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Abstracts

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The Mathematics of Electronmicroscopic Imaging

Organizers:

Jose M. Carazo García (Centro Nacional de Biotecnología CSIC)

Gabor T. Herman (City University of New York)

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Image processing in biological 3d electron microscopy

Jose M. Carazo García* (Universidad Autónoma de Madrid)

G. T. Herman (City University of New York)

Three-dimensional electron microscopy (3D EM) is a powerful technique for imaging complex biological macromolecules in order to further the understanding of their functions. It is achieving high goals and exceeding expectations unthinkable only a few years ago. However, there are still some problem areas where either not enough work has been invested or the work has not as yet been fruitful. We are engaged in a multidisciplinary approach to shed light on three of these areas by the application of image processing techniques: (i) Incorporation of realistic image formation models into new reconstruction algorithms which take into account image blurring models of the aberrations of the electron microscope and which are at the same time noise-resistant and flexible with respect to the different data collection geometries. (ii) Incorporation of knowledge regarding the specimen obtained by means other than EM, such as high resolution surface relief information and information regarding the chemical nature of the specimen. (iii) Improvement of the rendering and the analysis of the reconstructed volumes by the development of more accurate segmentation (of the specimen from its background) and visualization algorithms.

Computational Challenges in 3-D Reconstruction of Virus Particles

Wah Chiu (Baylor College of Medicine, Houston, Texas)

Electron cryomicroscopy is capable to generate 3-dimensional structure of large spherical virus particle with icosahedral symmetry at sub-nanometer resolutions (7-9 Å). Examples are P22 bacteriophage, rice dwarf virus and hepresvirus capsid which have a diameter ranging from 700 to 1250 Å. In these structures, alpha helices and beta sheets of the protein components have been clearly recognized. Modern microscope is capable of recording images of this class of biological particles towards 4 Å. In order to extend the structural determination towards this resolution, we need to address a number of computational and algorithmic issues. These include an increase in CPU to handle a larger number of particles in the data set, an improved accuracy in the estimate of initial particle orientation parameters from low S/N images and in the determination of the imaging parameters, and a need to correct for the focus gradient of the particle along the viewing direction. We will discuss our computational and algorithmic solutions to each of these factors with either simulated or experimental data.

Simplification of 3D densities

Herbert Edelsbrunner (Duke University)

Critial point theory, also known as Morse theory, is the appropriate mathematical framework for studying densities over three-dimensinal space. We consider the common case in which a Morse function over a 3-manifold is approximated by the piecewise linear extension of function values given at the vertices of a triangulation. We base the geometric simplification of this representation on successive edge contractions, and study conditions that guarantee these contractions do not alter the topological type of the 3-manifold. We base topological simplification on successive cancellations of critical points and describe this operation in terms of its effect on the Morse-Smale complex, which is obtained by overlaying the decompositions into stable and unstable manifolds.

Parallel and Distributed Computing for Efficient Tomographic Reconstructions

J. R. Bilbao-Castro (Centro Nacional Biotecnología)

J. M. Carazo (Centro Nacional Biotecnología)

J. J. Fernández (Universidad de Almería)

Inmaculada García Fernández* (Universidad de Almería)

Electron microscope tomography allows the investigation of structure of biological specimens over a wide range of sizes, from cellular structures to single macromolecules. Knowledge of 3D structure is critical to understanding biological function at all levels of detail.

Reconstruction algorithms are characterized for intensively requiring computational resources. These demands come from large memory requirements and long computation times. In practice, structural analyses of biological specimens imply huge reconstruction processes.

Moreover, reconstruction methods are also characterized by free parameters that have to be optimized to fully exploit their capabilities. Parameter optimization aims at tuning the reconstruction algorithm for the specimen under study. This process may involve launching thousands of reconstructions by following a certain optimization algorithm, which makes this process much heavier than the own reconstruction.

Structure determination of biological specimens at medium/high resolution is therefore a grand-challenge application. Parallel and distributed computing plays a critical role to make this problem affordable. In this work, we will describe the experience of our group in the development of parallel strategies for efficient tomographic reconstruction of subcellular structures and macromolecules.

Fourier Transforms of Trains of Pulses on Various Grids

Edgar Garduño (Department of Computer Science, City University of New York)

The sampling of a real-valued function can be mathematically seen as the multiplication of a train of pulses by the function; this is the extension of the concept of pointwise multiplication between two ordinary functions to the multiplication between a real-valued function and a distribution. By the convolution theorem, the result of multiplying a function by a train of pulses is equivalent to the inverse Fourier transform of the convolution of the Fourier transforms of the function and the train of pulses. The arrangement in space of the pulses will determine the final arrangement in space of the discretized, i.e., sampled, three-dimensional density function. For a three-dimensional application, it is customary to arrange the pulses of the sampled function over a simple cubic grid with distance Δ. The Fourier transform of a train of pulses arranged over a simple cubic grid has a train of pulses on the same simple cubic grid as its Fourier transform with distance $1/!\Delta$. However, it has been shown that the body-centered cubic grid is the most "efficient" sampling in three-dimensional Euclidean space when a function is bandlimited with a spectrum that is radially symmetric. We present a mathematical treatment of a method to obtain the Fourier transforms of trains of pulses on various grids using as example the body-centered cubic grid.

Algebraic reconstruction of 2D crystals from their projections

J. M. Carazo (Centro Nacional Biotecnología)

J. J. Fernández (Universidad de Almería)

Gabor T. Herman* (City University of New York)

R. Marabini (Universidad Autónoma de Madrid)

S. Matej

C. O. S. Sorzano (Centro Nacional Biotecnología (CSIC))

An algorithm for 3D reconstruction of 2D crystals from projections is presented, and its applicability to biological macromolecules imaged using electron microscopy (EM) is investigated.Its main departures from the traditional approach is that it works in real space, rather than in Fourier space, and it is iterative. This has the advantage of making it convenient to introduce additional constraints (such as the support of the function to be reconstructed, which may be known from alternative measurements) and has the potential of more accurately modeling the EM image foramtion process. Phantom experiments indicate the superiority of this new approach even without the introduction of constraints in addition to the projection data.

The work of the presenter is supported by NIH grant HL740742.

A method for stimating the CTF in electron microscopy and its application to 3D reconstruction

Roberto Marabini (Universidad Autónoma de Madrid)

The structural information of biological complexes, i.e., their shape and spatial conformation, is vital in molecular biology to understand the proteins function and therefore the molecular basis that support life. Three-dimensional electron microscopy (3D-EM) is a powerful technique for imaging these complex macromolecules. One of the limiting factors of 3D electron microscopy is that it is difficult to obtain high resolution structural details due to the strong effect of the microscope aberrations described, in Fourier space, by the so called contrast transfer function (or CTF). The CTF filters both high and low frequencies, introduces zones of alternate contrast and eliminates all information at certain frequencies. Although a well-established theory of image formation in biological electron microscopy exists, there is still a need for a good estimation method.

In this work, a powerful parametric spectral estimation technique, 2D-auto regressive moving average modeling (ARMA) is applied to CTF detection. ARMA models are generated from electron microscopy images and then a search algorithm is used to fit all the parameters of the theoretical CTF model.

A first comparison between several reconstruction methods (IDR, Chahine, ART) that have been modified to explicitly take into account the CTF is also shown.

Self-Organizing Maps for the Analysis of Electron Microscopy Images

Alberto Pascual-Montano (Centro Nacional de Biotecnología)

Accurate classification of single particles images is essential in Electron Microscopy (EM), especially as a step prior to the three-dimensional reconstruction of the biological specimen under study. All the methods for three-dimensional reconstruction used in EM rely on the strict requirement that the individual projection images considered for the reconstruction process, correspond to different views of the same biological specimen. The self-organizing maps (SOM) are excellent tools for classification, especially when using a large number of data. SOM takes the original large set of data and produces a reduced set of good-quality representatives of the same reality. These representatives, usually called code vectors in neural network terminology, have the property of being ordered over the grid, and in this way the map tends to preserve the topological characteristics of the input data. The capability of finding a set of code vectors that resemble as much as possible the probability density of the input data is a key problem in the process of data mapping. The driving force in this work has been to address this problem within a formal mathematical framework that also takes into account the conceptual good properties of SOM. In this work we will present a set of new SOMs algorithms and their applications in the classification problem of EM single particle images.

Angular assignment in 3D Electron Microscopy using PCA and wavelet decomposition

Carlos Oscar Sánchez Sorzano (Centro Nacional Biotecnología)

3D Electron Microscopy (3DEM) aims at the determination of the spatial distribution of the Coulomb potential of macromolecular complexes. This information is crucial in structural biology and provides key information about the way that macromolecules interact. 3D Electron Tomography computes the 3D reconstruction of a macromolecule based on the information provided by thounsands of 2D projections acquired with an electron microscope. One of the key parameters required to perform such a 3D reconstruction is the direction of projection of each projection image which is unknown a priori and must be determined using some algorithm. This information is usually coded with three Euler angles.

We propose the use of Principal Components Analysis (PCA) and Wavelets in order to match the experimental projections with those obtained from a model volume used as reference. The use of PCA prevents the algorithm from matching features that are not feasible given the reference model. On the other hand, the wavelet decomposition of the projection images provide a framework for a multiscale matching algorithm in which speed and robustness against noise is gained. Results obtained from computer simulations in terms of accuracy and speed encourages the use of this approach.

Reconstruction by Chahine's Method from Projections Corrupted by Electron Microscope Aberrations

G. T. Herman (IMPA)

R. Marabini (IMPA)

C. O. S. Sorzano (IMPA)

Jorge Zubelli* (IMPA)

A projection image obtained by an electron microscope can be conceived of as an "ideal" projection subjected to a contrast transfer function (CTF), which eliminates some frequencies and reverses the phase of others. The aberration caused by the CTF makes the problem of reconstruction from such data difficult. We reformulate the problem so that Chahine's method becomes applicable to it. We substantiate our results with numerical evidence.