3D Modeling of Chromosomes Territories in Normal and Aneuploid Nuclei

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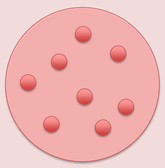
INTRODUCTION

- The spatial organization (SO) of chromosome territories (CTs). within the nucleus is non-random and any disruption leads to undesired changes, such as disease states.
- A 3D modeling approach to allow precise shape estimation and localization of CTs in the nucleus of human embryonic stem cells (hES) undergoing progressive but defined aneuploidy.
- The CTs were detected with chromosome specific DNA probes via multi-color fluorescence in situ hybridization (FISH) in conjunction with confocal microscopy.
- Spherical harmonic (SPHARM) surface modeling to generate a well-defined 3D surface for the nuclei and enclosed CTs, allowing precise quantification of their size and shape.

Figure 1: The maximum intensity projection of 22 optical sections of a diploid nuclei.

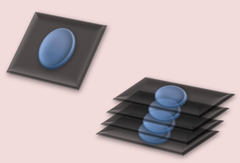
METHOD

FISH Slide Preparation and Image Acquisition

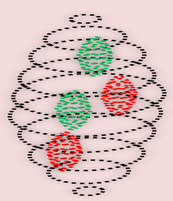


The hES cell line WA09 (H9) at passage 73 was provided by WiCell Research Institute.

Hybridizing fluorescent protein to chromosome X, 8, and 12. The images were acquired via confocal microscopy.



Serial optical sections were acquired at a z-interval of 0.25 μm (Fig. 1).



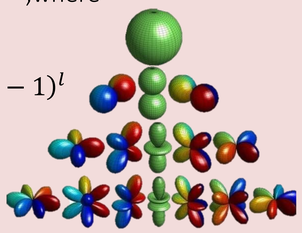
3D images were pre-processed, and 3D nuclear and CT objects were segmented using gray level thresholding and 3D region labeling algorithms.

Estimation of 3D surface using spherical harmonic modeling

Surface shapes for nuclei and CTs were estimated using spherical harmonics, $Y_l^m(\theta,\phi)$, a frequency-space shape descriptor based on sphere coordinates at order, l, and degree, m :

$$Y_l^m(\theta,\phi) \equiv \sqrt{\frac{2l+1}{4\pi}\frac{(l-m)!}{(l+m)}}\,P_l^m(cos\theta)e^{im\phi}$$,where

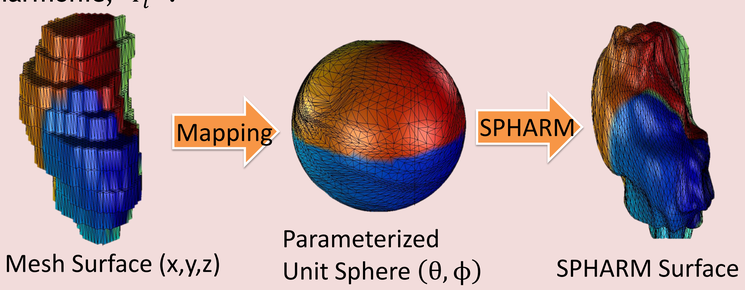
$$P_l^m(x) = \frac{(-1)^m}{2^l l!}(1-x^2)^{m/2}\frac{d^{l+m}}{dx^{l+m}}(x^2-1)^l$$



SPHARM Modeling

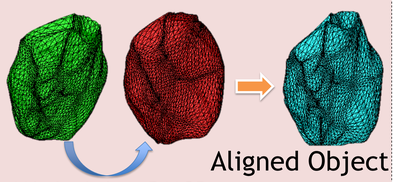
$$V(\theta,\phi) = \big(x(\theta,\phi), y(\theta,\phi), z(\theta,\phi)\big)^T = \sum_{l=0}^{\infty}\sum_{m=-1}^{l} C_l^m Y_l^m(\theta,\phi)$$

C_l^m is the coefficient matrix corresponding to spherical harmonic, Y_l^m.

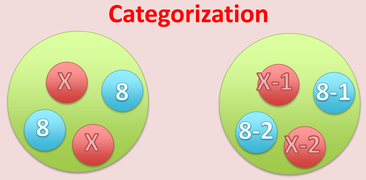


Realignment

Minimum Sum of Root Mean Square Distance (RMSD) :



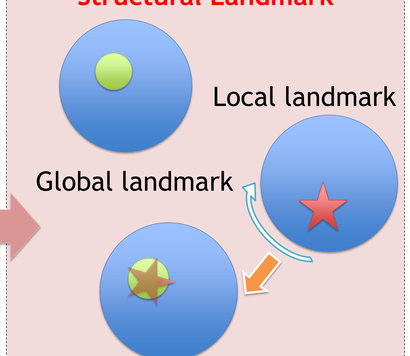
Chromosomes Class based Categorization



Statistical Analysis

- Chromosome Distance
- 3D Position
- Multidimensional scaling
- Spatial Point Patterns

Structural Landmark



Results

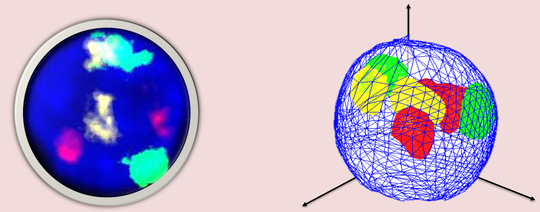


Figure 2: Results of analyzing images of nucleus and chromosome territories.

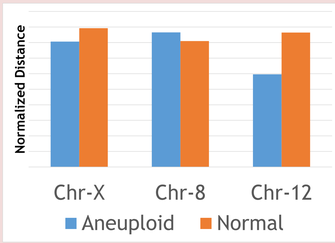


Figure 3: Intra-homologous distance.

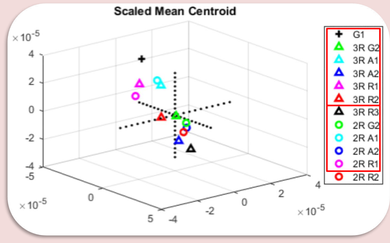


Figure 4: Average 3D position of chromosomes.

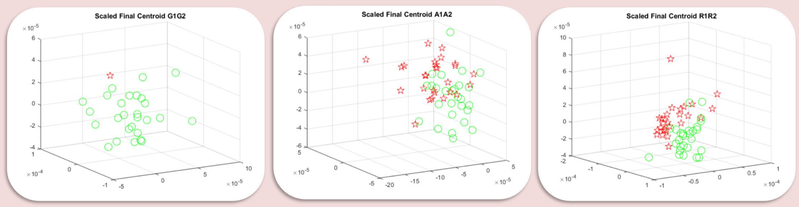


Figure 5: Aligned position of chromosomes in 3D

	ChrX-1	ChrX-2	Chr12-1	Chr12-2	Chr8-1	Chr8-2
F-test	7.39E-01	4.62E-02	1.91E-01	1.54E-01	3.80E-01	6.82E-01
T-test	1.00E+00	3.04E-01	2.29E-01	3.70E-02	5.31E-01	4.04E-02

Table 1. Paired t-test: 3D position of chromosomes in diploid and aneuploid cell.

Conclusions

- Demonstrated the use of spherical harmonic modeling for the quantitation of the 3D position of CTs.
- The computational framework presented can be used to compare the spatial distribution of CTs across multiple nuclei from a given population and/or between populations.
- Our results conform to previous studies in that we show changes in the spatial organization of CTs of aneuploid chromosome when compared to their diploid counterparts.
- Our data suggests, that computational modeling of chromosome territories may be useful in distinguishing normal and tumor cells.