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Cryo-electron tomography and deep learning based image denoising reveals chromatin landscape at the nanometer resolution in situ

Folding of nucleosome chains influences DNA availability for functional interactions necessary for the regulation of transcription, DNA replication and repair. Despite the existing models based on studies *in vitro*, the nucleosome chain geometry within the crowded cell nucleus has remained elusive. Cryo-electron tomography (Cryo-ET) is the only method that provides a sufficient resolution to address this question. Our previous studies using cryo-ET of vitreous sections demonstrated the feasibility of imaging nucleosomes in Drosophila nuclei *in situ* at a level of detail that allowed us to access their conformation. In this study, combining Cryo-ET and deep learning tools, we obtained the first direct observation of the path of linker DNA in chromatin imaged directly in its functional environment *in situ*. We quantify linker length and curvature characterizing a disordered zig-zag chromatin folding motif, with a low degree of DNA bending. In addition, the quality of visualization made it possible to explore the chromatin structure directly at the level of individual nucleosome conformation without structure averaging that was used by previous cryo-ET studies. Our results on identification of nucleosome conformational transitions and non-canonical nucleosome structures *in situ*, further highlighting potential of this methodology for deciphering chromatin organization.

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