Imaging and Modeling in Electron Microscopy - Recent Advances (14w5048)

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May 18 – May 23, 2014

The idea of this workshop is to bring together mathematicians and specialists in electron microscopy to discuss the future developments of the methods and approaches in assessing and understanding the data from materials at the nanoscale. There are several research areas in mathematics that can produce results beneficial for electron microscopy. While trying to establish connections between mathematicians working in these areas with scientists employing electron microscopy in their research, the goal is to go further than that and start fruitful collaborations that will provide new challenging mathematical problems, solutions of which will enhance the understanding of the materials in the nanoscale.

1 Overview of the Field

The field of Mathematical Electron Microscopy is to be developed and this workshop is one of the steps towards forming the general research area and identifying the research directions. The goal is to go outside the standard data and image processing research and address the challenging problems arising with the constantly developing nanoimaging instruments. It is about combining an accurate mathematical modeling of the processes that produces the data with successfully solving the mathematical problems needed for its faithful interpretation.

Previous small workshops at the University of South Carolina provided a first assessment of how new mathematical tools and theories could advance data analysis in modern electron microscopy and, in particular, in such areas as cryo-electron microscopy of biological matter and aberration-corrected scanning transmission electron microscopy. Based on these initial workshops a recently published book [56] entitled "Modeling Nanoscale Imaging in Electron Microscopy" (Springer, March 2012) summarized relevant methodologies such as super-resolution techniques, special de-noising and alignment methods, the application of mathematical and statistical learning theory, as well as a detailed introduction to compressed sensing and its possible influence on electron microscopy. The community is also very interested in implementing new measurement techniques based on ideas related to the single pixel camera and compressed sensing which could significantly reduce the measurement times and open up whole new fields of soft and/or hybrid materials to STEM imaging and tomography. Our goal to continue to push the boundaries of the electron imaging by enhancing data acquisition and state-of-the-art image analysis was also partially supported by a

highly competitive seed grant from the National Academies Keck Futures Initiative. The proposal for a BIRS workshop was an attempt to involve more members of the scientific community in the realization of this goal.

2 Recent Developments and Open Problems

The scope of the conference was purposefully allowed to be broad and talks bridged interests from quantum physics (Simulating core-loss scattering in the STEM by Christian Dwyer [8]) to biological applications (Chandrajit Bajaj [2], Yoel Shkolnisky [45], Amit Singer [46]). A series of talks on mathematical themes such as greedy algorithms (Deanna Needell [35]), compressed sensing approaches (Gitta Kutyniok [25]), de-noising techniques (Bin Han [17], Niklas Mevenkamp [32]) and image registration techniques (Benjamin Berkels [4]) was interspersed with talks on experimental approaches to imaging (Mark Davenport [7], Kevin Kelly [21], Thomas Vogt [55], Joachim Mayer [31], Sarah Haigh [14], Jarzy Sadowski [37], and Zineb Saghi [38]). Intriguing future directions were presented in presentations by Nigel Browning and Bryan Reed [36] on dynamic transmission electron microscopy (DTEM) which highlighted the need for better tool to correct and align terra-bytes of data in the near future. Dirk Van Dyck's talk ("Addressing Feynmans Challenge The 3D shape of nano-crystals from single projections at atomic resolution" [53]) reminded us that many new imaging tools were developed to establish structure-property relationships in nanomaterials and how much progress we have made in the past two decades.

Lively discussions after the talks and in the scheduled discussion sessions centered on broad ("How can Mathematics help Electron Microscopy?"[6]) as well as more focused issues ("Elemental quantification using energy dispersive x-ray spectrometry in the STEM"[16] and "Improving Precision and Signal to Noise Ratio in Electron Micrographs"[57]).

While the usual meaning of "imaging" is "visual representation of the information received from the data", it is often the case that it is perceived as a much broader process that includes the extraction of this information. To some extend this is the case in choosing the title of this workshop. One of the main points from this workshop is that the extraction of the information is better done with methods that are not image processing per se. There are several open questions in this field that remain to be answered. A number of them were posed in some of the talks and during the discussions. They are often problem specific but in general can be summarized in two main theme questions: **(i)** *How to better extract relevant information from the data received by the existing data gathering procedures?* and **(ii)** *How to change these procedures to allow more reliable and efficient information extraction?*

3 Presentation Highlights

The workshop featured 31 talks and three discussions. Due to the interdisciplinary nature of the workshop, the diversity of the subjects was significant and we had to go a bit against the guidelines suggesting fewer talks. In the summary below the talks are formally separated into six groups. This separation is for the purposes of the presentation and it should be clear that many of the talks could have been put in other group(s). The first two groups (Subsections 3.1 and 3.2) contain talks which are either mathematical in their nature or realize a new mathematical concept through processing experimental data. While in the first group (Subsection 3.1) the emphasis is on improving the acquisition process and formulating new theoretical results that could be relevant as a mathematical background for developing new methods in this direction, the second group (Subsection 3.2) features mathematical and algorithmic advances in processing the data. The quest of improving the instrumentation and creating new ways of collecting data is presented in the third group of talks (Subsection 3.3). The fourth group (Subsection 3.4) is rather small and includes only the talks in which modeling and simulation were the primary topics. Nevertheless, these topics were presented as part of the research in several other talks. The final two groups (Subsections 3.5 and 3.6) are devoted to receiving the 3D information of the observed object. Electron tomography is the primary subject of the talks from Subsections 3.5 while Subsections 3.6 features results for cryo-electron microscopy and research for biological applications.

3.1 Mathematics of Data Assimilation

The talk of B. Berkels [4] first considered the problem of averaging a series of noisy scanning transmission electron microscopy (STEM) images producing an improved image that surpasses the quality attainable by single shot STEM images. The main task in tackling this problem is the task of transform- ing two or more images into a common coordinate system, from the perspective of electron microscopy. The classical registration approach for image pairs is extended to handle the registration of hundreds of consecutive images to a single image with a special emphasis on input data with a low signal-to-noise ratio and periodic structures. One of the key ingredients is the use of a non-rigid transformation model that is able to cope with the frame-to-frame distortions resulting from the serial pixel-wise acquisition of STEM images. In the second part, it was discussed how to find global minimizers of a class of variational models that have a convex regularization term like total variation. This is achieved by constructing a convex minimization problem with a pointwise constraint in a higher dimension whose minimizers fulfill a thresholding theorem: The 0.5-level set of a minimizer of the convex problem is the subgraph of a minimizer of the original problem. Unlike the functional in the existing convexification models, the target functional in the proposed reformulation is strongly convex. Two immediate advantages of the strong convexity are that the reformulation has a unique solution and that more efficient minimization algorithms can be used.

The practical use of the above ideas was presented in the talk of A. Yankovich [60]. He considered atomic-resolution by scanning transmission electron microscopy (STEM) and the question *"how precisely can the positions of the atoms be measured?"*. Precision smaller than the resolution is routinely attainable, but in STEM it is limited by practical problems, such as image distortions caused by instabilities of the electron probe and the sample, before reaching the fundamental signal-to-noise ratio (SNR) precision limit. A non-rigid registration of a series of STEM images [5] is used to undo the effect of instabilities and enable averaging to improve the SNR and thus the precision. Non-rigit registration and averaging results in reproducible sub-pm precision [61], 5-7 times better than what is attainable with rigid registration and the best ever reported in electron microscopy. We have applied this high precision STEM method to measuring the surface atom distortions on a Pt nanocatalyst, for which the catalytic activity of the nanoparticles is determined by their atomic surface structure. Another important problem is determining three dimensional atomic structures of materials from the acquired two dimensional images. NR registration of STEM images enables extraction of 3D atomic structure information using the standardless atom counting method with the best-reported uncertainties. Previous results using the same method reported a few atom uncertainty and were limited by image Poisson noise. The extremely high SNR images resulting from NR registration allows for standardless atom counting with < 1 atom uncertainty for a majority of the atomic columns in the Pt nanocatalyst, with no limitation from Poisson noise.

The problem of recovering a sparse image from a small number of noisy measurements was considered in M. Davenport's talk [7]. In the case where the measurements are acquired in a nonadaptive fashion as in the standard compressive sensing framework, lower bounds on the minimax mean-squared error of the recovered vector very nearly match the performance of ℓ_1-minimization techniques, and hence in certain regimes these techniques are essentially optimal. Surprisingly, in the case where the measurements are acquired sequentially in an adaptive manner, the speaker showed that in certain worst-case regimes, adaptivity does not allow for substantial improvement over standard nonadaptive techniques in terms of the minimax mean-square error. Nonetheless, there are important regimes where the benefits of adaptive sensing are clear and overwhelming, and can be achieved via relatively simple algorithms.

The talk of K. Kelly [21] was giving insides about how to translate the mathematical breakthroughs of compressive sensing into actual imaging systems. A particular example are optical systems that acquire portions of the spectrum from ultraviolet to infrared. These cameras rely on making many multiplexed measurements over time summed into a single or a few detectors. In the case of video, the motion in the scene during acquisition disrupts the scene reconstruction. To overcome this, they designed and developed various algorithms to successfully reconstruct both the background and foreground. A few comments were made on how to exploit this in the design of compressive optical microscopy instrumentation for sum-frequency generation imaging of molecular vibrations and darkfield imaging of plasmon resonances.

The talk of A. Stevens [48] considered techniques in machine learning and compressive sensing with applications in electron microscopy. The contribution of compressive sensing is twofold- - it can be used to reduce dose (spatial compression) and increase acquisition speed (time compression). In the case of spa-

tial compressive sensing, Bayesian dictionary learning was used. This method infers the underlying basis space and a sparse representation from the compressed measurements. For temporal compressive sensing the Gaussian mixture model is used. Both of the approaches are relatively recent developments from statistical machine learning. Computational experiments in spatial and temporal compressive sensing will be presented.

D. Needell addressed in her talk [35] the problem of identifying a high resolution image from a subsampled, or lower resolution image. This is usually referred to as super-resolution. The problem can me modeled as a sparse recovery problem when the measurement operator has a pre-defined specific structure. The talk contained some new work on greedy algorithms which can handle the structure in the measurement operator for super-resolution. Experimental results as well as theoretical guarantees were presented.

In her talk R. Ward [58] presented a general framework which aims to address the question: *for which sets of points, using what randomized linear maps, and to what extent is dimensionality reduction in ℓ_1 possible?* Through the Johnson-Lindenstrauss Lemma and related results, it is known that a small set of points in a high-dimensional space can be linearly embedded into a space of much lower dimension in such a way that Euclidean distances between the points are nearly preserved, and that a random projection can be used for such embeddings. At the same time, it is known that a result of this kind is not possible if we replace Euclidean distance by the ℓ_1 norm, at least not for arbitrary sets of points. Certain sets, such as sparse vectors, can be linearly embedded in low dimension with respect to the ℓ_1 norm, and sparse random matrices work well for such embeddings.

3.2 Mathematics of Data Processing

G. Kutyniok considered in her talk [25] the important question about how to extract the individual components from imaging data composed of several geometrically distinct constituents. She utilized the novel methodology of Compressed Sensing to show that this geometric separation problem can indeed be solved both numerically and theoretically. For the separation of point- and curvelike objects, the solution of choice is to deliberately overcomplete a representation system made of wavelets (suited to pointlike structures) and shearlets (suited to curvelike structures). The decomposition principle is to minimize the ℓ_1-norm of the representation coefficients or to perform iterative thresholding. The theoretical results, which are based on microlocal analysis considerations, show that at all sufficiently fine scales, nearly-perfect separation is indeed achieved.

In his talk O. Scherzer [42] introduced variational motion estimation and decomposition for images that are defined on an evolving surface. While optical flow is traditionally computed from a sequence of flat images and used for motion estimation, the concept of optical flow is extended to a dynamic non-Euclidean setting to provide a concept for decomposition of flows. An application to biological imaging was presented.

The talk of Z. Shen [44] provided some insides about the wavelet frame-based image and video restorations. It started with some of main ideas and various examples including image and video inpainting, denoising, decomposition, image deblurring and blind deblurring, segmentation, CT image reconstruction, 3D reconstruction in electron microscopy, and etc. In all of these applications, spline wavelet frames derived from the unitary extension principle are used. This allows to establish connections between wavelet frame based method and various PDE based methods, that include the total variation model, nonlinear diffusion PDE based methods, and model of Mumford-Shah. A convergence analysis in terms of objective functionals and their approximate minimizers was discussed.

A new image processing tool that can find applications in different fields and in electron microscopy, in particular, was discussed in the talk of B. Han [17]. He introduced directional separable complex tight framelets and showed that directionality can be greatly improved by using separable complex tight framelets. While keeping the efficient tensor product structure, this approach has the advantages of much better improved directionality and the use of finitely supported complex tight framelets. For the image denoising problem, we show that separable complex tight framelets have significant performance gains (typically, 0.5db to 1db improvement) compared with several state-of-the-art image denoising methods such as undecimated wavelet transform, dual tree complex wavelet transform, shearlets, curvelets, total variation based method, and etc.

In his talk F. Krahmer [23] presented a recently introduced algorithm, called PhaseLift, for phase recovery that is computationally tractable, numerically stable, and comes with rigorous performance guarantees. PhaseLift is optimal in the sense that the number of amplitude measurements required for phase reconstruc-

tion scales linearly with the dimension of the signal. However, it specifically demands Gaussian random measurement vectors – a limitation that restricts practical utility and obscures the specific properties of measurement ensembles that enable phase retrieval. Two partial derandomizations of PhaseLift were presented. First one is a construction that only requires sampling from certain polynomial size vector configurations, called t-designs. Such configurations have been studied in algebraic combinatorics, coding theory, and quantum information. Reconstruction guarantees are given for a number of measurements that depends on the degree t of the design. If the degree is allowed to grow logarithmically with the dimension, the bounds become tight up to polylog-factors. Second one uses Fourier measurements with random masks as they are encountered in x-ray crystallography. Here the number of measurements is optimal up to a single logarithmic factor.

In his talk N. Mevenkamp [32] proposed modifications of the classical non-local means algorithm (NLM) to certain characteristics typical for Scanning Transmission Electron Microscopy (STEM) imaging. The focus was on three aspects: periodic recurrence of patterns, local horizontal distortions, and the noise type. The periodic distribution of the objects within the image is exploited to formulate an efficient strategy to search for similar patches. A periodic search grid is approximated from the images Fourier transform. The local horizontal distortions inherent to STEM images cause difficulties to recognize self similarities with the classical patch similarity measure. The proposition is to counter these horizontal distortions by allowing line shifts that improve patch regularity. The most dominant source of noise in STEM imaging is typically Poisson distributed. However, the NLM algorithm was originally designed to remove additive Gaussian noise. The proposed modifications have been shown to increase the denoising performance on STEM images, especially in high intensity regions. Finally, it was discussed a method to correct the horizontal distortions in STEM images based on the NLM weights.

3.3 Experimental Approaches to Nano Imaging and Data Processing

B. Reed introduced in his talk [36] a new data acquisition procedure Movie-Mode Dynamic Transmission Electron Microscopy (MM-DTEM) that can benefit greatly from recent developments in applied mathematics. The idea of doing experiments inside the microscope, of actually capturing the crucial during moments instead of merely before and after, is now one of the biggest growth areas in TEM. An essential difficulty with this is time resolution, the importance of which derives from general physical scaling laws. Simply put, small things tend to move fast. The nanometer- and micrometer-scale processes most relevant to materials science typically happen on nanosecond to microsecond scales, far faster than the multi-millisecond scales of conventional TEM. This need inspired the development of MM-DTEM, exemplified by the prototype instrument at Lawrence Livermore National Laboratory which is capable of capturing nine TEM images or diffraction patterns in the span of less than one microsecond. MM-DTEM enables direct visualization of details of phase transformations, microstructural evolution, and propagating chemical reactions at the actual time, length, and temperature scales of the real-world applications. MM-DTEM works by coupling a unique arbitrary-waveform laser, a photoemission-based TEM, and a high-speed fully programmable electrostatic deflector system. The development of such an instrument raises both challenges and opportunities. DTEM experiments must make maximal use of the information provided by every single precious electron, for any wasted beam current implies performance degradation because of finite brightness, space charge, and stochastic blur effects.

The focus S. Haigh's talk was on applications that have demanded the development of novel experimental approaches:
1) Two dimensional materials like graphene are widely studied using plan-view TEM/STEM imaging. However, this approach cannot be applied after the various individual atomic layers are used encapsulated so as to fabricate a complex heterostructured device. She demonstrated how a side-view approach to imaging these materials has facilitated new insights into electrical device performance including the use of elemental mapping to locate atomic layers [15, 12].
2) The vast majority of STEM imaging is in vacuum. In-situ liquid cell experiments are increasingly popular but these have not generally been considered compatible with elemental analysis due to the cell geometry. She reported on the first use of a redesigned liquid cell that has allowed them to perform the first elemental mapping of nanostructures submerged in liquid with nanometer spatial resolution [62].
3) She also reported on recent results using tomography to obtain full elemental distributions in three di-

mensions with nanometer spatial resolution for different nanoparticle compositions. This has allowed them to overcome the limitations of interpretation associated with two dimensional projections [47] providing a much clearer understanding of catalytic performance.

In his talk J. Mayer [31] reported about some initial results with the currently most advanced electron microscopy instrument, FEI Titan 60-300 PICO. PICO is a fourth-generation transmission electron microscope capable of obtaining high-resolution transmission electron microscopy images approaching 50 pm resolution in the CC- and CS-corrected mode at 300 keV. It is currently one of only two microscopes in the world capable of chromatic aberration correction [20]. In the PICO instrument, HRTEM images can be obtained with simultaneous correction of the spherical and the chromatic aberration. Furthermore, a spherical aberration corrector also exists in the illumination system for Cs-corrected STEM imaging. The benefits of chromatic aberration corrected imaging are particularly large for HRTEM imaging at low accelerating voltages and for energy filtered (EFTEM) imaging with large energy window width [51]. The recent results focusing on these two applications were reported.

The talk of S. Findlay [11] was dedicated to some of the challenges for scanning transmission electron microscopy (STEM) discussing the steadily improving high-angle annular dark-field (HAADF) mode acquisitions, as well as some recent developments such as annular bright field imaging. He reviewed some limitations of na¨ve interpretation of STEM images, in particular that an image with atomic scale features cannot automatically be interpreted as allowing perfect column-by-column analysis. Select recent advances in analysis which account for the detailed scattering of the probe were presented. One is the ability to put experimental HAADF images on an absolute scale, which through comparison with simulations allows the number of atoms in a column to be counted, and in some cases the depth of individual dopant atoms to be determined. Another is an approach for removing the effects of elastic and thermal probe scattering from a spectrum image, disentangling the fine structure signals from adjacent columns to allow a more direct and meaningful comparison with standard first-principles simulations of energy loss fine structure. However, both approaches require the basic structure of the specimen to be known. The outstanding challenge is whether the same quantitative rigor can be achieved on samples when the structure is not known in advance. Finally, some ideas were given as to how this might be achieved as the potential for simultaneous collection of multiple imaging modes is increasingly being realized.

In his talk J. Sadowski [37] introduced the direct imaging photoelectron emission microscope (PEEM) and low-energy electron microscope (LEEM) combined with an imaging analyzer and a tunable high-brilliance synchrotron radiation source (XPEEM mode). He presented examples of application of the LEEM/XPEEM technique to the in situ, real-time investigations of the 2D layered materials, including few-layer graphene on transition metals and dichalcogenides. LEEM is a powerful technique for studying the dynamic and static properties of surfaces and thin films including growth and decay, phase transitions, reactions, surface structure and morphology. It utilizes low energy electrons to image surfaces with $<$5nm lateral resolution and atomic layer depth resolution (see, [3] and [50]). In the LEEM/XPEEM setup, when using the electron irradiation, the elastically and inelastically backscattered electrons, Auger and secondary electrons may be used, while photoelectrons, Auger and secondary electrons are utilized for imaging when sample is irradiated with photons. The choice of the imaging, diffraction or spectroscopy mode depends upon the information to be obtained: structural, chemical, magnetic or electronic, from the topmost or rather deeper layers. The strength of the technique lies in the combination of the real-time structural and spectroscopic measurements in a single analytical system.

In his talk T. Vogt [55] discussed the use of scanning transmission electron microscopy data and images in materials science, He made the case to better integrate STEM with other analysis techniques and warned about the dangers of ‘cartoon science’ and the use of ‘selective imaging’ that could dominate the use of STEM in the near future.

3.4 Modeling and Simulation

One of the major challenges in simulating inelastic scattering in the TEM/STEM is the large number of inelastic channels that must be included, even for a specific energy loss. In his talk C. Dwyer [8] considered this problem from a formal perspective, combining ideas from symmetry (group) theory and information theory. These ideas enable a formal analysis, and thereby optimization, of the efficiency of inelastic scattering simulations (and quantum mechanical calculations in general). Applied to simulations of core-loss scattering in

the TEM/STEM, these ideas provide up to a 10-fold improvement in efficiency compared to current methods.

The talk of I. Lobato [29] presented a new parameterization of the electron scattering factor using five analytic non-relativistic hydrogen electron scattering factors as a basis functions. This new parameterization for the elastic electron scattering factors and its derived quantities such as the X-ray scattering factor, the electron charge density distribution and the atomic potential obey all the correct physical constraint conditions, have the correct asymptotic behavior and can be calculated analytically. The talk also presented an investigation of the accuracy of the main parameterized electron scattering factors for large variety of diffraction experiments including reflection that lies on the Zero Laue zones and Higher order Laue zones. The comparison of all these results allows to draw reliable conclusions about the range of applicability of the different parameterizations.

3.5 Electron Tomography

Electron tomography (ET) has become an important technique for the 3D characterization of nanomaterials [33]. Recently, significant advances in transmission electron microscopy have allowed spatial, temporal and spectroscopic imaging at unprecedented resolution. Extending these innovative techniques to 3D is of great interest for many nanotechnology applications. It necessitates, however, the development of powerful tomography algorithms that are capable of producing reliable reconstructions from datasets that are often limited due to constraints about e.g., sample geometry, total electron dose, total acquisition time and beam damage [34, 39].

In her talk Z. Saghi [38] presented some recent algorithmic developments with emphasis on compressed sensing ET (CS-ET) [40, 27]. By using the prior knowledge that the signal is sparse or compressible in a chosen transform domain (e.g. pixel or gradient domains), CS-ET employs a non-linear optimization algorithm to recover the sparsest solution consistent with the acquired projections. Based on simulations and experimental data, they compare CS-ET with traditionally employed algorithms and show that artifacts related to the limited number and angular range of available projections can be greatly reduced, making the segmentation and subsequent quantitative analysis much more reliable. Applied to innovative imaging modes, it is expected CS-ET to have a significant impact in the field of nanotechnology with unprecedented ability to follow changes in space and time, generate chemically-sensitive 3D reconstructions, and provide high quality 3D data that can be used as reliable starting point for detailed nanometrology and further simulations of the properties and behavior of nanodevices. There is a great potential in the 3D study of beam-sensitive materials, and in atomic scale ET using aberration-corrected microscopes and a small number of well-oriented projections.

In her talk I. Arslan [1] discussed the problems and specificity of electron tomography in the scanning transmission electron microscope (STEM) for recovering the 3D structure of nanoparticles with intricate shapes. considered advanced reconstruction algorithms for electron tomography. The standard 3-D reconstruction techniques of weighted back projection and simultaneous iterative reconstruction technique (SIRT) applied to the small number of projections available for beam sensitive materials typically leave elongation artifacts due to the missing wedge and no longer provide the necessary resolution. The suggested solution is to use a combination of a regularization using total variation (TV) minimization with the discrete algebraic reconstruction technique (DART). The presented examples of layered materials and small metal particles in supports are paving the road for future investigations towards in-situ/ex-situ 3-D imaging.

The mathematical part of this research was presented by T. Sanders [41]. He presented the issues arising in the combination of TV-minimization with the additional restriction by DART that the class of solutions should contain only piecewise constants with their values restricted to a few discrete levels. A critical one is the determination of these discrete levels based on a parameter selection. In the standard DART method even a semi-automated procedure for this selection is nontrivial. The suggested solutions are based on thorough analysis of all the steps in the 3D reconstruction from the original data to the final result and, in addition for the new method to select the discrete levels, make adjustments to the alignment and preprocessing of the tilt series.

The problem of limited angle in (STEM) electron tomography, also referred as the *missing wedge*, was considered in the talk of P. Lamby [26]. Motivated by the advances in the theory of sparse recovery, several algorithms have been recently developed that regularize the reconstruction problem using range constraints, the ℓ_1-norm and (possibly anisotropic) versions of the total variation semi-norm as priors. To solve the result-

ing typically underdetermined constrained optimization problems one needs iterative solvers which however converge only slowly because the data matrix A is badly conditioned. For example, with the regularized ART algorithm from [18] one can often observe notable improvements of the reconstruction appearing even after thousands of iterations which is computationally unacceptable for 3D reconstructions. Many algorithms developed for compressed sensing, like the Augmented Lagrangian Method [28] or Bregman iterations [30] accentuate the problem since they require iterative solution of the normal equation involving the matrix $A^{\mathrm{T}}A$ which is even worse behaved. These algorithms typically work well only in cases that the full range of angles is present. The idea presented in the talk is to combine the above mentioned algorithms with multigrid techniques, similar to the ones that have been proposed in [22] for overdetermined problems. Multigrid naturally acts as preconditioning of the system and one can hope for accelerated convergence. However, because of the structure of the system matrix, the standard multigrid theory is not applicable. The theoretical challenges for this approach were discussed and some experimental results with synthetical and real data were presented.

In his talk D. Van Dyck [53] referred to Richard Feynman who pointed out [10] in the fifties that, "It would be very easy to make an analysis of any complicated chemical substance; all one would have to do would be to look at it and see where the atoms are." since all structure-property relations are encoded in the 3D atom positions for a given set of elements. Nowadays, resolution and sensitivity of the latest generation aberration-corrected Transmission Electron Microscopes (TEM) suffice to detect even single light atoms from the Periodic Table of Elements [13, 24, 49, 19] and to pinpoint their position with a lateral precision that reaches the 2pm wavelength of the imaging electrons at 300kV of acceleration voltage [59] but the depth (z) information remains less certain. In the past, only a few favorable cases allowed for an extraction of atom positions in beam (z) direction with high precision. They included the study of a graphene double layer [54] and the study of nanocrystals of which the surfaces were protected by embedding in a sacrificial matrix [52]. Also, the combination of projections from different viewing directions yields remarkable results [43] as long as linear models for the interaction between the electron beam with the object apply and beam-induced sample alterations are ignored. However for the study of nanoparticles such as for catalysts there is a need for a tomographic method that allows a fast characterization of the shape of pristine particles at atomic resolution. The talk presented a new approach to atomic resolution tomography that meets these demands.

3.6 Cryo-Electron Microscopy and Biological Applications

In cryo-electron microscopy (cryo-EM), a microscope generates a top view of a sample of randomly-oriented copies of a molecule. The cryo-EM problem is to use the resulting set of noisy 2D projection images taken at unknown directions to reconstruct the 3D structure of the molecule.

The talk of Y. Shkolnisky [45] considered the recovery of the structure of large proteins (3D density maps) from their 2D cryo-EM images. A central stage in the method is to determine a three-dimensional model of the protein given many of its 2D projection images. The direction from which each image was taken is unknown, and the images are small and extremely noisy. The goal is to determine the direction from which each image was taken, and then to combine the images into a three-dimensional model of the molecule. The presented algorithm determines the viewing directions of all cryo-EM images at once, which is robust to extreme levels of noise. It is based on formulating a synchronization problem, that is, to estimate the relative spatial configuration of pairs of images, and then to estimate a global assignment of orientations that satisfies all pairwise relations. Information about the spatial relation of pairs of images is extracted from common lines between triplets of images. These noisy pairwise relations are combined into a single consistent orientations assignment, by constructing a matrix whose entries encode the pairwise relations. This matrix is shown to have rank 3, and its non-trivial eigenspace is shown to reveal the projection orientation of each image. In particular, it is shown that the non-trivial eigenvectors encode the rotation matrix that corresponds to each image.

The talk of A. Singer [46] considered tone of the fundamental challenges in cryo-EM, in which the molecule under examination exhibits structural variability. The heterogeneity problem is the task of mapping the space of conformational states of a molecule. It has been previously shown that the leading eigenvectors of the covariance matrix of the 3D molecules can be used to solve this problem. Estimating the covariance matrix is however challenging, since only projections of the molecules are observed, but not the molecules themselves. In the talk this problem was viewed as a noisy matrix completion problem, and an estimator for the covariance matrix was derived as a solution to a certain linear system. While it was proven that the

resulting estimator for the covariance matrix is consistent in the classical limit as the number of projection images grow indefinitely, an interesting open question regarding the sample complexity of the problem remains. Namely, how many images are required in order to resolve heterogeneous structures as a function of the volume size and the signal to noise ratio? Solving this question requires to extend the analysis of the spike model in principal component analysis (PCA) in high dimensions, as one encounters limiting distributions that differ from the classical Marcenko-Pastur distribution.

In his talk T. Zhang [63] proposed a semidefinite programming approach to determine the 3D structure of small macromolecules by extending Kam's theory for single particle reconstruction in cryo-EM. The 3D reconstruction requires us to solve for U and V in the equation $Z = XU + YV$, where X, Y, Z are matrices of size $n \times d$, and U, V are d by d orthogonal matrices. We relax this to a semidefinite program, and show that when $n > d$, we can recover U and V exactly. A phase transition is observed at $n = d$. Based on this, a new method is proposed that would potentially enhance the capabilities of three-dimensional electron microscopy techniques by being able to answer biological questions related to small protein structures that have so far remained unresolved. The method is tested by numerical experiments on the simulated data of the Kv1.2 potassium channel complex.

In his talk C. Bajaj [2] highlighted the current progress on several co-mingled computational mathematics algorithms for refinement of 3D Electron Microscopy map and models of macromolecular assemblies. The attempt is to recover the three-dimensional structure of an individual molecule, a protein or a macromolecular assembly at the finest possible resolution and in its natural environment. Despite the advances in X-ray imaging and Electron Microscopy (EM), it has been difficult to simultaneously achieve the goals of recovering shape and conformation at finer resolution, and the larger scale of protein/nucleic acid assemblies. The proposed algorithms are based on new improved solutions to low discrepancy sampling of rotational product spaces SO(3)n, and non-equispaced SO(3) Fourier transforms for fast multidimensional rotational correlations.

The talk of J. Evans [9] considered time-resolved imaging of biological or nanomaterial structural dynamics, a highly data intensive task. In it the attempt is not only to collect enough data to solve the three-dimensional structure of an object, but also to collect that same data at multiple time points during a reaction cycle to see how the object changes over time. Handling the data, which for a single dataset can be on the order of terabytes in size, is a barrier unto itself but analyzing the data and identifying slight changes from one image to the next can be even more daunting - especially when the timing offset or magnitude of changes is unknown a priori. The talk described some of the challenges identified from current ultrafast x-ray diffraction experiments and simulated Dynamic TEM datasets to highlight areas where the development of automated algorithms could dramatically improve throughput and reliability of interpretation.

4 Scientific Progress Made

Several recent scientific achievements of the participants in the workshop and their research groups were presented at the workshop and reflected upon in the highlights above.

5 Outcome of the Meeting

This workshop provided various newly formed collaborations the opportunity to present new results and join a growing community of mathematicians and experimentalists which has formed over the past 5 years with the goal to apply modern mathematical tools to data with unprecedented quality and complexity

The subject of advanced electron imaging is growing and starting to have impacts as evidenced by recent publications from the participants in this initiative [5, 61]. We anticipate that the growing use of aberration-corrected electron microscopes at universities and the emergence of new electron and x-ray sources such as DTEM and free electron lasers at national laboratories will entice more materials scientists and structural biologists to tackle grand challenges such as protein folding and ultra-fast imaging of chemical reactions. These will create an enormous need in new data management, automated mining and analysis approaches that calls for continuing collaborations of imaging experimentalists and mathematicians. We hope that we can continue and expand this collaboration within the next few years and look forward to other BIRS events.

References

[1] Ilke Arslan, Advanced reconstruction algorithms for electron tomography in the physical sciences, talk at *BIRS workshop* **14w5048** (2014).

[2] Chandrajit Bajaj, Macro-molecular Map and Model Refinement Techniques for Electron Microscopy, talk at *BIRS workshop* **14w5048** (2014).

[3] E. Bauer, Low energy electron microscopy, *Rep. Prog. Phys.* **57** (1994), 895-938.

[4] Benjamin Berkels, Image registration techniques for electron microscopy, talk at *BIRS workshop* **14w5048** (2014).

[5] B. Berkels, P. Binev, D.A. Blom, W. Dahmen, R.C. Sharpley, T. Vogt, Optimized imaging using non-rigid registration, *Ultramicroscopy* **138** (2014), 46-56.

[6] Nigel Browning and Peter Binev, How can Mathematics help Electron Microscopy?, moderated discussion at *BIRS workshop* **14w5048** (2014).

[7] Mark Davenport, Adaptive sensing for compressive imaging, talk at *BIRS workshop* **14w5048** (2014).

[8] Christian Dwyer, Simulating core-loss scattering in the STEM, talk at *BIRS workshop* **14w5048** (2014).

[9] James Evans, Data analysis challenges for observing protein dynamics with fast electrons and x-rays, talk at *BIRS workshop* **14w5048** (2014).

[10] R.P. Feynman, There's Plenty of Room at the Bottom, *Engineering and Science* **23** (1960), 22-36.

[11] Scott Findlay, Quantitative interpretation of atomic resolution scanning transmission electron microscopy images in the presence of multiple scattering: progress and challenges, talk at *BIRS workshop* **14w5048** (2014).

[12] T. Georgiou et al., Vertical field-effect transistor based on graphene–WS2 heterostructures for flexible and transparent electronics, *Nature Nanotech.* **8** (2013), 100103.

[13] Ç.Ö. Girit, J.C. Meyer, R. Erni, M.D. Rossell, C. Kisielowski, L. Yang, C.-H. Park, M.F. Crommie, M.L. Cohen, S.G. Louie, A. Zettl, Graphene at the Edge: Stability and Dynamics, *Science* **323** (2009), 1705-1708.

[14] Sarah Haigh, Exploring the limitations of energy dispersive X-ray mapping of nanomaterials with the Titan ChemiSTEM, talk at *BIRS workshop* **14w5048** (2014).

[15] S. J. Haigh et al., Cross-sectional imaging of individual layers and buried interfaces of graphene-based heterostructures and superlattices, *Nature Materials* **11** (2012), 764-767.

[16] Sarah Haigh and Zineb Saghi, Elemental quantification using energy dispersive x-ray spectrometry in the STEM, moderated discussion at *BIRS workshop* **14w5048** (2014).

[17] Bin Han, Image denoising using directional separable complex tight framelets, talk at *BIRS workshop* **14w5048** (2014).

[18] G. T. Herman and R. Davidi, Image reconstruction from a small number of projections, *Inverse Problems* **24** (2008), 45011-45028.

[19] P.Y. Huang, S. Kurasch, J.S. Alden, A. Shekhawat, A.A. Alemi, P.L. McEuen, J.P. Sethna, U. Kaiser, and D.A. Muller, Imaging Atomic Rearrangements in Two-Dimensional Silica Glass: Watching Silicas Dance, *Science* **342** (2013), 224-227.

[20] B. Kabius, P. Hartel, M. Haider, H. Müller, S. Uhlemann, U. Loebau, J. Zach, and H. Rose, First application of Cc-corrected imaging for high-resolution and energy-filtered TEM, *J. Electron Microscopy* **58** (2009), 147-155.

[21] Kevin Kelly, Multidimensional Compressive Imaging with a Two-Dimensional Modulator, talk at *BIRS workshop* **14w5048** (2014).

[22] H. Köstler, C. Popa, M. Prümmer, and U. Rüde, Towards an algebraic multi-grid method for tomographic image reconstruction improving convergence of ART. In *European Conference in Computational Fluid Dynamics ECCOMAS CFD, P. Wesseling, E. Onate, and J. Periaux, eds.)*, TU Delft, The Netherlands, 2006.

[23] Felix Krahmer, A partial derandomization of phase retrieval via PhaseLift, talk at *BIRS workshop* **14w5048** (2014).

[24] O.L. Krivanek, M.F. Chisholm, V. Nicolosi, T.J. Pennycook, G.J. Corbin, N. Dellby, M.F. Murfitt, S.S. Own, Z.S. Szilagyi, M.P. Oxley, S.T. Pantelides, S.J. Pennycook, *Nature* **464** (2010), 571-574.

[25] Gitta Kutyniok, A Compressed Sensing Approach to Component Separation in Imaging, talk at *BIRS workshop* **14w5048** (2014).

[26] Philipp Lamby, Solving the Regularized Reconstruction Problems Arising in Limited-Angle Tomography, talk at *BIRS workshop* **14w5048** (2014).

[27] R. Leary, Z. Saghi, P.A. Midgley, D.J. Holland, Compressed Sensing Electron Tomography, *Ultramicroscopy* **131** (2013), 70-91.

[28] Chengbo Li, *An efficient algorithm for total variation regularization with application to the single pixel camera and compressive sensing*, Masters thesis, Rice University, Houston, Texas, 2009.

[29] Ivan Lobato, On accurate modeling of electron scattering factors for TEM, STEM and diffraction, talk at *BIRS workshop* **14w5048** (2014).

[30] Y. Mao, B.P. Fahimian, S.J. Osher, and J. Miao, Development of optimization of regularized tomographic reconstruction algorithms utilizing equally-sloped tomography, *IEEE Transactions on Image Processing* **19(5)** (2010), 1259-1268.

[31] Joachim Mayer, PICO - Chromatic Aberration Correction in TEM and its impact on new experiments and signals, talk at *BIRS workshop* **14w5048** (2014).

[32] Niklas Mevenkamp, Non-local Means based Denoising and Reconstruction of STEM Images, talk at *BIRS workshop* **14w5048** (2014).

[33] P.A. Midgley et al, Nanotomography in the chemical, biological and materials sciences, *Chemical Society Reviews* **36** (2007), 1477-1494.

[34] P.A. Midgley and R.E. Dunin-Borkowski, Electron tomography and holography in materials science, *Nature Materials* **8** (2009), 271-280.

[35] Deanna Needell, Greedy algorithms in super-resolution, talk at *BIRS workshop* **14w5048** (2014).

[36] Bryan Reed, Movie Mode DTEM, talk at *BIRS workshop* **14w5048** (2014).

[37] Jerzy Sadowski, Spectro-microscopy of 2D materials: challenges and perspectives, talk at *BIRS workshop* **14w5048** (2014).

[38] Zineb Saghi, Compressed sensing approaches for novel 3D imaging modes in the TEM , talk at *BIRS workshop* **14w5048** (2014).

[39] Z. Saghi and P.A. Midgley, Electron Tomography in the (S)TEM: From Nanoscale Morphological Analysis to 3D Atomic Imaging, *Annual Review of Materials Research* **42** (2012), 59-79.

[40] Z. Saghi et al, 3D Morphology of Iron Oxide Nanoparticles with Reactive Concave Surfaces – a Compressed Sensing - Electron Tomography (CS-ET) Approach, *Nano Letters* **11** (2011), 4666-4673.

[41] Toby Sanders, Practical 3-D Reconstruction Techniques for Electron Tomography, talk at *BIRS workshop* **14w5048** (2014).

[42] Otmar Scherzer, Optical Flow Decomposition on Evolving Surfaces, talk at *BIRS workshop* **14w5048** (2014).

[43] M.C. Scott, C.-C. Chen, M. Mecklenburg, C. Zhu, R. Xu, P. Ercius, U. Dahmen, B. C. Regan, and J. Miao, Electron tomography at 2.4-ångström resolution, *Nature* **483** (2012), 444-447.

[44] Zuowei Shen, Image Restoration: Wavelet Frame Approach, Total Variation and Beyond, talk at *BIRS workshop* **14w5048** (2014).

[45] Yoel Shkolnisky, Viewing Direction Estimation in cryo-EM Using Synchronization, talk at *BIRS workshop* **14w5048** (2014).

[46] Amit Singer, Covariance Matrix Estimation for the Cryo-EM Heterogeneity Problem, talk at *BIRS workshop* **14w5048** (2014).

[47] T.J.A. Slater, A. Macedo, S.L.M. Schroeder, et al., *Nano Letters* **14** (2014), 1921-1926.

[48] Andrew Stevens, Machine Learning and Compressive Sensing for Electron Microscopy, talk at *BIRS workshop* **14w5048** (2014).

[49] K. Suenaga, Y. Sato, Z. Liu, H. Kataura, T. Okazaki, K. Kimoto, H. Sawada, T. Sasaki, K. Omoto, T. Tomita, T. Kaneyama, Y Kondo, Visualizing and identifying single atoms using electron energy-loss spectroscopy with low accelerating voltage, *Nature Chemistry* **1** (2009), 415-418.

[50] R.M. Tromp, Low energy electron microscopy, *IBM J. Res. Develop.* **44** (2000), 503-516.

[51] K.W. Urban, J. Mayer, J.R. Jinschek, M.J. Neish, N.R. Lugg, and L.J. Allen, Achromatic Elemental Mapping Beyond the Nanoscale in the Transmission Electron Microscope, *Phys. Rev. Lett.* **110** (2013), 185507.

[52] S. Van Aert, K.J. Batenburg, M.D. Rossell, R. Erni, and G. Van Tendeloo, Three-dimensional atomic imaging of crystalline nanoparticles, *Nature* **470** (2011), 374-377.

[53] Dirk Van Dyck, Addressing Feynman's Challenge - The 3D Shape of NanoCrystals from Single Projections at Atomic Resolution, talk at *BIRS workshop* **14w5048** (2014).

[54] D. Van Dyck, J.R. Jinschek, F.R. Chen, Big Bang tomography as a new route to atomic-resolution electron tomography, *Nature* **486** (2012), 243-246.

[55] Thomas Vogt, From Picture to Data - the iconoclastic struggle in materials science, talk at *BIRS workshop* **14w5048** (2014).

[56] T. Vogt, W. Dahmen, and P. Binev, eds., *Modeling Nanoscale Imaging in Electron Microscopy*, Nanostructure Science and Technology, Springer, New York, 2012.

[57] Paul Voyles and Wolfgang Dahmen, Improving Precision and Signal to Noise Ratio in Electron Micrographs, moderated discussion at *BIRS workshop* **14w5048** (2014).

[58] Rachel Ward, Linear dimension reduction in the L_1 norm: When and how is it possible?, talk at *BIRS workshop* **14w5048** (2014).

[59] X. Xu, S.P. Beckman, P. Specht, E.R. Weber, D.C. Chrzan, R.P. Erni, I. Arslan, N. Browning, A. Bleloch, C. Kisielowski,Distortion and Segregation in a Dislocation Core Region at Atomic Resolution, *Phisical Review Letters* **95** (2005), 145501.

[60] Andrew Yankovich, Applications of NR registration for enhanced signal to noise ratio, spatial precision, and standardless atom counting in STEM images, talk at *BIRS workshop* **14w5048** (2014).

[61] A.B. Yankovich, B. Berkels, W. Dahmen, P. Binev, S.I. Sanchez, S.A. Bradley, Ao Li, I. Szlufarska, and P.M. Voyles, Picometre-precision analysis of scanning transmission electron microscopy images of platinum nanocatalysts, *Nature Communications* **5** (2014), Article number: 4155.

[62] X-ray Energy-Dispersive Spectrometry During In Situ Liquid Cell Studies Using an Analytical Electron Microscope, *Microscopy and Microanalysis* **20** (2014), 323-329.

[63] Teng Zhang, A Semidefinite Programming Approach to 3D Reconstruction of Macromolecules, talk at *BIRS workshop* **14w5048** (2014).