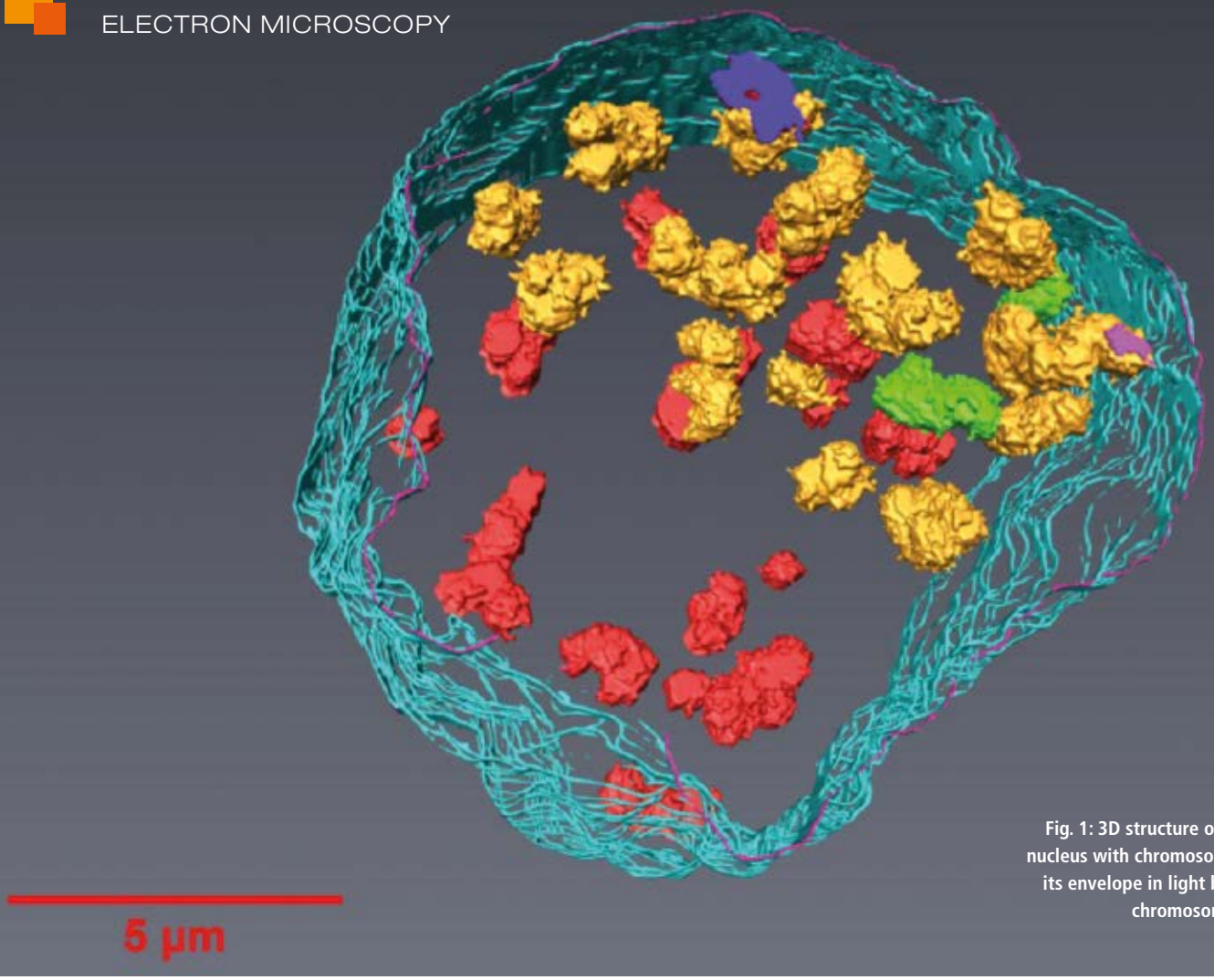

Fig. 1: 3D structure of the human nucleus with chromosomes in, with its envelope in light blue and the chromosomes in color.

3D Structure of A Nucleus and Chromosomes

Fine Structure Investigation of a Human Nucleus with Chromosomes

Bo Chen[1,2], JiaWei Lu[2], Teruo Hashimoto[3], George Thompson[3], Ian Robinson[1,2,4]

As lack of high-resolution tools for direct accesses, our understanding still remains controversial on the higher-order structure of human chromosomes between a few tens and hundreds of nanometers. In this work, the three-dimensional (3D) spatial structure of a human prophase nucleus and chromosomes was revealed by using a powerful 3D imaging tool, serial block-face scanning electron microscopy (SBFSEM). The acquired 3D image provided rich spatial structure information of the human prophase nucleus and chromosomes at a resolution of around 50 nm for quantitative analysis in three dimensions.

Introduction

When we are talking about chromosomes, the familiar images with X-shape would easily flash into our minds. Did you ever think that the chromosomes could be in other shapes, not the X-shape, with organized structure?

A team of researchers from the London Centre for Nanotechnology, UCL and Tongji University used serial block-face scanning electron microscopy (SBFSEM) to quantitatively reveal the spatial structure of human chromosomes and nucleus. SBFSEM uses a scanning electron microscope (SEM) with a built-in ultra-microtome to do automatic serial sectioning for three-dimensional (3D) imaging [1-3]. The work revealed the spatial structure of chromosomes in a human nucleus [4] by the 3D high-resolution microscopy method without flattening samples [5, 6]. The obtained 3D image provided us some unique and vital information which can determine the relative positions of the chromosomes within the nuclear inner space, and can also make us rather accurately identify the chromosomes by the statistic of their 3D structural information such as volumes/sizes, shape and centromere positions.

Results and Discussions

The original 2D backscattered electron (BSE) micrographs of the human nucleus sample were acquired by SBFSEM measurement. After stacking all the obtained

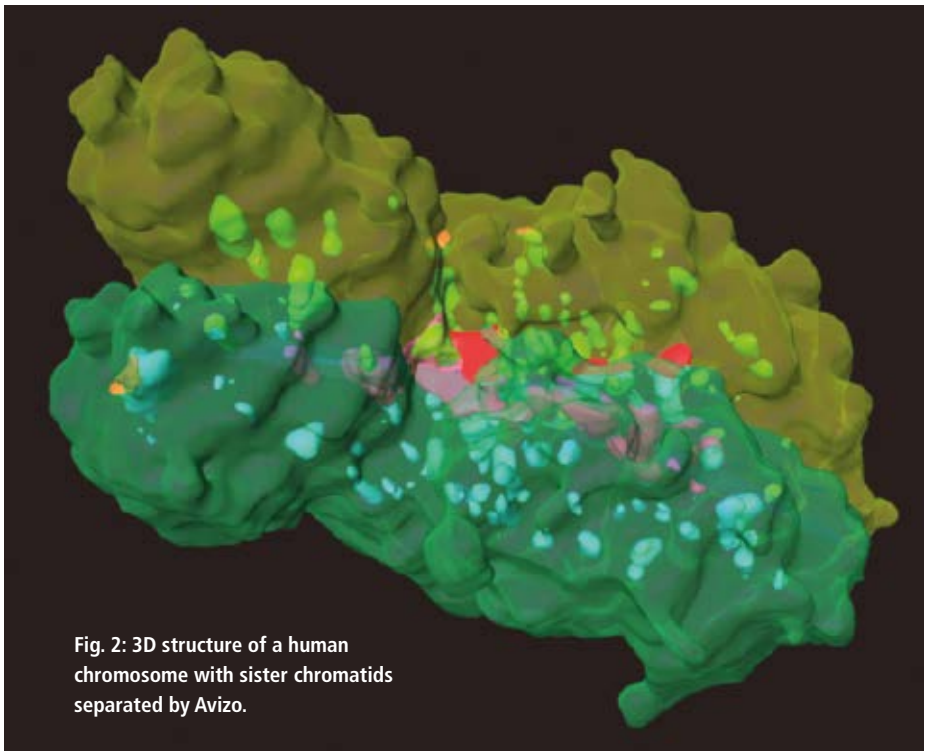

Fig. 2: 3D structure of a human chromosome with sister chromatids separated by Avizo.

2D BSE micrograph slices together, the 3D image of the observed human nucleus, with 36 chromosomes out of the whole set of 46 chromosomes, was segmented and rendered. The chromosomes were classified into the individual intact ones (shown as yellow and green ones in fig. 1) and the broken ones (shown as red in fig. 1).

The research found out that the chromosomes are also S-shaped and C-shaped, not only X-shaped, and the larger chromosomes were more likely to be in S shape or C shape, whereas the smaller chromosomes tend to be the familiar X-shape. It also found out that chromosomes are nonrandomly positioning in the prophase nucleus with the gene-rich chromosomes near the nuclear center and gene-poor ones near the periphery. This nonrandom positioning of the chromosomes in prophase also resembles the chromosome territory positioning pattern found in interphase: the smaller chromosomes are closer to the center of the nucleus, whereas the larger ones are nearer the periphery. The research team deduced that the chromatin condenses locally into "visible" chromosomes during the cell cycle. Furthermore, during the chromatin condensation, the sister chromatid pairs were found are not identical in morphology, but kept the volumes similar.

From the quantitative analysis of the obtained 3D structure of chromosomes, the volume of base pair was calculated to be 6.69 nm^3, and the sister chromatids have a well-conserved diameter of about 765nm in cylindrical shape regardless of their sizes (see fig. 2 as one of the examples). The research team also proposed a potential new method for identifying human chromosomes, in three dimensions, based on the analysis of their 3D morphology and sizes, but not conducting the multicolor fluorescence in situ hybridization (M-FISH) measurements as traditionally done. The method can be used in the future to identify human chromosomes through 3D imaging approaches.

Conclusions

The work has applied a powerful and persuasive method to the biological and biomaterials area and is able to go further in the investigation of the condensation process of the chromatin by comparing the 3D structure of chromosomes and nuclei at the different stages of cell cycle using the newly established SBFSEM facility at the Tongji University, Shanghai, China.

Acknowledgement

This work was supported by the Biotechnology and Biological Sciences Research Council (UK), the Engineering and Physical Sciences Research Council (UK) and partially by Tongji University (China).

Other Information

Text and data are partially courtesy of the London Centre for Nanotechnology. This report is based on the original publication "Three-dimensional positioning and structure of chromosomes in a human prophase nucleus" in Science Advances by Bo Chen, Mohammed Yusuf, Teruo Hashimoto, Ana Katrina Estandarte, George Thompson, Ian Robinson. Link to publication is presented as below: http://advances.sciencemag.org/content/3/7/e1602231

For the "Materials and Methods", please refer to the above original publication.

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More information on 3D imaging: http://bit.ly/IM3DIM

More about serial block-face scanning electron microscopy: http://bit.ly/SBF-IM

[1] All references: http://bit.ly/IM-Chen