have also started to study the inverse problem of expressing intrinsic volumes as rotational averages of suitably chosen measurements in sections in more detail. The focus has been on whether the available solution to this inverse problem is **unique**. In the case of volume expressed as a rotational integral with respect to lines passing through a reference point, it has been shown that the functional defined in the linear section is indeed unique in the class of rotation invariant functionals (Kiderlen & Jensen, 2012). This question will be further studied in 2012.

Apart from the close collaboration with Jan Rataj, Prague, and Johanna Ziegel, Heidelberg, this project has benefited from close collaboration with Günter Last, Daniel Hug and Wolfgang Weil, Karlsruhe Institute of Technology, and Klaus Mecke and Gerd Schröder-Turk, Institut für Theoretische Physik, Erlangen, with whom CSGB researchers have met three times during 2011. The AU-math group is the international research partner in a DFG Research Unit formed by the German researchers.

COURSE ON ADVANCED VALUATION THEORY

On 15-18 March 2011, professor Andreas Bernig, Goethe-Universität Frankfurt, gave a Course on Advanced Valuation Theory at Department of Mathematics, Aarhus University. The focal points were translation invariant valuations, the Klain embedding, algebraic structures on the space of valuations and integral geometry of $SO(n)$ and other groups.

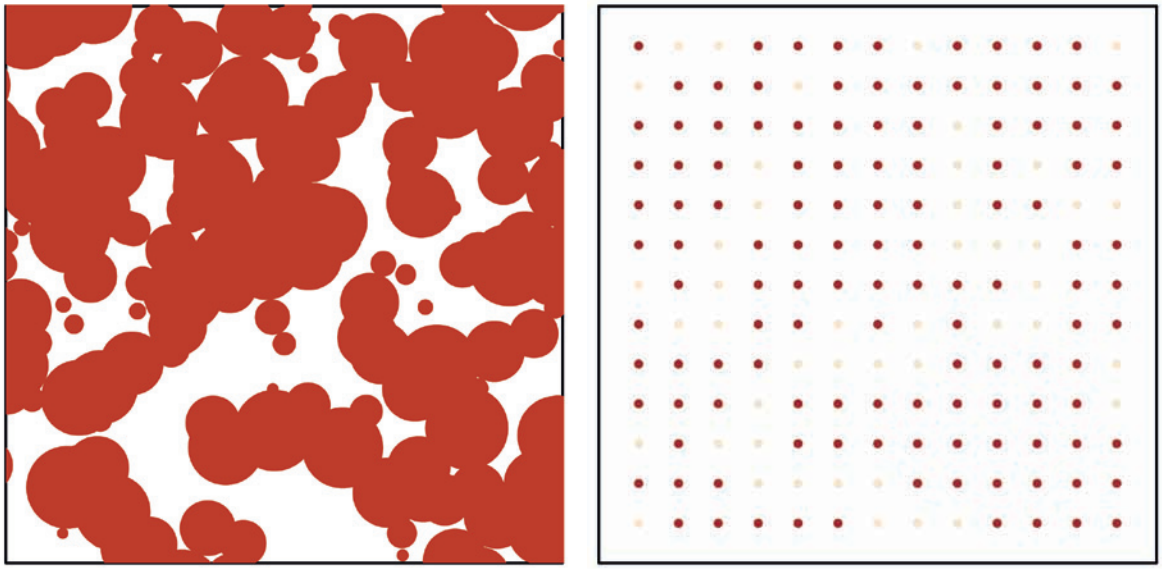


Figure 1:
Realization of a stationary Boolean model of random discs (left). Digital algorithms are based only on a digitization, that is a sample of the Boolean model on points of a regular lattice (right).

DIGITAL STEREOLOGY

Anne Marie Svane and Markus Kiderlen at the CSGB stochastic geometry group are currently working on an exhaustive analysis of the bias of digital specific intrinsic volumes in the planar case.

This project is concerned with the estimation of geometric characteristics from discrete binary images of a two- or three-dimensional structure.

Observing small pixel neighborhoods in a **digital image** containing both, fore- and background pixels, allows to get a rough idea on the location of the boundary of the structure. At least for sufficiently high resolution, this observation can be made rigorous to estimate properties of the boundary; cf. Gutkowski *et al.* (2004) and Ziegel & Kiderlen (2010) for surface area estimation in 3D. These results depend on asymptotic formulas for the increase of volumes of morphological transforms given in Kiderlen & Rataj (2006). However, the assumptions on the underlying structure in Kiderlen & Rataj (2006) appear to be intricate and difficult to handle. In collaboration with the CSGB cooperating scientist Jan Rataj, Prague, we were able to simplify these assumptions: based on inspiring work in Galerne (2011) we showed very recently that most of the asymptotic formulae hold for all structures that are **sets of bounded perimeter**, see Kiderlen & Rataj (2011).

With the exception of volume and surface area, very little is known about the quality of existing estimators for additive geometric characteristics, like the Euler

characteristic, integrated mean curvature or general intrinsic volumes. In order to compare existing local digital algorithms for intrinsic volumes, we intend to apply them to digitizations of standard (random) set models like the stationary Boolean model of balls in n-dimensional space, $n \geq 2$. None of the known local digital algorithms leads to unbiased estimates of all specific intrinsic volumes of this model. An analysis of the bias requires a purely geometric Laurent expansion of **large parallel volumes** for finite sets. This problem was solved in Kampf & Kiderlen (2011), where we showed such an expansion for arbitrary finite sets in the plane, and for finite sets satisfying a geometric condition when $n \geq 3$. It turns out that the coefficients of this expansion share many properties with the ordinary intrinsic volumes and were therefore named intrinsic power volumes.

They contain all the relevant geometric features of the finite set as far as parallel volumes are concerned. Anne Marie Svane and Markus Kiderlen at the CSGB stochastic geometry group are currently working on an exhaustive analysis of the bias of digital specific intrinsic volumes in the planar case ($n = 2$). Unlike earlier partial results, the bias is not only described asymptotically for the resolution tending to infinity, but will depend explicitly on the finite resolution of the digitization up to a desired finite order. In higher dimensions an individual treatment of digital algorithms, depending on the underlying adjacency system, appears to be necessary in order to assure the above mentioned geometric condition to hold. In the course of this analysis we in particular expect to find a digital algorithm for the integral of mean curvature that is tailor-made for **Boolean models** in 3-dimensional space.

References

Galerne B. (2011): Computation of the perimeter of measurable sets via their covariogram. Applications to random sets. *Image Anal. Stereol.* **30**, 39-51.

Gutkowski, P., Jensen E.B.V., & Kiderlen, M. (2004): Directional analysis of digitized three-dimensional images by configuration counts. *J. Microsc.* **216**, 175-185.

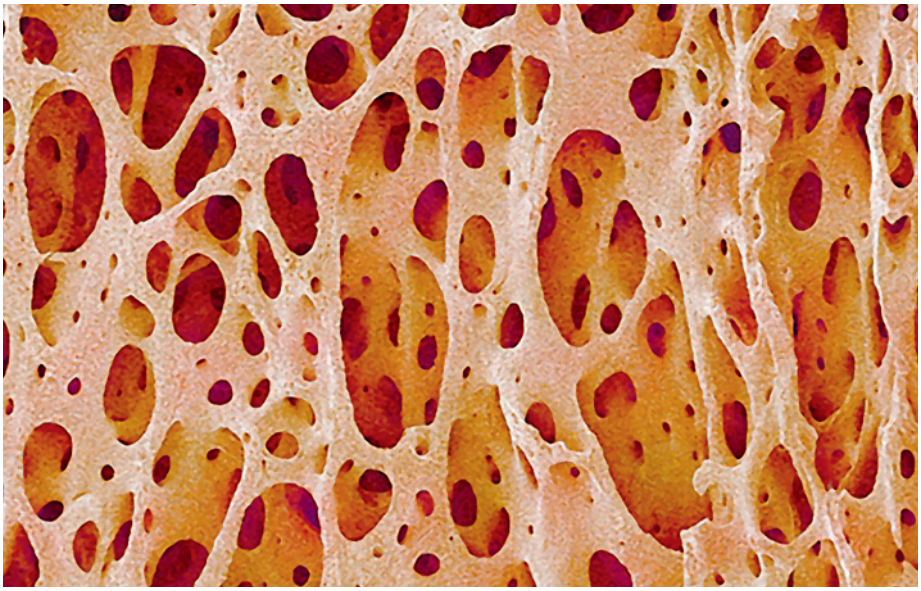
Kampf, J. & Kiderlen, M. (2011): Large parallel volumes of finite and compact sets in d-dimensional Euclidean space. *CSGB Research Reports*, **11-08**. Submitted.

Kiderlen, M. & Rataj, J. (2006): On infinitesimal increase of volumes of morphological transforms. *Mathematika* **53**, 103-127.

Kiderlen, M. & Rataj, J. (2011): Dilation volumes of sets of bounded perimeter. *CSGB Research Reports* **11-05**. Submitted.

Ziegel, J. & Kiderlen, M. (2010): Estimation of surface area and surface area measure of three-dimensional sets from digitizations. *Image and Vision Computing* **28**, 64-77.

TOPOLOGY AND DIGITAL IMAGE ANALYSIS



Andrew du Plessis

Sabrina Tang Christensen

Modern light-, laser- and electron microscopes, as well as scanners, yield digital pixel 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 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.

It remains an open question to what extent the full differential-geometric structure of the object's boundary can be reconstructed from a digitalisation - so that, for example, curvature and boundary length are well-approximated in a reconstruction.

A new approach to this question has made promising progress in 2011. A research report is in preparation. Advances in digital photography mean that these days a pixel represents rather faithfully the light intensity falling on the whole of the corresponding lattice square in the sensor, rather than just being a sampling of it. This leads to new methods of **boundary reconstruction** based both on differential-geometric and integral-geometric considerations. Preliminary experiments suggest that this yields very accurate reconstructions. If this is substantiated on a larger scale, the general availability of much more precise geometric information from low-resolution images will represent a considerable advance.

ADVANCES IN LOCAL STEREOLOGY

In classical stereology, **Wicksell's corpuscle problem** (Wicksell, 1925, 1926) is the most prominent example of shape estimation from planar sections. In 2011 we started to consider Wicksell's problem in a local stereological setting, where each spherical particle contains a reference point p, see Figure 1. Then the three-dimensional radius distribution of the particle is supposed to be estimated from profiles of the particle in an isotropic two-dimensional plane through p. In contrast to the classical Wicksell problem, the **shape distribution** of the particles is now described by two parameters: the radius R and the distance RQ of p from the particle centre (Q is therefore equal to this distance, relative to R). The profile is a circle containing p, with radius r, say. The relative distance of p to its centre is denoted by q. In Kiderlen & Thórisdóttir (2012), the case where R and Q are stochastically independent, that is, where the relative location of p is independent of the particle's size, is considered. They show that the joint distribution of the spatial variables $(R;Q)$ is uniquely determined by the distribution of the profile parameters $(r; q)$. They also derive a moment relation $ER^k = c_k Er^k$, $k = 0, 1, 2, ...$, similar to the classical case, where c_k can be determined from the distribution of q, and hence can be estimated from profile data. This allows to fit finitely many parameters in a model for R using the method of moments.

Even more generally, the explicitly known integral transforms connecting the distributions of r and q on the one side and R and Q on the other side, are of **generalized Abel type**. Hence they can be inverted numerically without model assumptions using adaptations of known inversion algorithms for the classical Abel transform. A Scheil-Schwartz-Saltykov type method (Saltykov, 1974; Stoyan *et al.*, 1995) is applied for the numerical unfolding of simulated data. In Figure 2, the spatial radius distribution of R is reconstructed from observations of 100 section profiles. The relative distance Q was chosen independent of R, uniformly in [0, 1].

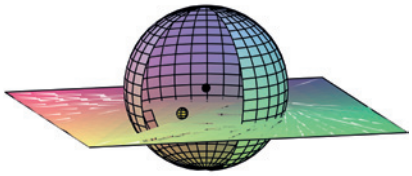


Figure 1:
Spherical particle with centre at the black point. An isotropic test plane through the reference point (yellow) is indicated.

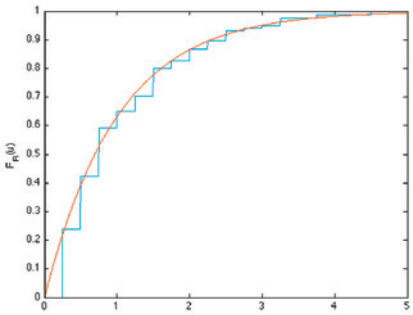


Figure2:
Scheil-Schwartz-Saltykov reconstruction of the distribution of R (blue) compared with the true exponential distribution (in red).

References

Kiderlen, M. & Thórisdóttir, Ó. (2012): Wicksell's problem in local stereology. In preparation.

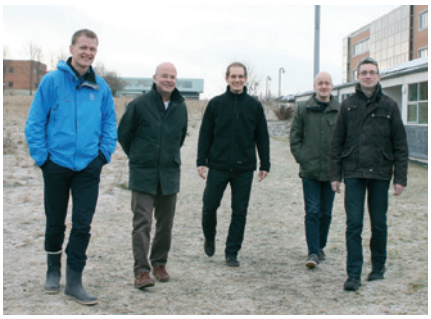
Saltykov, S.A. (1974): *Stereometrische Metallographie*. Deutscher Verlag für Grundstoffindustrie.

Stoyan, D., Kendall, W.S. & Mecke, J. (1995): *Stochastic Geometry and its Applications*. 2nd Edition. Wiley, New York.

Wicksell, S.D. (1925): The corpuscle problem I. *Biometrika* **17**, 84-99.

Wicksell, S.D. (1926): The corpuscle problem II. *Biometrika* **18**, 152-172.

SPATIAL AND SPATIO-TEMPORAL POINT PROCESSES



Contributions in 2011 to statistics for spatial point processes included the papers Jalilian *et al.* (2011) and Guan *et al.* (2011). The first paper studied an approach to **decomposition of variance** for spatial Cox processes with the aim of quantifying factors affecting the variation in realizations of Cox processes. The second paper introduced an **optimal quasi-likelihood** type estimating function for inference regarding the intensity function of a spatial point process. In 2012 it is the plan to develop parsimonious models for multivariate spatial Cox processes and inference procedures for such models.

Together with Håkon Toftager, Department of Mathematical Sciences, Norwegian University of Science and Technology, Jesper Møller studied in 2011 spatial point processes with a pair correlation function which depends only on the lag vector between a pair of points. They focused on statistical models with a special kind of `structured' anisotropy: the pair correlation function is geometric anisotropy if it is elliptical but not spherical. In particular they studied Cox process models with an **elliptical pair correlation** function, including shot noise Cox processes and log Gaussian Cox processes, and they developed estimation procedures using summary statistics and Bayesian methods. Their methodology was illustrated on real and synthetic datasets of spatial point patterns. Their paper (Møller & Toftager, 2012) has just been submitted for peer-reviewed journal publication.

The **Hawkes process** is a practically and theoretically important class of point processes, but parameter estimation for such a process can pose various problems. Rasmussen (2011) explored and compared two approaches to Bayesian inference. The first approach is based on the so-called conditional intensity function, while the second approach is based on an underlying clustering and branching structure in the Hawkes process. For practical use, MCMC (Markov chain Monte Carlo) methods are employed. The two approaches are compared numerically using three examples of the Hawkes process.

In collaboration with Dr. Mari Myllymäki, Aalto University, Kasper Berthelsen has investigated a class of marked point processes. The distribution of the random marks depends on the intensity of the point process. Further, the point process allows for pairwise interaction between points. These properties make this class of **marked point processes** particular interesting within as diverse fields as forestry and material

References

Baddeley, A., Rubak, E. & Møller, J. (2012): Score, pseudo-score and residual diagnostics for goodness-of-fit of spatial point process models. To appear in *Statistical Science* **27**.

Guan, Y., Jalilian, A. & Waagepetersen, R. (2011): Optimal estimation of the intensity function of spatial point process. *CSGB Research Reports* **11-07**. Submitted.

Jalilian, A., Guan, Y. & Waagepetersen, R. (2011): Decomposition of variance for spatial Cox processes. *CSGB Research Reports* **11-03**. To appear in *Scand. J. Statist.*

Møller, J. & Berthelsen, K.K. (2012): Transforming spatial point processes into Poisson processes using random superposition. To appear in *Adv. Appl. Probab.* **44**.

Møller, J. & Rasmussen, J.G. (2012): A sequential point process model and Bayesian inference for spatial point patterns with linear structures. To appear in *Scand. J. Statist.* **39**.

Møller, J. & Toftager, H. (2012): Geometric anisotropic spatial point pattern analysis and Cox processes. *CSGB Research Reports* **12-01**. Submitted.

Rasmussen, J.G. (2011): Bayesian inference for Hawkes processes. *CSGB Research Reports* **11-01.** Accepted for publication in *Methodology and Comp. Appl. Probab.*

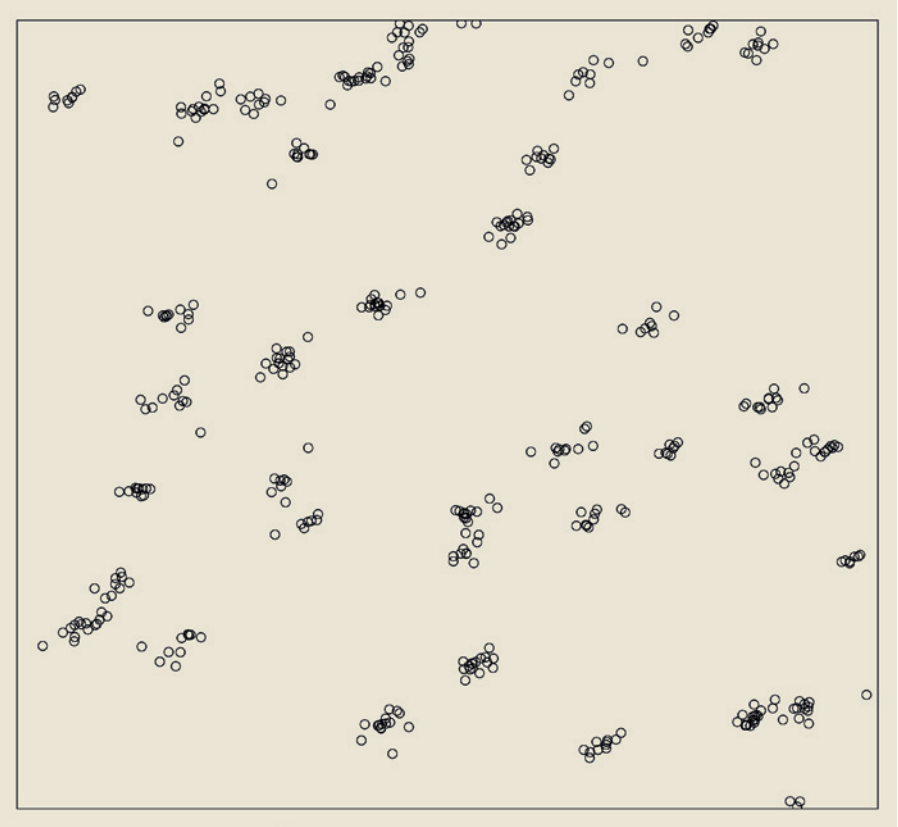


Figure 1: Simulated example of a geometrical anisotropic Cox process model studied in Møller & Toftager (2012).

sciences. In both areas of application object size (tree diameter, particle size) is random, and has a clear relationship with the abundance of objects. In addition both trees and particles exhibit obvious interaction due to non-overlapping objects and competition for resources (in case of trees). The class of marked point processes is an extension of or related to earlier work on **locally scaled point process**, preferential sampling and intensity dependent marking. For statistical inference, a pseudo Bayesian approach is adopted, where the likelihood function is replaced by a pseudo likelihood function. A conventional application of pseudo likelihood for point processes involves discretizing an integral over the product of the location and the mark spaces. However, in the present setting it turns out that it is feasible to perform the integral over the mark space without discretization, which in turn makes the approach computationally feasible.

During 2011, Ege Rubak together with Jean-François Coeurjolly, University of Grenoble, has initiated new research regarding the covariance between so-called innovations in relation to residuals for **Gibbs point processes**. In particular a fast method of estimating the innovation covariance has been developed, and it has been shown how this can be used to estimate the asymptotic covariance matrix for the maximum pseudo likelihood estimate (MPLE) of the parameters of a Gibbs point process. This makes it computationally feasible to provide asymptotic confidence regions for the MPLE.

Furthermore, Ege Rubak and Jesper Møller have initiated research in **determinantal point processes** in collaboration with Frédéric Lavancier, University of Nantes. Finally, the work on the papers Baddeley *et al.* (2012), Møller & Berthelsen (2012) and Møller & Rasmussen (2012) have been completed.

SPACE-TIME LATTICE DATA

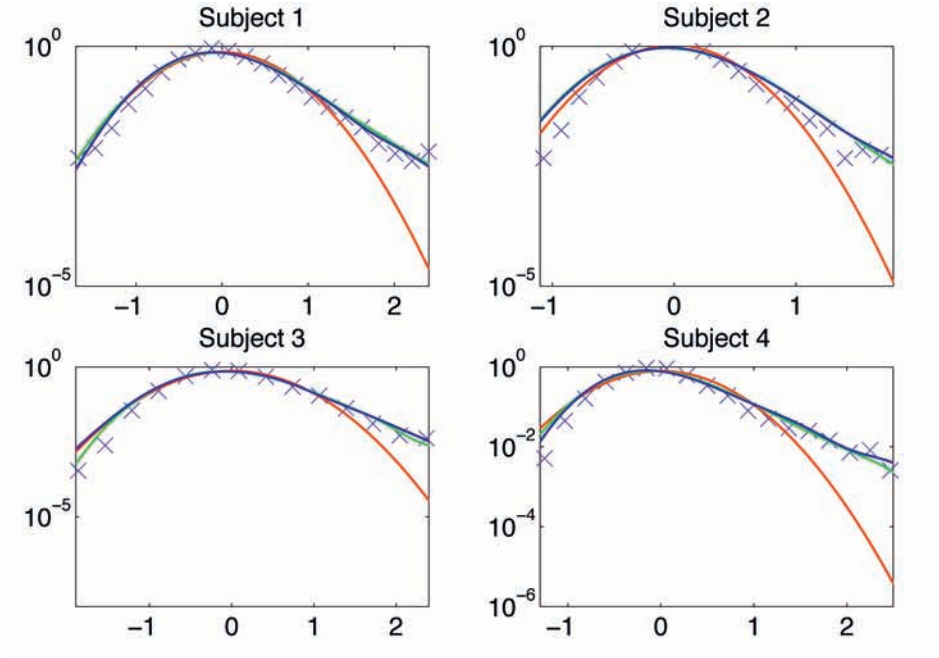


Figure 1:
Log-histograms for the data (×) in the selected region for four healthy subjects together with the fitted Gaussian densities and the densities based on a NIG (normal inverse Gaussian) random field model. The Gaussian density is shown as the red curve, the NIG based density estimated using the method of moments is shown as the blue curve and the NIG based density estimated using the EM algorithm is shown as the green curve.

Kristjana Jónsdóttir | MIND*Lab*

In 2011, CSGB has together with MINDLab researchers developed new models for **non-Gaussian random fields**, see Jónsdóttir *et al.* (2011).

Traditional methods of analysis in brain imaging based on Gaussian random field theory may leave small, but significant changes in the signal level undetected, because the assumption of Gaussianity is not fulfilled. In group comparisons, the number of subjects in each group is usually small so the alternative strategy of using a non-parametric test may not be appropriate either because of low power.

This has been our motivation for proposing in Jónsdóttir *et al.* (2011) a flexible, yet tractable model for a random field, based on **kernel smoothing** of a so-called **Lévy basis**. The resulting field may be Gaussian, but there are many other possibilities, e.g. random fields based on Gamma, inverse Gamma and normal inverse Gaussian (NIG) Lévy bases.

Figure 1 shows log-histograms for MTT (mean transit time) measurements of four subjects together with fitted densities based on a Gaussian random field (red curve) and a NIG random field (blue and green curves). The two different NIG densities represent two different ways of fitting the NIG model. The NIG model provides a

References

Hansen, L.V., Thorarinsdottir, T.L. and Gneiting, T. (2011): Lévy particles: modelling and simulating star-shaped random sets. *CSGB Research Reports* **11-04**. Submitted.

Jónsdóttir, K.Y., Rønn-Nielsen, A., Mouridsen, K. and Jensen, E.B.V. (2011): Lévy based modelling in brain imaging. *CSGB Research Reports* **11-02**. Submitted.

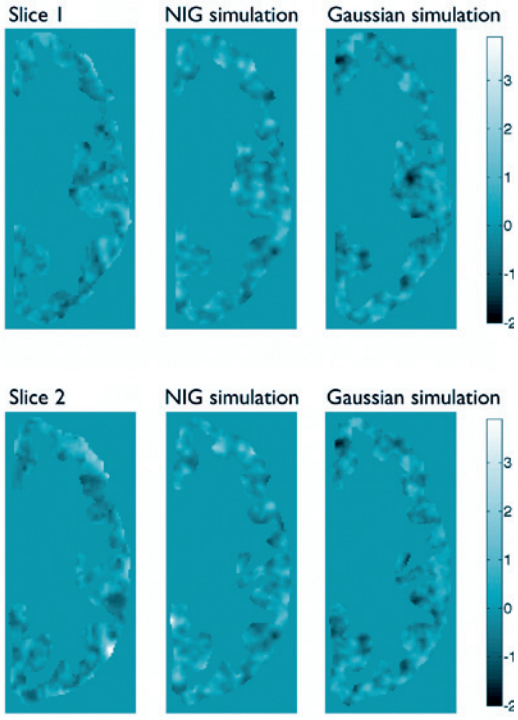


Figure2:
Observed MTT measurements (left) together with simulations under the fitted NIG model (middle) and the fitted Gaussian model (right) for subject 4.

more satisfactory fit. Figure 2 shows simulations of the fitted normal inverse Gaussian random field together with simulations of the fitted Gaussian random field model and the observed random field in slice 1 and 2, respectively, for subject 4. It is seen that the NIG based simulations capture more satisfactorily the feature of the data that occasionally very high values are observed at some voxels.

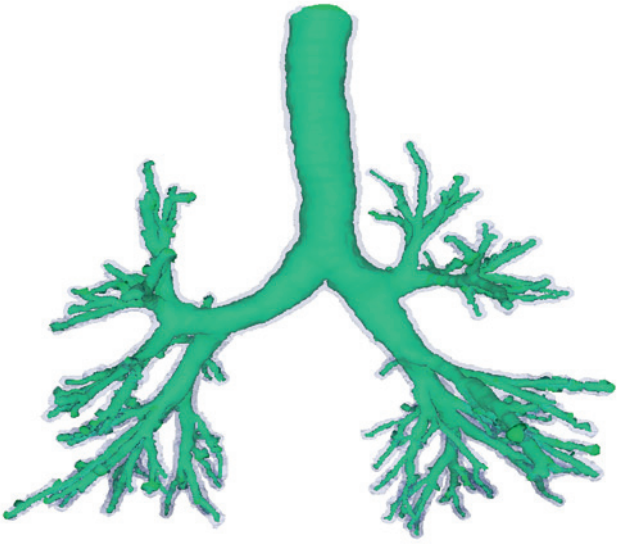
A widely used procedure in brain imaging for testing the hypothesis of no difference between two groups of subjects is to calculate a *t*-test statistic of no difference between groups at each voxel and declare a voxel as significant if the observed value of the *t*-test statistic in the voxel exceeds the 95 percentile in the **distribution of the maximal test statistic** under the null hypothesis. This procedure is very sensitive to the distributional assumptions of the underlying random field. A method of determining correctly the 95 percentile in the non-Gaussian case is provided in Jónsdóttir *et al.* (2011).

Lévy-based modelling has also been the focus in Hansen *et al.* (2011) where this type of modelling has been used to model random star-shaped particles in 3D. One of the topics taken up in this publication is the **Hausdorff dimension** of the boundaries of the particles.

RANDOM SHAPES

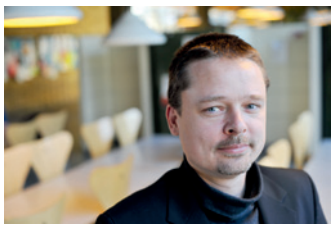
Quantifying the dimensions of the human airways are important with respect to diseases such as chronic obstructive pulmonary disease, asthma and cystic fibrosis.

The figure shows the interior (green) and exterior (transparent blue) surface of a human airways extracted from a CT image using an automatic graph based approach. The optimal solution is found using a minimum cut of a graph construction as illustrated in the figure to the right.



Aasa Feragen

Stefan Sommer



Jon Sporring

François Lauze

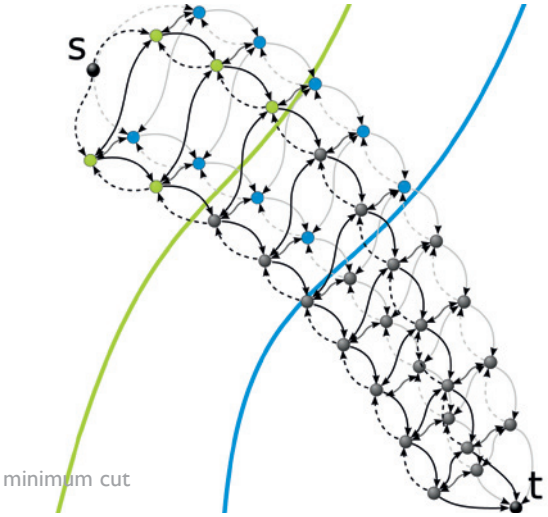
This year the three major methodological areas of interest relating to the random shape project have been the definition of proper structures to analyze **geometric trees**, to further develop the **large deformation** diffeomorphic metric mapping (LDDMM) framework, and the maximum a posteriori estimation of **covariance matrices**. The future plans are to further develop these areas to apply them in medical image analysis, as well as entering the field of brain imaging and especially the area of high angular resolution diffusion imaging for fibre analysis.

Tree-shape analysis

Geometric trees form an important class of shapes, which appear as skeletal or hierarchical representations as well as anatomical networks such as blood vessels, dendrite trees or airway trees from lungs. The statistical analysis of tree-structured data is gathering attention both in mathematical statistics, biomathematics, computer vision and medical image analysis. In 2011, we have published the first algorithms for computing meaningful **average geometric trees** (Feragen *et al.*, 2011a). We continued the development of the mathematical framework for spaces of tree-structured shapes (Feragen *et al.*, 2012a) and used this for doing automatic anatomical labeling of airway trees from the lungs (Feragen *et al.*, 2011b). With support from CSGB we have, moreover, started a collaboration with Megan Owen from the University of Waterloo, who is an expert on **algorithms for computations in tree-spaces**, and we are currently collaborating with her on fast anatomical airway tree labeling (Feragen *et al.*, 2012b).

LDDMM: medical image registration

Computational representations and statistical models for **diffeomorphism groups** constitute important tools for analyzing anatomical changes. The brain tissue degeneration caused by Alzheimer's disease can for example be modeled using diffeomorphisms. By introducing the kernel bundle framework (Sommer *et al.*, 2012)



and higher order kernels (Sommer *et al.*, 2011) for use with large deformation frameworks, we have made important contributions to compact and low-dimensional description of **anatomical change**. The promise is improved statistics on larger data sets leading to new clinical results. The work comes as a result of collaboration with Professor Xavier Pennec from INRIA Sophia-Antipolis, France.

Covariance estimation

The estimation of covariance matrices is a crucial step in several statistical tasks. Especially when using few samples of a high dimensional representation of shapes, the standard maximum likelihood estimate (ML) of the covariance matrix can be hard to determine, is often rank deficient, and may lead to unreliable results. In this work, we study **regularization by prior knowledge** using maximum a posteriori (MAP) estimates. We compare ML to MAP using a number of priors and to Tikhonov regularization. We favorably evaluated the covariance estimates on both synthetic and real data and analyzed the influence of the estimates on a missing-data reconstruction task, where high resolution vertebra and cartilage models are reconstructed from incomplete and lower dimensional representations (Crimi *et al.*, 2011).

References

Crimi, A., Lillholm, M., Nielsen, M., Ghosh, A., de Bruijne, M., Dam, E.B., & Sporring, J. (2011): Maximum à posteriori estimation of linear shape variation with application to vertebra and cartilage modeling. *IEEE Transactions on Medical Imaging* **30**, 1514-1526.

Feragen, A., Hauberg, S., Nielsen, M. & Lauze, F. (2011a): Means in spaces of treelike shapes. In: *International Conference of Computer Vision 2011*, 736-746.

Feragen, A., Lo, P., Gorbunova, V., Nielsen, M., Dirksen, A., Reinhardt, J., Lauze, F. B. & de Bruijne, M. (2011b): An airway tree-shape model for geodesic airway branch labeling. In: *Mathematical Foundations for Computational Anatomy: Workshop at MICCAI 2011, the 14th International Conference on Medical Image Computing and Computer Assisted Intervention.*

Feragen, A., Lo, P., de Bruijne, M., Nielsen, M. & Lauze, F. B. (2012a): Towards a theory of statistical tree-shape analysis. Submitted.

Feragen, A., Petersen, J., Owen, M., Lo, P., Hohwu, L., Wille, M., Dirksen, A. & de Bruijne, M. (2012b): A hierarchical scheme for geodesic anatomical labeling of airway trees. Submitted.

Sommer, S., Nielsen, M. & Pennec, X. (2012): Sparsity and scale: compact representations of deformation for diffeomorphic registration. *MMBIA Workshop at WACV 2012, Breckenridge, Colorado.*

Sommer, S., Nielsen, M., Darkner, S. & Pennec, X. (2011): Higher order kernels and locally affine LDDMM registration. Submitted.

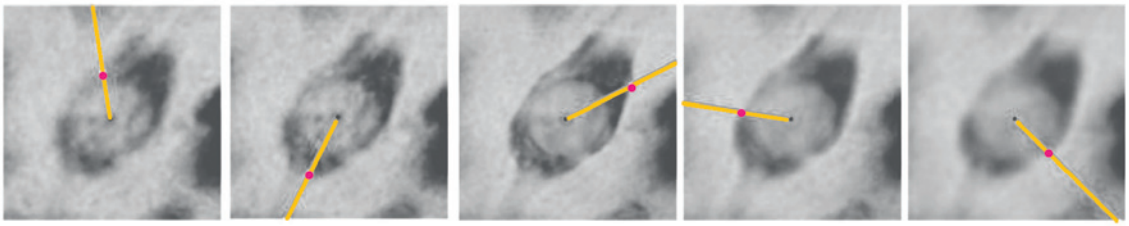


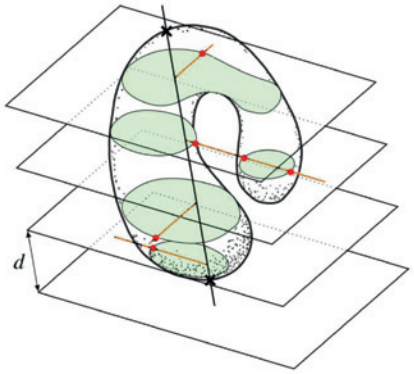
Figure 2: Five consecutive optical serial sections of a neuron, with test lines overlaid on screen. The intersection with the boundary was marked by mouse click (red dot).

NON-UNIFORM SAMPLING

Ute Hahn

Allan Rasmusson

Figure 1:
Volume of a particle is estimated using a spatial rotator with *n* parallel equidistant sections that are perpendicular to a given axis (here, *n*=4). On every section, the intersections (red dots) of the profile boundary with a test line (orange) are marked, and their distance to the central axis is measured. The direction of the test lines changes systematically from section to section.



Cell volume distribution is a very important geometric characteristic of biological tissue at a microscopic level. Its estimation requires that a large number of cells be inspected using stereological methods that work on a per cell level. The usual method of choice, the planar rotator (Jensen & Gundersen, 1993), is based on the evaluation of a single section through the object, correspondingly with limited accuracy. It is therefore desirable to **include spatial information**, and to evaluate several sections per cell when possible. Commonly, this would be done with the point counting Cavalieri estimator, which however means a prohibitively high work load. Therefore, members of the two Aarhus groups have developed a new method, **the spatial rotator**, which only requires intersection measurement with one test line per section, see Rasmusson *et al.* (2011). The principle of this unbiased estimator is explained in Figure 1. The volume of the particle is estimated as

$$\hat{V} = d\pi \sum_{i=1}^{n} \ell_i^2, \quad \text{where} \quad \ell_i^2 = \sum_k \ell_{ik}^2 \cdot (-1)^{k+1}.$$

On the *i*th section, l_{ik} is the distance to the axis of the *k*th intersection of particle boundary and test line, $l_{i1} > l_{i2} > \ldots$

References

Jensen, E.B.V. & Gundersen, H.J.G. (1993): The rotator. *Journal of Microscopy* **170**, 35-44.

Rasmusson, A., Hahn, U., Larsen, J.O., Gundersen, H.J.G., Jensen, E.B.V. & Nyengaard, J.R. (2011): The spatial rotator. *CSGB Research Reports* **11-06**. Submitted.

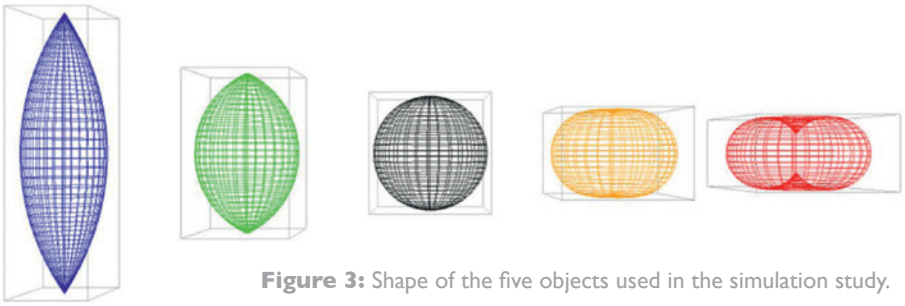


Figure 3: Shape of the five objects used in the simulation study.

Practical implementation

The spatial rotator has been implemented for use with **stacks of digital sections**, see Figure 2. In the practical application, the focus plane is moving in direction of the rotator axis, and top and bottom section have to be determined to obtain the projection length L of the cell. The sections that are to be evaluated are chosen systematic random with distance $d=L/n$ by the software. A test line is displayed on every section.

Simulation study

The variance of the spatial rotator estimate depends on the number n of test lines, the shape of the object, direction and placement of the rotator axis, and on the randomization scheme for the direction of test lines. An **extensive simulation** study was carried out, including five different cell like shapes, see Figure 3, various positioning and direction of the rotator axis, and three randomization regimes for the test line angle, namely independent uniform and systematic uniform with one and two revolutions on $[0,2\pi]$.

For realistic sample size $n=4, 5, ..., 20$, systematic uniform sampling with two revolutions yielded the lowest variance. Furthermore, we compared the spatial rotator with the planar rotator. The results are shown in Figure 4. Perhaps not surprisingly, the extra spatial information yields a **gain in precision**, the spatial rotator being about ten times more efficient than the planar rotator when using the same number $n=10$ of test lines in both estimators.

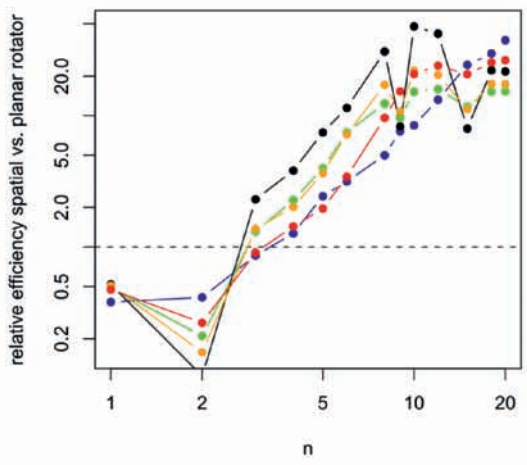


Figure 4:
Relative efficiency = ratio of the precision (inverse variance), of the spatial rotator compared to a planar rotator with the same number of test lines, for the five objects (colours correspond to Figure 3). The rotator axis was chosen isotropic random, with non central nucleus, thus reflecting a realistic practical setting.

FLUORESCENCE MICROCOPY TAKEN TO THE MOLECULAR LEVEL

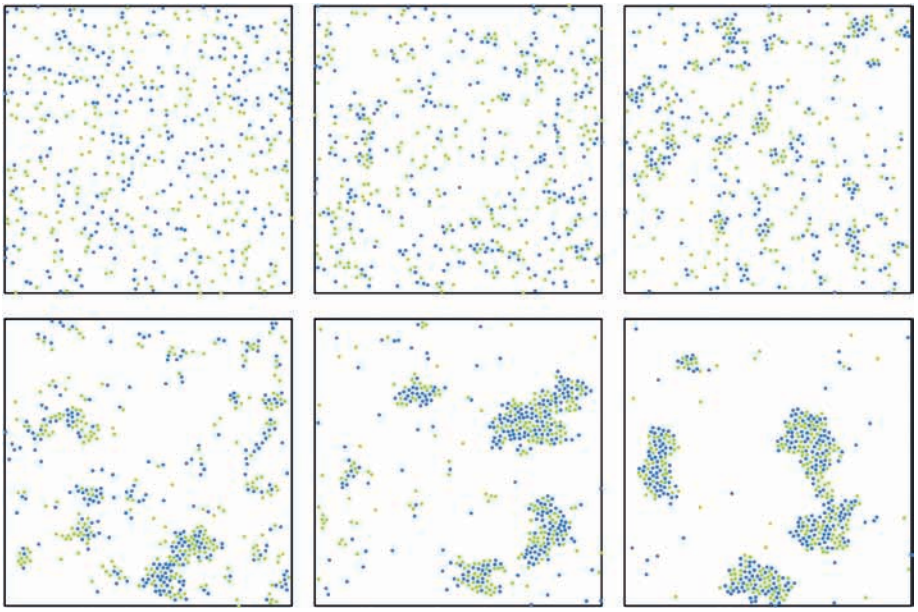


Figure 1: Simulations of clustered spatial point processes that are used in the modelling of protein interactions at an inner pixel level. It is planned to use implicit likelihood based inference methods to find appropriate parameter settings within the different point process cluster models. The simulations shown in the figure are from so-called Multi-type hard core Strauss processes.

Ege Rubak

Jan-Otto Hooghoudt

Merete Raarup

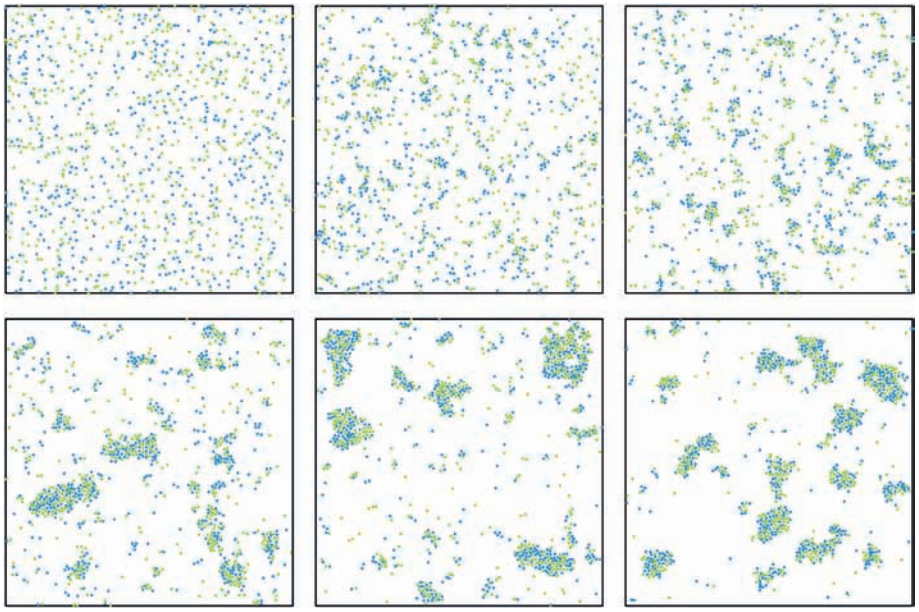
In this project, we study **intracellular protein interactions** by Förster resonance energy transfer (FRET). This type of microscopy has become one of the preferred tools to obtain information concerning the distribution of proteins throughout living cells. FRET is an electrodynamic phenomenon, occuring between a donor molecule in the excited state and an acceptor molecule in the ground state. Although the interactions between donors and acceptors are at the molecular level (1-10 nm), the pixel resolution of FRET microscopy is typically of the order of 100x100 nm. This implies that in general a large number of proteins are confined within one pixel and therefore only an average value of the distance between multiple donor and acceptor pairs can be obtained.

In 2011, we have continued the work on the statistical performance of **estimates of equilibrium parameters** and furthermore, we have started to develop point process models at the protein level. The FRET projects are collaborative projects between three of the four research groups participating in CSGB, viz. the spatial statistics group (AAU), the biomedical group (AU-bio) and the stochastic geometry group (AU-math).

FRET data consists of three noisy digital fluorescence images representing three different light intensities indirectly quantifying the concentration of each of the

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.



two proteins and the ratio of interacting proteins. In Chen *et al.* (2007), the protein interactions are quantified in terms of a chemical equilibrium parameter denoted K_d and an intrinsic FRET efficiency $E_{\max}$. In Chen *et al.* (2007), population based estimates of K_d and $E_{\max}$ are obtained from a sample of cells. During 2011, we have developed statistical tools for estimating the parameters for individual cells which allow us to study the biological variations between cells. Right now, we are in the process of writing a paper for a statistical journal concerning the new statistical method of analysis.

As an alternative to the approach above based on data at the pixel level, we have in 2011 developed **spatial point process models** to capture fundamental aspects of the distribution of proteins and their interactions. These models aim at describing the distribution of proteins at an inner pixel level throughout living cells. The aim is to use these models to obtain information concerning the interaction processes that take place at the molecular level between different types of proteins. **Implicit likelihood** based inference methods will be used in order to find appropriate parameter settings within different point process cluster models. Figure 1 shows an example of simulations of a point process model that is used to describe the distribution of two interacting proteins. The model can be characterized as a so-called Multi-type hard core Strauss process.

MOLECULAR CRYO-EM

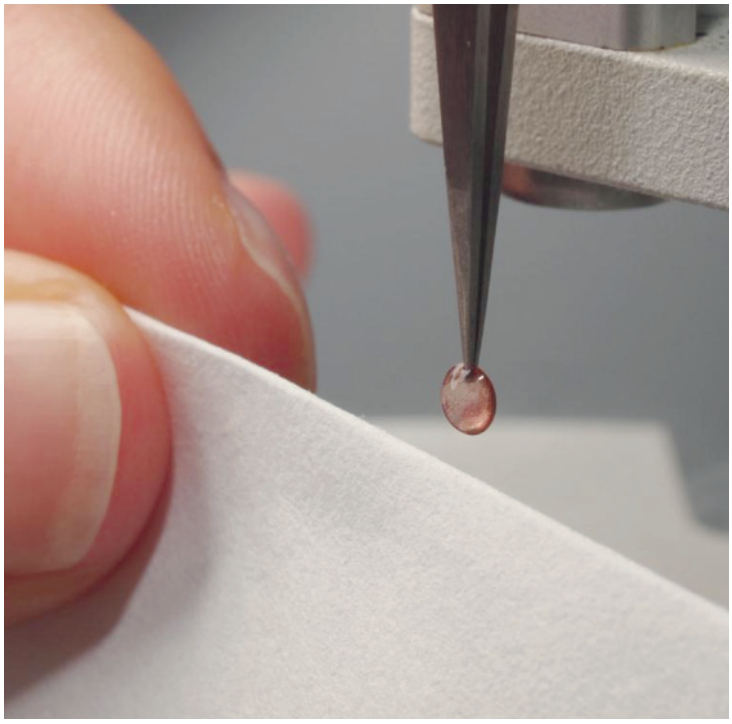
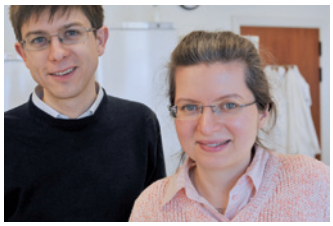


Figure:
Electron microscopical Sample Preparation of Biological Specimens. An electron microscopical copper grid is held by a pair of tweezers. A few microliters of sample is pipetted on the grid and subsequently blotted with a piece of filter paper. The resulting thin aqueous layer is then rapidly frozen by plunging into liquid ethane. Thereby, the amorphous state of the solution is maintained. The specimen is then ready for transfer into the electron cryomicroscope and can be imaged under cryogenic (about -180°C) conditions.



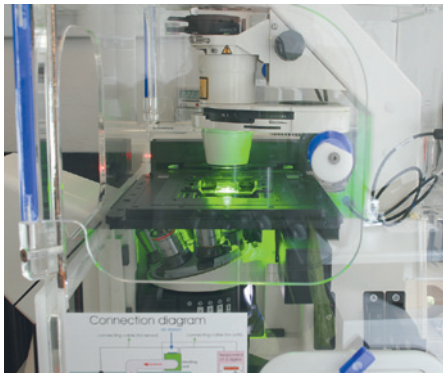
Project leaders AU-Bio:
Björn Sander *(Department of Clinical Medicine, AU),*
M. Monika Golas
(Department of Biomedicine, AU)

Participating Ph.D. student:
Jay Rai *(Department of Clinical Medicine, AU)*

The purification of **macromolecular samples** suitable for imaging in a cryo-electron microscope is a central part of electron cryomicroscopy (cryo-EM). Among the prerequisites for cryo-EM samples, biochemical purity and integrity, sufficient concentration, compatible buffer conditions as well as a solid biochemical and functional knowledge about the proteins and other biomolecules constituting the complex of interests are the most important aspects. We use baker's yeast (**Saccharomyces cerevisiae**) and, to a lesser extent, the bacterium **Escherichia coli** as model organisms to accomplish this task. In the recent months, we therefore designed and constructed DNA vectors suitable for the genetic modification of endogenous yeast proteins. The genetic modification represents a condition for the purification of cellular protein assemblies from cultured cells under most native conditions. Additionally, **the genetic modification** has also been used to functionally and structurally modify a protein of interest: the introduction of a bulky domain can be used as a structural landmark to identify a protein's location in a multi-component assembly by cryo-EM. Furthermore, these domains bear additional functions such as fluorescent properties which in turn facilitate further **in vivo** and **in vitro** studies of the protein of interest. We have constructed two different types of **DNA vectors**. The first type allows tagging a protein of choice with a purification tag, while the second type allows adding a combination of a choice of different fluorescent proteins coupled to a purification tag for protein complex purification under gentle conditions.

By using these DNA vectors, we set out to replace the natural C-termini of a number of yeast proteins by the engineered termini, and we achieved to establish novel, stable yeast strains that express tagged versions of our proteins of interest. The successful integration into the yeast genome could be verified by performing control polymerase chain reactions (PCRs) to assess the PCR fragment lengths as well as subsequent sequencing of the **modified gene**, and could also be monitored by growth on selective cell culture media. During the last months, we have started to grow larger amounts of the new yeast strains in order to establish purification conditions suitable for cryo-EM. To facilitate the purification of intact macromolecular assemblies, we established an optimized milling system for **protein complex purification** from yeast and bacteria cells under liquid nitrogen conditions which only recently has been introduced in the field. The isolates are currently subjected to biochemical analysis. This is a critical step to assess the identity of the proteins purified as well as to optimize the purification quality. By SDS PAGE (a type of gel electrophoresis) followed by Western blotting we could show that full-length versions of the genetically modified proteins were expressed in the yeast strains. The biophysical properties of these proteins in their complexes are currently analyzed by different combinations of affinity chromatography and size fractionation, and we have also started to screen the first samples by electron microscopy.

In the first half of 2011, the **Titan Krios cryo electron microscope** has been installed at the Faculty of Science, AU. In summer until late autumn, the device was ready for several rounds of user training by the manufacturers of the microscope hardware which we attended. This was followed by a period of maintenance and required hardware and software updates by the microscope company, and we now expect the microscope to be ready for user work in spring 2012. Our first task will thus be the purification of sufficient amounts of various samples with the aim to use the samples in the development of **algorithms for image processing**. Also, the extension of the GPU computer cluster we have access to at the Danish Center for Scientific Computing - Aarhus University (DCSC/AU) took place in the first half of 2011. We have thus also adapted our single-particle image processing software to the new network architecture.




37
36
35
34
33
32
0.05
0.10
0.15
0.02
0.04
0.06
0.08
0.10
122
120

CENTRE ACTIVITIES

OVERVIEW - PAST AND PLANNED INTERNATIONAL ACTIVITIES

International conferences and workshops

- *16th Workshop on Stochastic Geometry, Stereology and Image Analysis*, 5-10 June 2011, Sandbjerg
- *BioImaging Workshop*, 22-23 June 2011, Copenhagen
- *5th Workshop on Theory of Randomized Search Heuristics*, 8-9 July 2011, Copenhagen
- *Workshop on Convexity and Geometric Tomography*, 7 June 2012, Aarhus
- *Workshop on Geometry and Statistics in Bioimaging: Manifolds and Stratified Spaces*, 8-12 October 2012, Sandbjerg

International minisymposia

- *Minisymposium on Bayesian Inference in Spatial Statistics*, 24 February 2011, Aarhus
- *Minisymposium on the Proportionator*, 26 August 2011, Aarhus
- *Lectures on Stereology, with Emphasis on the Invariator*, 14 - 15 December 2011, Aarhus. Lecturer Luis Cruz-Orive (University of Cantabria)

International Ph.D. courses

- *Course on Advanced Valuation Theory*, 15-18 March 2011, Aarhus
- *Course on Quantitative Medical Graphics*, 23 and 30 March 2011, Aarhus
- *Summer Camp on the Analysis of Spatial Point Patterns*, 1-5 June 2011, Sandbjerg
- *Summer School on Graphs in Computer Graphics, Image and Signal Analysis*, 14-19 August 2011, Bornholm
- *Summer School on Advances in Image, Motion and Video Coding and Processing*, 22-26 August 2011, Copenhagen
- *Stereology Course*, 29 August-2 September 2011, Bern
- *Stereology Course*, 13-15 September 2011, Sandbjerg
- *Bayesian Computing with INLA*, 7 November 2011, Aalborg
- *Course on Quantitative Medical Graphics*, 16 and 23 November 2011, Aarhus
- *Practical Confocal Fluorescence Microscopy*, 12-15 December 2011, Aarhus
- *Summer School on Image Registration*, 13-15 June 2012, Copenhagen
- *Summer School on Domain Adaptation Theory and Applications*, 20-24 August 2012, Copenhagen
- *Topics in Space-Time Modelling and Inference*, 27-31 May 2013, Aalborg

SUMMER CAMP SPATSTAT 2011



Prior to the 16th Workshop on Stochastic Geometry, Stereology and Image Analysis, a course on the analysis of spatial point patterns was held 1-5 June 2011 at Sandbjerg Estate. The teaching team included Adrian Baddeley (CSIRO, Perth) and CSGB researchers from Aarhus and Aalborg.

Workshop on Geometry and Statistics:

Manifolds and Stratified Spaces

8-12 October 2012, Sandbjerg Estate, Sønderborg, Denmark

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

Scope of the workshop:

This workshop is dedicated to geometric and statistical modeling in biomedical image analysis. The workshop is a result of our desire to bring together researchers from biomedical image analysis, who have an interest in the underlying mathematical constructions, along with mathematicians who have an interest in the underlying practical problems.

Invited speakers:

Alfred Bruckstein, Israel Institute of Technology | **James Damon**, University of North Carolina | **Herbert Edelsbrunner**, Duke University and Institute of Science and Technology Austria | **Stephan Huckemann**, Universität Göttingen | **Sarang Joshi**, University of Utah | **Steve Marron**, University of North Carolina | **Peter W. Michor**, Universität Wien | **Ezra Miller**, Duke University | **David Mumford**, Brown University | **Megan Owen**, University of Waterloo | **Xavier Pennec**, INRIA Sophia Antipolis | **Stephen Zucker**, Yale University

For further information, please see the homepage:

www.csgb.dk

RESEARCH TRAINING

In 2011, a total of ten international Ph.D. courses were arranged by CSGB researchers in a wide range of the study areas of CSGB, including Bayesian inference, computer graphics, fluorescence microscopy, graphical models, integral geometry, spatial point processes and stereology. The Ph.D. students and postdocs at CSGB attended these courses that also in the majority of the cases had international participants. In addition, the research students at CSGB were offered participation in a number of other international workshops and conferences.

The donation from the Villum Foundation involves a total of four full Ph.D. stipends. At the end of 2011, ten Ph.D. students were associated to CSGB, four of these students come from abroad. In 2012, we expect to be able to hire two more Ph.D. students. This increased research training activity has been made possible by cofinancing from the three participating Danish universities.

In 2011, the following five collaborative projects were up running (the participating research groups are shown in parenthesis):

- modelling microcolumns by point processes (AU-bio, AAU)
- intelligent sampling (AU-math, AU-bio)
- point processes and protein interactions (AU-bio, AAU)
- fluorescence microscopy taken to the molecular level (AU-math/bio, AAU)
- reconstruction algorithms in cryo-EM (AU-bio, KU)

CSGB Ph.D. students are involved in four of these five collaborative projects. In each of these cases, the Ph.D. student has a main supervisor from one of the research groups and a cosupervisor from a collaborative research group. In 2012, two more collaborative projects are planned with the image group, KU, as the main partner.

CSGB Research Reports 2011 can be downloaded at www.csgb.dk (publications).

CSGB RESEARCH REPORTS 2011

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. Guan, Y., Jalilian, A. & Waagepetersen, R. (2011): Optimal estimation of the intensity function of a spatial point process. *CSGB Research Reports* **11-07**. Submitted.

2. Hansen, L.V., Thorarinsdottir, T.L. & Tilmann, G. (2011): Lévy particles: Modelling and simulating star-shaped random sets. *CSGB Research Reports* **11-04**. Submitted.

3. Jalilian, A., Guan, Y. & and Waagepetersen, R. (2011): Decomposition of variance for spatial Cox processes. *CSGB Research Reports* **11-03**. To appear in *Scandinavian Journal of Statistics*.

4. Jónsdóttir, K.Y., Rønn-Nielsen, A., Mouridsen, K. & Jensen, E.B.V. (2011): Lévy based modelling in brain imaging. *CSGB Research Reports* **11-02**. Submitted.

5. Kampf, J. & Kiderlen, M. (2011): Large parallel volumes of finite and compact sets in *d*-dimensional Euclidean space. *CSGB Research Reports* **11-08**. Submitted.

6. Kiderlen, M. & Rataj, J. (2011): Dilation volumes of sets of bounded perimeter. *CSGB Research Reports* **11-05**. Submitted to *Advances in Applied Probability*.

7. Rasmussen, J.G. (2011): Bayesian inference for Hawkes processes. *CSGB Research Reports* **11-01**. Accepted for publication in *Methodology and Computing in Applied Probability*.

8. Rasmusson, A., Hahn, U., Larsen, J.O., Gundersen, H.J.G., Jensen, E.B.V. & Nyengaard, J.R. (2011): The spatial rotator. *CSGB Research Reports* **11-06**. Submitted.

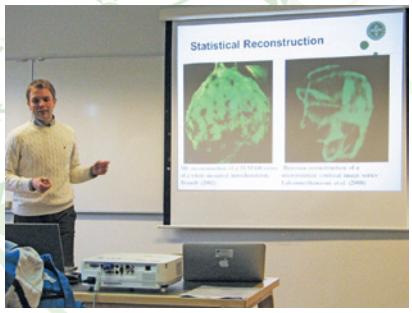
Third Internal CSGB Workshop - Aalborg

The internal CSGB workshops are held twice a year. The third internal workshop was arranged by the spatial statistics group and took place at Aalborg University 25-26 May 2011.

Fourth Internal CSGB Workshop - Aarhus

The internal CSGB workshops are held twice a year. They are arranged alternately 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. The fourth internal workshop was arranged by the Biomedical group and took place at Aarhus University 17-18 November 2011.



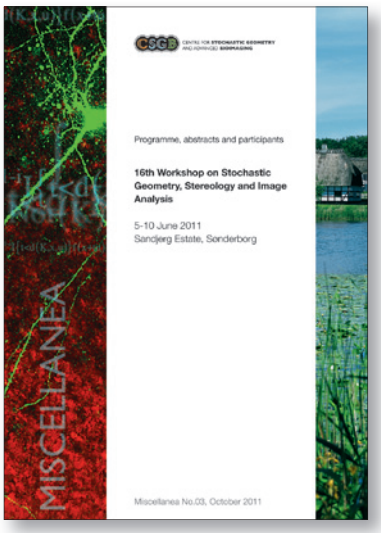
CSGB MISCELLANEA 2011

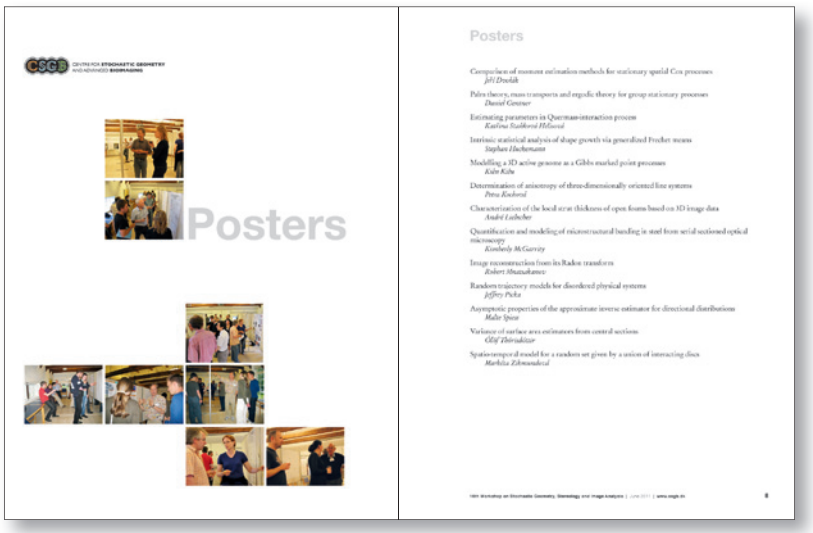
In 2011, a new publication series started that contains various internal publications such as lecture notes, conference abstracts, etc. Three such publications appeared in 2011.

1. Baddeley, A. (2011): Analysing spatial point patterns in R. *CSGB Miscellanea* **11-02**. 233 pages.

2. Bernig, A. (2011): Course on advanced valuation theory. *CSGB Miscellanea* **11-01**. 19 pages.

3. Proceedings from the 16th Workshop on Stochastic Geometry, Stereology and Image Analysis. *CSGB Miscellanea* **11-03**. 48 pages.





CSGB Miscellanea 2011 can be downloaded at www.csgb.dk (publications).

CSGB JOURNAL AND PROCEEDINGS PUBLICATIONS, BOOK CHAPTERS

1. Bianchi, G., Gardner, R.J., & Kiderlen, M. (2011): Phase retrieval for characteristic functions of convex bodies and reconstruction from covariograms. *J. Amer. Math. Soc.* **24**, 293-343.

2. Birkedal, V., Dong, M., Golas, M.M., Sander, B., Andersen, E.S., Gothelf, K.V., Besenbacher, F. & Kjems, J. (2011): Single molecule microscopy methods for the study of DNA origami structures. *Microscopy Research and Technique* **74**, 688-698.

3. Boyce, R.W., Dorph-Petersen, K.-A., Lyck, L. & Gundersen, H.J.G. (2011): Stereological solutions for common quantitative endpoints in neurotoxicology. Chapter 15 in *Fundamental Neuropathology for Pathologist and Toxicologists: Principles and Techniques.* Eds. B. Bolon & M.T. Butt. J Wiley and Sons, Hoboken, 209-228.

4. Brandt, S., Karemore, G.R., Karssemeijer, N. & Nielsen, M (2011): An anatomically oriented breast coordinate system for mammogram analysis. *IEEE Transactions on Medical Imaging* **30**, 1841-1851.

5. Crimi, A., Lillholm, M., Nielsen, M., Ghosh, A., de Bruijne, M., Dam, E.B, & Sporring, J. (2011): Maximum à posteriori estimation of linear shape variation with application to vertebra and cartilage modeling. *IEEE Transactions on Medical Imaging* **30**, 1514-1526.

CSGB meets the Danish-Icelandic artist Olafur Eliasson at the ARoS Kunstmuseum.

6. Cullen-McEwen, L.A., Armitage, J.A., Nyengaard, J.R., Moritz, K.M. & Bertram, J.F. (2011): A design-based method for estimating glomerular number in the developing kidney. *American Journal of Physiology: Renal Physiology* (16 March, 2011). DOI 10.1152/ajprenal.00055.2011.

7. Darkner, S., Hansen, M.S., Larsen, R. & Hansen, M.F. (2011): Efficient hyperelastic regularization for registration. In: *Lecture Notes in Computer Science* **6688**, 295-305.

8. Darkner, S. & Sporring, J.: (2011): Generalized partial volume: An inferior density estimator to Parzen windows for normalized mutual information. In: *Information Processing in Medical Imaging - 22nd International Conference, IPMI 2011*. Eds. Gábor Székely & Horst K. Hahn. Springer Lecture Notes in Computer Science **6801**, pp. 436-447.

9. Feragen, A., Hauberg, S., Nielsen, M. & Lauze, F.B. (2011): Means in spaces of treelike shapes. In: *International Conference of Computer Vision 2011*, 736-746.

10. Feragen, A., Lo, P., Gorbunova, V., Nielsen, M., Dirksen, A., Reinhardt, J., Lauze, F.B. & de Bruijne, M. (2011): An airway tree-shape model for geodesic airway branch labeling. In: *Mathematical Foundations of Computational Anatomy: Workshop at MICCAI 2011, the 14th International Conference on Medical Image Computing and Computer Assisted Intervention.*

11. Fioretto, E.T., Rahal, S.C., Borges, A.S., Mayhew, T.M., Nyengaard, J.R., Marcondes, J.S., de Carvalho Balieiro, J.C., Teixeira, C.R., de Melo, M.P., Lobo Ladd, F.V, Lobo Ladd, A.A.B., de Lima, A.R., da Silva, A.A.P. & Coppi, A.A. (2011): Hypertrophy and neuron loss: Structural changes in sheep CSG induced by unilateral sympathectory. *International Journal of Developmental Neuroscience* **29**, 475-481.

12. Ganz, M., Nielsen, M. & Brandt, S. (2011): Patch-based generative shape model and MDL model

selection for statistical analysis of archipelagos. *Machine Learning in Medical Imaging* **6357**. *Lecture Notes in Computer Science*, p. 34.

13. Goodey, P., Kiderlen, M. & Weil, W. (2011): Spherical projections and liftings in geometric tomography. *Adv. Geom.* **11**, 1-47.

14. Hagensen, M.K., Raarup, M.K., Mortensen, M.B., Thim, T., Nyengaard, J.R., Falk, E. & Bentzon, J.F. (2011): Circulating endothelial progenitor cells do not contribute to regeneration of endothelium after murine arterial injury. *Cardiovascular Research* (19 October, 2011). DOI 10.1093/cvr/cvr278.

15. Hahn, U. (2011): A studentized permutation test for the comparison of spatial point patterns. To appear in *J. Amer. Statist. Assoc.*

16. Hansen, L.V., Kiderlen, M. & Jensen, E.B.V. (2011): Image-based empirical importance sampling: an efficient way of estimating intensities. *Scand. J. Statist.* **38**, 393-408.

17. Hansen. L.V., Nyengaard, J.R., Andersen, J.B. & Jensen, E.B.V. (2011): The semi-automatic nucleator. *J. Microsc.* **242**, 206-215.

18. Kamper, P., Bendix, K., Hamilton-Dutoit, S., Honoré, B., Nyengaard, J.R. & D'Amore, F. (2011): Tumor-infiltrating macrophages correlate with adverse prognosis and Eptsein-Barr virus status in classical Hodgkin's lymphoma. *Haematologica* **96**, 269-276.

Short course | Aalborg University

Bayesian computing with INLA

This course was held 7 November 2011 at Aalborg University by Daniel Simpson, Norwegian University of Science and Technology. The focus was on Bayesian inference using Integrated Nested Laplace Approximations. Examples and case-studies in R were given.

19. Kamper, P., Ludvigsen, M., Bendix, K., Hamilton-Dutoit, S.J., Rabinovich, G., Møller, M., Nyengaard, J.R., Honoré, B. & D'Amore, F.A. (2011): Proteomic analysis identifies galectin-1 as a predictive biomarker for relapsed/refractory disease in classical Hodgkin lymphoma. *Blood* **117**, 6638-6649.

20. Kraugerud, M., Aleksandersen, M., Nyengaard, J.R., Ostby, G.C., Gutleb, A.C., Dahl, E., Farstad, W., Schweder, T., Skaare, J.U., Ropstad, E. & Berg, V. (2011): In utero and lactational exposure to PCB 118 and PCB 153 alter ovarian follicular dynamics and GnRH-induced luteinizing hormone secretion in

CSGB Minisymposium on Bayesian Inference in Spatial Statistics

On 24 February 2011, a minisymposium on Bayesian inference in spatial statistics was arranged. Bayesian inference for spatial point processes was discussed, including Bayesian model selection. Another topic taken up was Bayesian inference for graphical models.

CSGB JOURNAL AND PROCEEDINGS PUBLICATIONS, BOOK CHAPTERS

CSGB meets the Danish-Icelandic artist Olafur Eliasson at the ARoS Kunstmuseum.

female lambs. *Environmental Toxicology* (22 February, 2011). DOI 10.1002/tox.20679.

21. Møller, J. (2011): Contribution to the discussion of Lindgren, F., Rue, H. and Lindstrøm, J. (2011): An explicit link between Gaussian fields and Gaussian Markov random fields: The stochastic partial differential equation approach. To appear in *J. Roy. Statist. Soc.* **B 73**.

22. Møller, J. & Yiu, M.L. (2011): Probabilistic results for a mobile service scenario. *Adv. Appl. Prob.* **43**, 322-334.

23. Pedersen, M., Karstoft, K., Lødrup, A., Jespersen, B. & Nyengaard. J.R. (2011): Advantages and controversies in the era of intrarenal volumetry. *American Journal of Nephrology* **33**, 40-45.

24. Petersen, J., Nielsen, M., Lo, P.C.P., Saghir, Z., Dirksen, A. & de Bruijne, M. (2011): Optimal graph based segmentation using flow lines with application to airway wall segmentation. In: *Information Processing in Medical Imaging - 22nd International Conference, IPMI 2011*. Eds. Gábor Székely & Horst K. Hahn. Springer Lecture Notes in Computer Science **6801**, pp. 49-60.

25. Riber-Hansen, R., Nyengaard, J.R., Hamilton-Dutois, S.J., Sjoegren, P. & Steiniche, T. (2011): Automated digital volume measurement of melanoma metastases in sentinel nodes predicts disease recurrence and survival. *Histopathology* **59**, 433-440.

26. Sander, B. & Golas, M.M. (2011): Visualization of bionanostructures using transmission electronmicroscopical techniques. *Microscopy Research and Technique* **74**, 642-663.

27. Schlafer, S., Raarup, M.K., Meyer, R.L., Sutherland, D.S., Dige, I., Nyengaard, J.R. & Nyvad, B. (2011): pH landscapes in a novel five-species model of early dental biofilm. *P L o S One* (23 September, 2011). DOI 10.1371/journal.pone.0025299.

28. Sommer, S.H. (2011): Accelerating multi-scale flows for LDDKBM diffeomorphic registration. In: *GPUCV workshop at ICCV 2011*. IEEE/ACM, pp. 499-505.

29. Sommer, S.H., Lauze, F.B., Nielsen, M. & Pennec, X. (2011): Kernel bundle EPDiff: Evolution equations for multi-scale diffeomorphic image registration. In: *Scale Space and Variational Methods in Computer Vision 2011: Lecture Notes in Computer Science*. Springer.

Lectures by Andreas Bernig Goethe-Universität Frankfurt

As part of an Erasmus exchange, Andreas Bernig gave four lectures on Advanced Valuation Theory 15-18 March 2011 at Aarhus University.

30. Sommer, S.H., Nielsen, M., Lauze, F.B. & Pennec, X. (2011): A multi-scale kernel bundle for LDDMM: Towards sparse deformation description across space and scales. In: *Information Processing in Medical Imaging - 22nd International Conference, IPMI 2011.* Eds. Gábor Székely & Horst K. Hahn. Springer Lecture Notes in Computer Science **6801**, pp. 624-635.

31. Stark, A.K., Gundersen, H.J.G., Gardi, J.E. Pakkenberg, B. & Hahn, U. (2011): The saucor, a new stereological tool for analysing the spatial distributions of cells, exemplified by human neocortical neurons and glial cells. *J. Microsc.* **242**, 132-147.

32. van Es, N., Schulz, A., Ijpelaar, D., van der Wal, A., Kuhn, K., Schütten, S., Kossmehl, P., Nyengaard, J.R., de Heer, E. & Kreutz, R. (2011): Elimination of severe albuminuria in aging hypertensive rats by exchange of 2 chromosomes in double-consomic rats. *Hypertension* **58**, 219-224.

33. Vaegter, C.B., Jansen, P., Fjorback, A.W., Glerup, S., Skeldal, S., Kjølby, M.F., Richner, M., Erdmann, B., Nyengaard, J.R., Tessarollo, L., Lewin, G.R., Willnow, T.E., Chao, M.V., & Nykjaer, A. (2011): Sortillin associates with Trk receptors to enhance anterograde transport and nurotrophin signaling. *Nature Neuroscience* **14**, 54-61.

34. Yiu, M.L., Jensen, C.S., Møller, J. & Lu., H. (2011): Design and analysis of a ranking approach to private location-based services. To appear in *ACM Transactions on Database Systems.*

35. Ziegel, J., Jensen, E.B.V. & Dorph-Petersen, K.-A. (2011): Variance estimation for generalized Cavalieri estimators. *Biometrika* **98**, 187-198.

WORKSHOP SGSIA 2011

16th Workshop on Stochastic Geometry, Stereology and Image Analysis - Sandbjerg Estate

This interdisciplinary workshop brought together scientists from integral geometry, stereology, stochastic geometry, applied probability, spatial statistics and bioimaging. An important scope of the workshop was to promote the advance of stochastic geometry.

The workshop had longer talks by invited speakers and shorter contributed talks by the participants as well as a poster session. The workshop was a big success and very well attended with 70 participants.

CSGB SEMINARS

2 March, 2011 | Ürün Dogan (Ruhr Universität Bochum): **A unified view on multi-class support vector classification**

14 March 2011 | Manna Valerie (VTT Technical Research Centre of Finland): **Extraction of features from MRI to identify early biomarkers for Alzheimer**

16 March 2011 | Johanna Ziegel (Heidelberg University): **Stereological analysis of volume tensors for particle distributions**

17 March 2011 | Jürgen Kampf (Karlsruhe Institute of Technology): **On weighted parallel volumes and spaces of continuous functionals of convex bodies.**

11 April, 2011 | Tom Olesen (Unisensor): **Image analysis at Unisensor**

25 May, 2011 | Adrian Baddeley (CSIRO and University of Western Australia): **The strange history of spatial logistic regression**

31 May, 2011 | Guochun Shen (Sun Yat-sen University): **What determines alpha diversity of a given community?**

17 June 2011 | Peter Husen (University of Southern Denmark): **Spherical surface images of vesicles from confocal microscopy stacks**

CSGB meets the Danish-Icelandic artist Olafur Eliasson at the ARoS Kunstmuseum.

22 June 2011 | Jon Sporring (University of Copenhagen): **Fast Lebesgue registration**

27 June, 2011 | Yongtao Guan and Chong Deng (Yale University): **On measurement error problems with predictors derived from stationary stochastic processes and application to cocaine dependence treatment data**

27 June, 2011 | Paolo Viappiani (Aalborg University): **Principled machine learning techniques for preference elicitation: recommendation sets and choice queries**

30 August, 2011 | Megan Owen (University of Toronto): **Means in the space of phylogenetic trees**

5 September, 2011 | Megan Owen (University of Toronto): **Statistics in the space of metric trees**

25 October, 2011 | Sepp de Raedt (Aarhus University): **Localized statistical shape models for detection of osteoarthritic changes of the trapezium**

31 October, 2011 | Ron Kupers (Panum Institute): **Brain imaging at BRAINLab**

7 December, 2011 | Bent Jørgensen (University of Southern Denmark): **The ecological footprint of Taylor's universal power law**

15 December, 2011 | Neil Roberts (Edinburgh): **Dynamic MRI: Nothing happens until something moves**

CSGB VISITORS

Tilman Davies (Massey University), 5-25 January, 2011

Håkon Toftaker (Norwegian University of Science and Technology), 16 - 21 January, 2011

Frédéric Lavancier (Université de Nantes) 17-21 January, 2011

Frank Alexander Lenkoski (Heidelberg University) 20-27 February, 2011

Thordis Linda Thorarinsdottir (Heidelberg University)
20-27 February, 2011

Corinna Cortes (Head of Google Research New York)
1-5 March 2011

Manna Valerie (VTT Technical Research Centre of Finland), 10-16 March 2011

Andreas Bernig (Goethe-Universität Frankfurt)
13-19 March, 2011

Daniel Hug (Karlsruhe Institute of Technology)
14-18 March, 2011

Johanna Ziegel (Heidelberg University)
14-18 March, 2011

Jürgen Kampf (Karlsruhe Institute of Technology)
14-19 March, 2011

Pinar Naile Gürgör (Hitit University)
15 March - 15 September, 2011

Mari Myllymäki (Aalto University), 3 - 31 May, 2011

Gouchun Shen (Sun Yat-sen University)
23 May - 7 June, 2011

Elsa Angelini (Telecom Paris Tech), 26-28 May 2011

Bram van Ginneken (University Nijmegen)
26-27 May 2011

Yongtao Guan (Yale University), 1 June - 31 July, 2011

Semyon Alesker (Tel Aviv University), 5-10 June, 2011

Mathew Penrose (University of Bath), 5-10 June, 2011

Håvard Rue (Norwegian University of Science and Technology), 5-10 June, 2011

Gennady Samorodnitsky (Cornell University)
5-10 June, 2011

Johanna Ziegel (Heidelberg University), 5-10 June, 2011

Michaela Prokesova (Charles University)
5-18 June, 2011

Chong Deng (Yale University)
22 June - 10 July, 2011

Natalia Slabiak-Blaz (Medical University of Silesia)
11-15 July, 2011

Michael Gleicher (University of Wisconsin)
13-20 August 2011

Marcello Pelillo (University of Venice)
13-20 August 2011

Martin Reuter (Harvard Medical School and Massachusetts General Hospital), 13-20 August 2011

Ali Shokoufandeh (Drexel University)
13-20 August 2011

Xiaolin Wu (McMaster University), 21-27 August 2011

Joachim Weickert (Saarland University)
21-27 August 2011

Fernando Pereira (Instituto Superior Tecnico)
21-27 August 2011

Horst Bischof (TU Graz). 21-27 August 2011

Megan Owen (University of Toronto)
27 August - 7 September, 2011

Werner Nagel (Friedrich-Schiller Universität)
2-3 October, 2011

Martin Roberts (University of Manchester)
15-17 November 2011

Michaela Prokesova (Charles University)
11 - 16 December, 2011

Luis M. Cruz-Orive (University of Cantabria)
12 - 16 December, 2011

Neil Roberts (Edinburgh), 14 - 17 December, 2011

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)


EBVJ


CI


JLJ


JM


MN


JRN


RPW

ASSOCIATE PROFESSORS

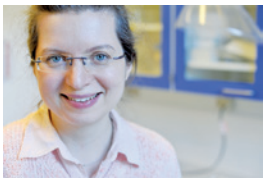
- Johnnie B. Andersen (JBA)
- Kasper Klitgaard Berthelsen (KKB)
- Sami Brandt (SB)
- Karl-Anton Dorph-Petersen (KADP)
- Monika Golas (MG)
- Ute Hahn (UH)
- Asger Hobolth (AH)
- Markus Kiderlen (MK)
- François Lauze (FL)
- Kim Stenstrup Pedersen (KSP)
- Andrew du Plessis (AP)
- Jakob G. Rasmussen (JGR)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


JBA


KKB


SB


KADP


MG


UH


AH


MK


FL


AP


JGR


BS


JS


MR

ASSISTANT PROFESSORS

- Merete Raarup (MR)


JAC


SD


AF

POSTDOCS

- Jérémy Auneau-Cognacq (JAC)
- Sune Darkner (SD)
- Aasa Feragen (AF)
- Allan Rasmusson (AR)
- Ege Rubak (ER)
- Anne Marie Svane (AMS)


AR


ER


AMS


ITA


CMA


STC

PH.D. STUDENTS

- Ina Trolle Andersen (ITA)
- Camilla Mondrup Andreassen (CMA)
- Sabrina Tang Christensen (STC)
- Mohammad Ghorbani (MG)
- Jan-Otto Hooghoudt (JOH)
- Katrine Hommelhof Jensen (KHJ)
- Jay Rai (JR)
- Farzaneh Safavimanesh (FS)
- Stefan Sommer (SS)
- Ólöf Thorisdottir (OT)


MG


JOH


KHJ


JR


FS


SS


OT

RESEARCH ASSOCIATE

- Ali Hoseinpoor Rafati (AHR)


AHR

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

Annual Report 2011, published April 2012

CSGB - Centre for Stochastic Geometry and Bioimaging
Department of Mathematics
Aarhus University, Ny Munkegade 118, Bldg. 1530
DK-8000 Aarhus C, Denmark
www.csgb.dk

Stochastic geometry group
Department of Mathematics
Aarhus University, Ny Munkegade 118, Bldg. 1530
DK-8000 Aarhus C, Denmark
www.imf.au.dk

Biomedical group
Danish Neuroscience Centre
Aarhus University, Building 10G, 3rd Floor
Aarhus Sygehus, Aarhus University Hospital, Nørrebrogade 44
DK-8000 Aarhus C, Denmark
www.ki.au.dk/stereo/stereologi

The spatial statistics group
Department of Mathematical Sciences
Aalborg University, Fredrik Bajers Vej 7G
DK-9220 Aalborg, Denmark
www.math.aau.dk

The image group
Department of Computer Science
University of Copenhagen, Universitetsparken 1
DK-2100 Copenhagen, Denmark
www.diku.dk

Editors: Eva B. Vedel Jensen, Jens R. Nyengaard

Text: Eva B. Vedel Jensen, Sami Brandt, Monika Golas, Ute Hahn, Markus Kiderlen, Jesper Møller, Mads Nielsen, Jens R. Nyengaard, Andrew du Plessis, Ege Rubak, Björn Sander

Photo: Petra Steiner, Daniela Mayer, CSGB staff

Design and layout: DesignZone, Daniela Mayer, daniela@designzone.info, (supported by Simone)

Printed in Denmark by SUN-Tryk

ISSN: 1904-9404

www.csgb.dk


37
36
35
34
33
32
0.00
0.05
0.10
0.15
0.02
0.04
0.06
0.08
0.10
122
120