

TeloView: Image analysis for structural genomics

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Introduction

The three dimensional (3D) genome organization in the nucleus is important for both research and diagnostics. It can be studied by analyzing the telomeres, centromeres and other nuclear bodies. The goals of this study:

- Develop tools to analyze 3D multiple-probe signals in the nucleus.
- Determine the 3D organization of these signals in normal & cancer cells.

TeloView: a set of DIPimage tools in MatLab

Load images

Automatic localization of probe signals

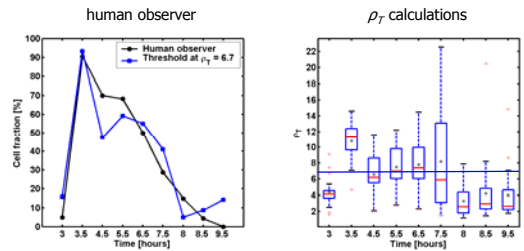
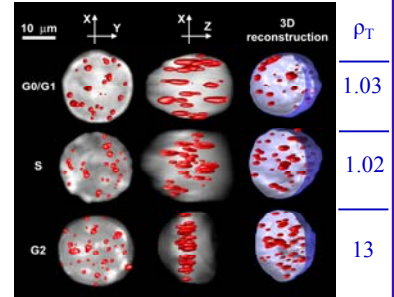
Interactive correction

Analyze probe signals:
e.g. calculate intensities, organizational parameter, find aggregates etc.

Telomere distribution is cell-cycle dependent

By analyzing cell-cycle sorted primary mouse lymphocytes we found that the 3D telomere organization changes during the cell cycle (1,2).

Telomeres are widely distributed throughout the nucleus in the G0/G1 and S phases. During late G2 their 3D organization changes into a telomeric disk (TD).



Nuclei in S phase are labeled with BrdU.
At 0 hours all nuclei are in S phase

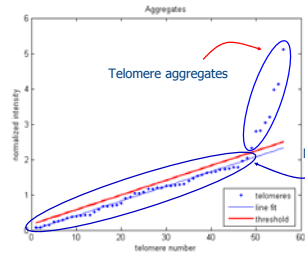
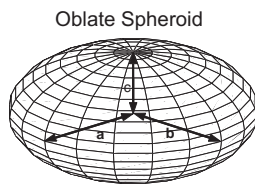
Output and analysis

The basic output of TeloView consists of:

- the location of the probes
- the integrated intensity of the probe

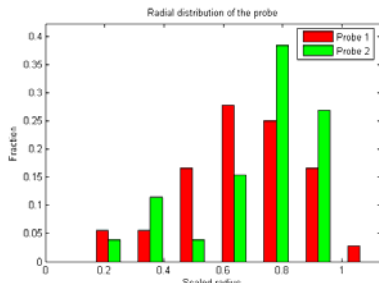
This output can be used for numerous kinds of analysis for example:

TeloView characterizes the volume (i.e. sphere or a disk) in which telomeres are distributed in the nucleus. The volume is then described by one number, $\rho_T = a/c$, which is the ratio of the two main axes of the spheroid. If $\rho_T = 1$, the volume is spherical, if $\rho_T > 1$, the spheroid is oblate (1).

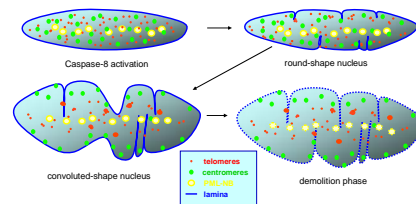


TeloView calculates the intensities of the telomere signal in the image. Using statistical analysis it will find outliers. In this particular example, the outliers are defining telomere aggregates.

TeloView can create histograms of the radial position of one or two probes within the nucleus. In this example probe 1 is CenpA (a centromeric protein) and probe 2 is trf1 (a telomeric protein).

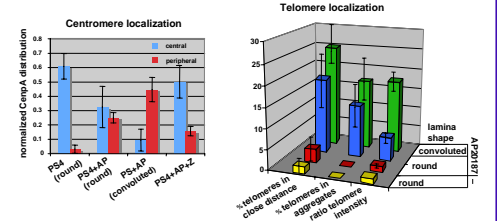


Changes in nuclear spatial organization induced by the caspase-8 pathway



Here we have activated apoptosis in human mesenchymal stem cells, by expressing an inducible caspase-8 (4). Left we see a cartoon of the changes appearing in the nucleus.

We find that caspase-8 induces alteration of the nuclear lamina, which triggers spatial reorganization of telomeres and centromeres.



Conclusion and future

TeloView has proven to be a useful tool in the research area of nuclear organization. The ongoing collaboration with biology research groups in need of problem specific image analysis solutions will help continuous development of new tools in TeloView. In the recent future we also hope to make the software freely available.

References:

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- Chuang, T.C.Y. *et al*, The three-dimensional organization of telomeres in the nucleus of mammalian cells. *BMC Biology*, 2004. **2**(12).
- Louis, S.F. *et al*, c-Myc induces chromosomal rearrangements through telomere and chromosome remodeling in the interphase nucleus. *PNAS*, 2005. **102**(27).
- Raz, V. *et al*, Changes in the nuclear lamina triggers spatial reorganization of heterochromatic regions in Caspase-8-activated human mesenchymal stem cells, *JCB*, 2006, *in print*.