representative for the class. The traditional cross correlation method searches a large space of rotations and translations since information about the alignment is not known a priori. Furthermore, that method requires an initial reference image to be provided by the user. In contrast, in our new version of the cross correlation method, the size of the search space is reduced by preprocessing class images as described below, and this peprocessing step circumvents the need for a reference image.
During preprocessing, the centers of mass and the principal axes of images within a class are aligned, resulting in a blurred version of the underlying image. This blurry image is then used in place of an initial reference image. Even though the initial alignment is coarse, the statistics of the resulting misalignment can be estimated well based on the ergodic properties of the additive background noise. Using the statistical properties of the misalignments, a targeted search within the set of all translations and rotations of images is performed, resulting in reduced computational time and increased alignment accuracy. Using synthetic data, we compare the new method to both the classical cross correlation approach and the maximum likelihood method, and demonstrate the improvement in performance that results when using our method.
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1750-Pos Board B660
Novel Methods for Rapid Comparison and Multimeric Protein Complex Fitting for Low-Resolution Electron Microscopy Data
Lee Sael, Juan Esquivel-Rodriguez, **Daisuke Kihara**.
Recent advancements of experimental techniques for determining protein tertiary structures raise significant challenges for protein bioinformatics. Previously, we have introduced a method for protein surface shape representation using the 3D Zernike descriptors (3DZDs). The 3DZD enables fast structure database searches, taking advantage of its rotation invariance and compact representation. The 3DZD has been successfully applied for global protein surface shape comparison, local pocket shape comparison, protein docking prediction, and rapid small ligand molecule search. Here, we apply the 3DZD for comparing low-resolution structure data from the electron microscopy (EM). Two applications are presented. First, we use the 3DZD for rapid comparison for an EM density map of a protein structure to a database of EM data. We examined EM maps of varying resolutions and found that the method has good performance in identifying the structures of the same fold even for EM maps at a resolution of 15 Angstroms (Sael, Kihara , BMC Bioinformatics, in press). Next, we applied the 3DZD for fitting multiple component proteins into an EM map. The method integrates a multiple protein docking procedure and the 3DZD, which compares surface shape of docking conformation to the EM map. The multiple docking is performed by the Multi-LZerD algorithm, which starts by computing pairwise docking prediction of component chains by using the LZerD docking program, which our group have developed recently (Venkatraman et al., BMC Bioinformatics, 2010). Multi-LZerD combines the pairwise docking results generating a couple of hundreds solutions. Then the fitness of the multiple docking decoys and the EM map is quantified by using the 3DZD. Overall, we show that the 3DZD is powerful in comparing low-resolution structure data for comparison and multiple-docking guided by the low-resolution data.

1751-Pos Board B661
Helex: an Evolutionary Tabu Search Strategy for the Identification of Helical Regions in cryo-Electron Microscopy Reconstructions
Mirabela Rusu, Stefan Birmanns.
Cryo-electron microscopy (cryo-EM) enables the imaging of macromolecular complexes in near-native environments at resolutions that in many instances approach atomic level of detail. Already covering 9.8% of the EBI database for cryo-EM reconstructions, the maps at intermediate- to high-resolution (better than 8A) potentially allow the identification of secondary structure elements. Especially, alpha helices which frequently show consistent patterns in volumetric maps, may be annotated using pattern matching methods. Previously introduced approaches predict secondary structure elements in cryo-EM datasets by applying multi-step heuristics to characterize the geometric features of the volumetric data. Here, we introduce helex (Helix Extractor) - a novel technique for the identification of helical regions in cryo-EM data sets. Helex is a hybrid optimization technique that combines a genetic algorithm, a tabu-search strategy, and a one-dimensional iterative optimization to locate and characterize helical regions. Our method takes advantage of the stochastic nature of genetic algorithms to identify optimal placements for a template helix. These placements are then used to characterize the length of the helical region, using an adaptive one-dimensional search that allows suboptimal steps during the optimization. Moreover, the tabu-search strategy prevents further exploration of already characterized helical regions. The method was extensively evaluated using maps at various resolutions, sampling rates and system complexity. Helex reliably identified medium to large helices (> 6 amino acids) in both synthetic and experimental test cases, placing them frequently with root mean square deviations of 1A or less from the correct helical axes. Helex is distributed in our molecular modeling software Sculptor, freely available at http://sculptor.biomachina.org.

1752-Pos Board B662
Scanning Transmission Electron Microscopy of Eukaryotic Cells in Liquid
Niels de Jonge, Madeline J. Dukes, Elizabeth A. Ring, Diana B. Peckys.
We have recently introduced liquid scanning transmission electron microscopy (STEM) [1-3], a novel electron microscopy technique for the imaging of whole cells in liquid. Eukaryotic cells in liquid were placed in a microfluidic chamber with a thickness of ~5 μm enclosed between two ultra-thin electron-transparent windows. Images were obtained by scanning a focused electron beam over the sample and detecting the elastically scattered electrons with an annular dark field detector. On account of the atomic number (Z) contrast of the STEM, nanoparticles of a high-Z material, e.g. gold, can be detected within the background signal produced by a micrometers-thick layer of a low-Z liquid, e.g. water, or cellular material. Nanoparticles specifically attached to proteins can be used to study protein distributions in whole cells in liquid, similar as proteins tagged with fluorescent labels can be used to study cellular function with fluorescence microscopy. COS7 fibroblast cells were labeled with gold nanoparticles conjugated with epidermal growth factor (EGF). Intact fixed cells in liquid were imaged with STEM with a spatial resolution of 4 nm and a pixel dwell time of 20 μs [1]. In addition, proteins were labeled with quantum dots (QDs), fluorescent nanoparticles visible both with light- and with electron microscopy. STEM images showed individual QDs, and their locations were correlated with the cellular regions, as imaged with fluorescence microscopy [4]. Liquid STEM also obtains contrast on the native structure of live cells. Wild type S. pombe cells and several mutants were imaged with a spatial resolution of 30 nm.
[1] N. de Jonge et al., Proc. Natl. Acad. Sci., 106, 2159 (2009).
[2] D.B. Peckys et al., PLoS One, 4, e8214 (2009).
[3] E.A. Ring & N. de Jonge, Microsc. Microanal. 16, 622 (2010).
[4] Dukes et al., ACS Nano 4, 4110 (2010).

1753-Pos Board B663
Orbweaver: A New Graphical User Interface for Particle Selection in Single-Particle Reconstruction with Cryo-Em
Robert Ezra Langlois, Joachim Frank.
Computer algorithms play a key role in nearly every step of single-particle reconstruction of data collected by cryo-electron microscopy (cryo-EM). A three-dimensional (3D) reconstruction of a macromolecular complex requires tens of thousands of 2D experimental projections to be handpicked from hundreds of film micrographs (or thousands of CCD micrographs). To handle this deluge of data, semi-automated particle-picking algorithms have been developed to assist in locating particles on a micrograph, but only in a few easy cases do these algorithms perform a significant portion of the work. In most cases, particle picking comprises most of a researcher's time in building a 3D reconstruction, often taking weeks to months.
Two current trends in cryo-EM substantially increase the load on particle picking. One is the need to improve the resolution of the density maps, to aid in the interpretation in terms of atomic structures. The other is the need to characterize heterogeneous samples by an entire array of reconstructions, one for every class encountered.
We are working on optimizing every step of the particle-picking process, developing new machine-learning algorithms and designing a better graphical user interface. To this end, we have recently developed an unsupervised learning algorithm to extract potential particles from the micrograph, in combination with an active learning algorithm aimed to drastically reduce the number of manually selected particles required to build an accurate supervised classifier. Since active learning requires a new type of manual particle picking interface, we now present a new graphical user interface to improve both the speed and accuracy in manual selection through active learning.

1754-Pos Board B664
Using Sculptor for the Simultaneous Assembly of Atomic Components into Volumetric Maps
Stefan Birmanns.
An important challenge, especially from a computational standpoint, is the integration of data from different biophysical sources, by providing efficient algorithms and user-friendly software tools. We propose a new, integrated software system that combines extensive visualization capabilities with molecular