CALCULATION OF DELETION, INVERSION, AND RING SPECTRA USING A COMPUTATIONAL MODEL OF THE RADIATION-INDUCED CHROMOSOME ABERRATIONS WITH STOCHASTIC AND AMORPHOUS PARTICLE TRACKS

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PROJECT OVERVIEW

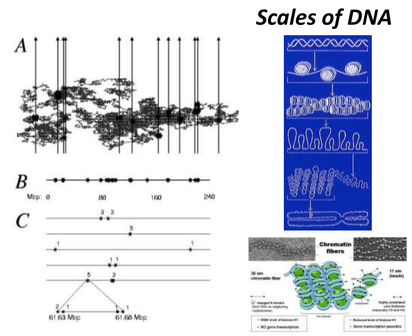
At the NASA Johnson Space Center, we produced new results with a computational chromosome and radiation-induced DNA damage model, named BDSTRACKS (Biological Damage by Stochastic Tracks), which simulates general types of chromosome aberrations (CA) from low- and high-LET (linear energy transfer) radiations, using two different physical models of particle tracks: stochastic and amorphous. The chromosomes were simulated by a polymer random walk (RW) algorithm. The stochastic dose to the nucleus was calculated with the code RITRACKS [1]. The new simulation results were compared with results calculated with amorphous tracks, a common model for ionizing radiation transport in matter [2]. The number and spatial location of DSBs (DNA double-strand breaks) were calculated using the simulated chromosomes and local (voxel) dose. Assuming that DSBs led to chromosome breaks and simulating the rejoining of damaged chromosomes occurring during repair, BDSTRACKS predicted the yield of various types of chromosome aberrations. We reported some of these data in previous work and, herein, we focus on deletions, inversions, and rings, which are relevant biological endpoints for the prediction of risk from space radiation in astronauts. Specifically, we simulated, previously hard to model, ring-size distributions. We calculated these new data for a number of ions: $^{1}H^{+}$, $^{4}He^{2+}$, $^{12}C^{6+}$, $^{28}Si^{14+}$, and $^{56}Fe^{26+}$, with energies varying from 7.7 to 1,000 MeV/u. We also present calculated RBE's (relative biological effectiveness) for deletions, inversions and rings, which predict a realistic peak for LET values around 100 keV/μm. We suggest using this model for situations that are hard to obtain experimentally and are looking forward to comparing this model of the experimental data, when they become available.

[1] Plante I. et al (2013) *Phys. Med. Biol.* 58, 6393-6405. [2] Ponomarev A.L. et al (2014) *Rad Res* 181, 284-292.

COMPUTATIONAL MODELING

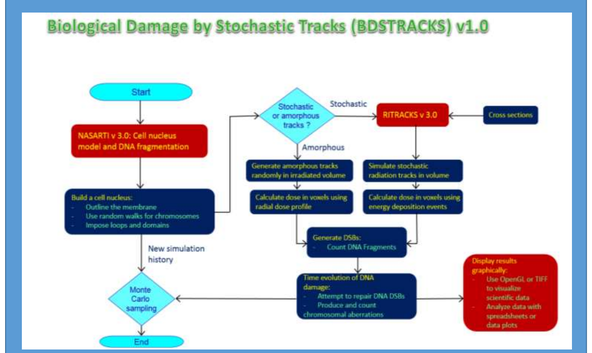
BDSTRACKS: Biological Damage by Stochastic (and Amorphous) Tracks

This new algorithm developed on massively parallel Linux architecture is based on functions developed in other similar models. These models include NASARTI with the amorphous track structure and RITRACKS with the stochastic track structure. BDSTRACKS improves predictions of high-LET DNA damage in human cells, and produces DNA repair/misrepair in physical time. Results from BDSTRACKS are expected to improve our understanding of how CA's form and what physical factors impact their statistics.



High-LET irradiation produces more clustered damage, as shown on a single simulated chromosome (Panels A, B, C), which is based on DNA geometry (Panels on the right).

BDSTRACKS flowchart



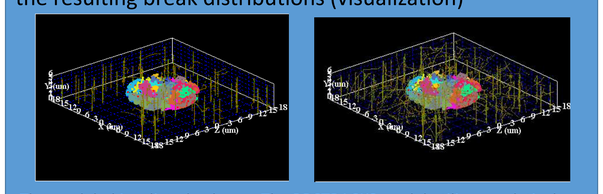
The BDSTRACKS code and the flowchart showing its contributing modules, RITRACKS and NASARTI.

Model of NHEJ (non-homologous end joining):

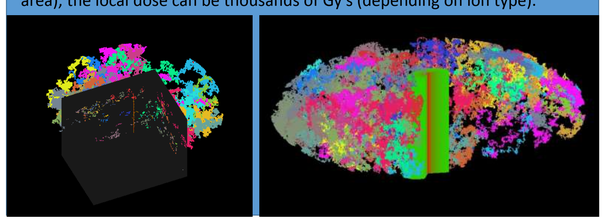
$$I = \frac{1}{W} e^{-\frac{r^2}{\sigma^2}}$$

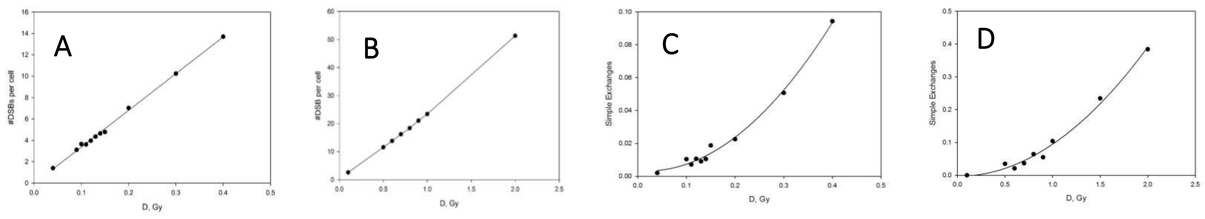
W is an empirically calibrated parameter, *r* is a Euclidian *(x, y, z)* distance between reacting DSB free end (μm), and *σ* is an adjustable parameter with the dimension of microns. As NHEJ is a predominant process in the G0/G1 phase, other types of repair have not been modeled.

Track structure interaction with chromosome domains and the resulting break distributions (visualization)

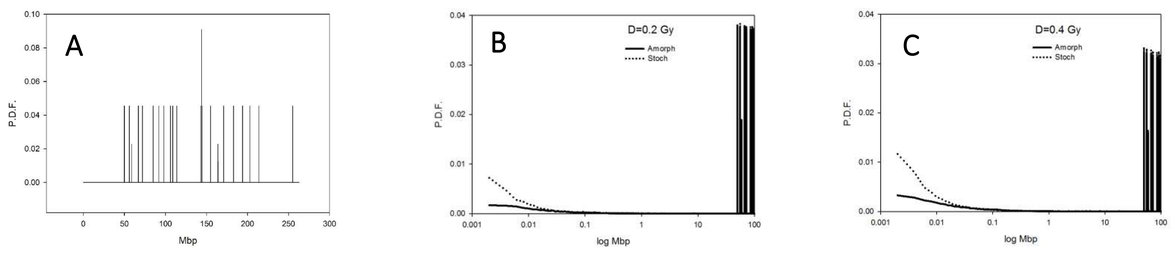


The modeled irradiated volume. The BDSTRACKS model utilizes a relatively large (but adjustable) irradiated volume in comparison to a cell nucleus. The particles are impinging through the bottom surface of the box randomly. For this simulation, $^{12}C^{6+}$ ions of 25 MeV/u are used corresponding to a dose of 0.1 Gy, without periodic boundary conditions (PBC), Panel A, and with PBC, Panel B. Panel C shows an amorphous track radiation profile against a background of a nucleus with chromosomes represented by RWs. Local dose values are represented by a colored cylinder, in which the "warmer" colors correspond to a higher local dose, centered on the particle trajectory. The radius of the cylinder is 1 micron. Greener colors correspond to the local dose of almost 0 in this model, while at the center of the cylinder (redder area), the local dose can be thousands of Gy's (depending on ion type).



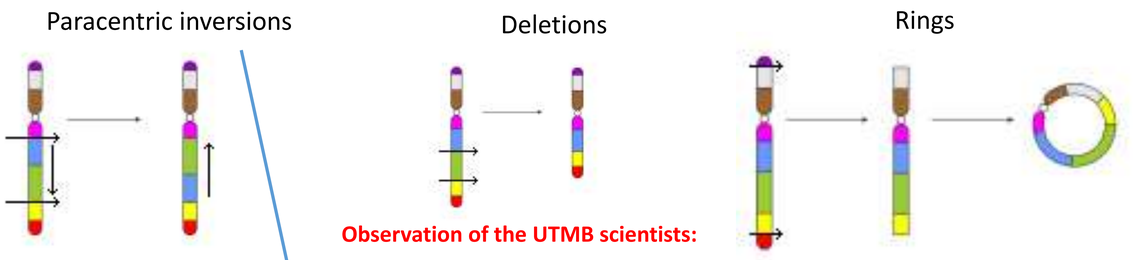


Benchmark simulations (a general model check before fitting to the experiment) of the expected linear and linear-quadratic behaviors of the simulated data for human fibroblasts. Panel A. Number of DSBs as a (linear) function of dose for He ions, *E*=100 MeV/u. Panel B. Number of DSBs as a (linear) function of dose for gamma rays. Panel C. The number of simple exchanges as a (linear-quadratic) function of dose for He ions, *E*=100 MeV/u. Panel D. The number of exchanges as a (linear-quadratic) function of dose for gamma rays.



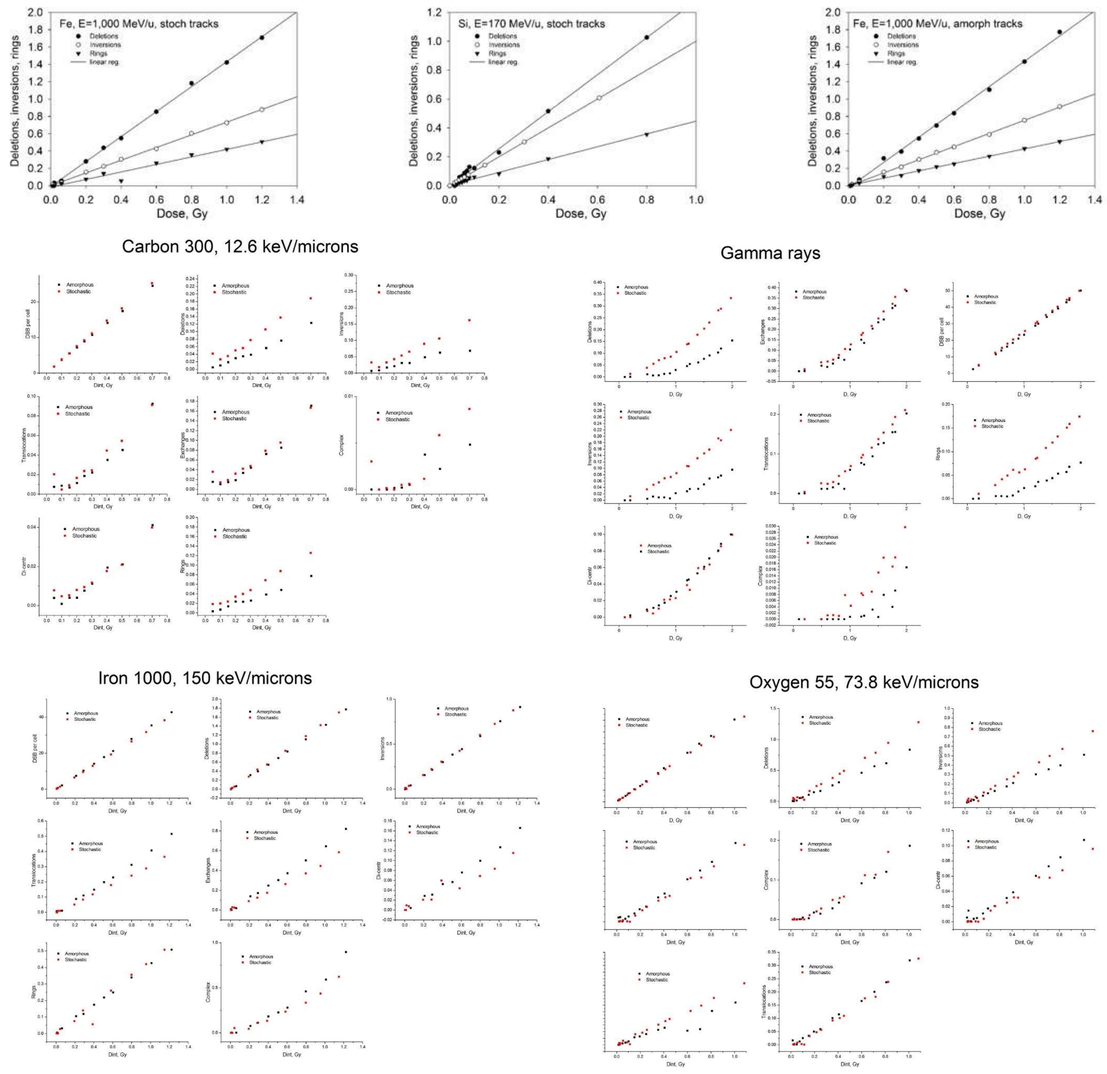
Panel A. Baseline simulation, D=0 Gy. The baseline fragment-size P.D.F. (probability density function) for human fibroblasts, Fe ions, E = 1,000 MeV/u, at D=0 Gy. It shows no fragments due to irradiation; the spikes beginning with 50 Mbp (Y chromosome) correspond to intact chromosomes. Panel B. Fragment-size P.D.F. for a simulated nucleus irradiated with 0.2 Gy of 1,000 MeV/u Fe particles, using the amorphous track model and the stochastic track model. The stochastic algorithm produces a larger yield of fragments smaller than 100 kbp. Panel C. Fragment-size P.D.F. for a simulated nucleus irradiated with 0.4 Gy of 1,000 MeV/u Fe particles, using the amorphous track model and the stochastic track model. The stochastic algorithm produces a larger yield of smaller fragments (<100 kbp) and slightly fewer larger-sized fragments. The spikes beginning with 50 Mbp (Y chromosome) correspond to intact chromosomes, which are also counted as fragments.

EXPERIMENTAL DATA and CLASSIFICATION of CAs (in collaboration with Drs. M. Cornforth and B. Loucas (UTMB, TX))

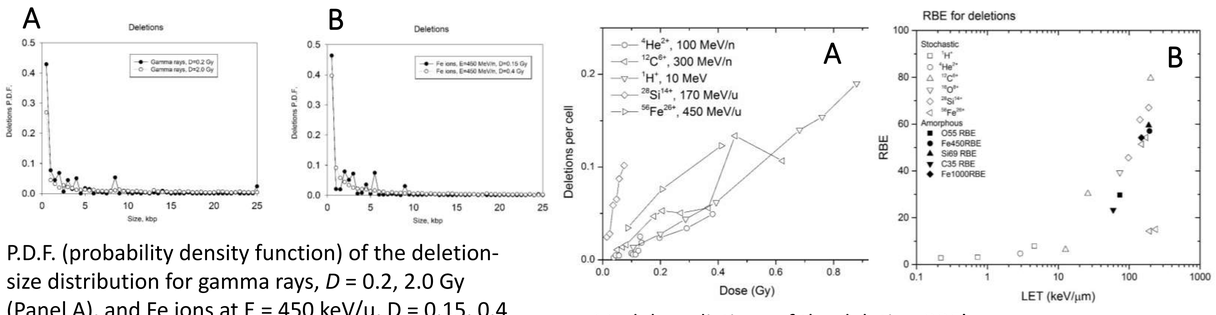


- Specific types: Deletions, Terminal Deletions, Inversions, Translocations, Exchanges, Dicentrics, Rings
- Acentric rings are deletions
- Banding is less than ideal for studying inversions
- Whole genome sequencing yet to prove useful
- Strand-specific FISH is robust for inversion detection
- ~1 Mb (500 BDSTRACKS monomers) for whole genome "discovery"
- < 6 kb (3 BDSTRACKS monomers) for recurrent or "targeted" applications
- Strand-Specific FISH has other uses

RECENT SIMULATIONS



CALCULATED DELETION-SIZE DISTRIBUTION and RBE'S FOR DELETIONS



P.D.F. (probability density function) of the deletion-size distribution for gamma rays, *D* = 0.2, 2.0 Gy (Panel A), and Fe ions at E = 450 keV/u, D = 0.15, 0.4 Gy (Panel B). The probabilities drop sharply for sizes >2.5 kb (b = DNA base pair). At higher doses the larger deletions are more frequent. The simulated ellipsoidal nucleus is parallel to the beam. Higher LET produces smaller deletions more frequently, which could be more cytotoxic. Notice that that these ARE P.D.F.'s, which show the relative frequencies of certain deletion sizes. The total number of deletions is linear with the dose (see Recent Simulations).

Model predictions of the deletion RBE's:

Panel A. Dose dependence for deletions, the basis for the RBE calculation.

Panel B. RBE's for deletions. Data by the amorphous and stochastic tracks models are compared in each panel, for different ion types.

Table for F-, G-, I-, C-ratios

F-, G-, I-, C-ratios (amorph/stoch; Fe, 1 GeV/u)	Translocations (inter-chromo)	Dicentrics (inter-chromo)	Centric rings (intra-chromo)	(small) rings (intra-chromo)	Translocations (inter-chromo)	Simple Exchanges (inter-chromo)
Rings (intra-chromo)	F=1.641 /1.527	F=0.247 /1.130				
Interstitial deletions (intra-chromo)	F=0.251 /0.202	F=0.078 /0.091	G=TBD			
Inversions (intra-chromo)	F=0.460 /0.775	F=0.144 /0.591				
Pericentric Inversions (intra-chromo)			G=TBD			
Paracentric Inversions (intra-chromo)				G=TBD		
Insertions (inter-chromo)					I=TBD	
Complex exchanges (inter-chromo)						C=0.669/ 0.814

FUTURE WORK

- The implemented DNA damage model (BDSTRACKS) will undergo more tests for different particles types and energies; simulation results will be compared with the experimental data
- We will continue using the computational model to extrapolate results for deletions, inversions and rings from the available experimental data to a wider range of doses, particle types, and energies. Model outputs will be used to calculate RBE's for DNA damage and chromosome aberrations of various types
- An analytical model of the ratios of frequencies of deletions to rings and inversions is necessary, as these are three closely related CA pathways, and maybe related by a geometric factor
- We will continue expanding and refining the theoretical values for F-, G-, I-, C-ratios, and comparing them to the experimental ones. LET and dose dependence of these ratios is of importance for CA-based radiation quality analysis