Simulation of radiation-induced DNA damage with the code RITRACKS

National Aeronautics and Space Administration

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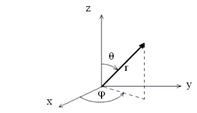
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Introduction

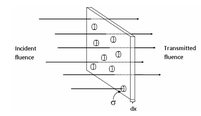
- DNA damage is one of the primary mechanisms mediating the health risks of exposure to ionizing radiation.
- Various types of DNA damage are induced by ionizing radiation, but clustered types have the strongest radiobiological effects [1].
- Damage can be caused by direct ionizations, dissociative electron attachment, or by the free radicals created in the vicinity of the DNA [2].
- Radiation-induced correlated cleavage with sequencing (RICC-Seq) experiments are used to probe sub-chromosome scale chromatin structure using ionizing radiation [3].
- In this work, the code RITRACKS (Relativistic Ion Tracks) [4], which is a program used to simulate stochastic radiation track structures, was used to simulate DNA damage by various types of ions.
- The code was adapted for DNA damage simulations by changing the radiation transport algorithm and the radiation chemistry simulation.
- The simulations were done using selected ions ($^{1}H^{+}$, $^{4}He^{2+}$, $^{12}C^{6+}$, $^{16}O^{8+}$, and $^{56}Fe^{26+}$) at different energies, and photons, covering a wide range of LET.
- The target DNA is the core nucleosome structure (PDB:1kx5) [5].

Radiation transport

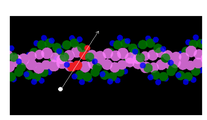
- Particles are assigned a position (x,y,z), an energy (E), and a direction (θ,ϕ).
- The probability of interaction between radiation and matter is given by cross sections
  - $dI = -IN\sigma dx$
  - $I(x) = I(0)\exp(-\frac{x}{\lambda(E)})$, where $\lambda(E) = \frac{1}{N\sigma(E)}$, N is the density and σ(E) is the cross section.
- Near DNA, the particle trajectories can intercept the DNA structure. Each base, sugar, and phosphate (BSP) is modeled as a sphere. The cross sections for electron interactions inside that sphere depends on the type of BSP and of the electron's energy [6].



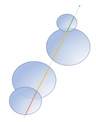
Direction vector of particle



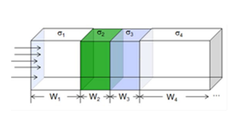
Cross sections



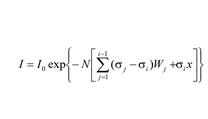
Electron crossing a DNA structure



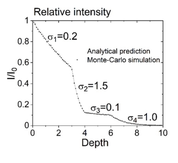
Find the entrance and exit of the trajectory in BSP



Calculate the length and total cross sections in each media



Solve the differential equation for multiple cross sections

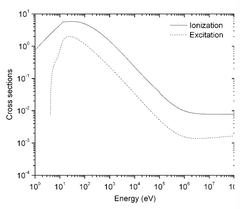


Determine position of next interaction by sampling

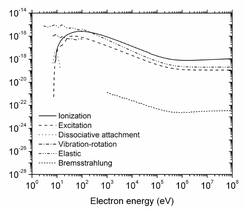
Cross sections

- Cross sections are used for particle transport. Differential cross sections are used to determine energy loss, change of direction, etc.
- In the DNA bases, there are many internal and valence electrons. The Binary encounter Bethe (BEB) model is used for to calculate the ionization cross sections for each electron of the molecule [6].
- Additionally, it is now well established that low-energy electrons can damage DNA, including DSB, by dissociative electron attachment (DEA) to resonant states [7].
- Ionization and DEA cross sections for all bases, sugar, phosphate, and all amino acids have been recently included in RITRACKS.

Ions



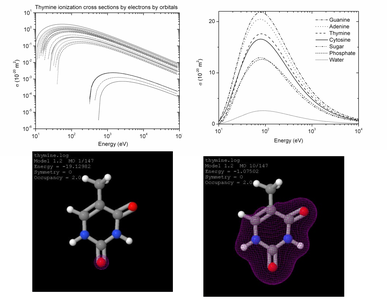
Electrons



Cross sections for particle transport for ions and electrons in water.

Thymine

	No	U (eV)	B (eV)	N
Internal electrons [18]	1	794.1	559.41	2
	2	794.1	559.18	2
	3	603.5	425.6	2
	4	603.5	425.48	2
	5	435.9	311.36	2
	6	435.9	310.43	2
	7	435.8	308	2
	8	435.7	306.41	2
	9	435.8	305.8	2
Valence electrons [44]	10	66.26	40.06	2
	11	71.74	39.14	2.04
	12	63.05	36.16	1.86
	13	57.89	34.56	1.85
	14	44.95	30	2.3
	15	43.96	26.22	2.35
	16	47.64	25.14	2.11
	17	40.64	24.85	2.15
	18	41.92	21.32	2.18
	19	39.28	20.94	2.02
	20	36.32	19.4	1.86
	21	44.53	18.7	2.05
	22	55.89	18.56	1.92
	23	54.72	17.59	1.99
	24	39.88	16.62	2.01
	25	46.93	16.15	2.03
	26	39.89	15.44	1.78
	27	47.3	13.96	1.83
	28	59.96	13.15	1.86
	29	54.12	12.31	2.07
	30	60.23	12.10	1.78
	31	60.38	9.27	1.97



Calculations of MO from the site www.chemeddl.org

Radiation chemistry

- Simulation of chemical reactions between the radiolytic species and DNA bases by using an approach based on the Green's functions of the diffusion equation (GFDE) [8].
- GFDE $p(r,t|r_0)$ for partially diffusion-controlled reaction with rate k_a, diffusion coefficient D, reaction radius R, and initial distance r_0.
- Reactions between the radicals H·, ·OH and e^-_{aq} and the bases, sugar, phosphate, and all amino acids have been recently added to RITRACKS.

$$A + B \xrightarrow{k_a} C \qquad \text{(Reaction)}$$

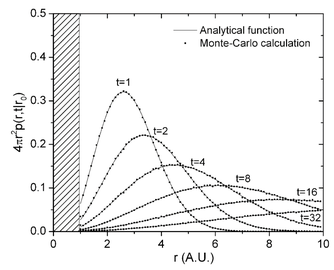
$$4\pi R^2 D \left.\frac{\partial p(r,t\,|\,r_0)}{\partial r}\right|_{r=R} = k_a\, p(R,t\,|\,r_0) \qquad \text{(Boundary condition)}$$

$$4\pi r r_0 p(r,t\,|\,r_0) = \frac{1}{\sqrt{4\pi Dt}}\left\{\exp\left[-\frac{(r-r_0)^2}{4Dt}\right] + \exp\left[-\frac{(r+r_0-2R)^2}{4Dt}\right]\right\} + \alpha W\left(\frac{r+r_0-2R}{\sqrt{4Dt}}, -\alpha\sqrt{Dt}\right) \qquad \text{(Green's function)}$$

$$Q(t\,|\,r_0) = \int_R^\infty 4\pi r^2 p(r,t\,|\,r_0)\,dr = 1 + \frac{R\alpha+1}{r_0\alpha}\left[W\left(\frac{r_0-R}{\sqrt{4Dt}}, \alpha\sqrt{Dt}\right) - \mathrm{Erfc}\left(\frac{r_0-R}{\sqrt{4Dt}}\right)\right] \qquad \text{(Survival probability)}$$

$$\alpha = -\frac{k_a + 4\pi RD}{4\pi R^2 D}$$

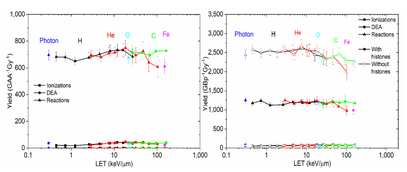
The Green's function of the diffusion equation p(r,t|r_0) is the probability distribution of interparticle distances r at time t, given that the distance was r_0 at t=0. The survival probability is obtained by integration over space. The probability of reaction P(t|r_0) = 1 – Q(t|r_0). At each time step, the probability of reaction is assessed. If the particles have not reacted, their relative distance is obtained by sampling the Green's function using the algorithm described in Plante et al. (2013).



Green's function $4\pi r^2 p(r,t|r_0)$ for D=1, R=1, r_0=1.5 and α=-2 at t = 1, 2, 4, 8, 16 and 32. Analytical functions (—) and result of sampling (□).

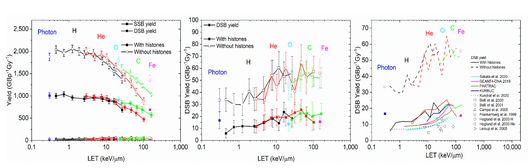
Results

- DNA damage yield by cause



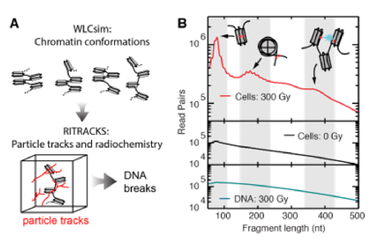
Yield by cause of damage (ionizations, DEA, or chemical reactions) for DNA (left) and for amino acids (right), for $^{1}H^{+}$, $^{4}He^{2+}$, $^{12}C^{6+}$, $^{16}O^{8+}$, and $^{56}Fe^{26+}$ as a function of the LET, with and without histones [9].

- SSB and DSB yields

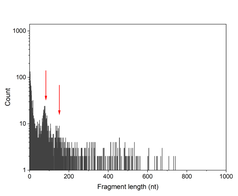


Left. SSB and DSB yield, for $^{1}H^{+}$, $^{4}He^{2+}$, $^{12}C^{6+}$, $^{16}O^{8+}$, and $^{56}Fe^{26+}$ as a function of the LET, with and without histones. Center. Same as left figure, focus on DSB yield vs LET. Right. DSB yields for $^{1}H^{+}$, $^{4}He^{2+}$, $^{12}C^{6+}$, $^{16}O^{8+}$, and $^{56}Fe^{26+}$ as a function of the LET, with histones. Comparison with calculations from other codes and experiments [9].

- Fragment length distribution



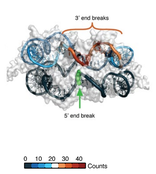
(A) Strategy to combine Monte Carlo sampling of chromatin conformation ensembles followed by prediction of DNA damage for sampled conformations. (B) RICC-seq fragment length distributions for 300 Gy g-ray irradiated cells. [3].



FLD calculated by RITRACKS for a 10-nucleosome extended DNA structure irradiated with 10-MeV protons, showing the first and second peaks at 78 and 150 base pairs, corresponding to 1 and 2 DNA wraps around a nucleosome.

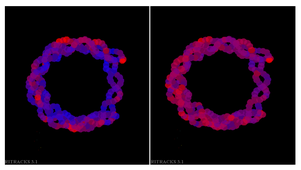
- Evidence of histone protection

Nucleosome structure

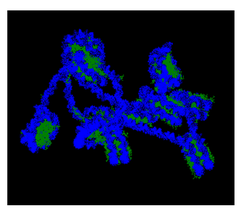


The DNA has a periodicity of about 10 base pairs (bp). The DNA in direct contact with the histone proteins also has a periodicity of 10 bp. Coloring of DNA chain represents density of 3' end breaks of fragments with a 5' end on the green nucleotide. [3]

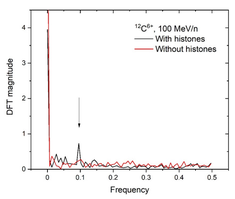
With histones present | Without histones present



Nucleosomal DNA, with color indicating the probability of damage events (blue=low to red=high), with and without histones present. The inner DNA is in contact with the histone proteins and is harder to damage. The ion used is $^{12}C^{6+}$, 50 MeV/n.



Chromosome structure generated by RITRACKS, built from nucleosome units.



Discrete Fourier Transform (DFT) of the damage base pair number for $^{12}C^{6+}$, 100 MeV/n. The peak indicate periodicity of 10 bp, suggesting histone protection. The peak is not present when simulations are done without histones

Conclusions

- DNA damage simulations have been implemented in RITRACKS.
- We simulated radiation-induced DNA damage using several ions, covering a range of LET.
- The results show evidence of histone protection
  - SSB and DSB yields are much smaller in the presence of histones.
  - Peak in the DFT of damage by base pair number, indicating periodicity of 10 bp.
- The calculated fragment length distributions show peaks at ≈75 bp and 160 bp, corresponding to a loop of DNA around a nucleosome and a full nucleosome unit. Calculations will be done with different DNA structures to model RICC-SEQ experiments.

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Acknowledgements

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