Distribution of chromosome breakpoints in human epithelial cells exposed to low- and high-LET radiation

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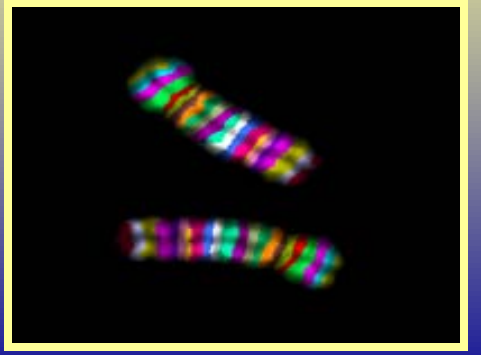
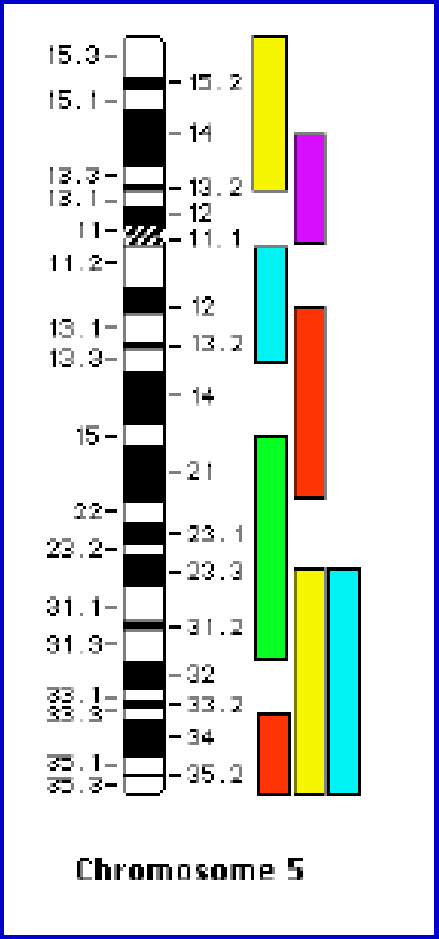
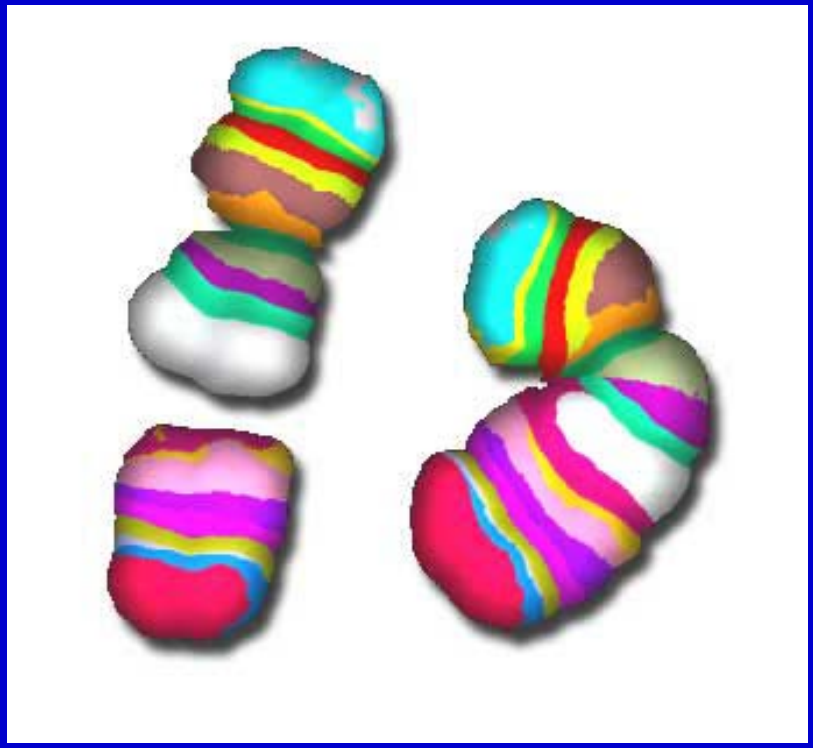


mBAND Analysis

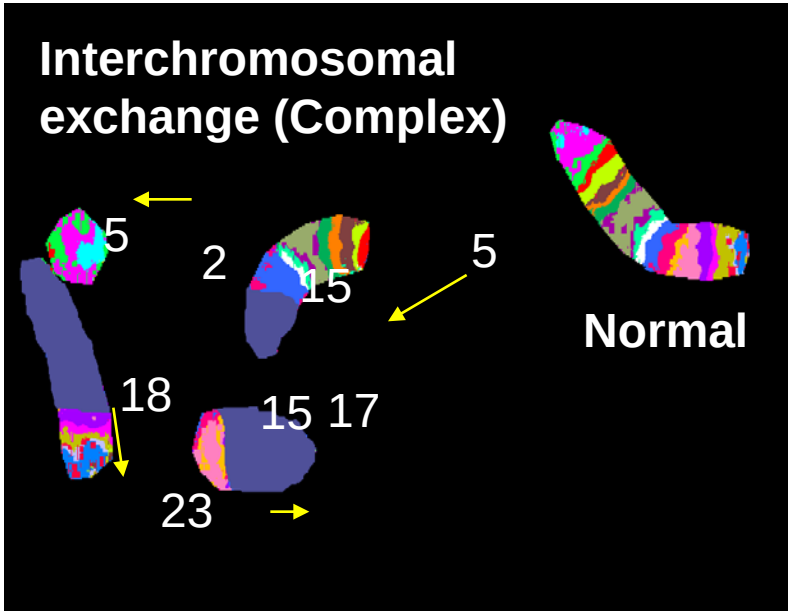


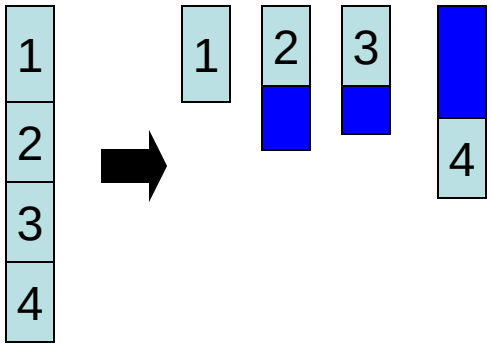
XCyte 5-labeling scheme

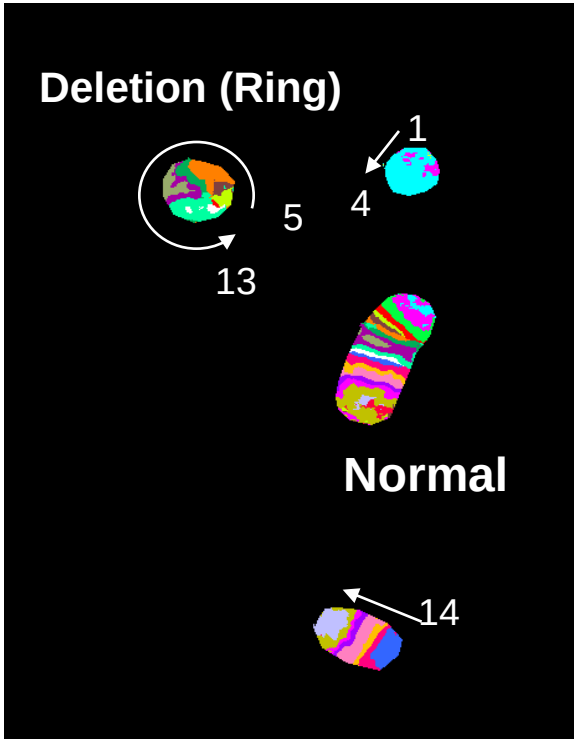


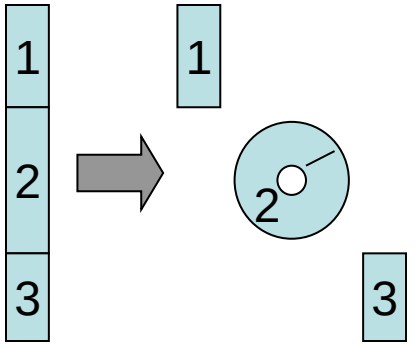
- DEAC (Ex 426 nm / Em 480 nm)
- FITC (Ex 502 nm / Em 530 nm)
- Spectrum Orange (Ex 559 nm / Em 588 nm)
- Texas Red (Ex 595 nm / Em 615 nm)
- Cy5 (Ex 649 nm / Em 670 nm)

Example of chromosome 3 painted with mBAND









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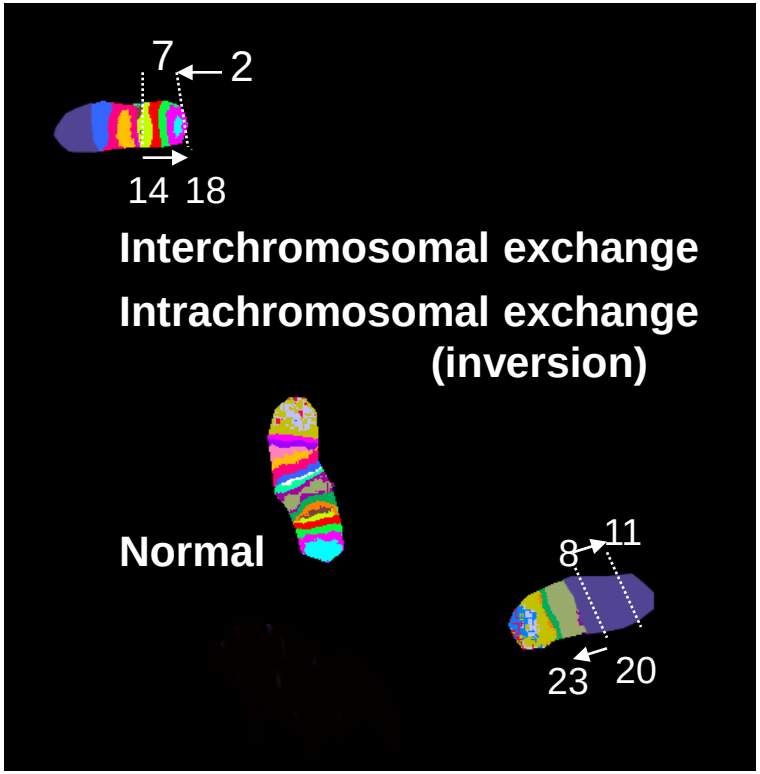
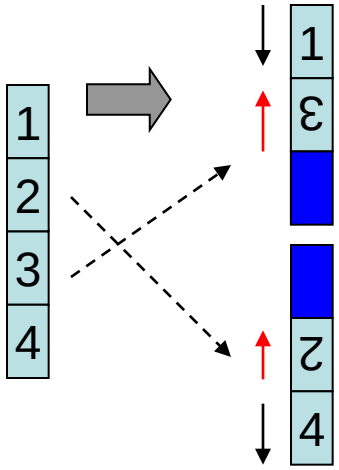
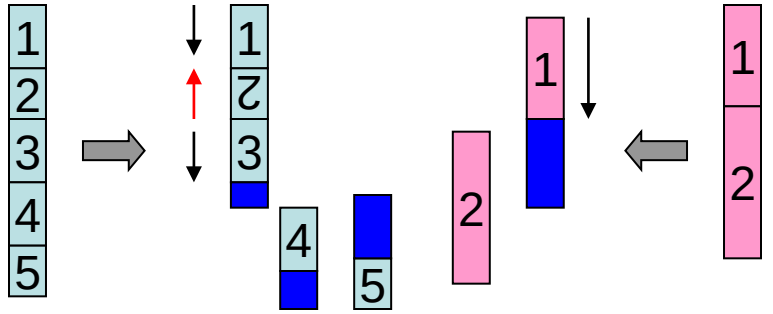
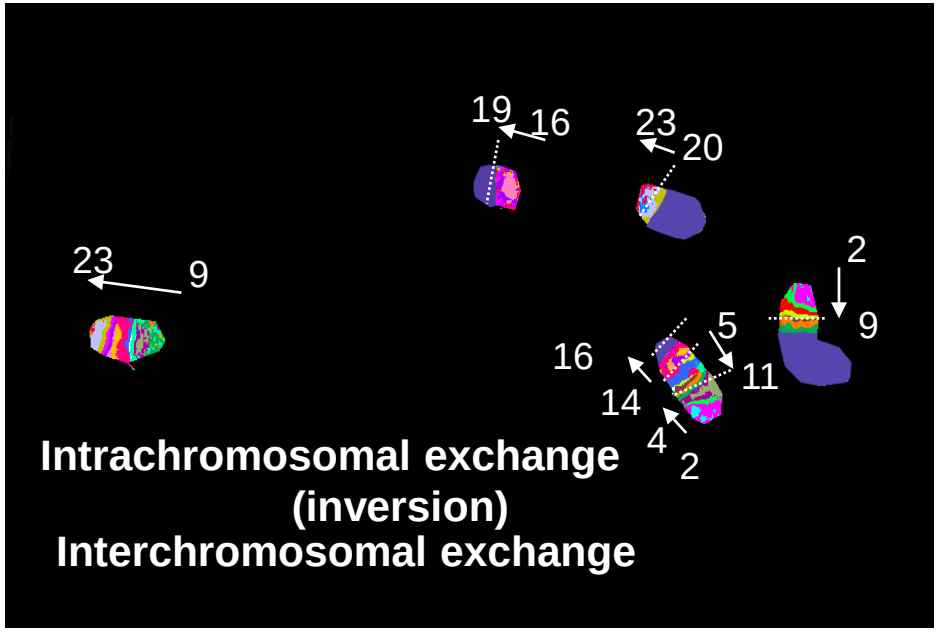




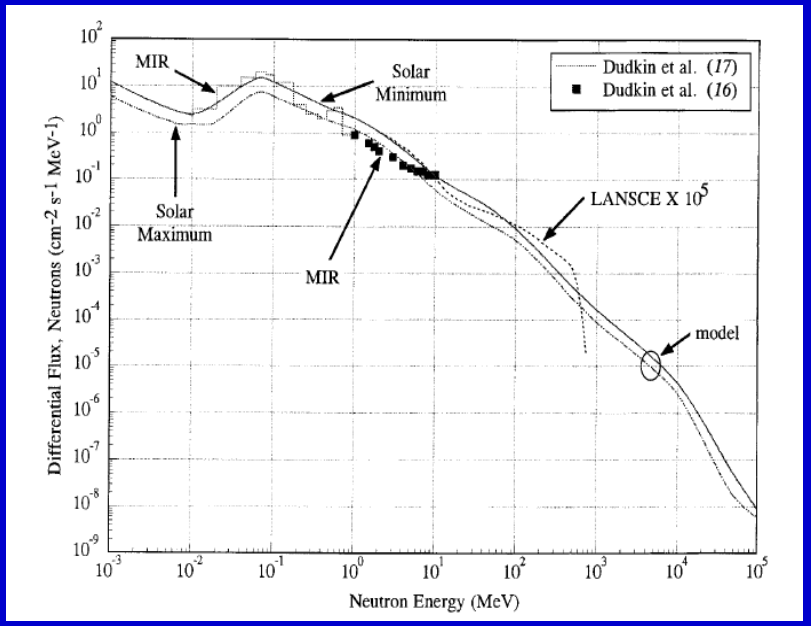




Irradiation

High Dose Rate		
^{137}Cs γ-ray	2.0 Gy/min	University of Texas, MD Anderson Cancer Center
Fe ions	0.5 Gy/min	NASA Space Radiation Laboratory / BNL
Low Dose Rate		
^{137}Cs γ-ray	1.7 cGy/h	NASA/JSC
Neutron	2.5 cGy/h	Los Alamos Nuclear Science Center (LANSCE) 30L

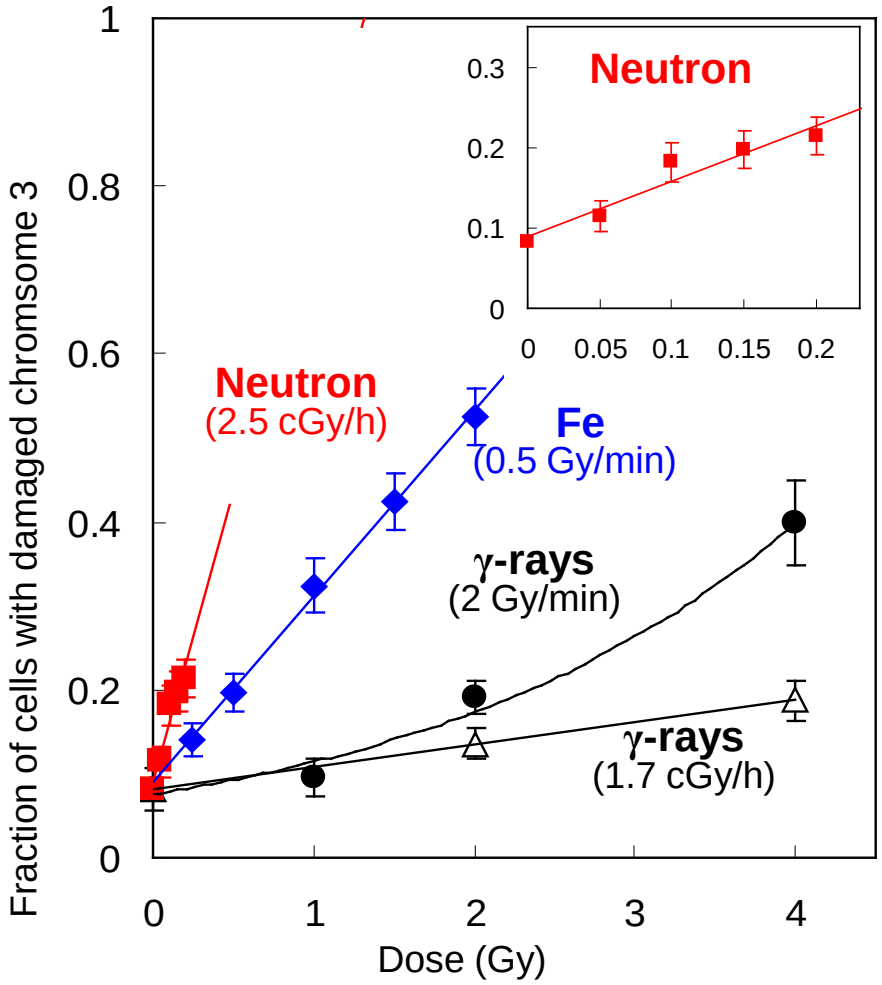
Neutron energy spectrum on the ISS, measured spectra on Mir and the normalized LANSCE energy spectra.



The LANCE neutron energy spectrum is similar over a wide energy range to expected spectrum inside the International Space Station (ISS).

Badhwar G.D. et al. (2000)

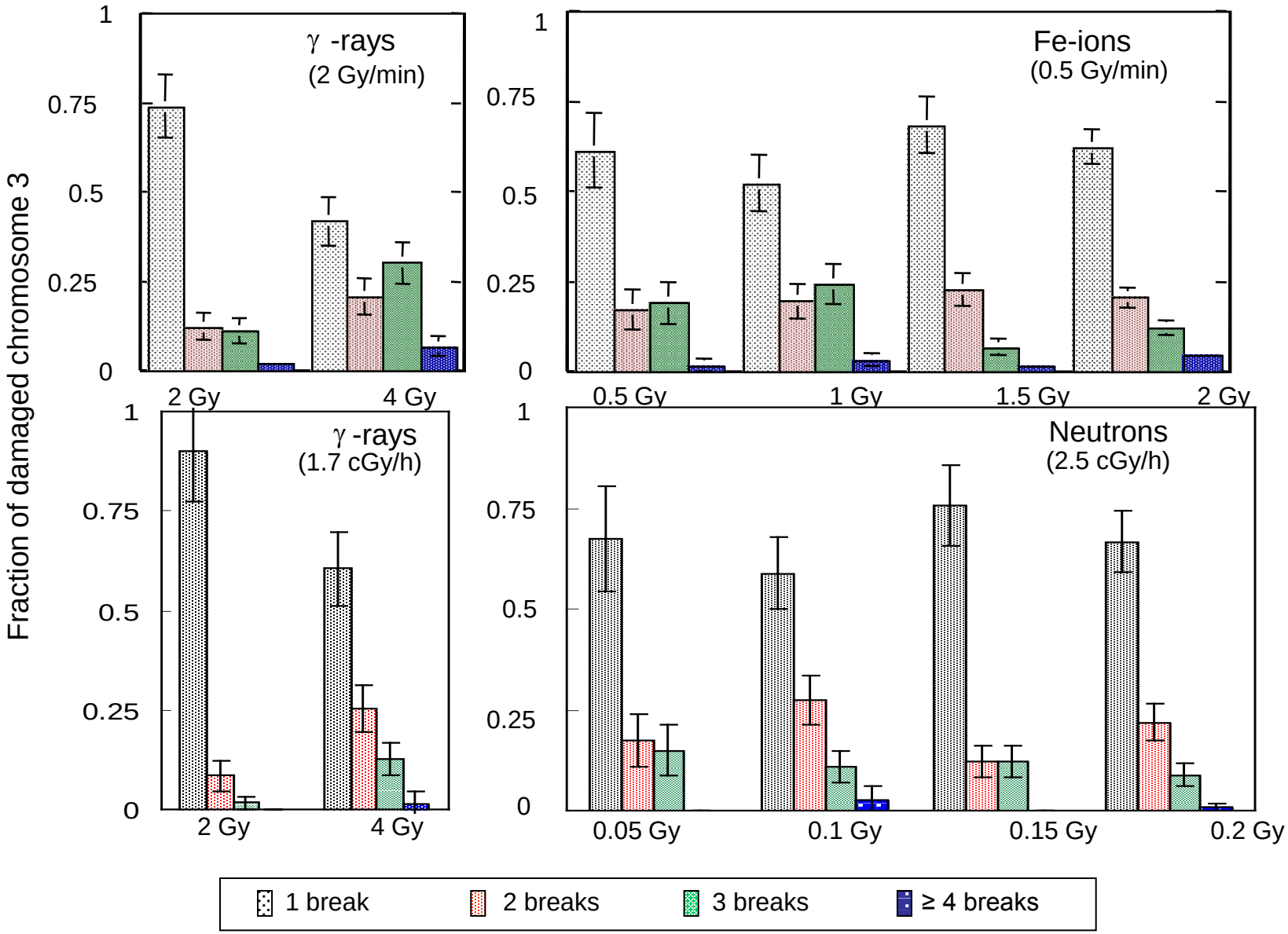
Induction of chromosome 3 aberration in human cells by neutrons, Fe-ions or γ-rays



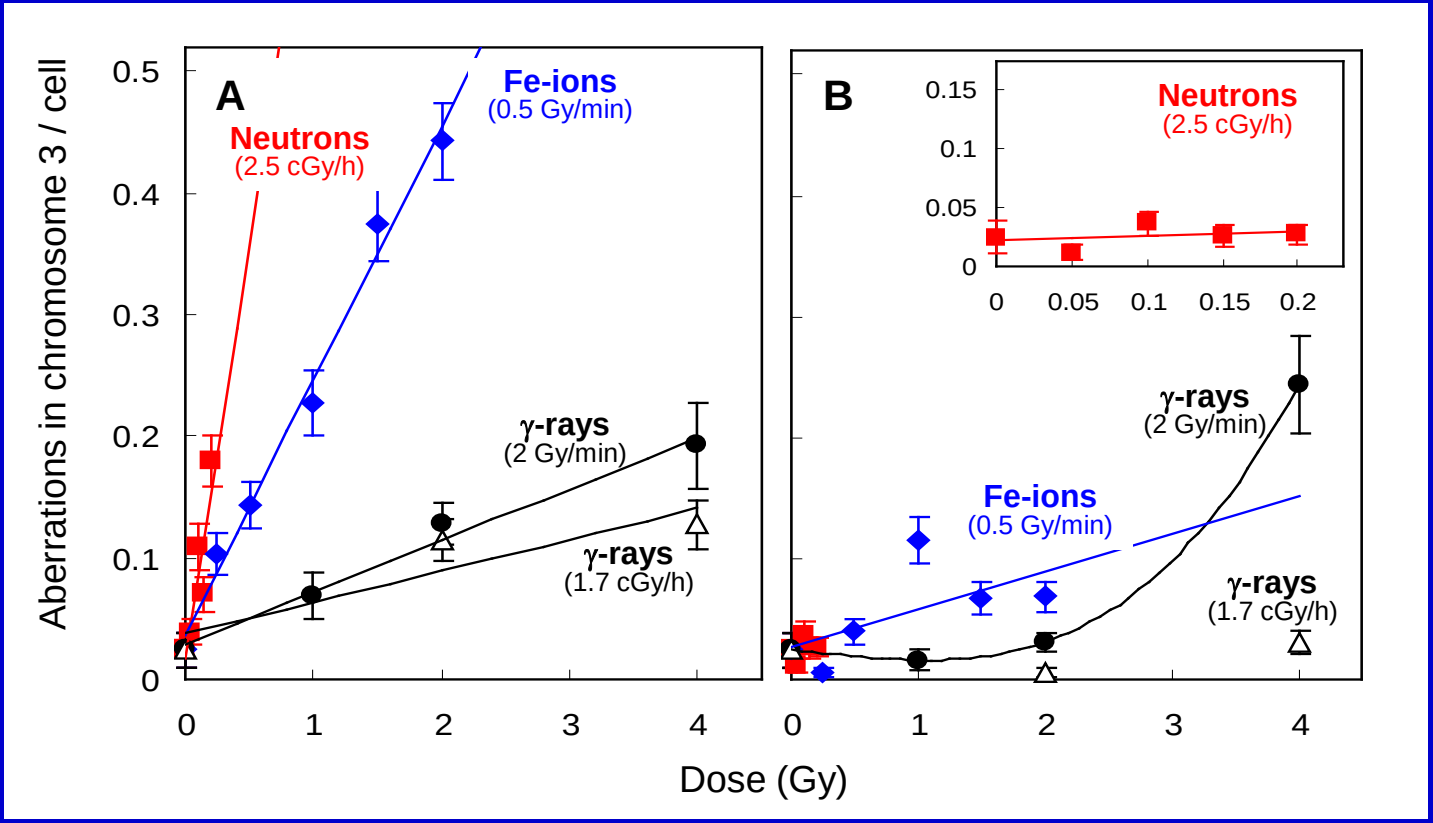
Relative Biological Effectiveness (RBE) **Fe: 8.4**

Neutron: 26.4

Frequency distributions of breaks/chromosome 3

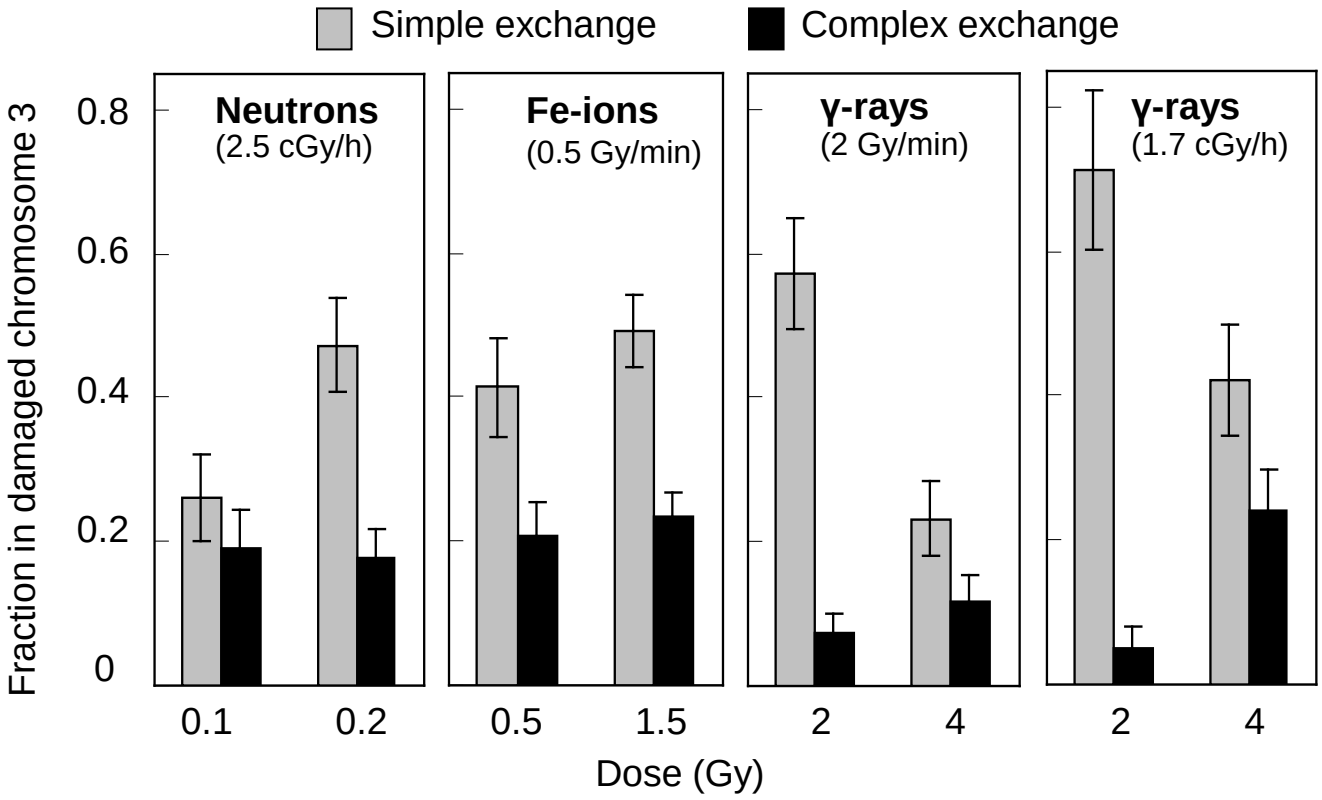


Induction of interchromosome exchanges (A) and intra-chromosome exchanges (B) in human chromosome 3 by neutrons, Fe-ions or γ-rays.

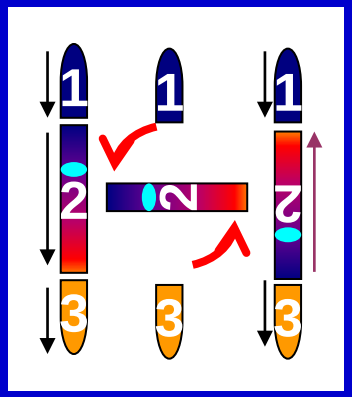


The dose responses for interchromosomal exchanges were linear in all four exposures. However, the dose response for intrachromosomal exchanges were none linear. Increasing dose of high dose rate exposure (Fe-ions or γ-rays) increase the fraction of cells with intrachromosome aberrations, whereas increasing dose of low dose rate exposure (neutrons or γ-rays) does not affect the fraction of cells with intrachromosome aberrations.

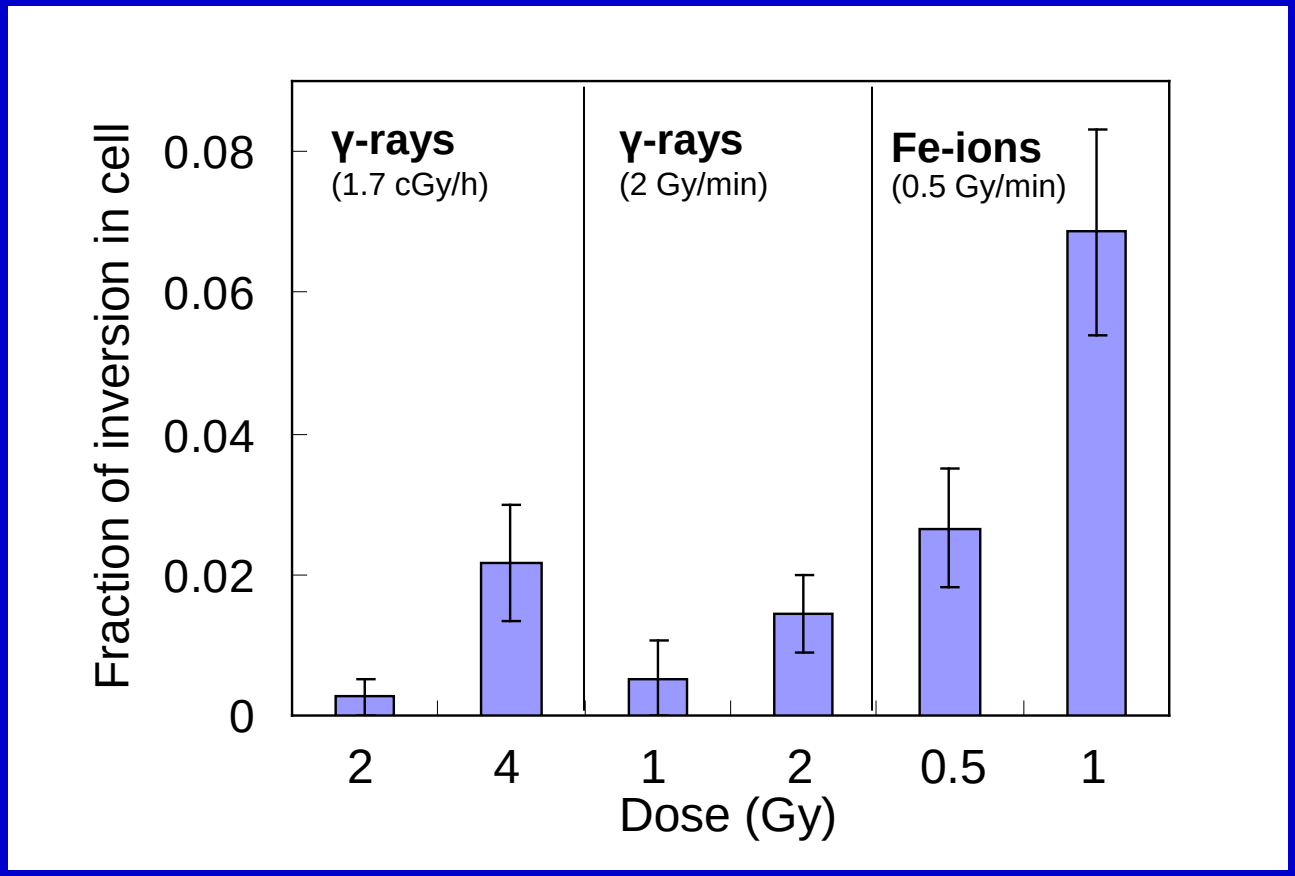
Interchromosome exchanges broken down as simple and complex types



Complex exchange: Chromosome interexchanges involving at least 3 breaks in two or more chromosomes

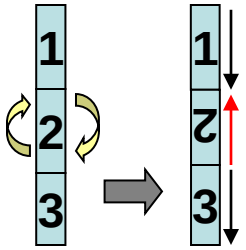


Induction of inversion

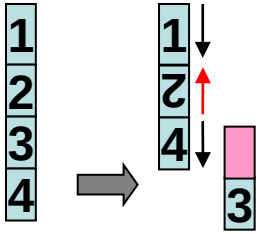


Classification of inversion involved aberrations in chromosome 3

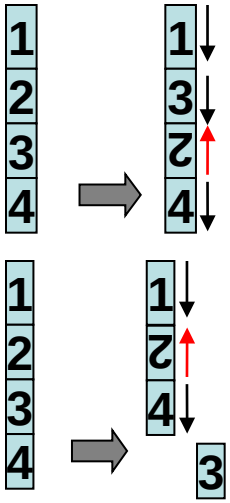
Inversion (simple)



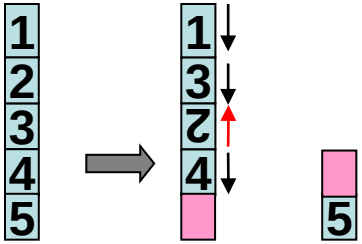
Inter-exchange involved Inversion

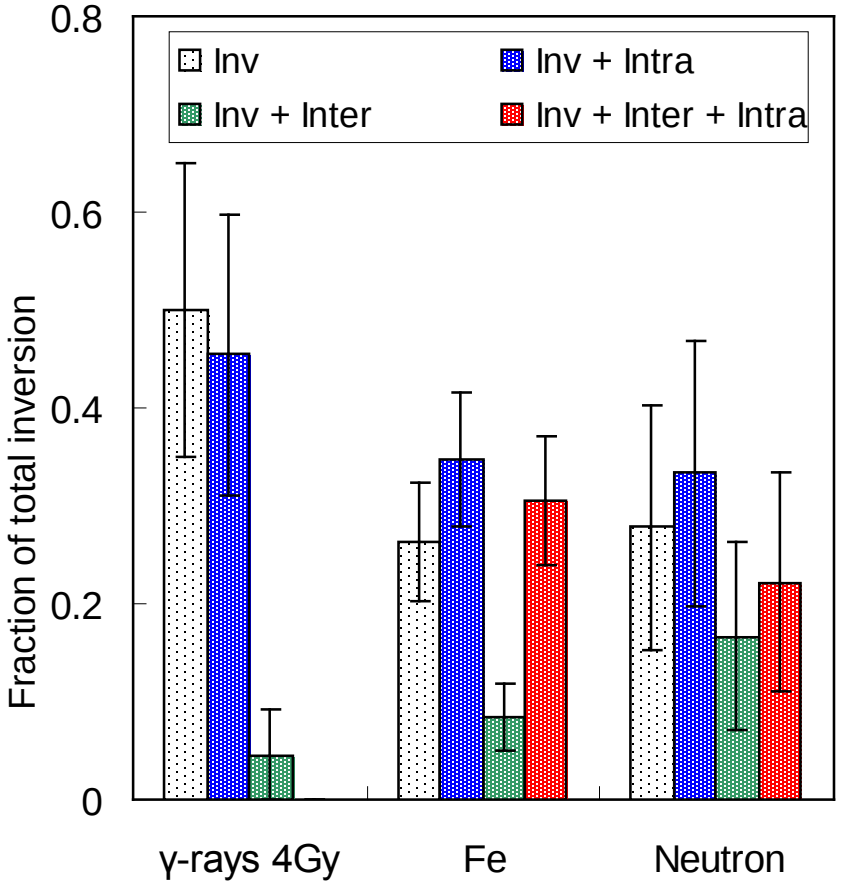


Intra-exchange involved Inversion



Inter-exchange and Intra exchange involved Inversion

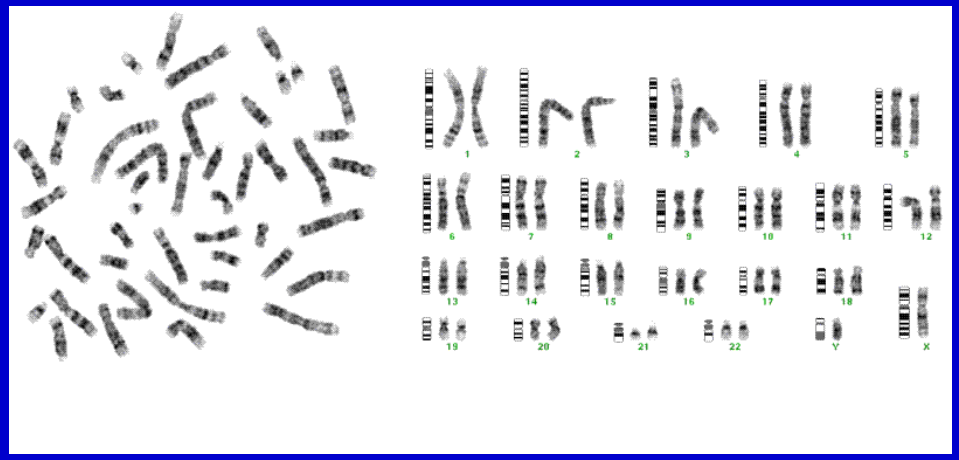


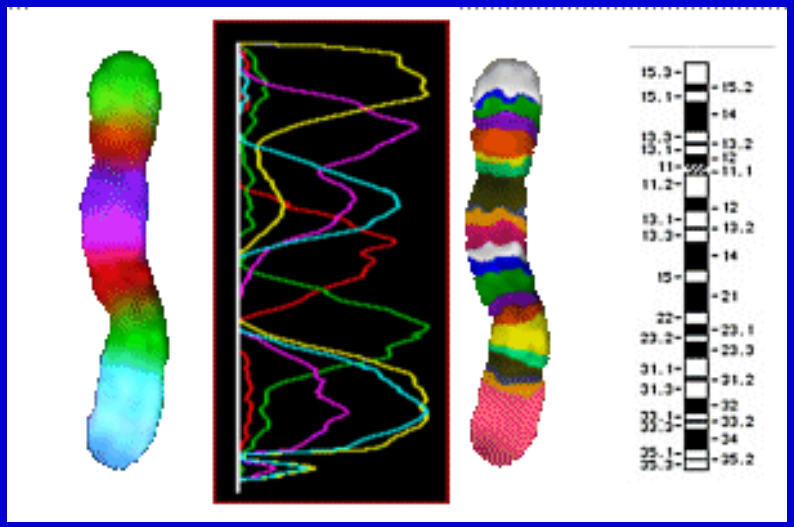


Distribution of breakpoints on chromosome 3

Table 6.2 Nonrandom Chromosome Abnormalities in Malignant Myeloid Diseases

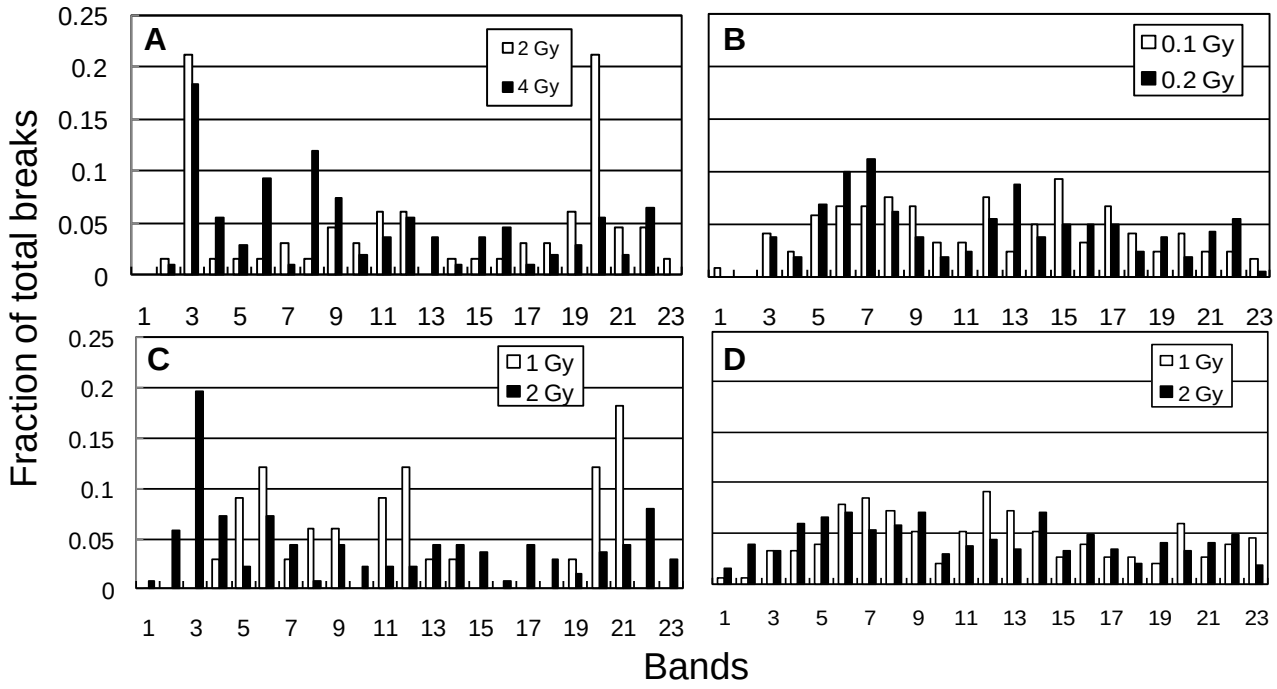
Disease*	Chromosome Abnormality	Involved Genes
CML	t(9;22)(q34;q11)	*BCR-ABL*
CML blast phase	t(9;22)(q34;q11) with +8, +Ph^1, +19, or i(17q)	*BCR-ABL*
CMMoL	t(5;12)(q33;p13)	*PDGFRB-TEL*
AML-M2	t(8;21)(q22;q22)	*ETO-AML1*
APL-M3, M3V	t(15;17)(q22;q11-12)	*PML-RARA*
Atypical APL	t(11;17)(q23;q12)	*PLZF-RARA*
AMMoL-M4Eo	inv(16)(p13q22) or t(16;16)(p13;q22	*MYH-CBFB*
AMMoL-M4 or M5	t(6;11)(q27;q23)	*AF6-MLL**
	t(9;11)(p22;q23)	*AF9-MLL*
AmegL-M7	t(1;22)(p13;q13)	
AML	t(3;3)(q21;q26) Or inv(3)(q21;q26)	*RPN1-EVI1*
	t(3;5)(q21;q31)	
	t(3;5)(q25;q34)	*MLF1-NPM1*
	t(6;9)(p23;q34)	*DEK-CAN (NUP214)*
	t(7;11)(p15;p15)	*HOXA9-NUP98*
	t(8;16)(p11;p13)	*MOZ-CBP*
	t(9;12)(q34; p13)	*TEL-ABL*†
	t(12;22)p13;q13)	*TEL-NM1*
	t(16;21)(p11;q22)	*TLS(FUS)-ERG*
	–7 or del(7q)	
	–5 or del(5q)	
	t(12p) or del(12p)	*TEL, p27^{KIP1}*
	del(20q)	
Therapy-related AML	–7 or del(7q) and/or	
	–5 or del(5q)	*IRF1*
	t(11q23)	*MLL*
	t(3;21)q26;q22)	EAP/MDS1/EVI1-AML1

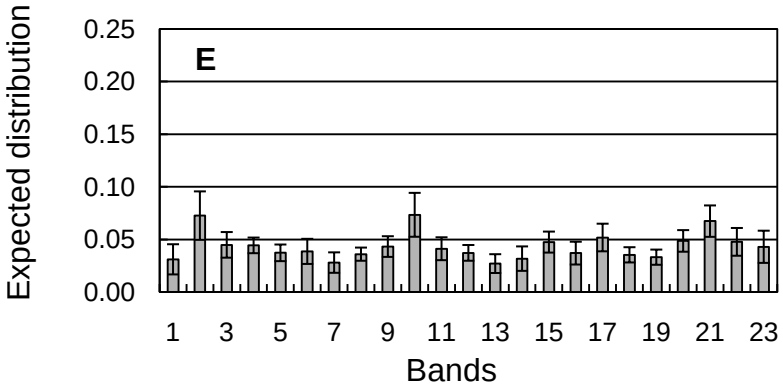




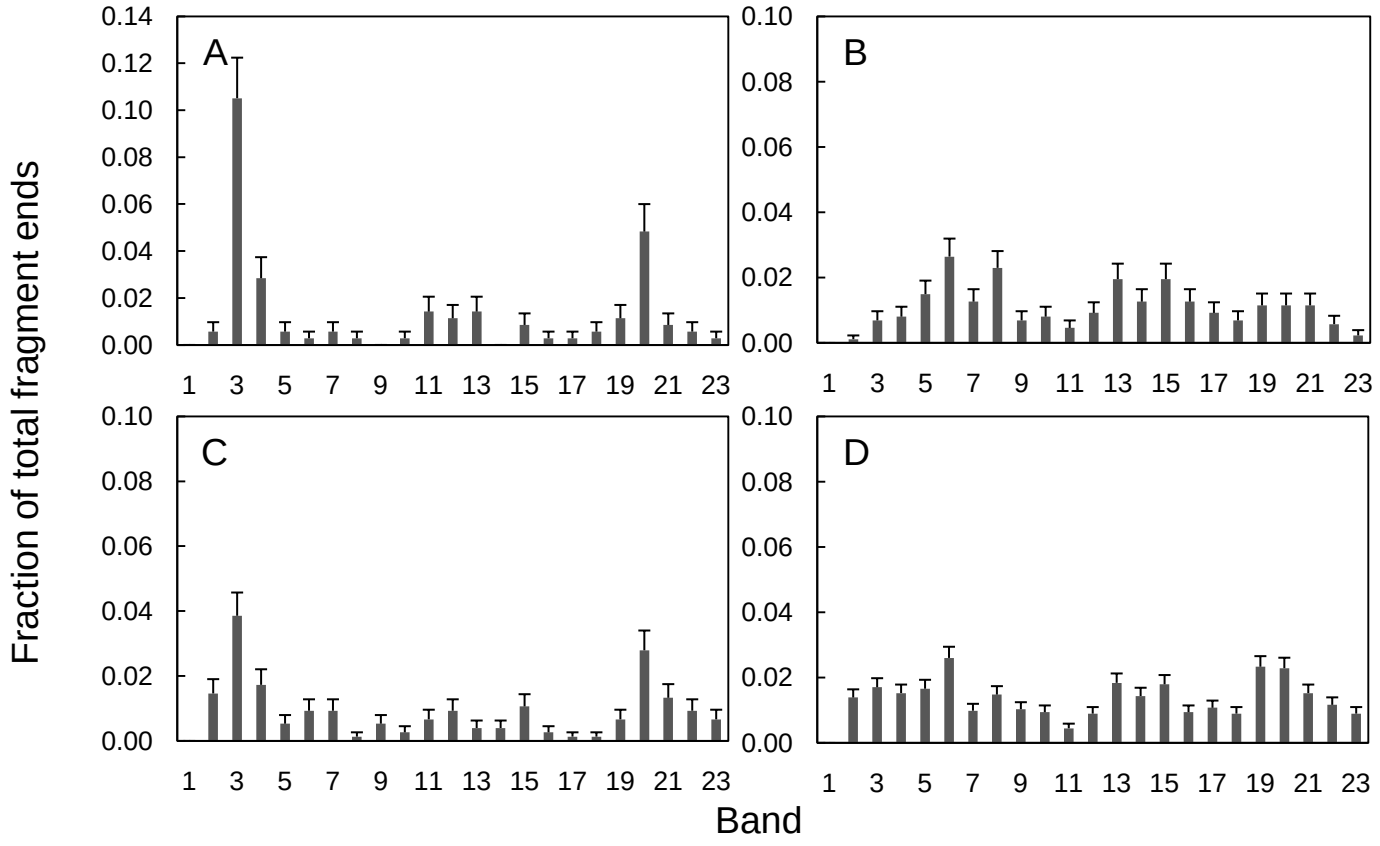
Chromosome rearrangements in human cancer (Olopade et al.)

Distribution of total breaks

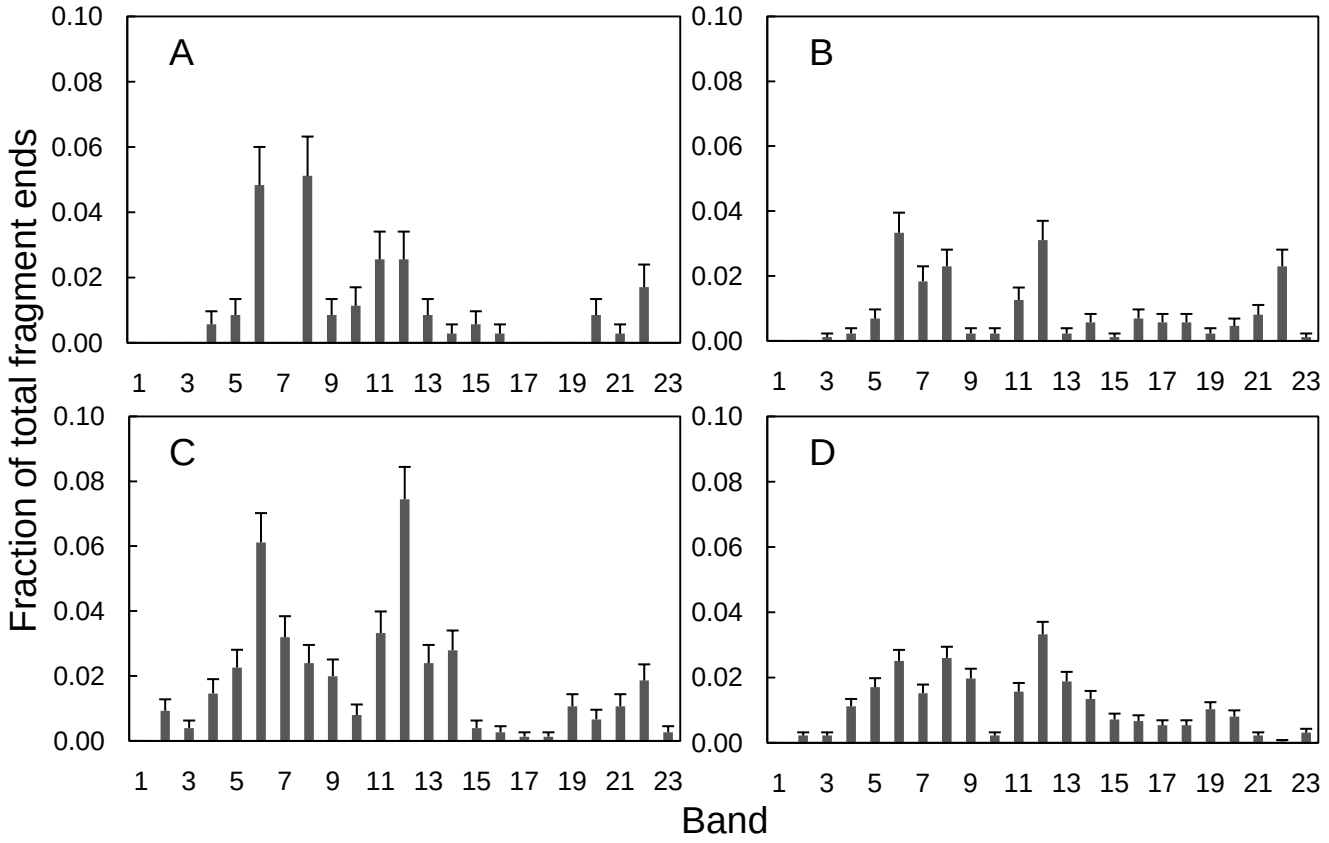




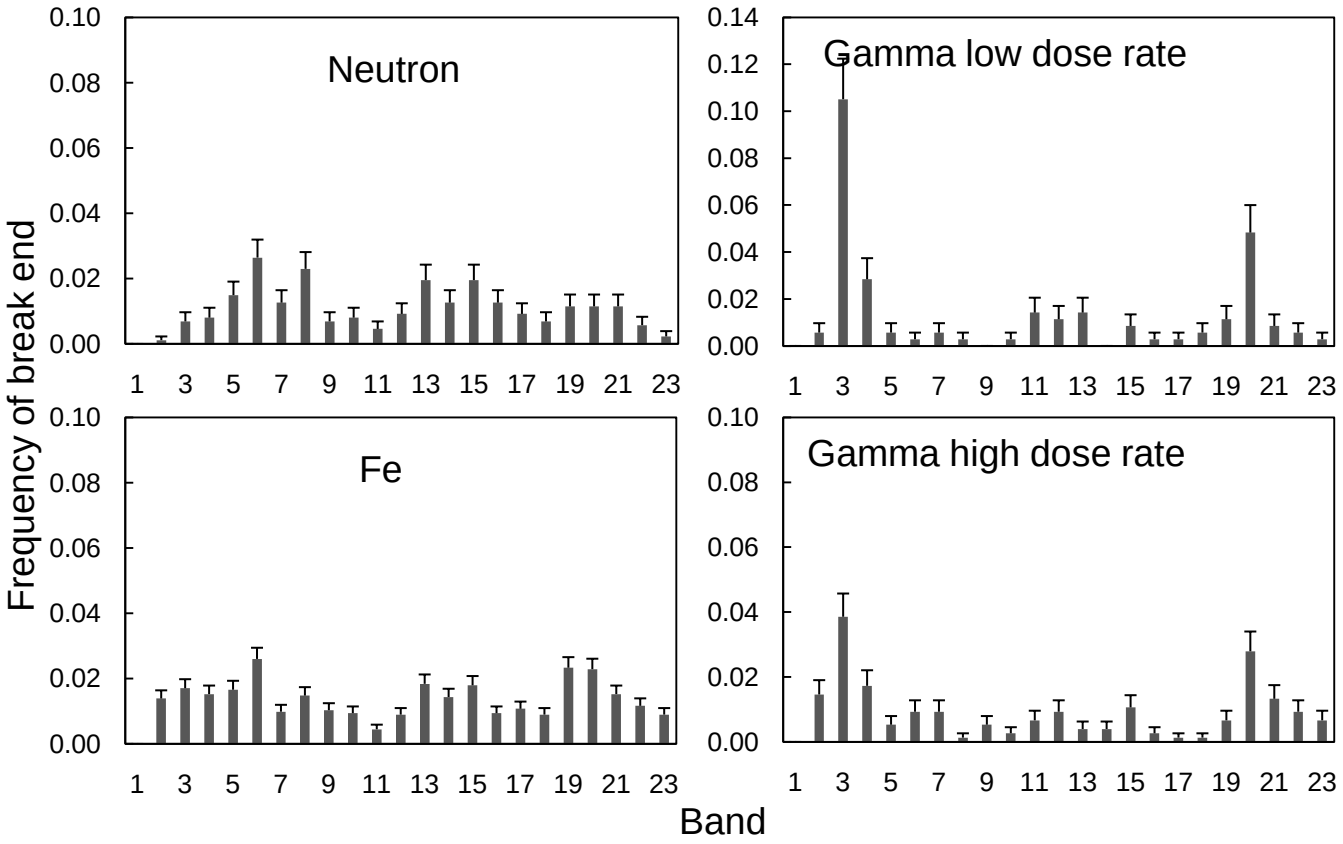
Fragment ends participating in interchromosomal exchanges



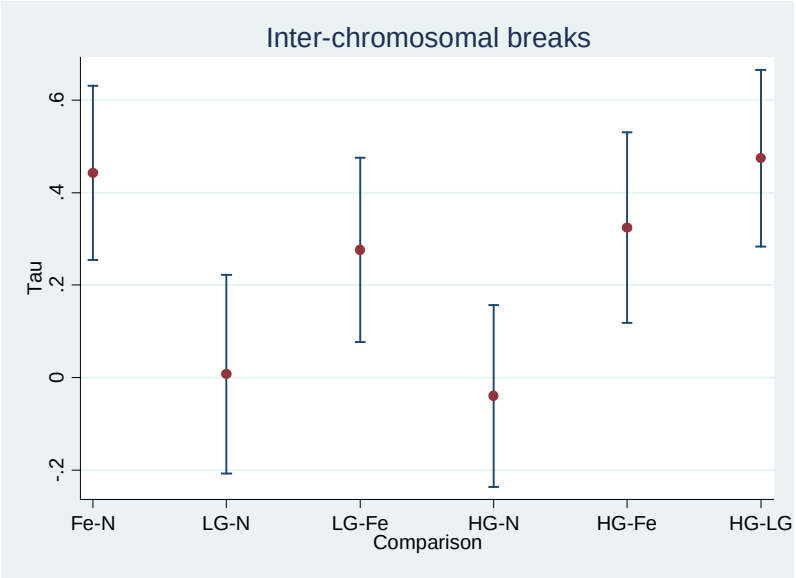
Fragment ends participating in intrachromosomal exchanges

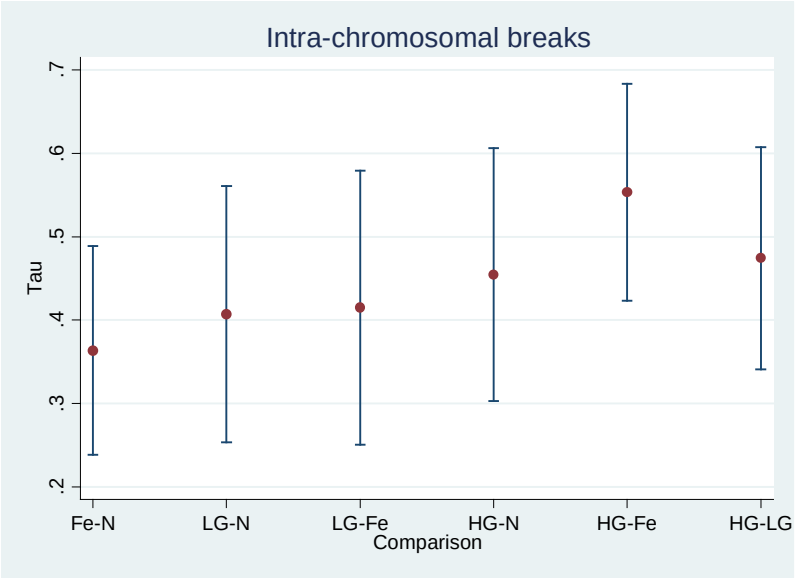


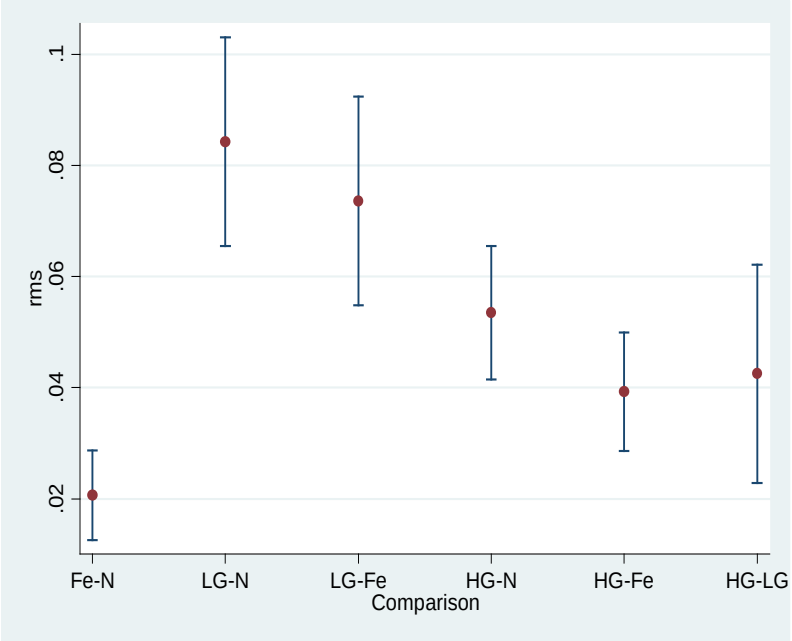
Interchromosome exchanges



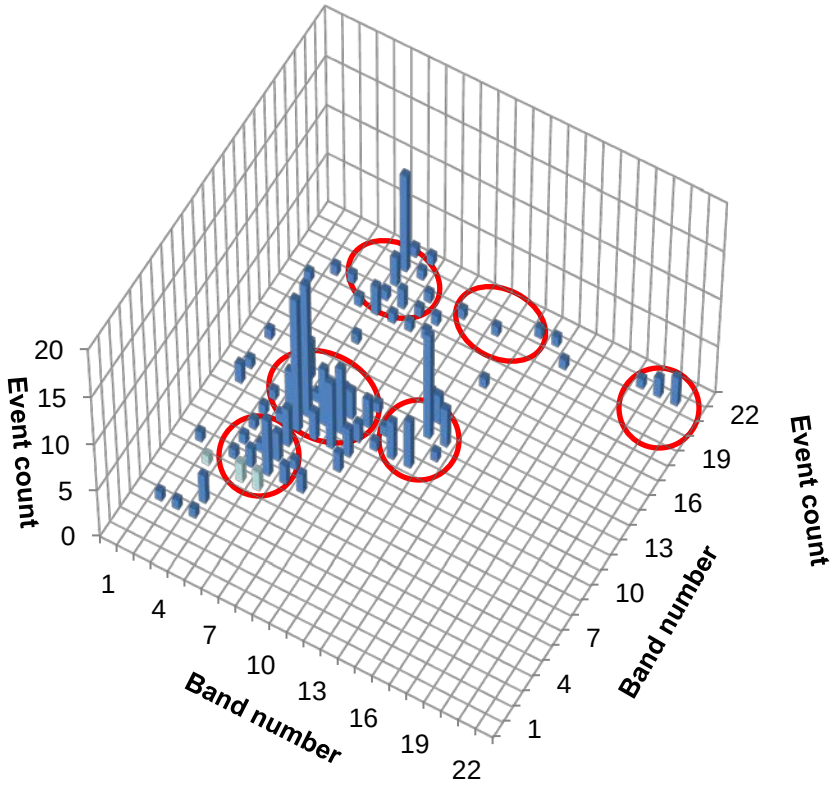
Statistical analysis



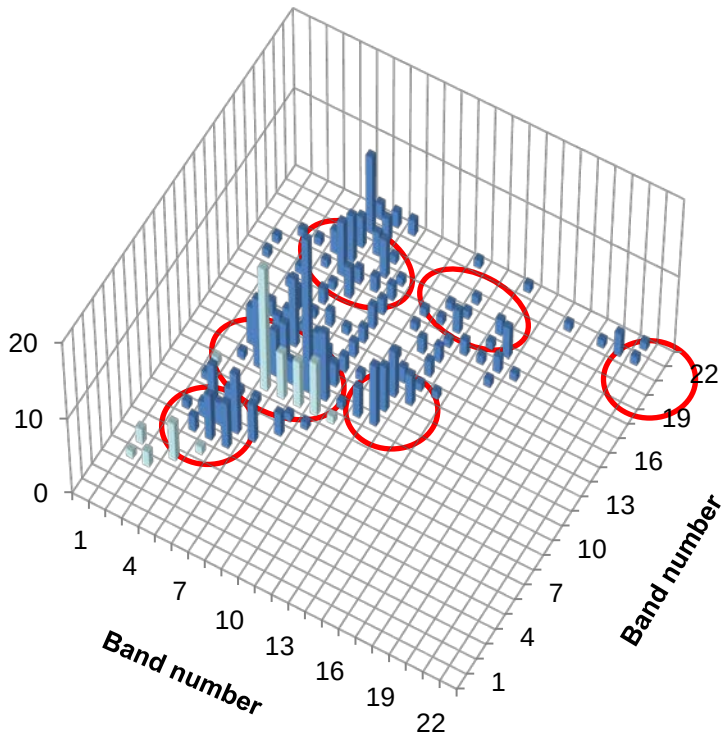




intrachromosomal exchange events between two fragment ends



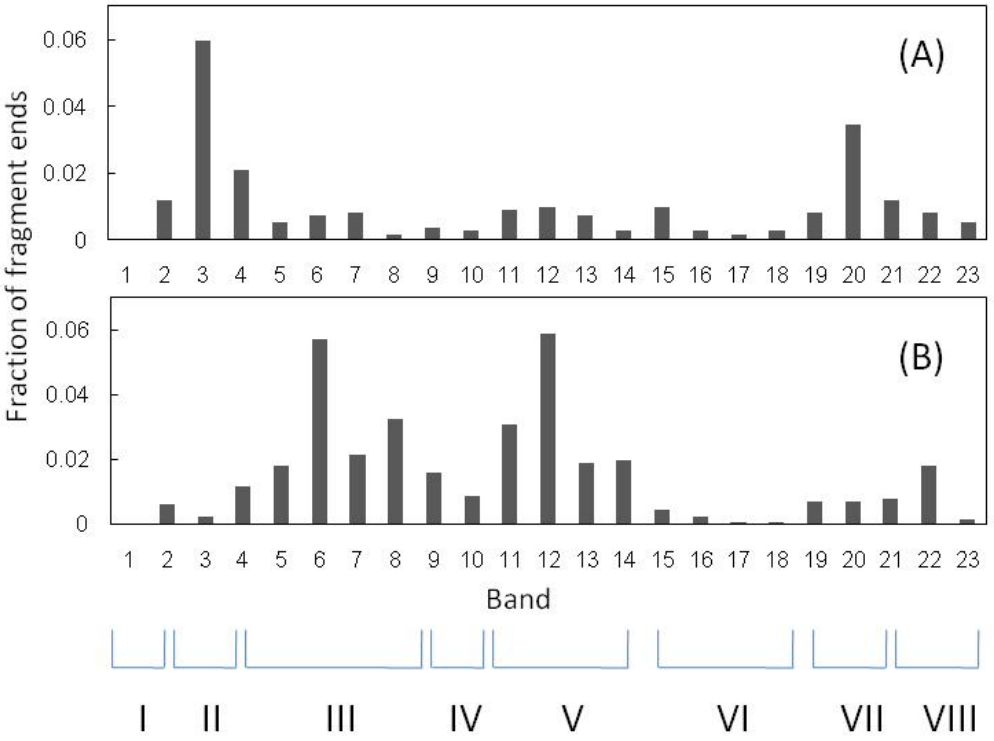
Low-LET



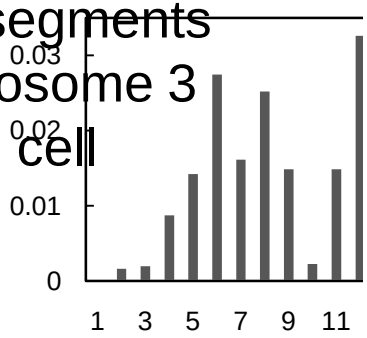
High-LET

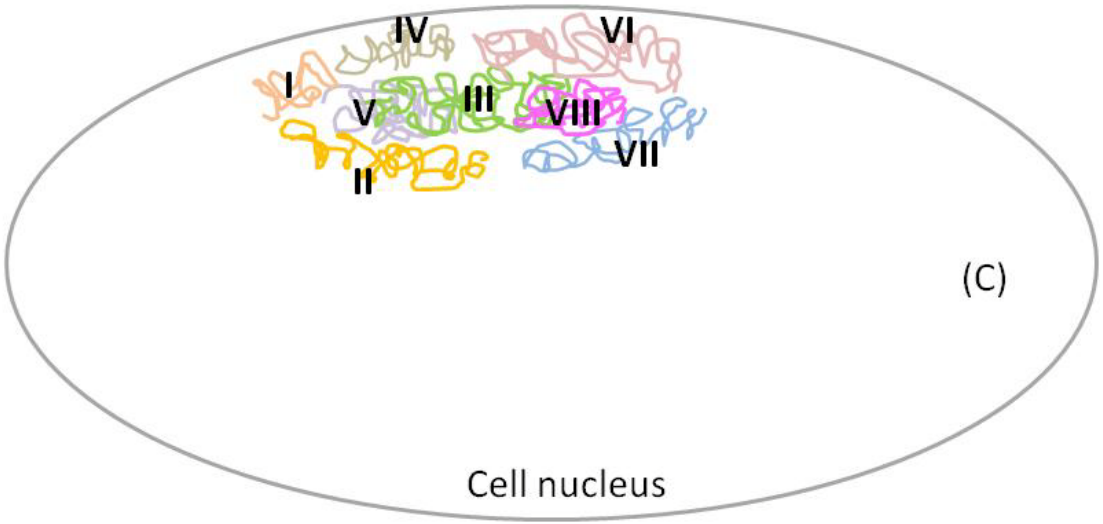
Interchromosome exchange

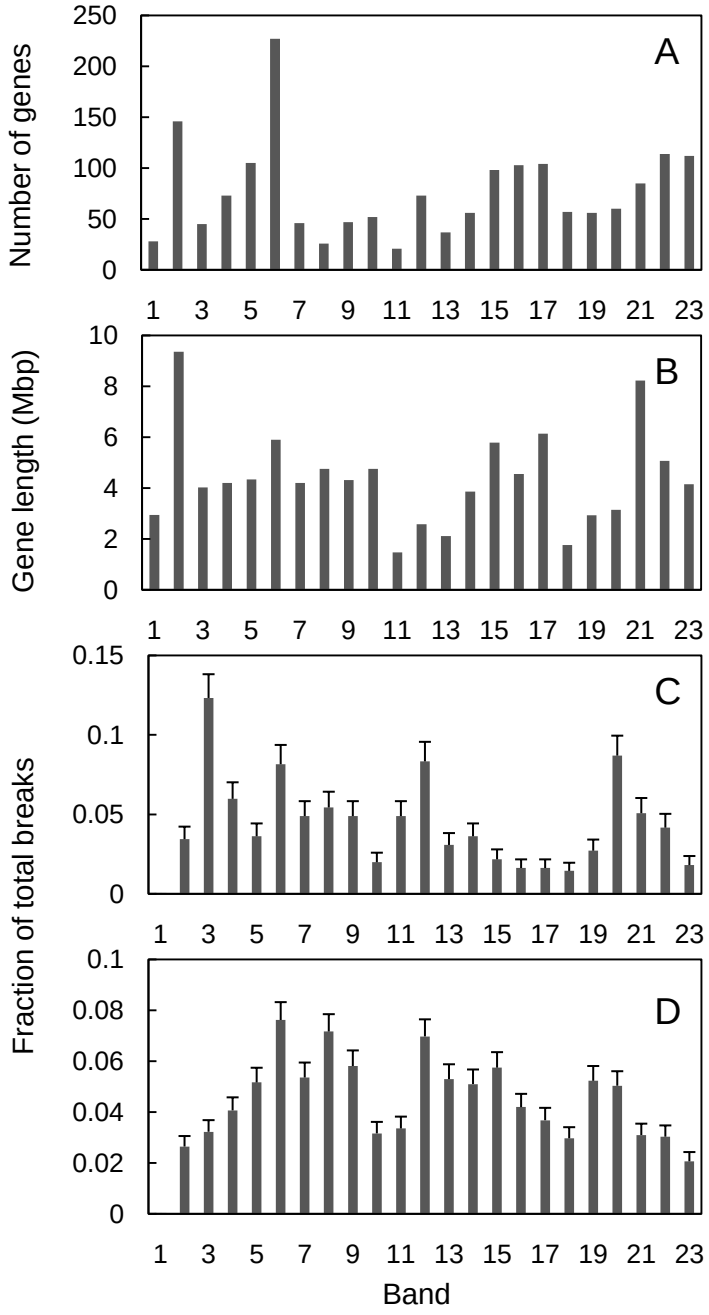
Intrachromosome exchange



2-D representation of the locations of different segments of Chromosome 3 inside the cell nucleus







Comparison between the distributions of the genes and of the breakpoints

Conclusions

- Low- and high-LET radiations produced distinct breakpoint distributions.

- The difference of the breakpoint distributions between low- and high-LET only appeared in break ends involved in interchromosome exchanges.

- The breakpoint distributions for break ends participating in intrachromosome exchanges were similar.

- Gene-rich regions do not necessarily have more chromosome breaks.

- High-LET appeared to produce long live (data not shown) or longer live breaks that can migrate a longer distance before rejoining with other breaks.

- Domains occupied by different segments of the chromosomes may be responsible for the breakpoint distribution.

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