Interphase Chromosome Conformation and Chromatin-chromatin Interactions in Human Epithelial Cells Cultured under Different Gravity Conditions

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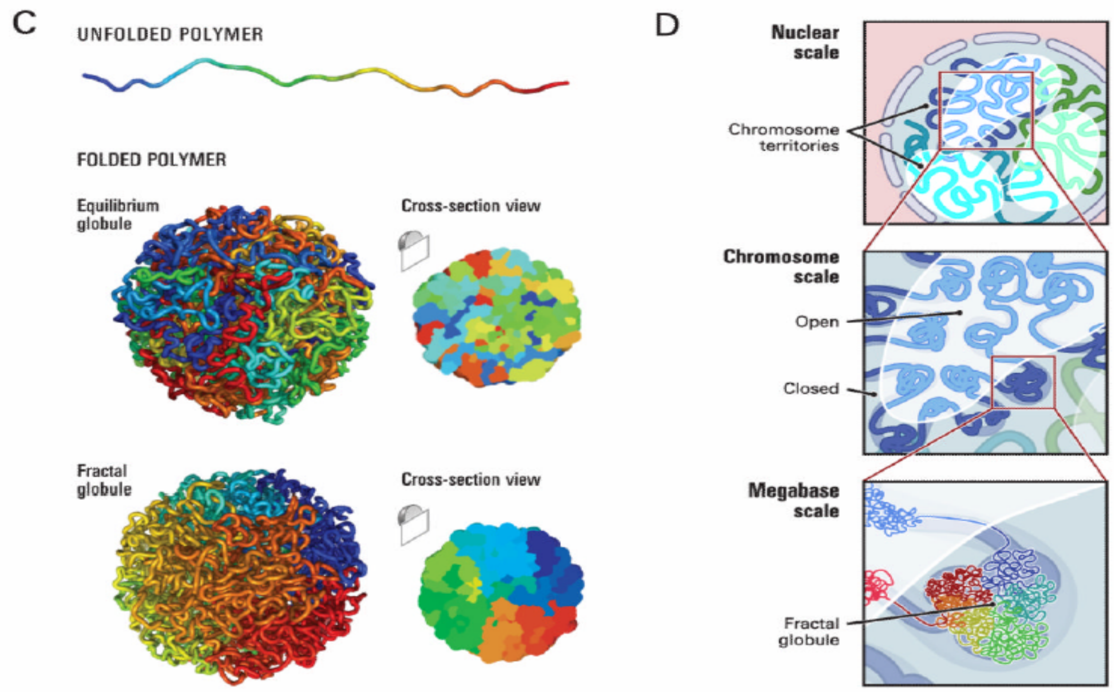
Chromatin Folding Models

Random walk/polymer model of chromatin folding on 0.5-5 mbp scales



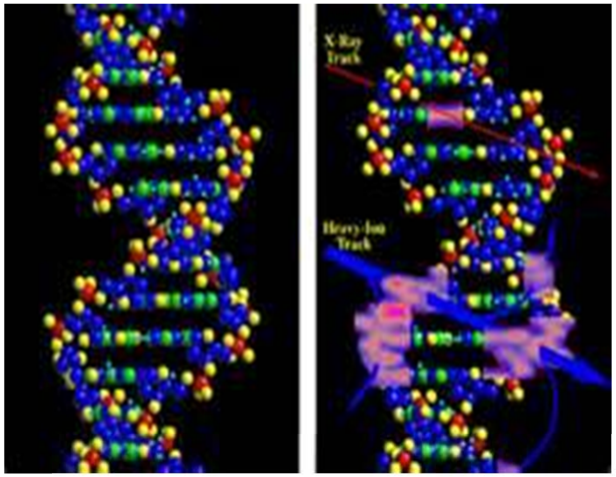
Lieberman-Aiden et al., Science, 2010

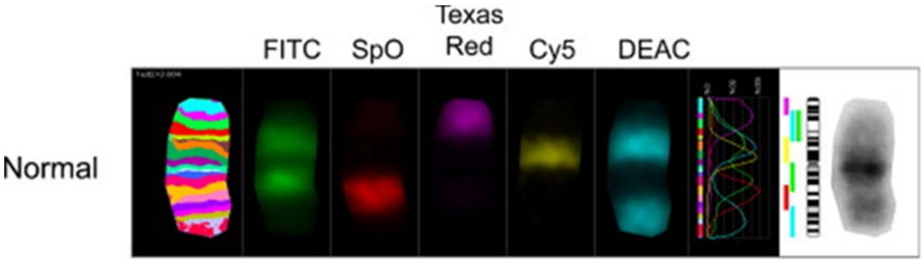
Non-randomness of chromatin folding on multi-megabase scales

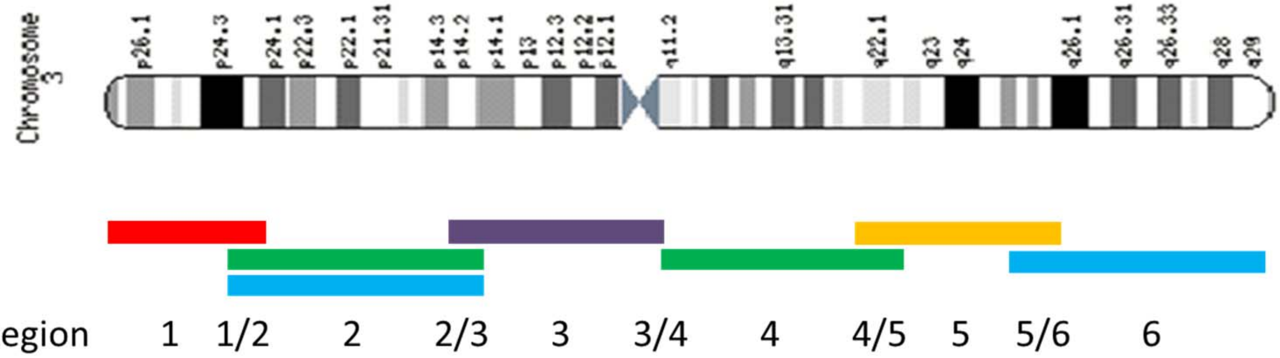
- Being confined in localized chromosome domains
- Limiting the spatial extension of the chromatin
- With regions of different transcriptional activities and gene densities

Distributions of low- and high-LET radiation-induced breaks in chromosome 3 are associated with inter- and intra- chromosomal exchanges in human mammary epithelial cells

Hada *et al*, *Radiation Research*, 2011



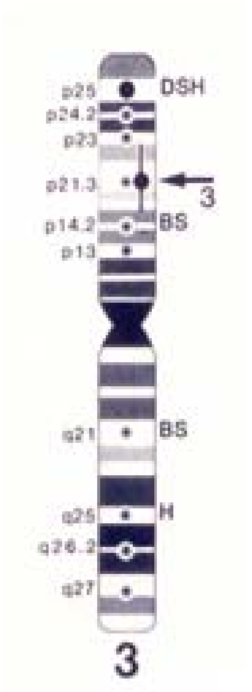




Chromosome 3 is hybridized with mBAND probes in 5 fluorophore dyes. The chromosome is separated in six colored regions and 5 junction regions.

Chromosome 3

Chromosome 3 spans almost 200 million base pairs, representing about 6.5 percent of the total DNA in cells, and containing about 1,980 genes (Human genome overview page, Build 36.3 http://www.ncbi.nlm.nih.gov/mapview/maps.cgi?taxid=9606&build=previous&chr=3)



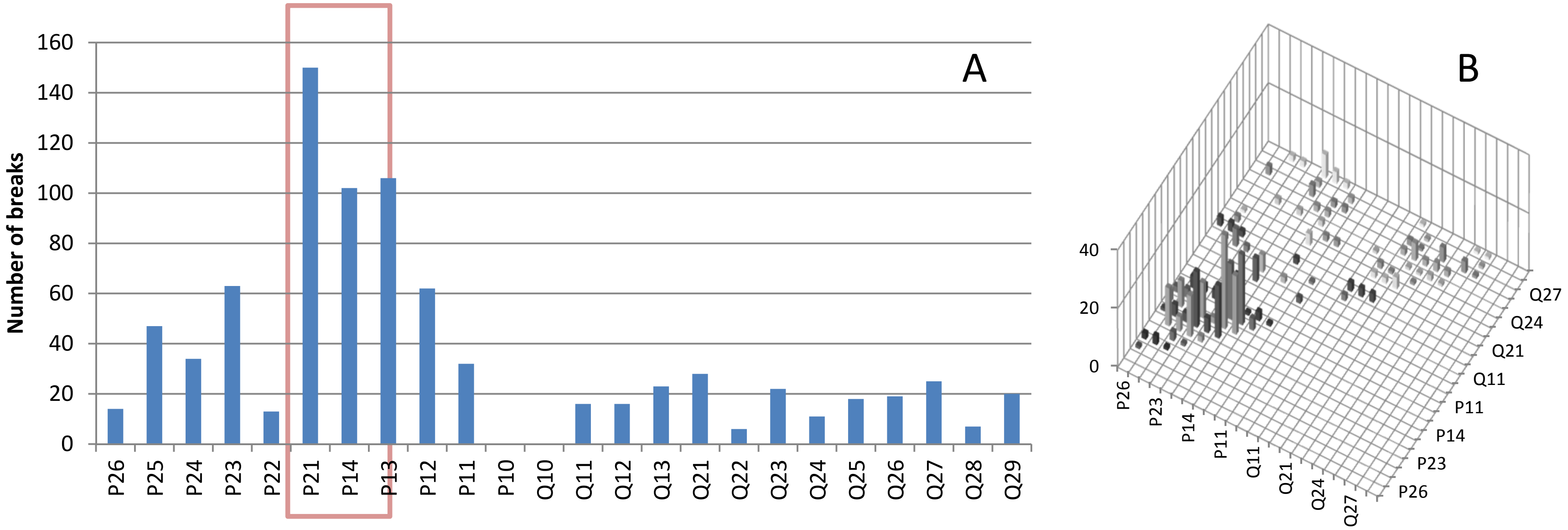
Yunis and Hoffman 1989

Topography	Case	Case with Ch 3 Aberration	%	Case Analyzed
Bone and Soft Tissues	3406	576	16.9	500
Breast	1128	293	25.9	245
Cadiovascular	48	2	4.2	1
CNS	2511	208	8.3	175
Digestive System	2285	543	23.8	492
Endocrine System	605	115	24.8	107
Female Genital Organs	1552	266	17.1	225
Male Genital Organs	609	94	15.4	63
Respiratory System	1128	365	32.4	319
Skin	331	76	22.9	71
Urinary Tract	2166	640	29.5	569
Overall	15769	3178	20.2	2767

Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer (2013). Mitelman F, Johansson B and Mertens F (Ed.), http://cgap.nci.nih.gov/Chromosomes/Mitelman

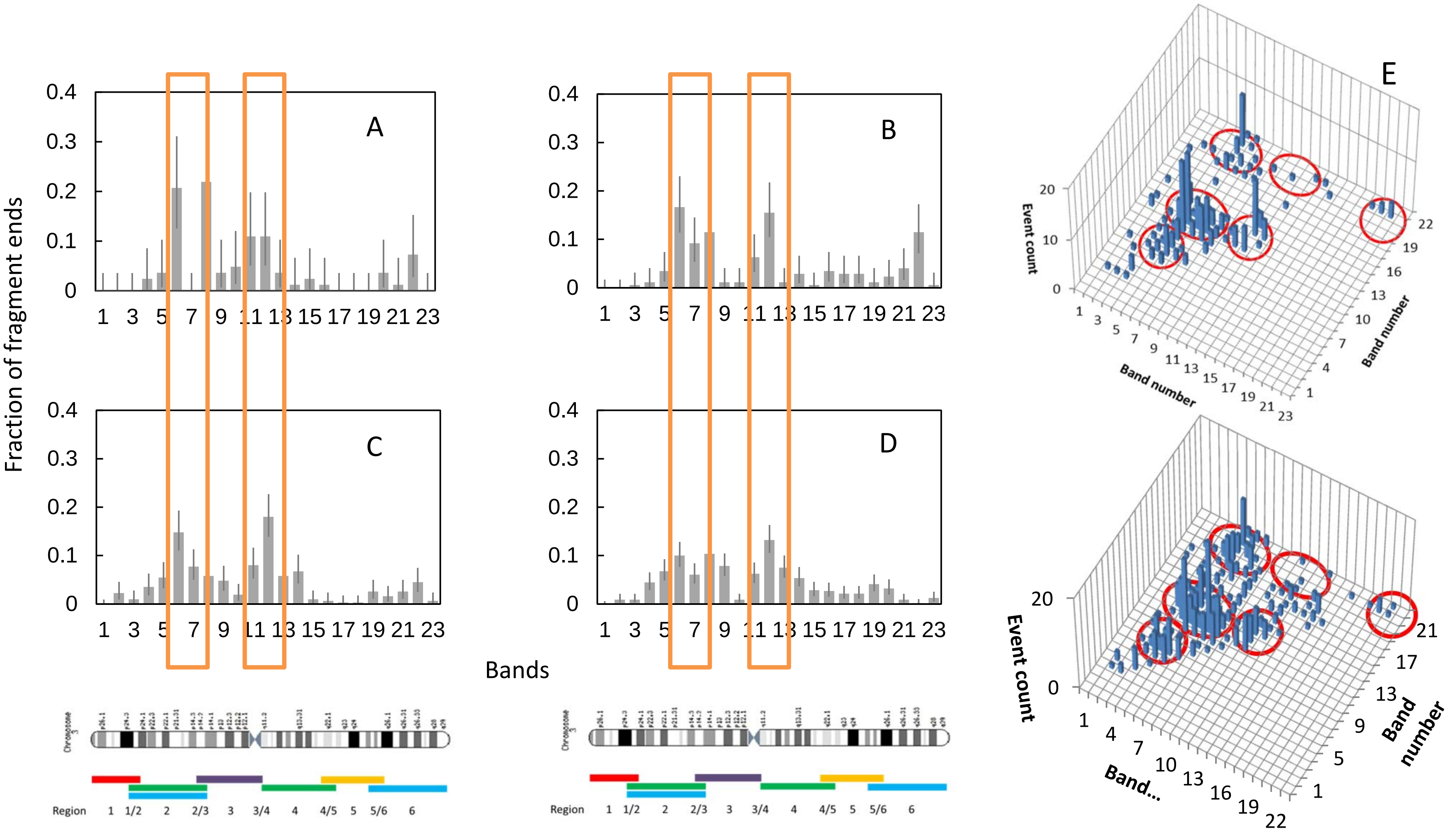
Distributions of intra-chromosome 3 exchanges in cancer patients

The hotspots for radiation exposure coincide with some but not all hotspots for solid cancers. The region of 3p21.3 (band 6 within region 2) is a known fragile site and contain several tumor suppression genes/regions.



Distributions of breaks involved in intra-chromosome 3 exchanges in cancer patients

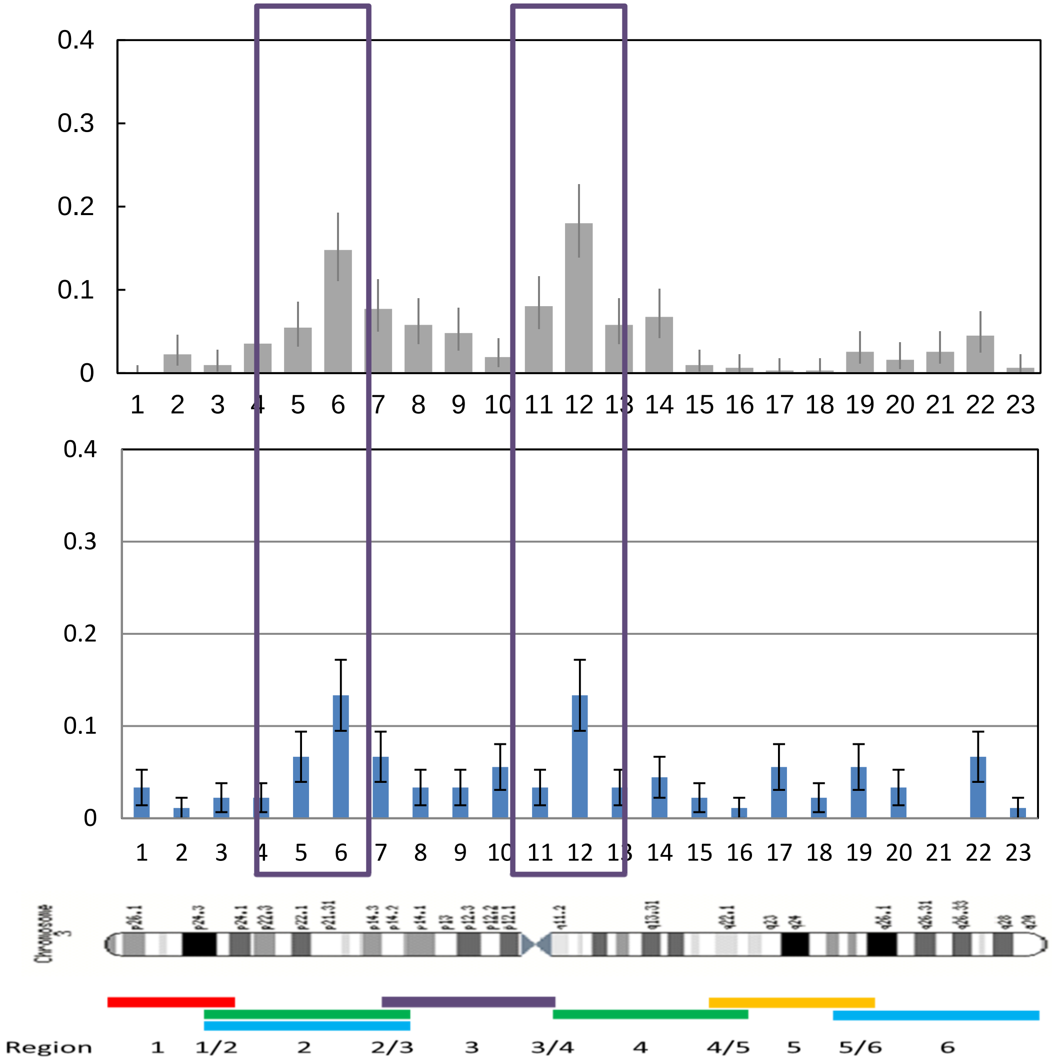
Distributions of radiation-induced intra-chromosomal exchanges in human epithelial cells

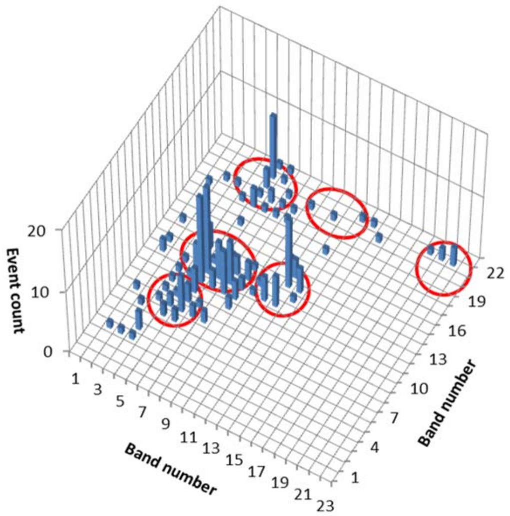


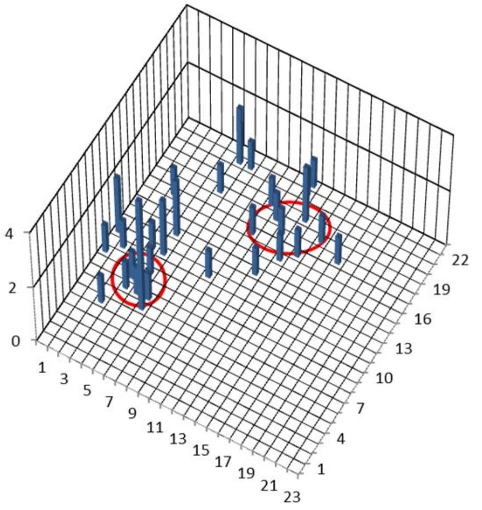
γ-rays of low dose rate (Panel A), neutrons (Panel B), γ-rays of high dose rate (Panel C) or Fe ions (Panel D). Panel E: Most of the intra-chromosomal exchanges occurred between a break in band 5-9 (region 2) and one in band 11-13 (junction 3/4).

Hada *et al*. *Rad Res.,* 2011

Distributions of radiation-induced intra-chromosomal exchanges in human lymphocytes

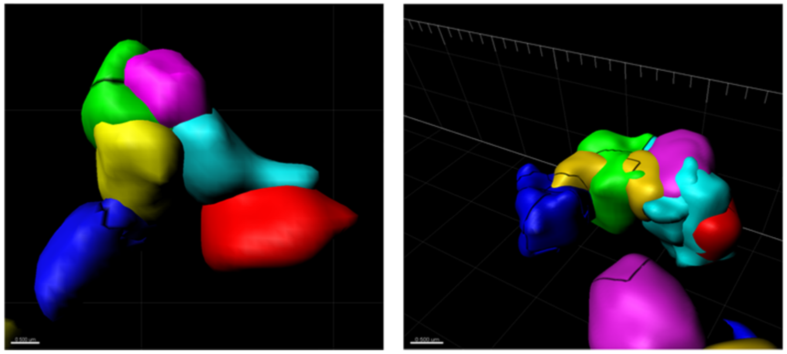




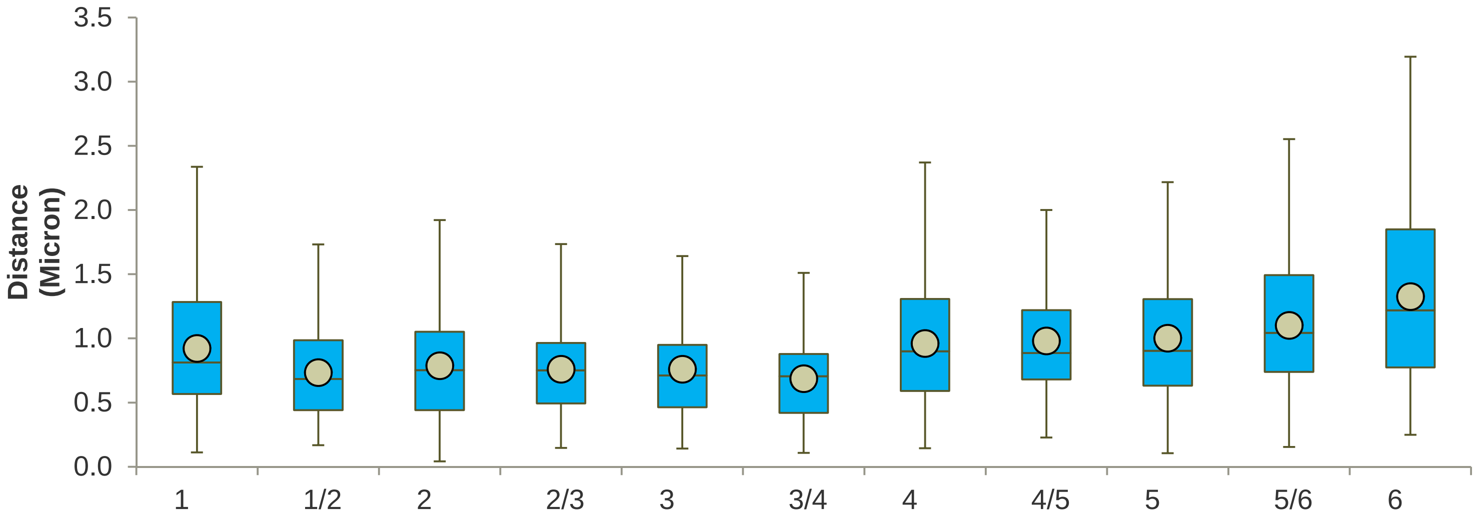


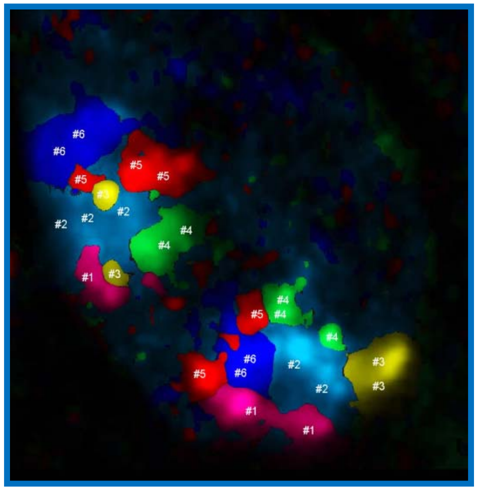
Proximity within interphase chromosome contributes to the breakpoint distribution in radiation-induced intra-chromosomal exchanges

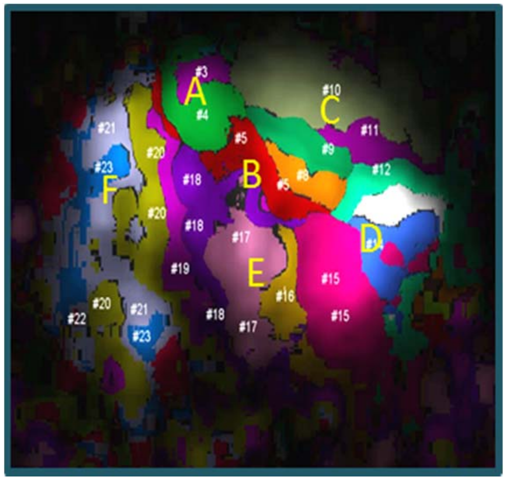
Zhang *et al*, *LSSR*, 2014



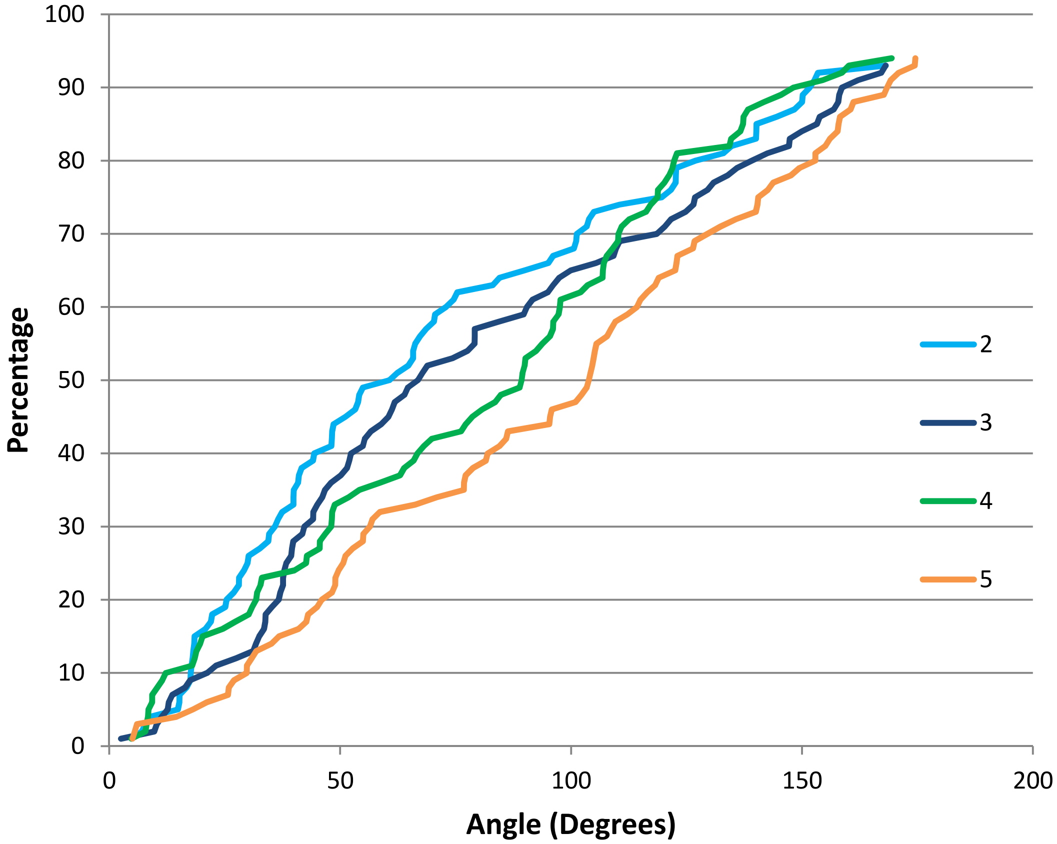
Distances between the center of each region and the center of the chromosome domain

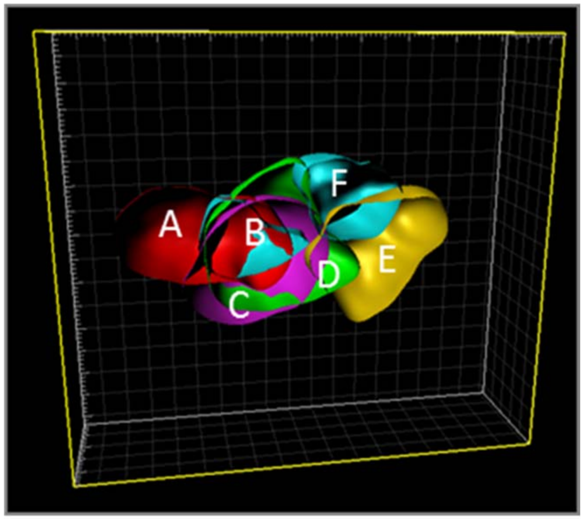




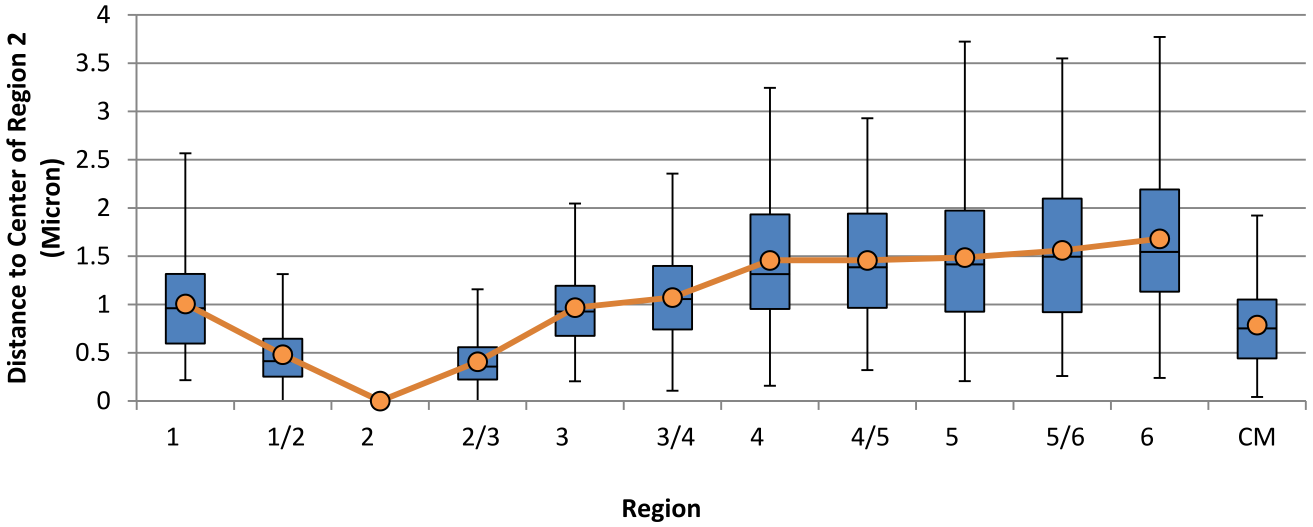


Integral distribution of the angles extended from the center of each colored region to the neighboring colored regions

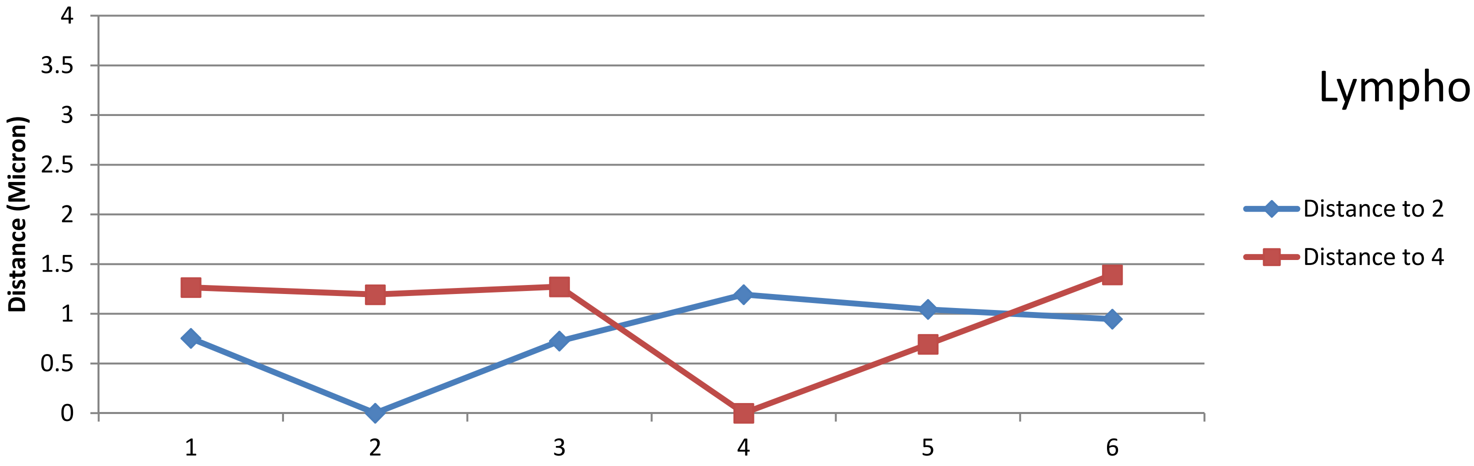




Distances between regions 2 or 4 and other regions



Epithelial cells

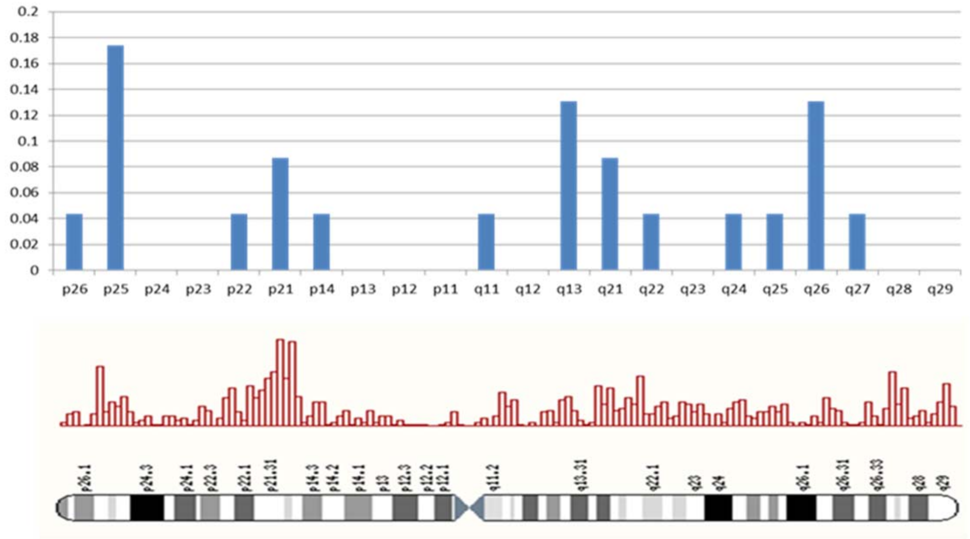


Lymphocytes

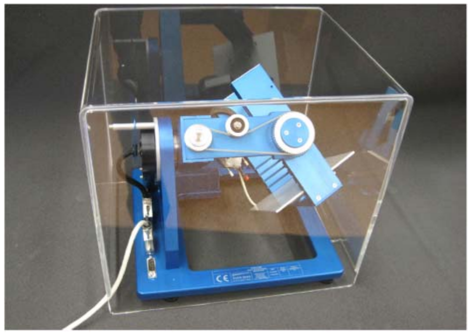
In Simulated Microgravity:

- Transcriptional changes

Distribution of genes with significantly altered expression on chromosome 3 in lymphoblastoid cells

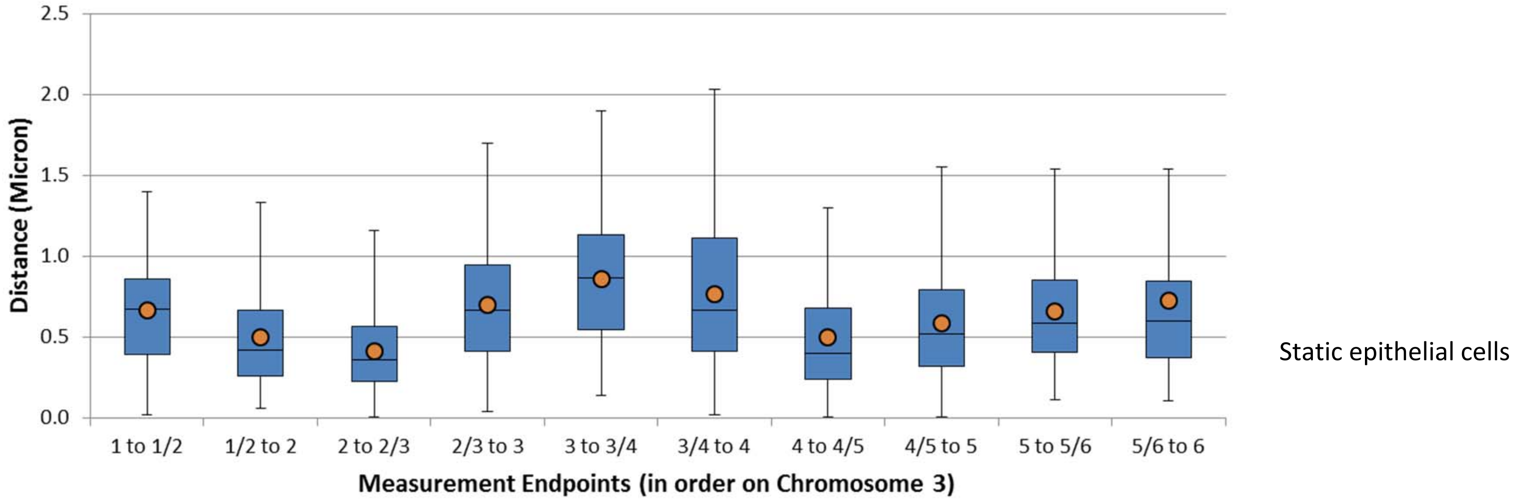


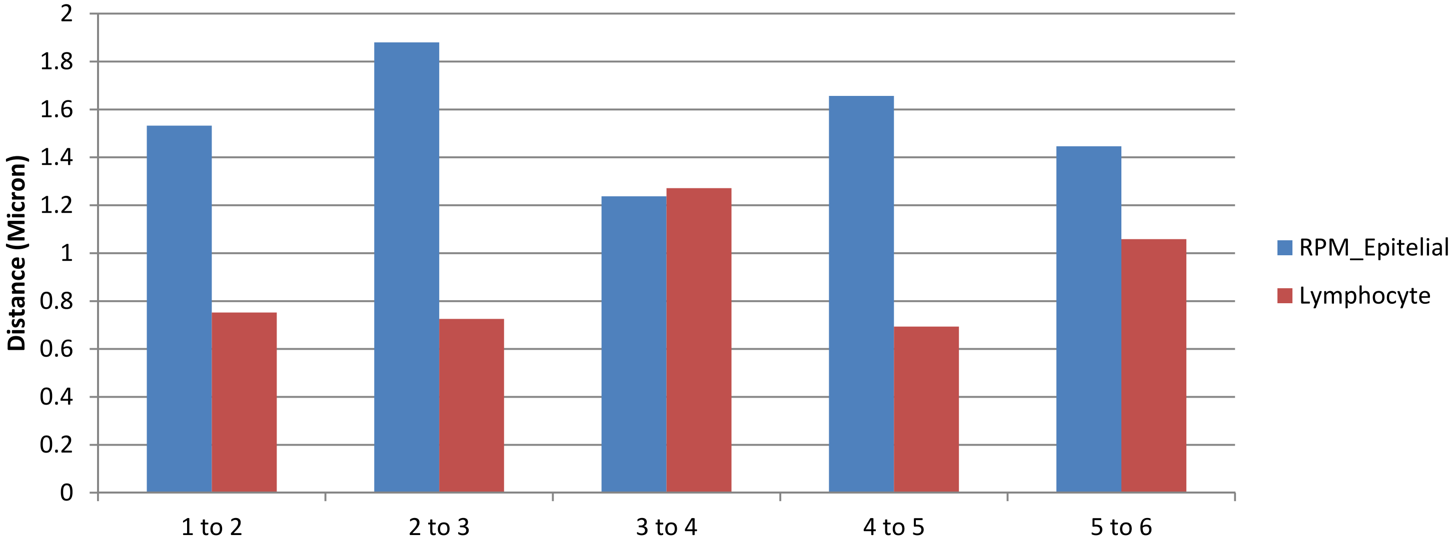
Mangala *et al*, 2011



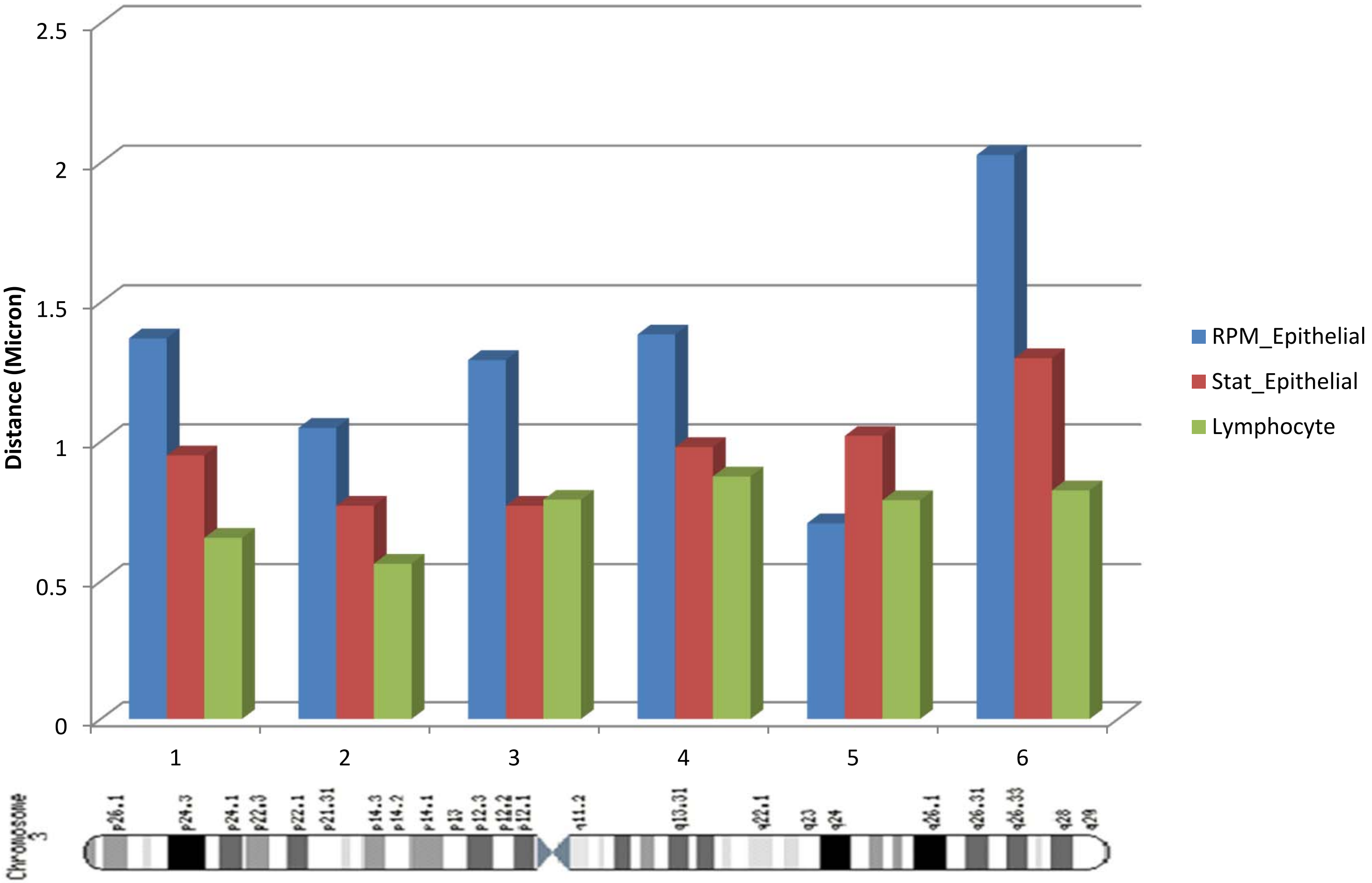
- Chromatin folding
- Adaptation

Distance between the neighboring regions

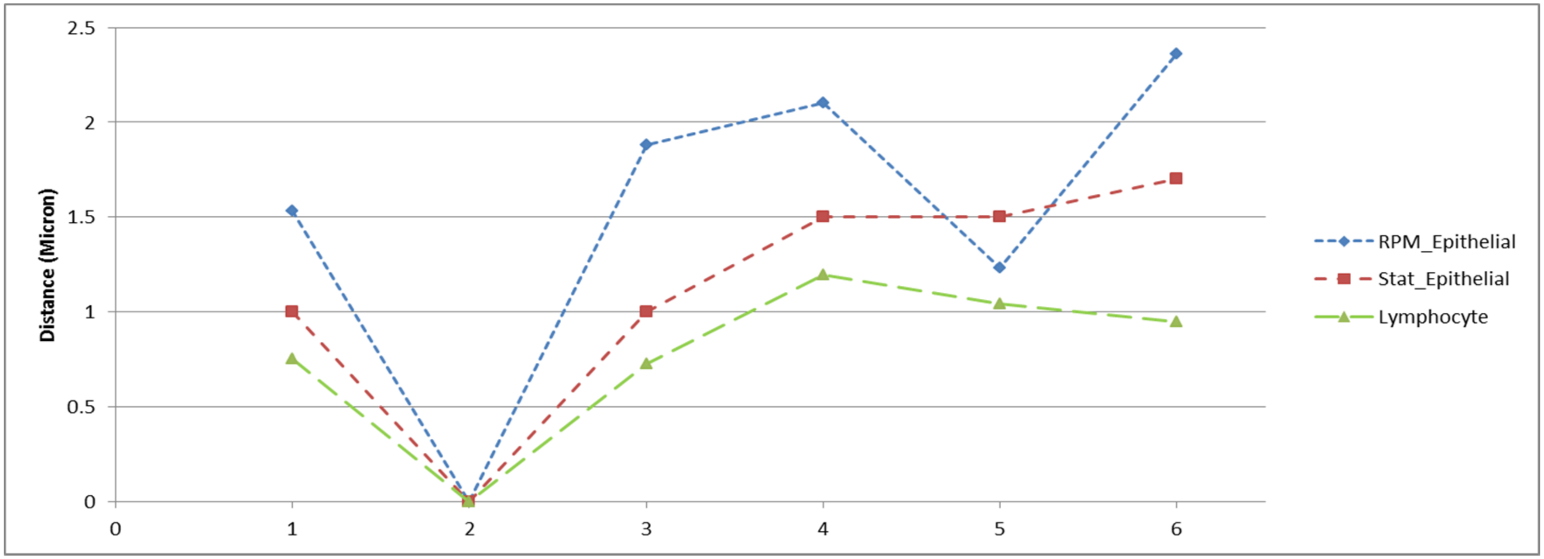




Distances between the center of each region and the center of the chromosome domain



Distances between Region 2 and other regions



Questions to be investigated:

- Changes of distribution of radiation induced chromosome aberration in simulated microgravity culture condition
- Gene-gene interaction and transcriptional regulation
- Other chromosomes
- Normal vs Cancerous cells

In Space: *unknown*

Conclusion

- On a multi-mega base pair scale of the DNA, the arrangement of chromatin is non-random.

- In M10 epithelial cells, both telomere regions tend to be located towards the exterior of the chromosome domain, whereas the rest p-arm of the chromatin region towards the interior. In contrast, most of the q-arm of the chromatin is found in the peripheral of the domain.

- In lymphocytes, the p-arm chromatin regions towards the interior in close proximity with each other, whereas two q-arm regions are nearness in space. It indicates that G0 lymphocytes may lack secondary 3D chromatin folding.

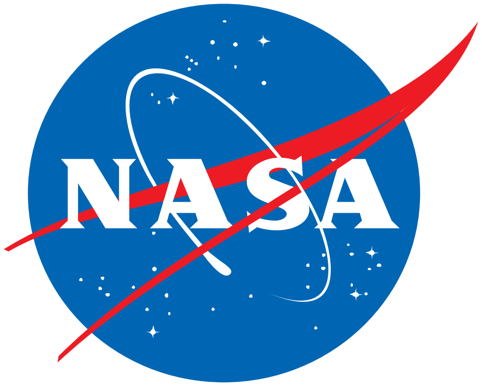
- There chromatin folding patterns are consistent with our previous finding of non-random distribution of intra-chromosomal exchanges.

- In simulated microgravity conditions, the chromosome conformation may be altered and new regions in close proximity, especially to region 2 are suggested.

Acknowledgement

- Space Biology Program
- Space Radiation Program

- NASA-Johnson Space Center
    - **Biomedical Research & Environmental Sciences Division**
    - Bioanalytical Core Laboratory
    - Radiation Biophysics Laboratory
- Brookhaven National Lab
- UT Southwestern Medical Center


NASA