Voronoi-Tessellation based High Content Nanoscopy of nuclear Genome Structure

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Abstract

Super-resolution light microscopy (SRM) methods1 have provided new possibilities to investigate quantitatively the spatial consequences of current models of nuclear genome organization2 at nanoscale resolution. To achieve the high structural resolution required, “high content” approaches of Single Molecule Localization Microscopy (SMLM) have been developed, such as fluctuation based binding activated localization microscopy (fBALM)3,4. Using this technique, up to about 10 million individual DNA sites in an optical section of an individual mammalian cell nucleus have been localized with high precision, corresponding to about 1 Single Molecule localization (SM) per 60 base pairs, or about 3 per nucleosome. To draw from such large amounts of SM positions meaningful conclusions with respect to nuclear chromatin organization, a variety of algorithms may be used. Here, we report on recent results of a Voronoi tessellation approach applied to the entire data set. This allowed us to determine the absolute 3D DNA densities of chromatin assemblies in entire nuclear sections at a lateral resolution of 10-20 nm, and an axial resolution down to 600 nm. The results revealed a high heterogeneity of the DNA density distribution, with absolute 3D DNA compaction levels ranging from a few Mbp/µm³ up to >40 Mbp/µm³. Our results support a model2, where higher order chromatin networks are built up from chromatin nanodomains, pervaded by a contiguous network of interchromatin channels, called the interchromatin compartment (IC). How this structure of the nuclear landscape and its space-time dynamics may affect the accessibility of nanodomains for individual factors and pre-assembled aggregates remains to be explored.