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Non-Rigid Registration of Cell Microscopy Images and Statistical Shape Analysis of Chromosome Structure

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The 3D folding structure formed by different genomic regions of chromatin in cellular interphase is still poorly understood. In this work, different computational approaches are developed to determine the 3D structure of chromatin based on fluorescent microscopy images.

First, since different cell nuclei in 3D multi-channel microscopy images are analyzed, it is necessary to perform a geometric normalization. To this end, an intensity-based non-rigid registration approach is presented. A main problem with cell nuclei images is that the intensity structure of different nuclei differs very much, thus an intensity-based registration scheme cannot be used directly. Instead, in this work first a segmentation of the images from the cell nucleus channel is performed, then the resulting images is smoothed by a Gaussian filter, subsequently an intensity-based registration algorithm is applied. The obtained transformation is applied to the images from the nucleus channel as well as to the images from the other channels. An adaptive step length optimization approach combined with a multi-resolution scheme is proposed to improve the convergence rate of the algorithm. This approach has been successfully applied using 2D cell-like synthetic images, 3D phantom images as well as 3D multi-channel microscopy images representing different chromosome territories and genomic regions. Furthermore, this approach is extended for the registration of 3D+t (4D) image series of moving cell nuclei.

Second, since so far only relatively simple geometric features, like distances and angles between different genomic regions (BACs) on chromatin fiber have been evaluated, this work is concerned with more complex geometric properties, i.e., the complete shape formed by genomic regions. Different approaches based on statistical shape theory are described to analyze the considered structures, e.g., shape uniformity test, 3D point-based registration, Fisher distribution, and the aforementioned 3D non-rigid image registration for geometric normalization. These approaches have been applied to statistically analyze the triangles or tetrahedrons which are built by the different BACs of chromosome 1 and X as well as centromeres and centrosomes in 3D microscopy images. The experimental results show that for most datasets the considered 3D structure is statistically non-random, and the shapes formed by certain active and inactive BACs of X-chromosome are statistically independent. Moreover, the average 3D structure of chromatin was

reconstructed based on five BACs resulting from 2x4 BACs overlapping on three positions. Finally it turned out that geometric normalization based on the non-rigid image registration has a significant influence on the location of the genomic regions.