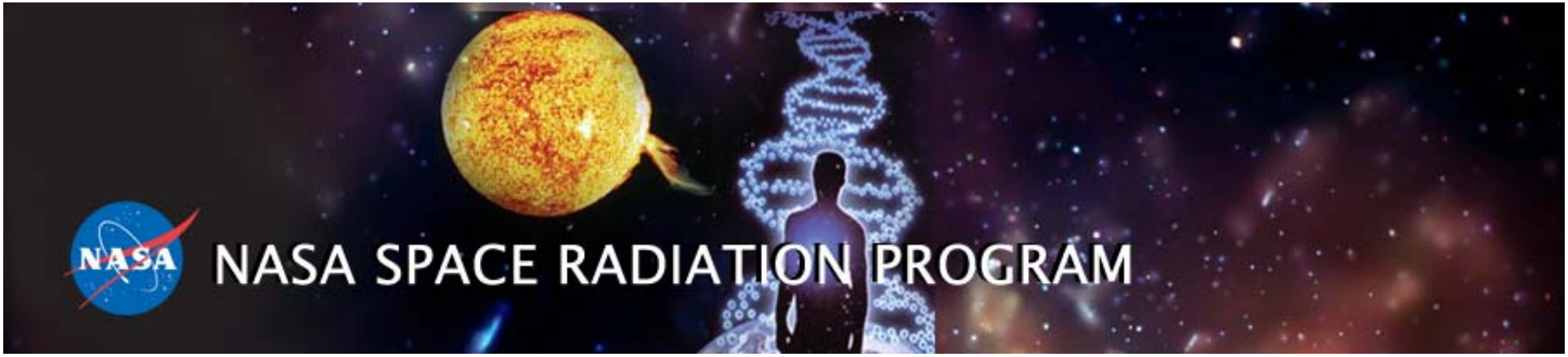


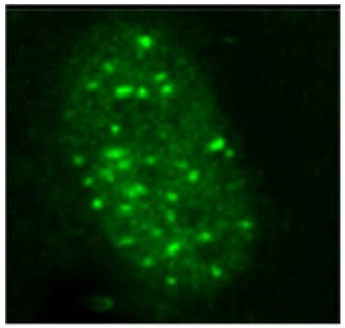
Simulation of ionizing radiation tracks and its applications

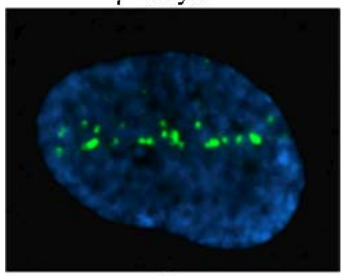
Ianik Plante
Universities Space Research Association
Division of Space Life Sciences
NASA Johnson Space Center, Houston TX

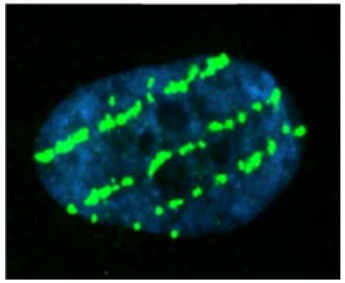
NASA Space Radiation Summer School 2014
Brookhaven National Laboratory
May 30 – June 20, 2014

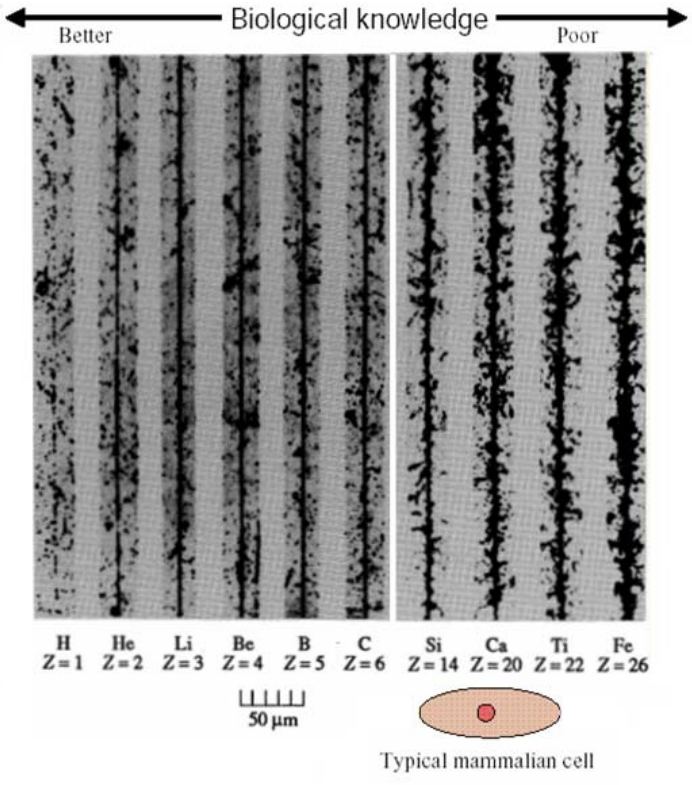
The space radiation problem

- Space radiation is comprised of high-energy protons and heavy ions (HZE's) and secondary protons, neutrons, and heavy ions produced in shielding
- Unique damage to bio-molecules, cells, and tissues occurs from HZE ions that is qualitatively distinct from X-rays and gamma-rays on Earth
- No human data to estimate risk from heavy ions, thus requiring use of biological models and theoretical understanding to assess and mitigate risks
- Shielding has excessive costs and will not eliminate galactic cosmic rays (GCR)







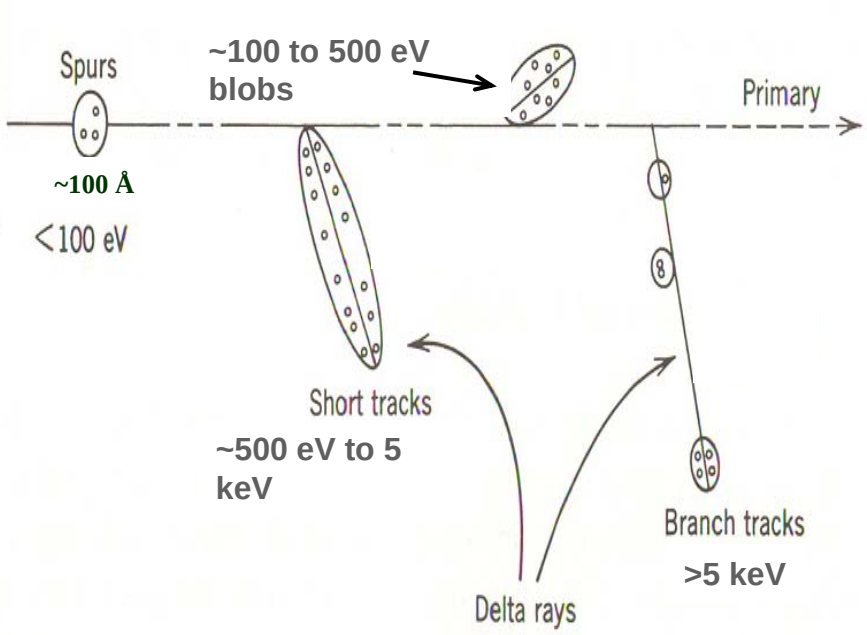


Cucinotta and Durante, *Lancet Oncology (2006)*

Radiation tracks and energy deposition

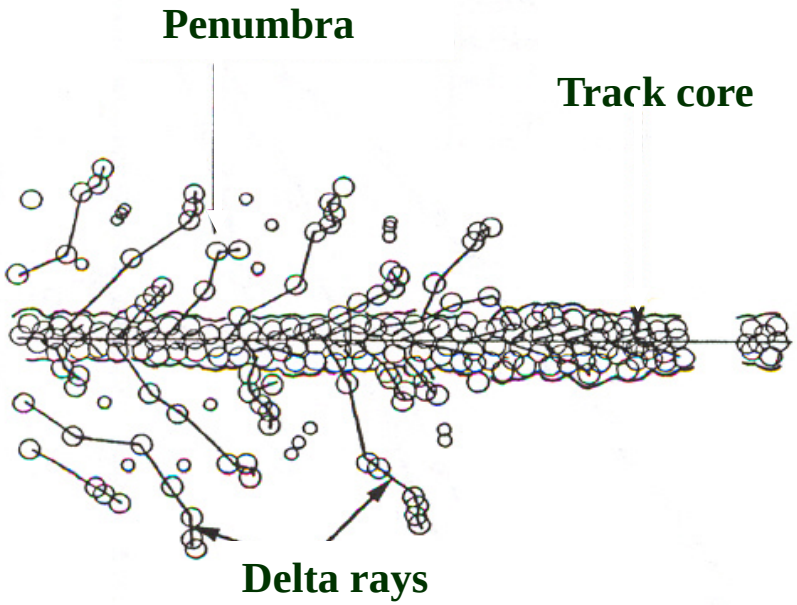
- The energy deposition by heavy ions is highly heterogeneous and dependent on the type and energy of the ion
- The interactions of radiation with matter are stochastic in nature and therefore often studied by Monte-Carlo simulations

Primary energy loss events in low-LET tracks



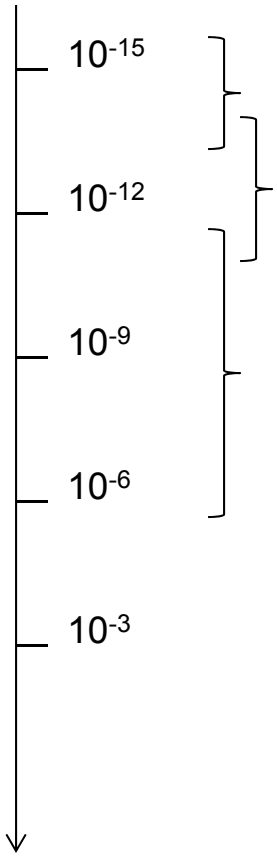
A. Mozumder and J.L. Magee (1966) *Radiat. Res.* **28**, 203

Primary energy loss events in high-LET tracks



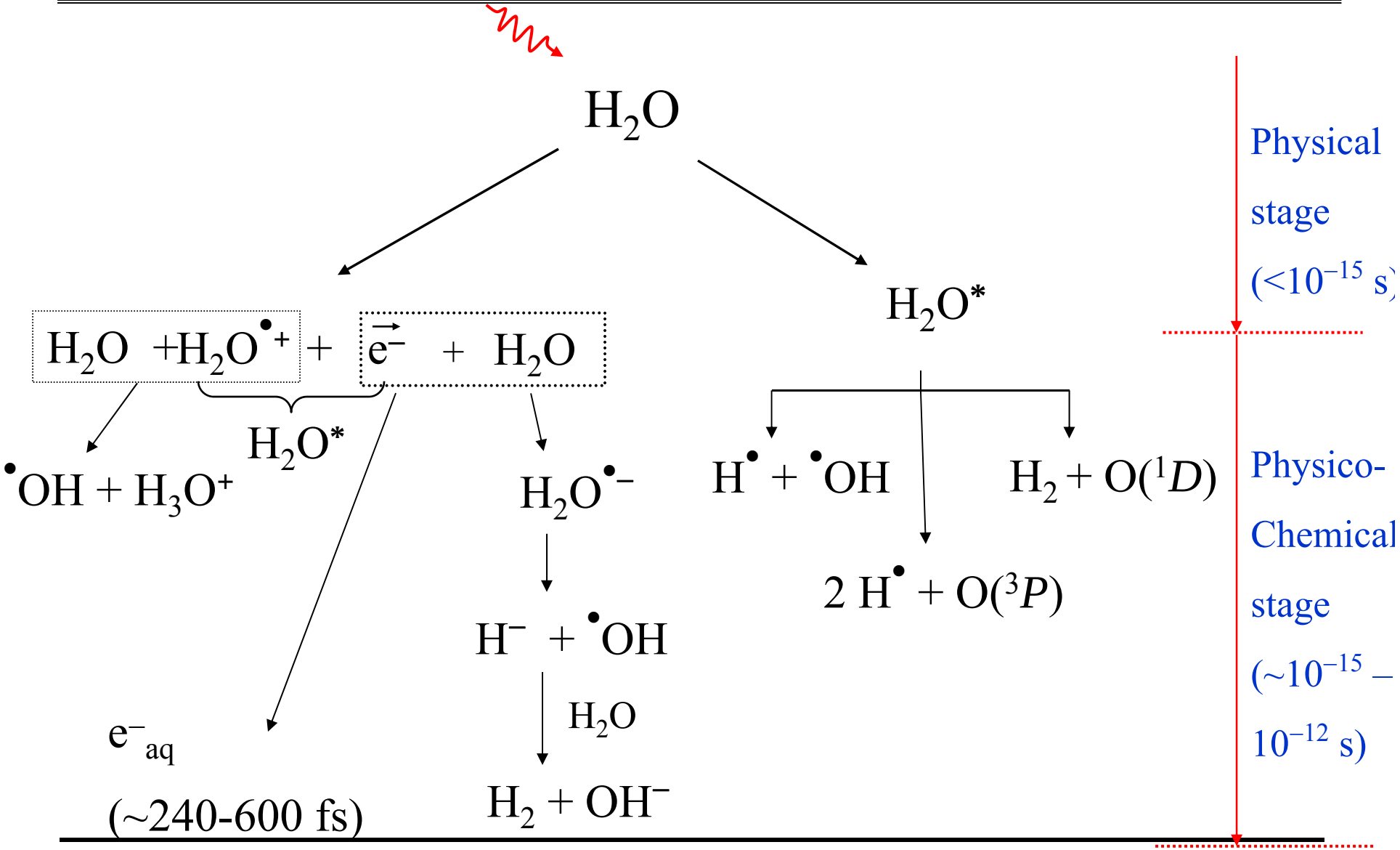
C. Ferradini (1979) *J. Chim. Phys.* **76,** 636

Radiation effects: time sequence of events



Time (s)	Stage	Events	Modeling
10^{-15}	Physical	Energy absorption	Particle transport Cross sections
10^{-12}	Physico-chemical	Reorganization Electron thermalization	
10^{-9}	Chemical	Radical diffusion Chemical reactions	Green's functions
10^{-6}			
10^{-3}	Biological	DNA repair	Kinetics models Molecular dynamics

Radiation effects: time sequence of events



Particle transport basics

- **The trajectory of a particle and all its interactions is followed in the medium**
- **A particle is followed until**
  - It leaves the volume of interest
  - Its energy decrease below a threshold
  - It disappears by a physical process (e.g. absorption of a photon during a photo-electric effect
- **Many other particles are generated by the interactions of the "primary" particle. The trajectories of these secondary particles should also be followed.**

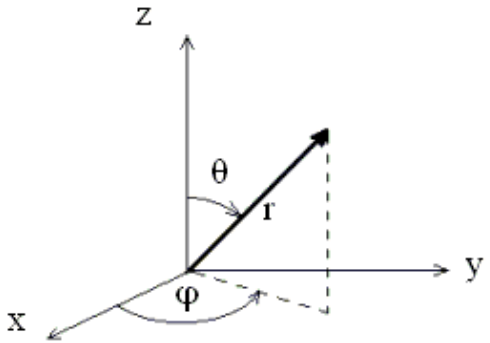
Plante, I. and Cucinotta, F.A. (2011) Monte-Carlo Simulation of Ionizing Radiation Tracks. In: Mode, C.J. (Ed.) Applications of Monte Carlo Methods in Biology, Medicine and Other Fields of Science. InTech, Rijeka, Croatia. www.intechopen.com

Particle transport basics

❑ Particles

- Position (x,y,z)
- Energy (E)
- Direction (θ,φ)

$$\vec{v} = \begin{bmatrix} \sin(\theta)\cos(\varphi) \\ \sin(\theta)\sin(\varphi) \\ \cos(\theta) \end{bmatrix}$$



❑ Cross sections

- Probability of interaction between radiation and matter

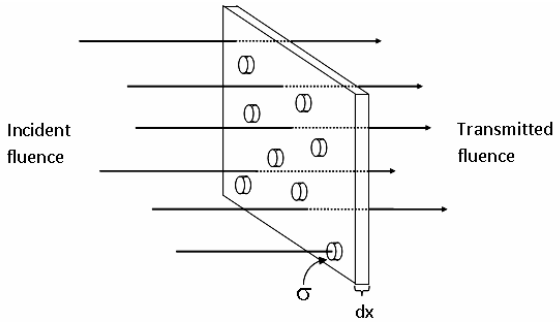
$$dI = -In\sigma dx$$

I: Incident fluence

n: Density of targets

dx: Width

σ: Cross section



- Cross sections (units: cm^2)
- Mean free path λ (units: cm)

$$I(x) = I(0)\exp(-x/\lambda(E))$$

$$\lambda(E) = 1/(N\sigma(E))$$

Plante, I. and Cucinotta, F.A. (2011) Monte-Carlo Simulation of Ionizing Radiation Tracks. In: Mode, C.J. (Ed.) Applications of Monte Carlo Methods in Biology, Medicine and Other Fields of Science. InTech, Rijeka, Croatia. www.intechopen.com

Particle transport basics

- Cross sections (total and differential in energy, angle,… i.e. $d\sigma/dW$, $d\sigma/d\theta$, $d^2\sigma/dWd\sigma$,…) are needed for particle transport
- The total cross section is the sum of the cross sections for each interactions
- A distance to the next interaction (s) is sampled from the exponential distribution:

$$s = -\lambda \log(U)$$

$$\lambda(E) = 1/(N\sigma(E))$$

- The particle is moved to the next interaction site:

$$x' = x + s\sin(\theta)\cos(\varphi)$$

$$y' = y + s\sin(\theta)\sin(\varphi)$$

$$z' = z + s\cos(\theta)$$

- The phenomenon (e.g. ionization) is determined by the ratio of the cross section a phenomenon over the total cross section
- The energy loss and change of direction are determined by sampling the differential cross sections

Plante, I. and Cucinotta, F.A. (2011) Monte-Carlo Simulation of Ionizing Radiation Tracks. In: Mode, C.J. (Ed.) Applications of Monte Carlo Methods in Biology, Medicine and Other Fields of Science. InTech, Rijeka, Croatia. www.intechopen.com

Cross sections

❑ **RITRACKS includes accurate cross section models for all ions and secondary electrons or photons**

❑ **For electrons:**

- Ionization
- Excitation
- Elastic collisions
- Dissociative electron attachment
- Bremsstrahlung

❑ **For ions:**

- Ionization
- Excitation

❑ **For photons:**

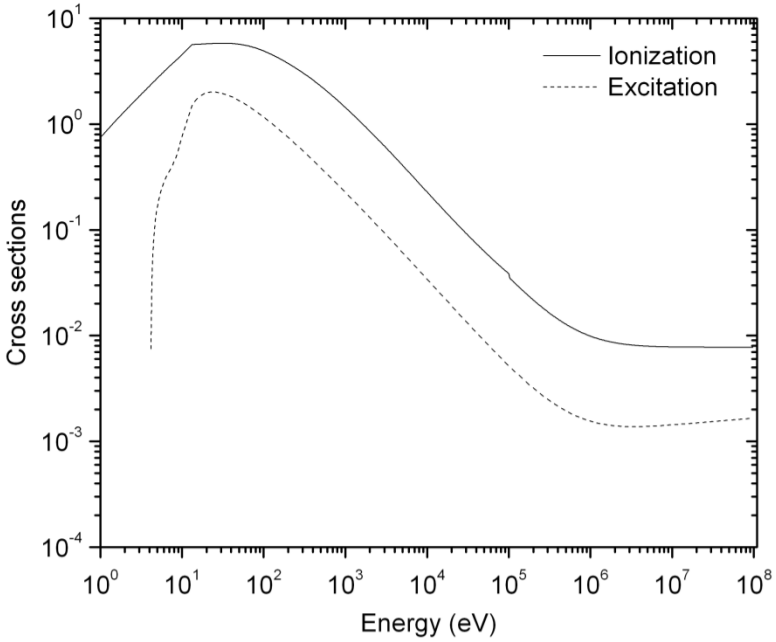
- Compton effect
- Coherent diffusion
- Photoelectric effect
- Pair production

Plante, I. and Cucinotta, F.A. (2011) Monte-Carlo Simulation of Ionizing Radiation Tracks. In: Mode, C.J. (Ed.) Applications of Monte Carlo Methods in Biology, Medicine and Other Fields of Science. InTech, Rijeka, Croatia. www.intechopen.com

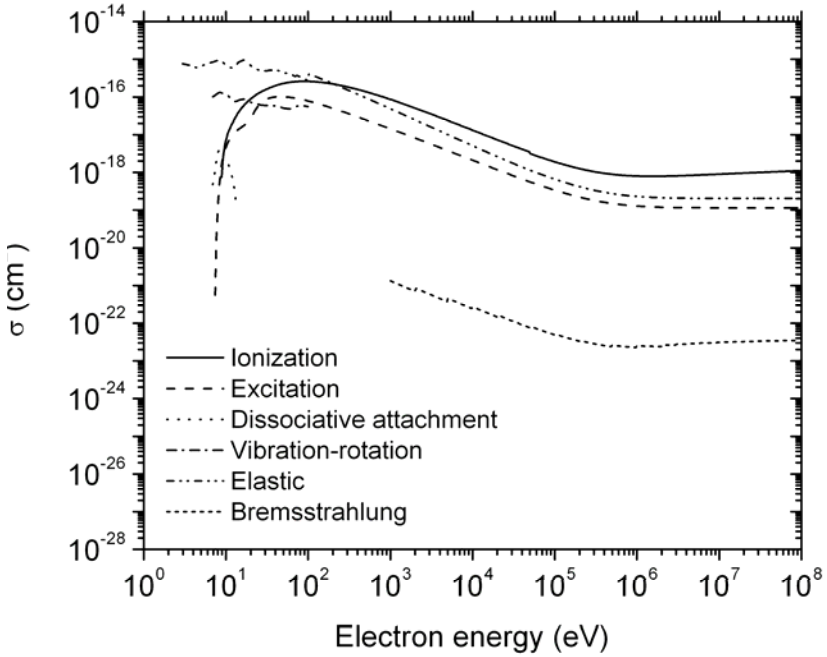
Cross sections

❑ Cross sections used in RITRACKS

Ions



Electrons



The cross sections for ions are scaled with Z_{eff}:

$$\frac{d\sigma_{ion}(v)}{dW} = Z_{eff}^2 \frac{d\sigma_{proton}(v)}{dW}$$

$$Z_{eff} / Z = 1 - \exp(-125\beta^2 / Z^{2/3})$$

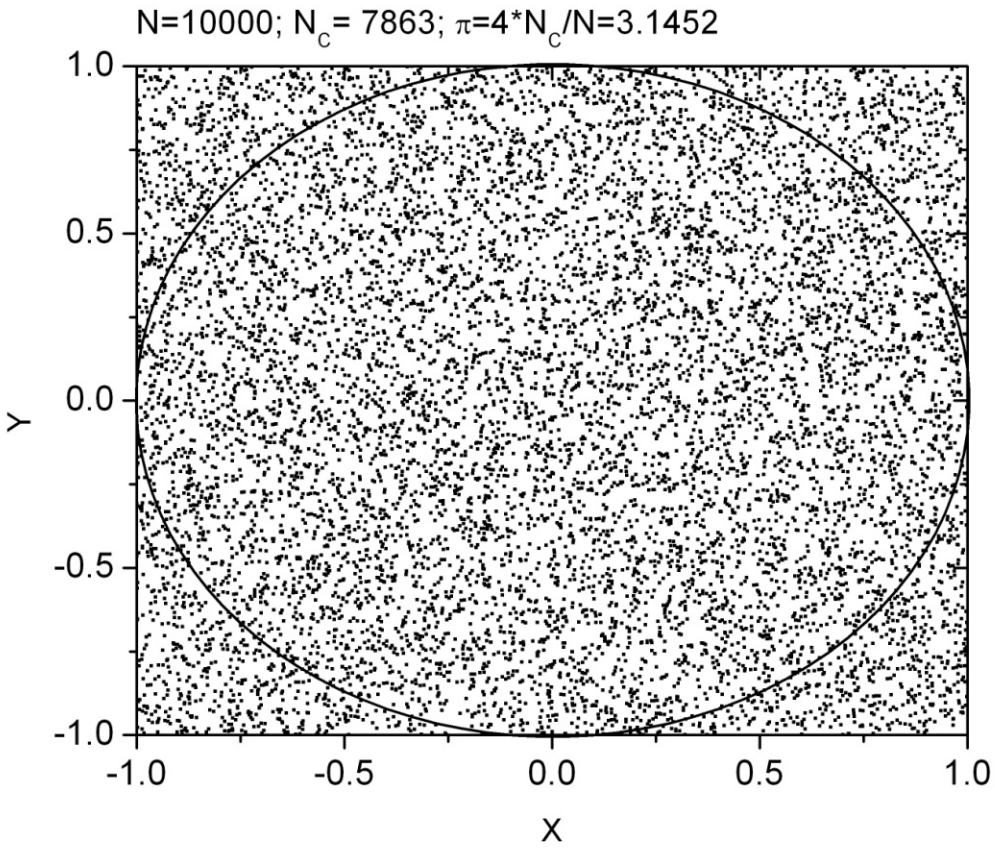
v: velocity of the ion

β: relativistic v/c

Plante, I. and Cucinotta, F. A. (2009). *New J. Phys.* **11**, 063047

Monte-Carlo simulations

- **Used to simulate stochastic systems**



$\Rightarrow$By increasing the number of random points, $4N_C/N$ converges to the value of π

Example: Calculation of π

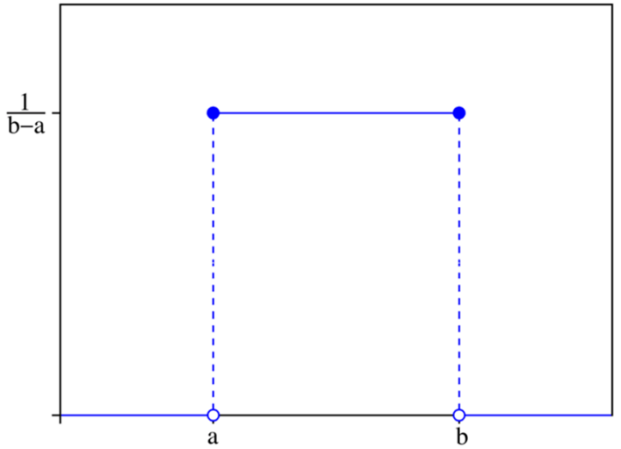
Monte-Carlo simulations

- **Random numbers**
- **Probability distributions**
- **Normalization**

$$\sum_{i=1}^{N} p_i = 1$$ Discrete

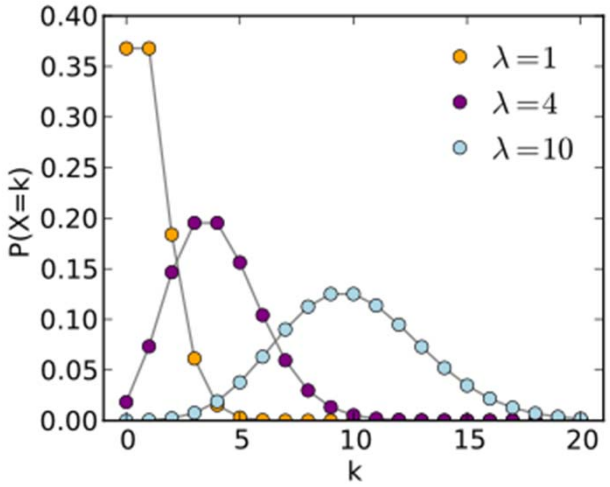
$$\int_{-\infty}^{\infty} f(x')dx' = 1$$ Continuous

Uniform distribution



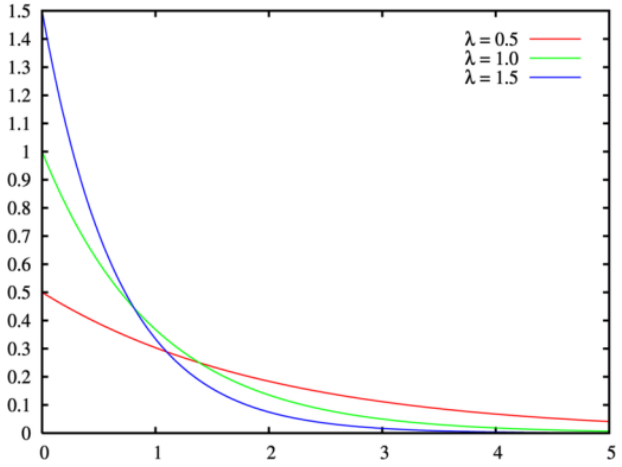
Poisson distribution

$P(x=k)=\lambda^x e^{-\lambda}/x!$



Exponential distribution

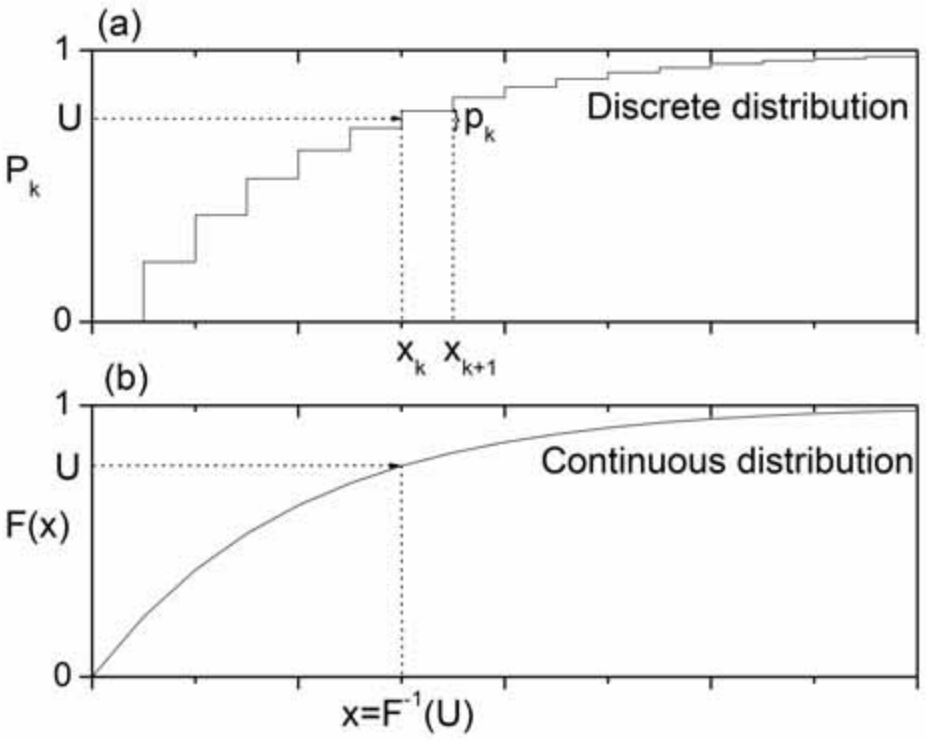
$p(x)=\lambda e^{-\lambda x}$



From http://en.wikipedia.org/wiki/List_of_probability_distributions

Monte-Carlo simulations

❑ Generating probability distributions



Example: Exponential distribution

$f(x)=\lambda e^{-\lambda x}$, $\lambda>0$, $x\geq 0$

$F(x)=1-e^{-\lambda x}=U$

$X=-Log(1-U)/\lambda$ or $X=-Log(U)/\lambda$

U is a random number between 0 and 1

F(x) is the cumulative probability distribution

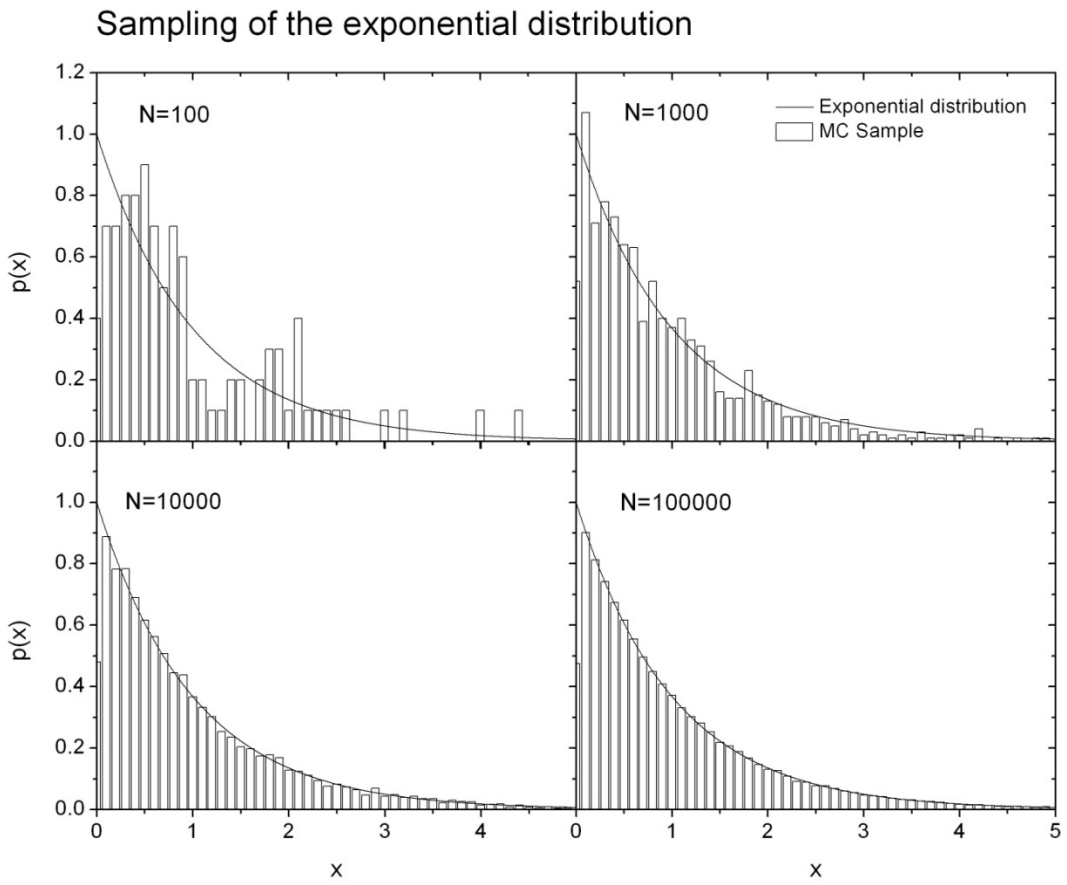
$$F(x) = \int_{-\infty}^{x} f(x')dx'$$

$$P_k = \sum_{i=1}^{k} p_i$$

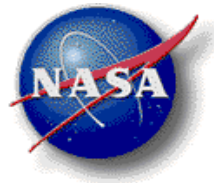
Plante, I. and Cucinotta, F.A. (2011) Monte-Carlo Simulation of Ionizing Radiation Tracks. In: Mode, C.J. (Ed.) Applications of Monte Carlo Methods in Biology, Medicine and Other Fields of Science. InTech, Rijeka, Croatia. www.intechopen.com

Monte-Carlo simulations

❑ Generating the exponential distribution



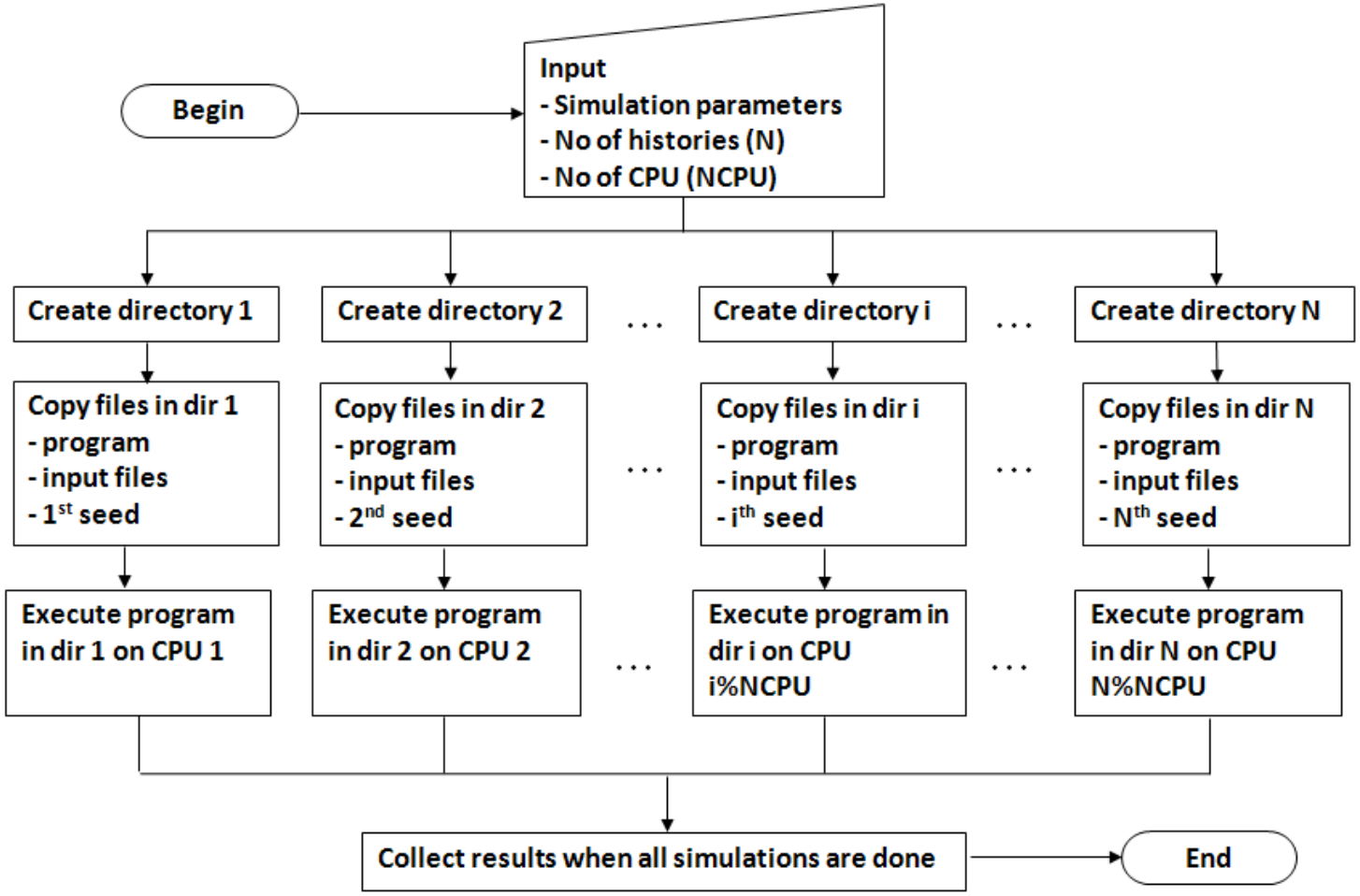
The software RITRACKS



- **The software RITRACKS comprises several parts**
  - The calculation part includes:
    - ✓ The cross sections, which are necessary for particle transport
    - ✓ The particle transport routines
    - ✓ Post-simulation data management
  - The Graphic User Interface (GUI), comprises several windows:
    - ✓ The main window
    - ✓ Incident radiation window
    - ✓ Cross sections windows (electrons and ions)
    - ✓ Results (events) details
  - The 3D visualization window
  - The help file
- **All necessary files are included in an installer for Windows**

The software RITRACKS

❑ Multiple CPU computing

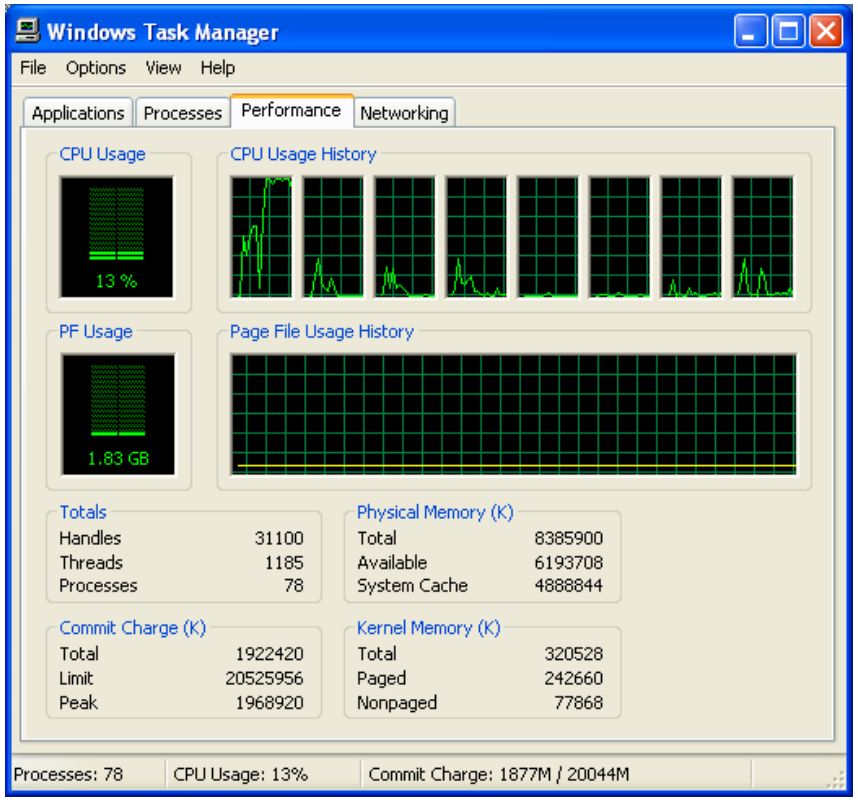


Plante, I. and Cucinotta, F. A. (2013). *Lecture Notes in Computer Sciences* **7845**, 12-25

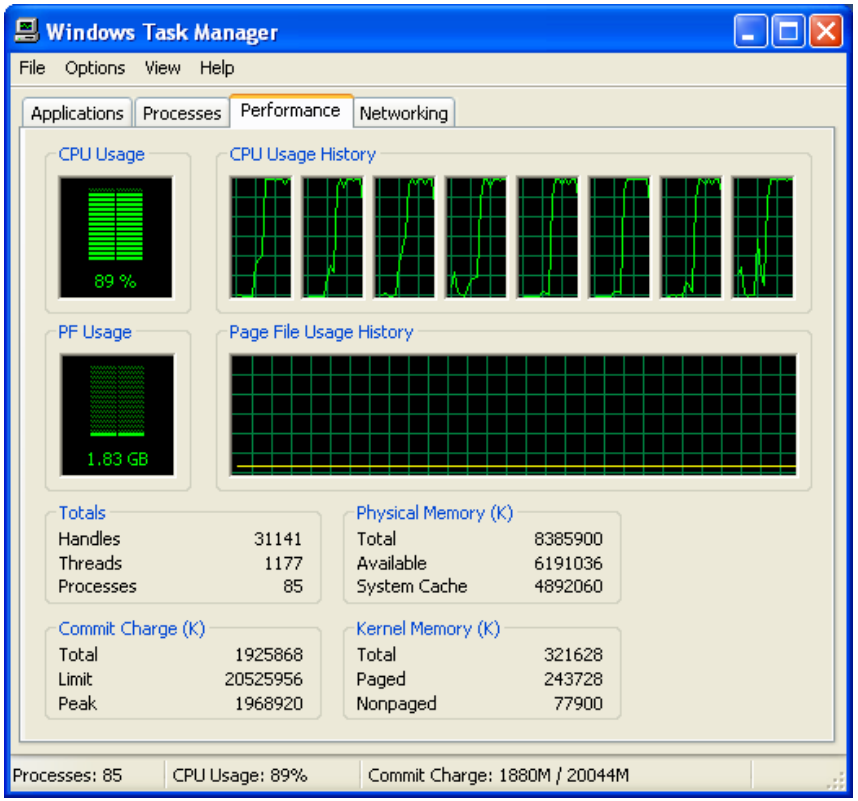
The software RITRACKS

❑ Multiple CPU computing (Windows)

RITRACKS V1



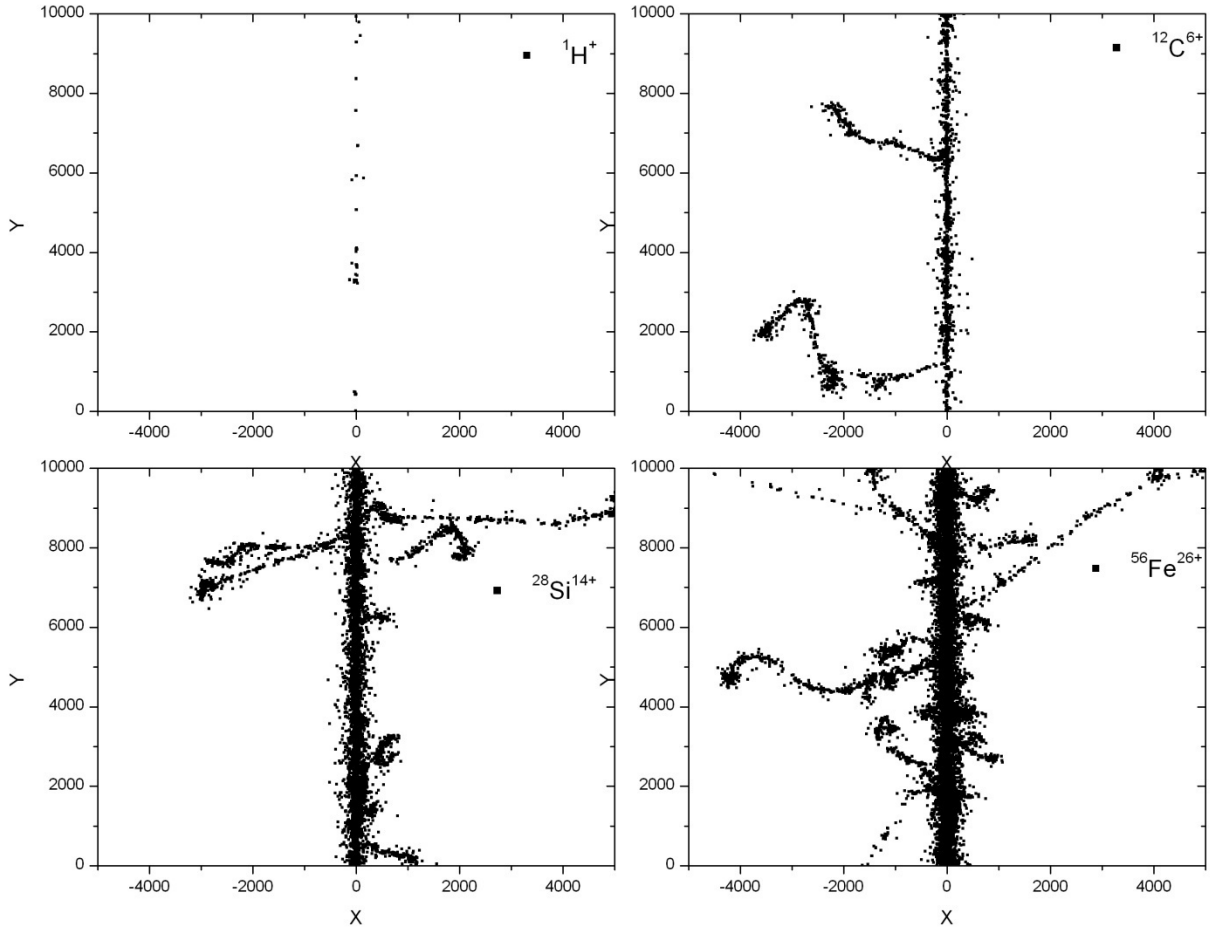
RITRACKS V2



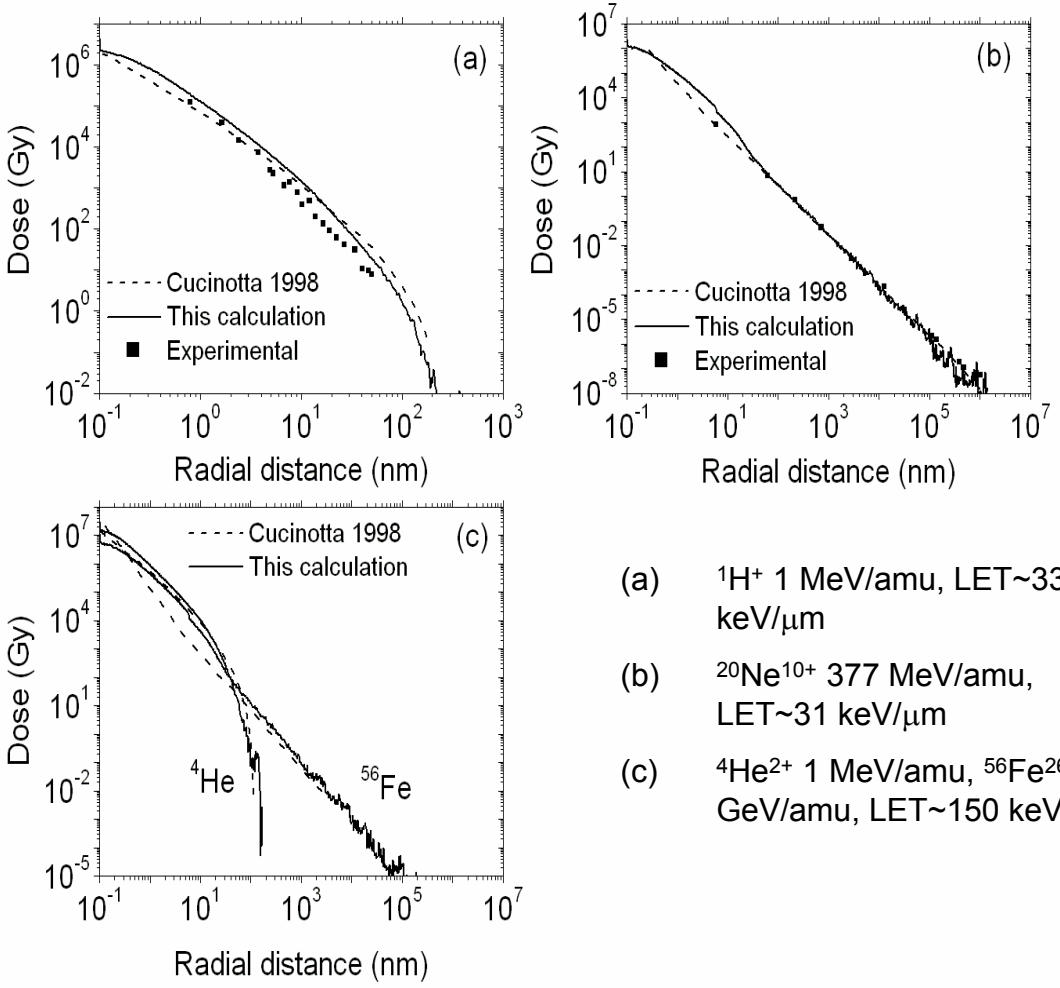
Plante, I. and Cucinotta, F. A. (2013). *Lecture Notes in Computer Sciences* **7845**, 12-25

Heavy ion track structure simulation

Simulation fo $^{1}H^{+}$, $^{12}C^{6+}$, $^{28}Si^{14+}$ and $^{56}Fe^{26+}$ tracks, 100 MeV/amu



Radial dosimetry



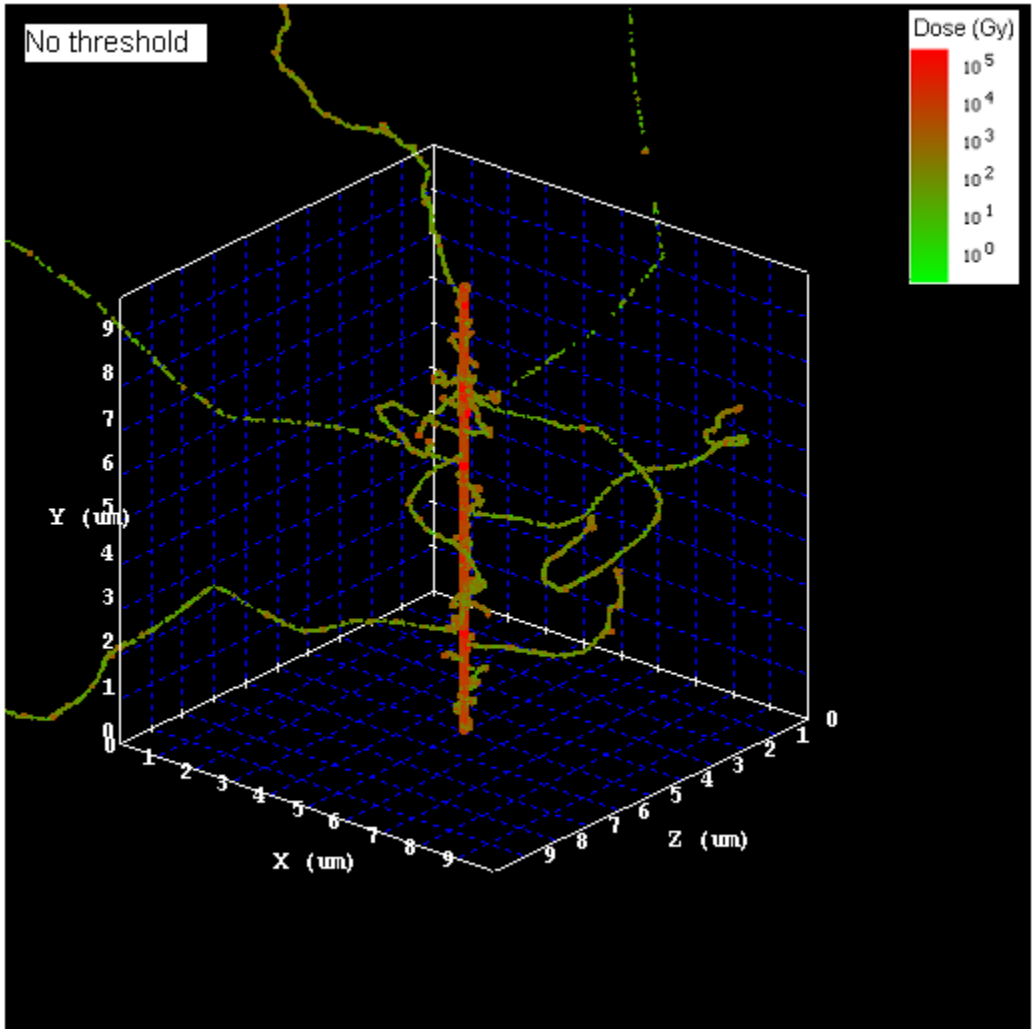
(a) $^1H^+$ 1 MeV/amu, LET~33 keV/μm

(b) $^{20}Ne^{10+}$ 377 MeV/amu, LET~31 keV/μm

(c) $^4He^{2+}$ 1 MeV/amu, $^{56}Fe^{26+}$ 1 GeV/amu, LET~150 keV/μm

Plante, I. and Cucinotta, F.A. (2008), *New J. Phys.* **10**, 125020

Voxel dosimetry



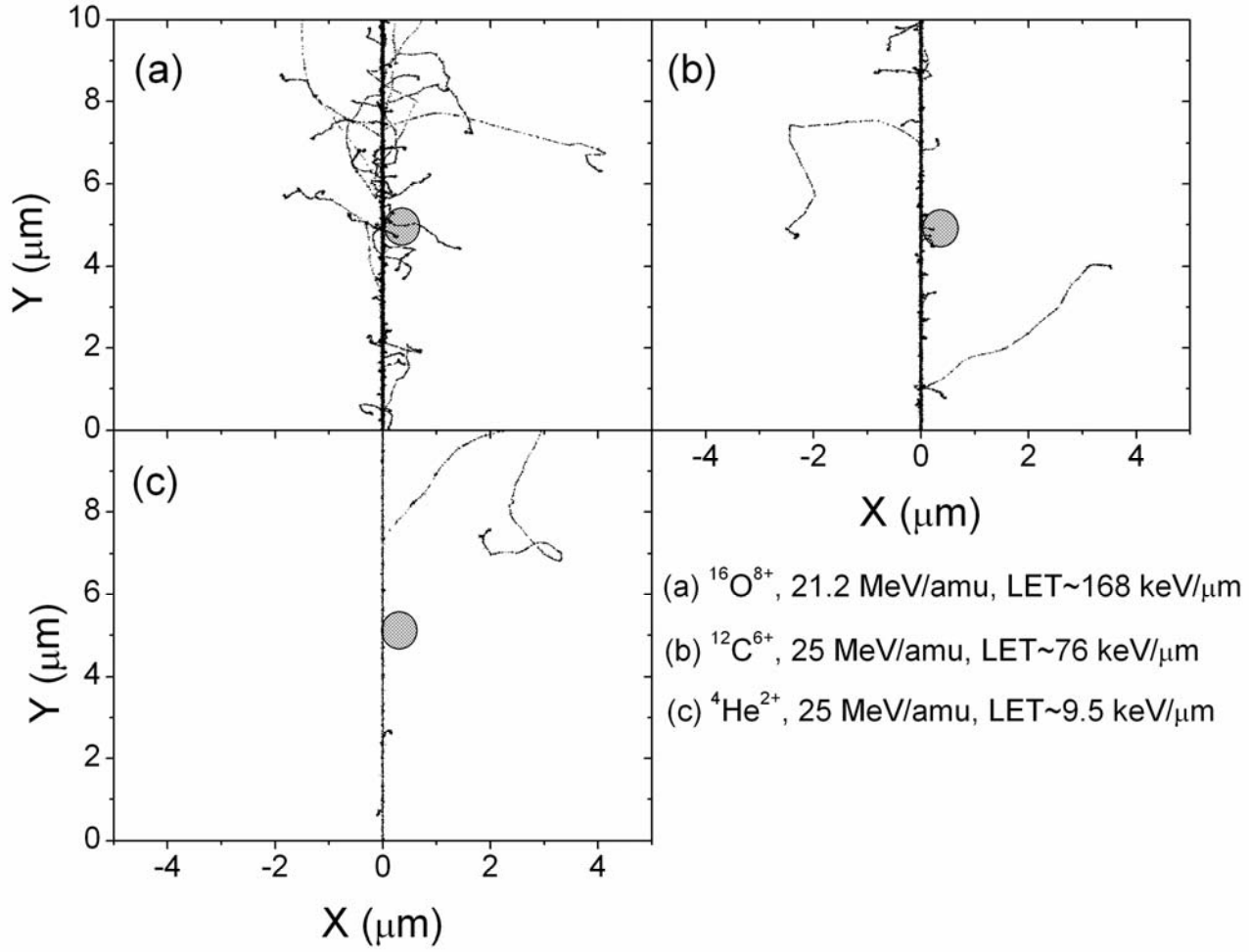
1 GeV/amu $^{56}Fe^{26+}$ ion

LET~150 keV/μm

Voxels: 40 nm x 40 nm x 40 nm

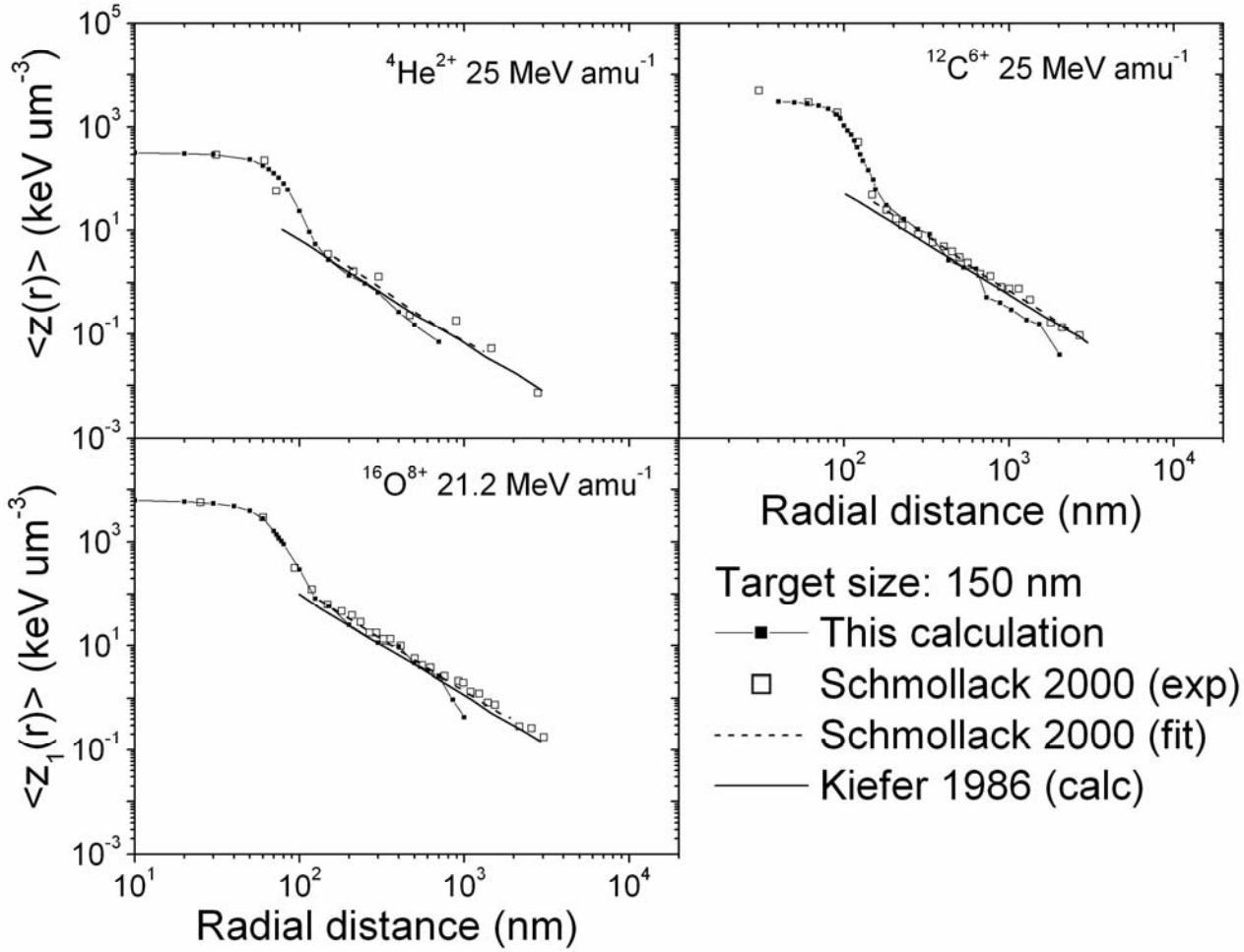
Plante I. et al. (2011). *Radiat. Prot. Dosim.* **143**, 156-161.

Target dosimetry



Plante, I. and Cucinotta, F.A. (2009), *Radiat. Env. Biophys.* **49**, 5-13

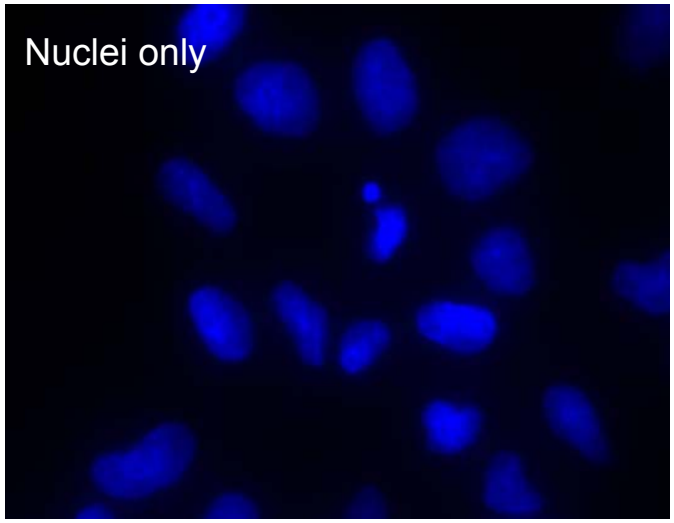
Target dosimetry

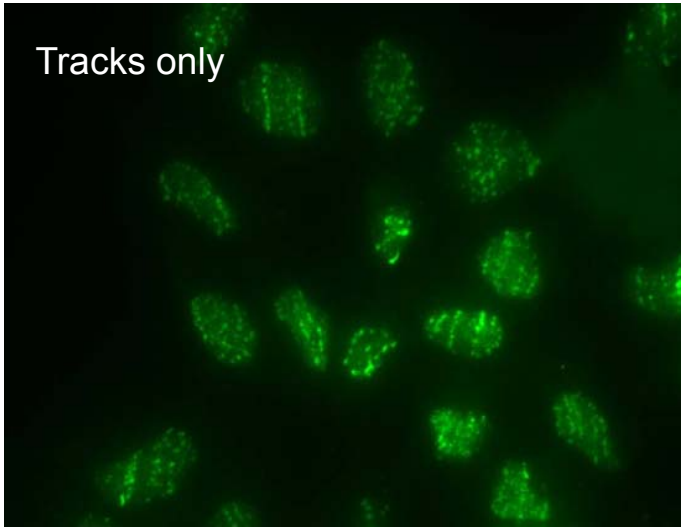


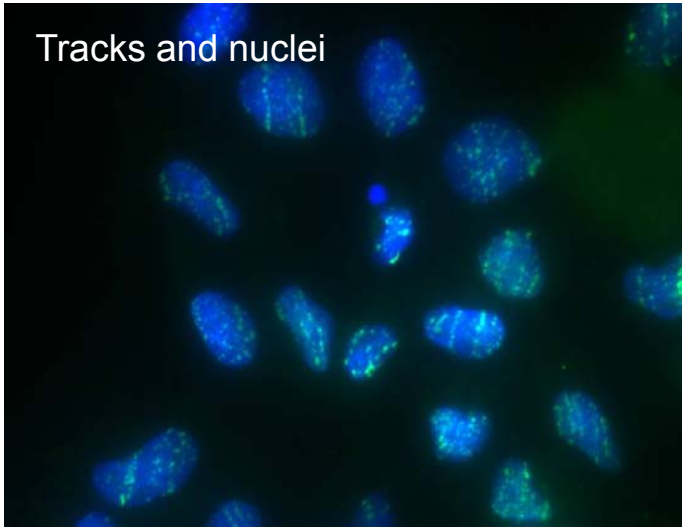
Plante, I. and Cucinotta, F.A. (2009), *Radiat. Env. Biophys.* **49**, 5-13

DNA damage / γH2AX foci studies

- Irradiation by 1 GeV/amu Fe ions
- 100 cGy
- LET ~ 149 keV/µm

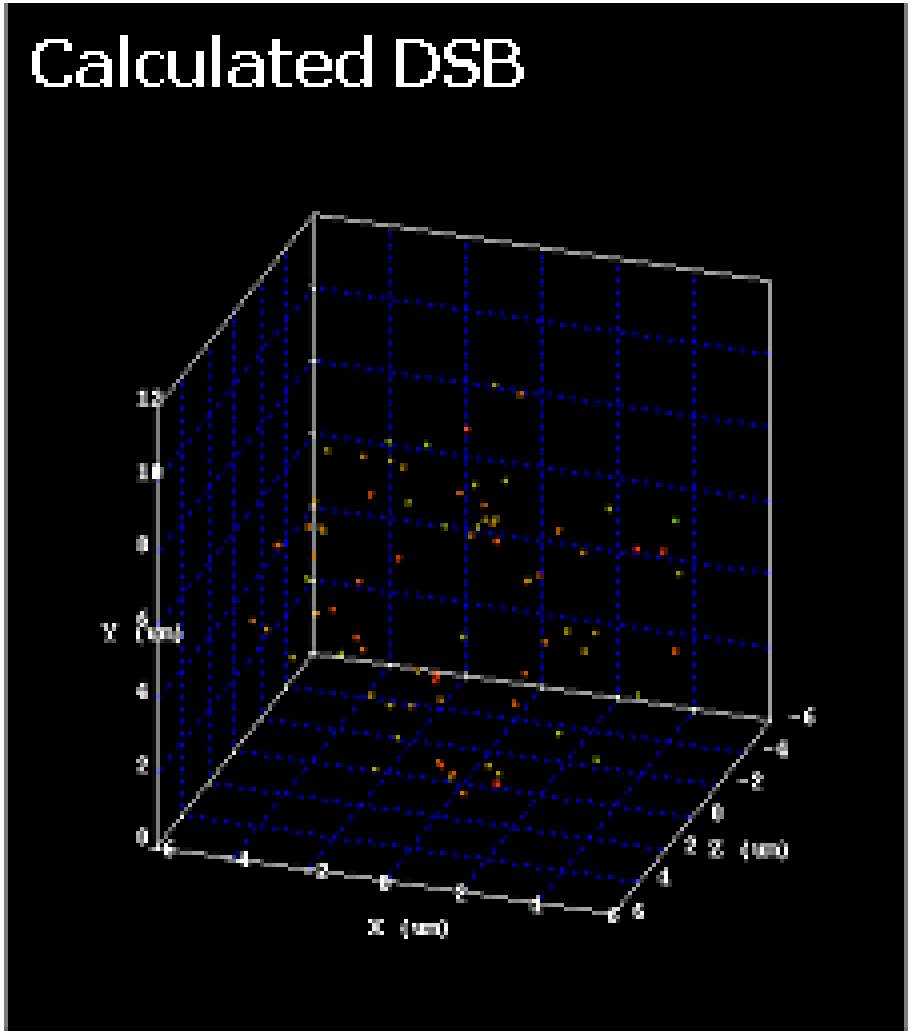






Experiments performed at the NASA Space Radiation Laboratory (2007)

DNA damage



2700 x $^{1}H^{+}$, 300 MeV (1 Gy)

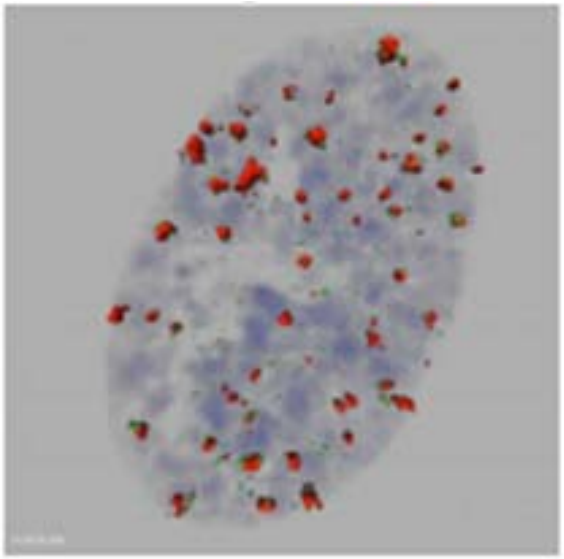
Dose in voxels (20 nm)

Chromosomes (RW model)

Intersection voxels

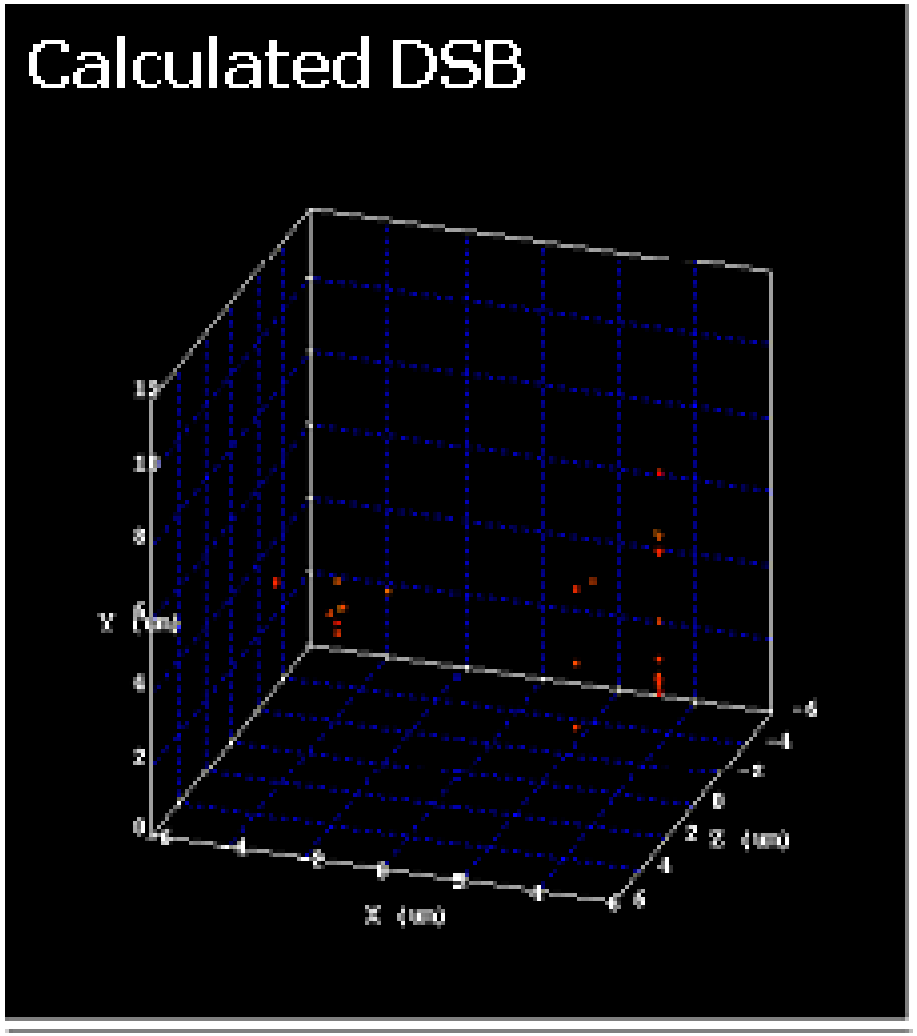
H2AX foci experiments

Application of DSB probability



Mukherjee, B. et al. (2008), *DNA repair* **7** 1717-1730; Plante, I. et al. (2013), *Phys. Med. Biol.* **58**, 6393-6405

DNA damage



6 x $^{56}Fe^{26+}$, 1 GeV/u (1 Gy)

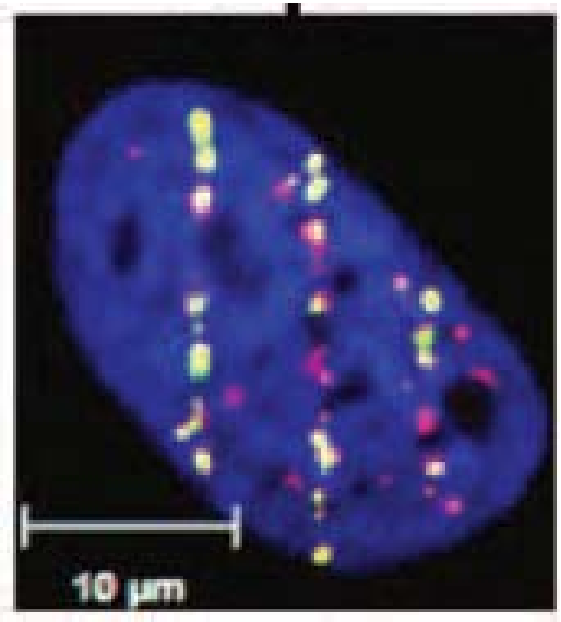
Dose in voxels (20 nm)

Chromosomes (RW model)

Intersection voxels

H2AX foci experiments

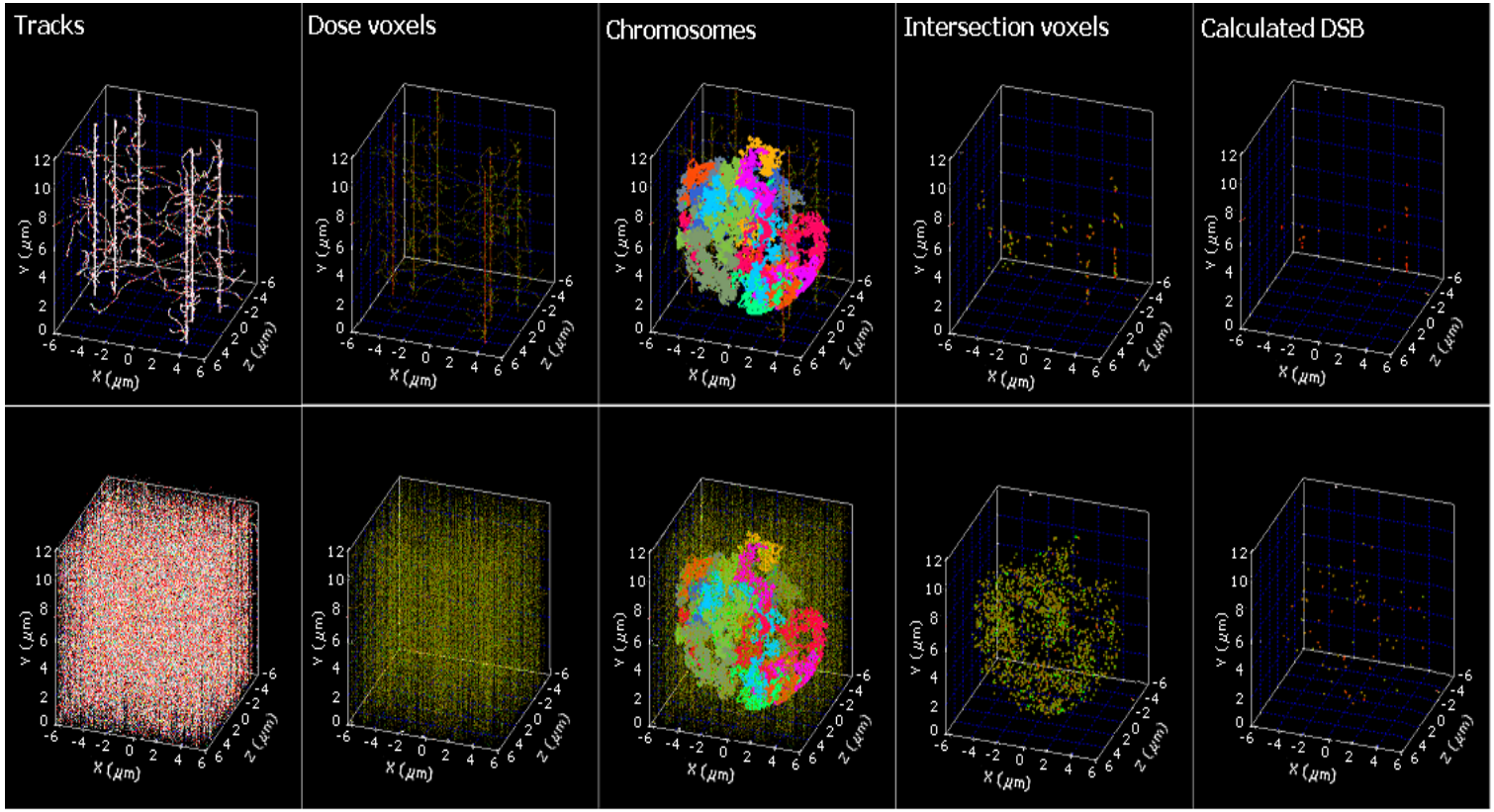
Application of DSB probability



Asaithamby, A. et al. (2008) *Radiat. Res.* **169**, 437-446; Plante, I. et al. (2013), *Phys. Med. Biol.* **58**, 6393-6405

DNA damage / γH2AX foci studies

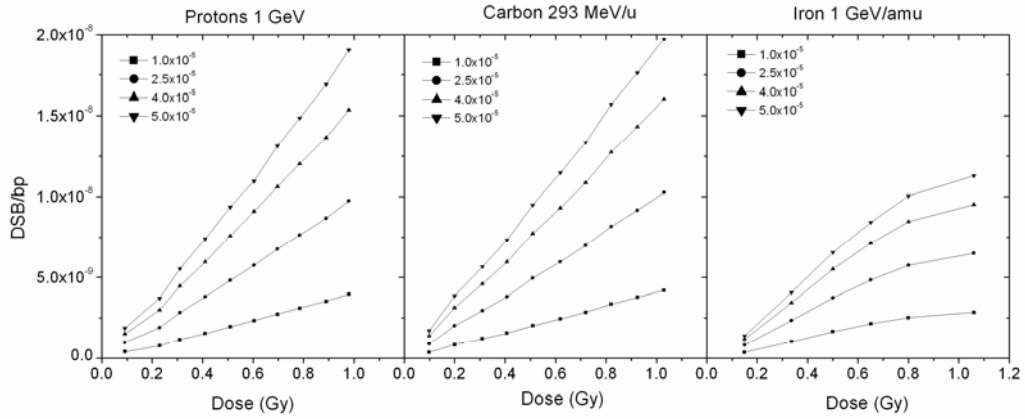
- Calculation of DSBs by low- and high-LET radiation

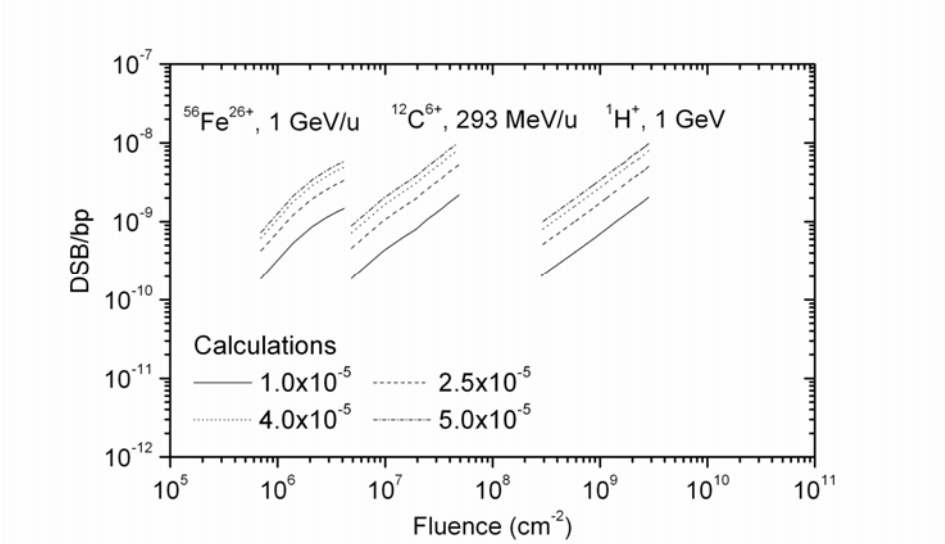


Plante, I. et al. (2013), *Phys. Med. Biol.* **58**, 6393-6405

DNA damage / γH2AX foci studies

- Calculation of DSBs by $^{1}H^{+}$, $^{12}C^{6+}$ and $^{56}Fe^{26+}$ ions

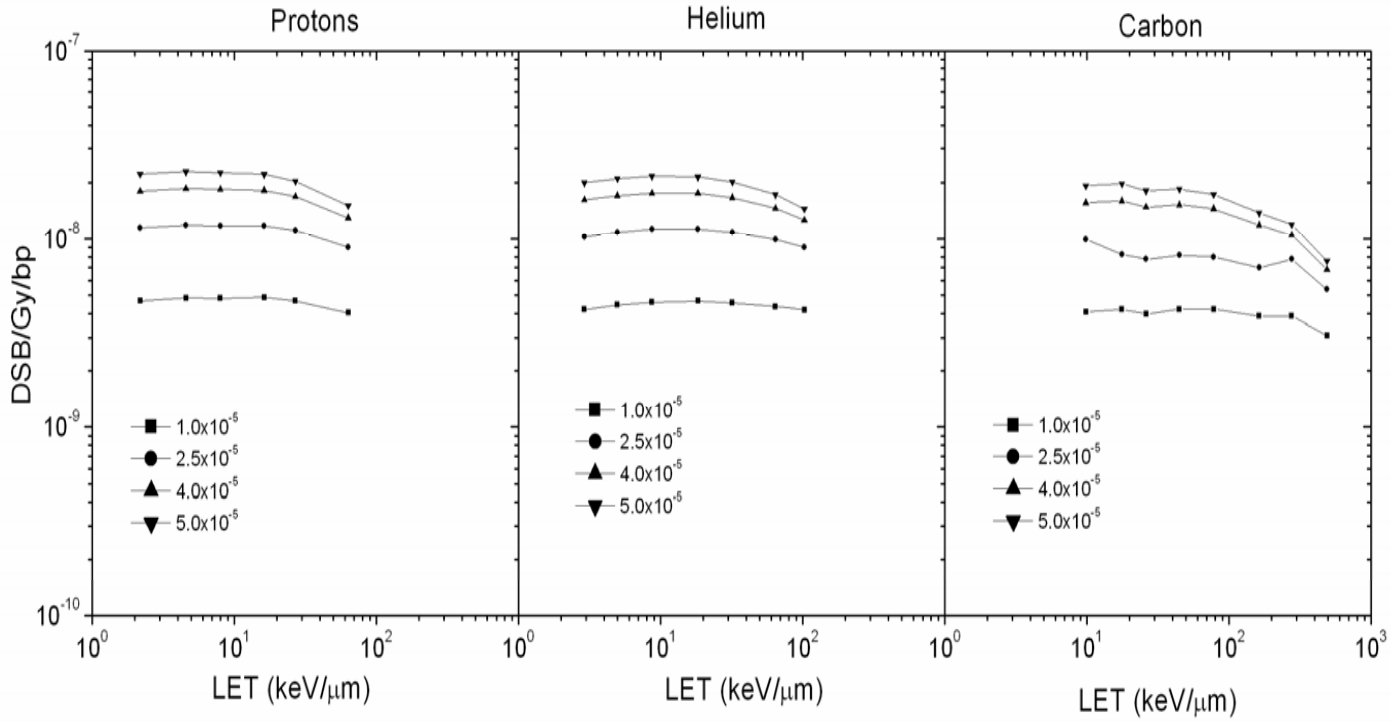




Plante, I. et al. (2013), *Phys. Med. Biol.* **58**, 6393-6405

DNA damage / γH2AX foci studies

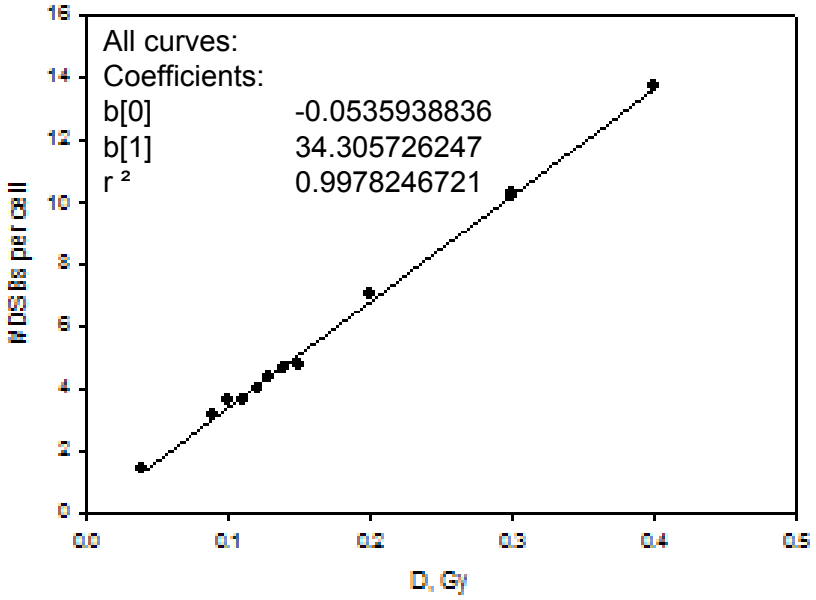
- Calculation of DSBs vs LET by $^{1}H^{+}$, $^{12}C^{6+}$ and $^{56}Fe^{26+}$ ions

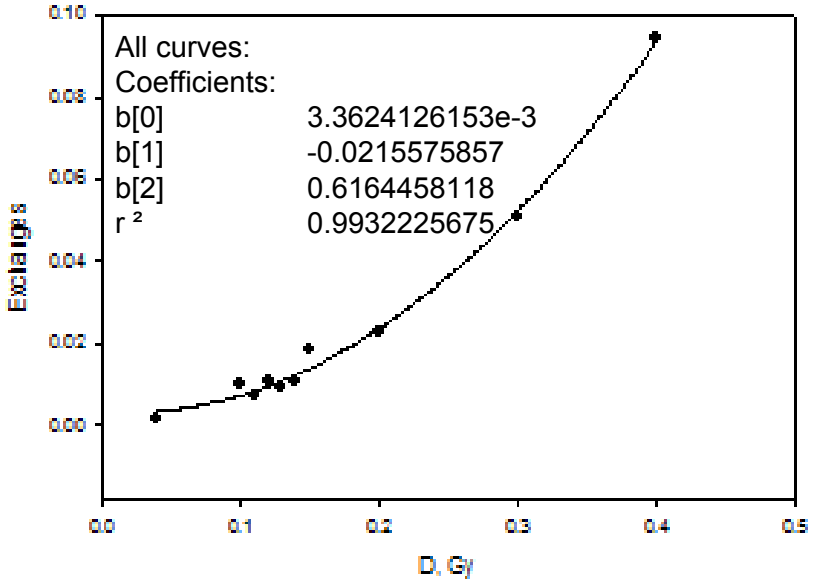


Plante, I. et al. (2013), *Phys. Med. Biol.* **58**, 6393-6405

DNA damage / γH2AX foci studies

- DSBs per cell vs dose is linear
- Exchanges per cell vs dose is linear-quadratic



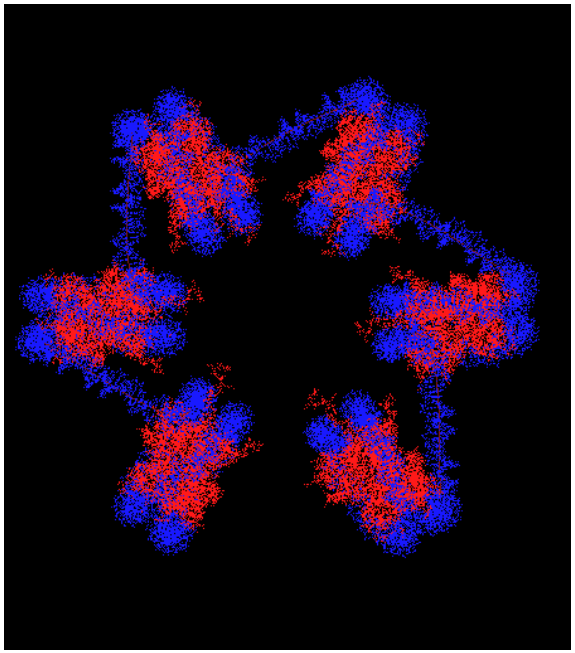


From Dr. Artem Ponomarev

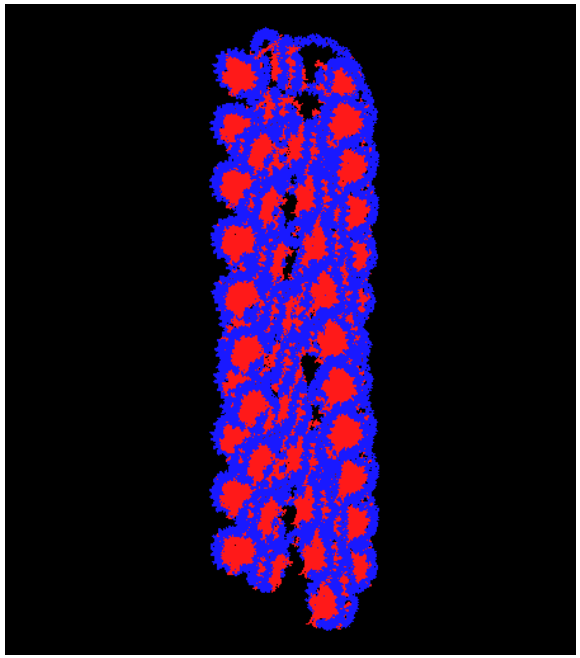
DNA damage simulations

- **To better understand the formation of DSBs, a chromatin fiber is build from nucleosome units and linker DNA**

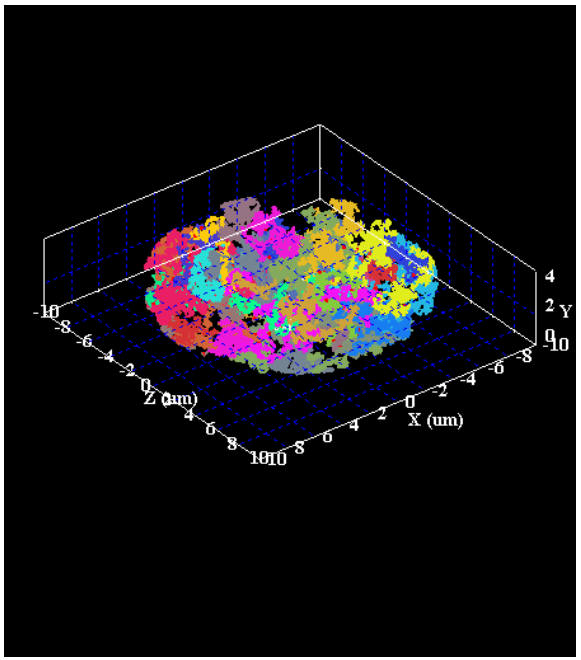
Nucleosome (DNA fragments)



Chromatin fiber



Nuclei



Nuclei simulations courtesy of Dr. Artem Ponomarev

DNA damage simulations

- **The Binary-Encounter-Bethe (BEB) model of ionization cross section**

$$\frac{d\sigma}{dw} = \frac{s}{t+u+1}\left\{\frac{1}{(t-w)^2}+\frac{1}{(1+w)^2}-\frac{1}{1+t}\left[\frac{1}{t-w}+\frac{1}{1+w}\right]+\left[\frac{1}{(t-w)^3}+\frac{1}{(1+w)^3}\right]\log(t)\right\}$$

- **The energies are expressed in units of ionization potential of the orbital (B):**
  - t=T/B is the kinetic energy of the incident electron
  - w=W/B is the kinetic energy of the ejected electron
  - u=U/B is the kinetic energy of the electron in the orbital

- **The total cross section is obtained by integration**

$$\sigma = \int_0^{(t-1)/2} \frac{d\sigma}{dw}\,dw = \frac{s}{t+u+1}\left\{1-\frac{1}{t}+\frac{1}{2}\left[1-\frac{1}{t^2}\right]\log(t)-\frac{\log(t)}{t+1}\right\}$$

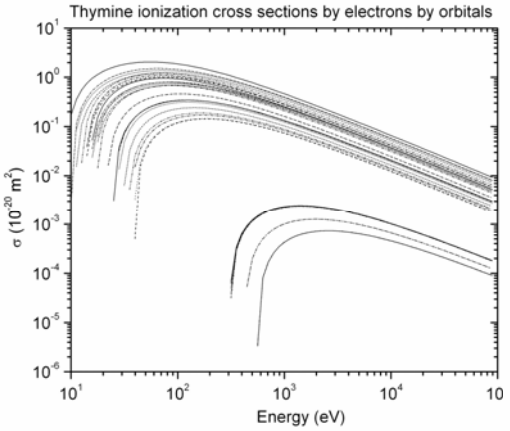
Adapted from S. Edel, PhD Thesis, Université de Toulouse (2006)

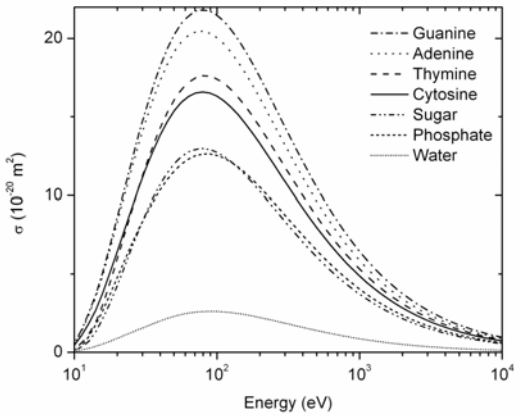
DNA damage simulations

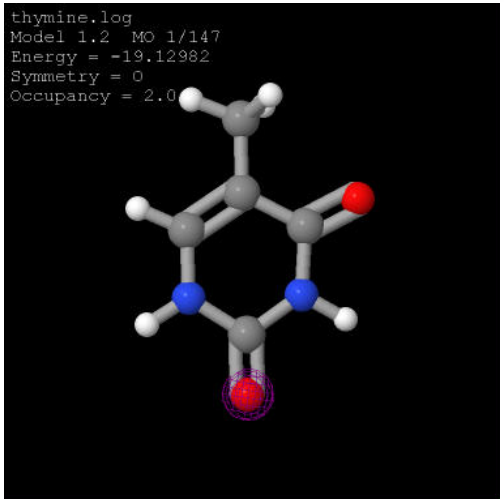
- **In the DNA bases, there are many internal and valence electrons. The BEB model allows to model the ionization for each electron of the molecule.**

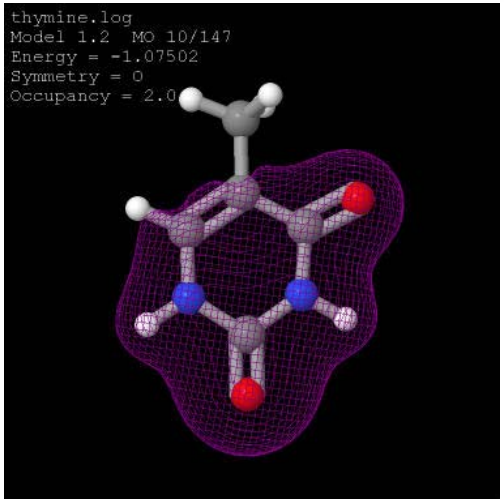
Thymine

	No	U (eV)	B (eV)	N
Internal electrons (18)	1	794.1	559.41	2
	2	794.1	559.18	2
	3	601.5	425.6	2
	4	601.5	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	40.38	9.27	1.97









Calculations of MO from the site www.chemeddl.org

DNA damage simulations

- **The BEB cross section can be written in a form suitable for sampling by a composition method:**

$$\frac{d\sigma}{dw} = \frac{s}{t+u+1}\left\{\frac{1}{(t-w)^2}+\frac{1}{(1+w)^2}-\frac{1}{1+t}\left[\frac{1}{t-w}+\frac{1}{1+w}\right]+\left[\frac{1}{(t-w)^3}+\frac{1}{(1+w)^3}\right]\log(t)\right\}$$

$$\frac{d\sigma}{dw} = \sum_{i=1}^{3} k_i(w) = \sum_{i=1}^{3} A_i g_i(w) h_i(w)$$

where

$$\int_0^{(t-1)/2} g_i(w)dw = 1$$

$$0 \le h_i(w) \le 1$$

$$A_i \ge 0$$

$$A_1 = \frac{s}{t+u+1}\left(\frac{t}{t+1}\right)\left(\frac{t-1}{t+1}\right) \qquad h_1(w) = \frac{t+1}{t}\left[1-\frac{w+1}{t+1}\right] \qquad g_1(w) = \frac{t+1}{t-1}\frac{1}{(w+1)^2}$$

$$A_2 = \frac{1}{2}\left(\frac{s}{t+u+1}\right)\left[\frac{t-1}{t(t+1)}\right] \qquad h_2(w) = 2\left[1-\frac{t-w}{t+1}\right] \qquad g_2(w) = \frac{t(1+1)}{t-1}\frac{1}{(t-w)^2}$$

$$A_3 = 2\log(t)\left(\frac{s}{t+u+1}\right)\left[\frac{(t+1)^2-4}{2(t+1)^2}\right] \qquad h_3(w) = \frac{1}{2}\left[1+\left(\frac{w+1}{t-w}\right)^3\right] \qquad g_3(w) = \left[\frac{2(t+1)^2}{(t+1)^2-4}\right]\frac{1}{(w+1)^3}$$

Adapted from S. Edel, PhD thesis, Université de Toulouse

DNA damage simulations

❑ Sampling algorithm and results

Algorithm to sample the energy of the ionized electron w_x from the BEB model of ionization cross sections

CALCULATE A_1, A_2, A_3 and $A_{123}=A_1+A_2+A_3$
REPEAT {
GENERATE random numbers R_1, R_2 and R_3
IF ($R_1<A_1/A_{123}$) {
{

$$w_x = \frac{R_2(t-1)}{(t+1)-R_2(t-1)}$$

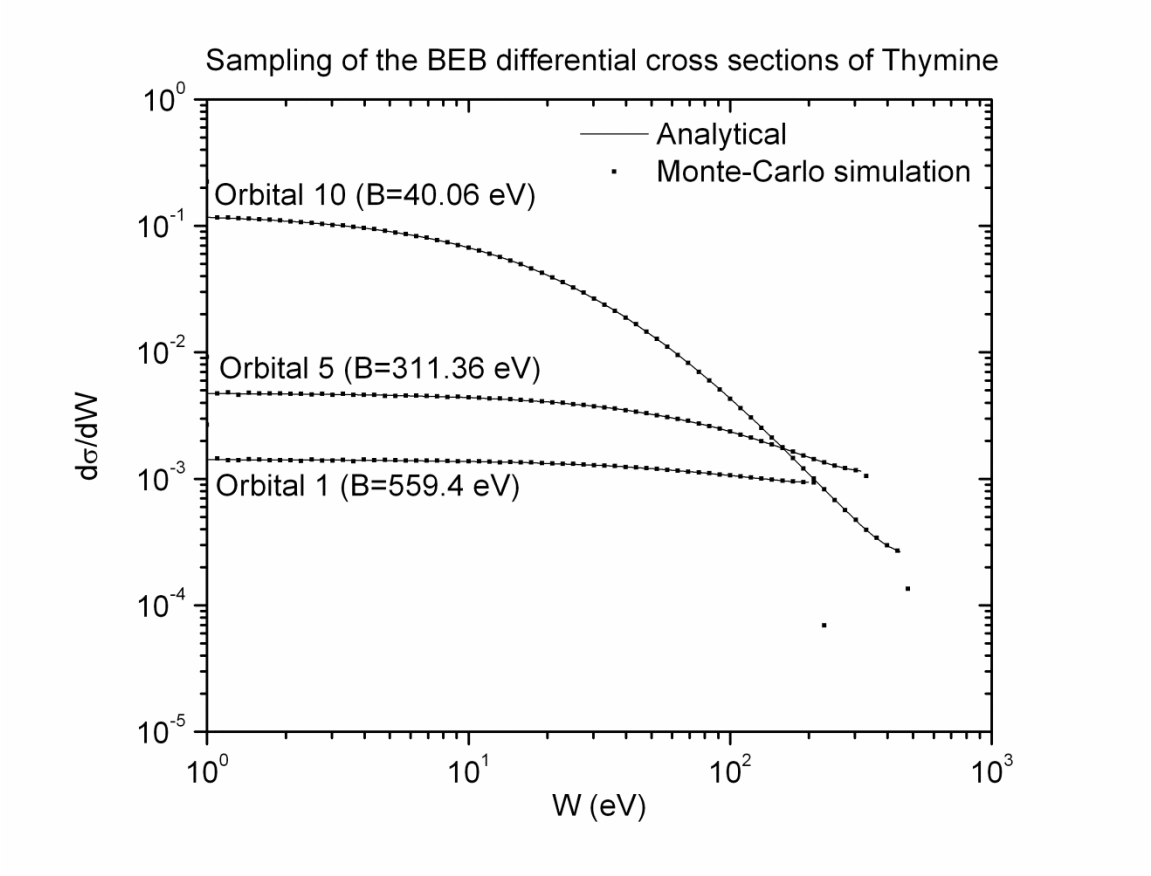
IF ($R_3 \le \frac{t-w_x}{t}$) EXIT loop
}
IF ($A_1/A_{123} \le R_1 < (A_1+A_2)/A_{123}$) {

$$w_x = \frac{R_2 t(t-1)}{(t+1)+R_2(t-1)}$$

IF ($R_3 \le 2\left(1-\frac{t-w_x}{t+1}\right)$) EXIT loop
}
IF ($R_1 \ge (A_1+A_2)/A_{123}$) {

$$w_x = \frac{t+1}{\sqrt{4+(R_2-1)((t+1)^2-4)}} - 1$$

IF ($R_3 \le \frac{1}{2}\left[1+\left(\frac{w_x+1}{t-w_x}\right)^3\right]$) EXIT loop
}
}
RETURN w_x



Adapted from S. Edel, PhD thesis, Université de Toulouse

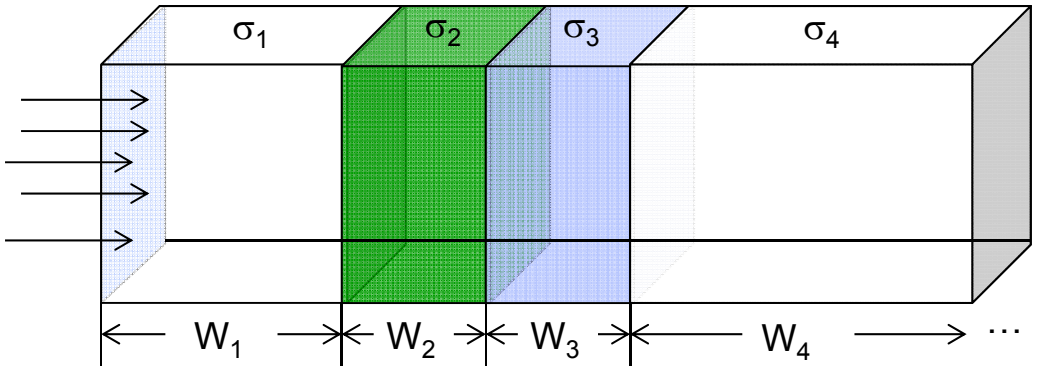
DNA damage studies

- **Cross sections can be calculated for the bases, sugars and phosphates.**
- **In this case, the medium is considered a succession of homogeneous media.**

$$dI = -IN\sigma dx$$

$$\ln(I / I_0) = -\int_0^x \sigma(u) N du$$

$$I = I_0 \exp\left\{ -N\left[\sum_{j=1}^{i-1} (\sigma_j - \sigma_i) W_j + \sigma_i x \right] \right\}$$

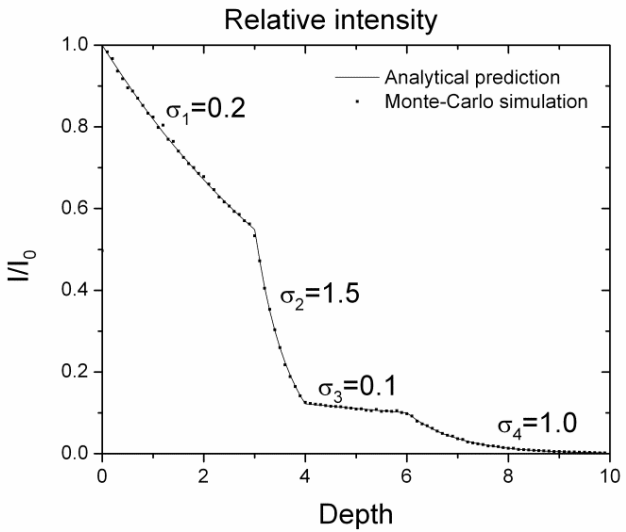


Relative weight

$$p_i = I_0 \frac{\exp(-N\sum_{j=1}^{i-1} W_j \sigma_j)(1 - \exp(-NW_i\sigma_i))}{N\sigma_i}$$

Sampling of W_s

$$W_s = \sum_{j=1}^{i-1} W_j - \frac{1}{N\sigma_i} \log[1 - V(1 - e^{-\sigma_j NW_j})]$$



Adapted from S. Edel, PhD Thesis, Université de Toulouse (2006)

Radiation chemistry

- **~10^{-12} – 10^{-6} s**
  - Particles diffusion
  - Chemical reactions

$$G(X) = \frac{\text{Number of chemical species created}}{\text{100 eV deposited energy}}$$

- **The radiolytic species are not uniformly distributed. Therefore, an approach based on Green's functions of the diffusion equation (DE) is used.**

Examples of chemical reactions:

$$e^-_{aq} + e^-_{aq} \xrightarrow{2H_2O} H_2 + 2\,OH^-$$

$$^\bullet OH + e^-_{aq} \longrightarrow OH^-$$

$$^\bullet OH + {}^\bullet OH \longrightarrow H_2O_2$$

$$^\bullet OH + H_2O_2 \longrightarrow HO_2^\bullet + H_2O$$

$$H^+ + O_2^{\bullet -} \rightleftharpoons HO_2^\bullet$$

$$H^\bullet + H_2O_2 \longrightarrow {}^\bullet OH + H_2O$$

(More than 60 reactions...)

Bimolecular reactions

❑ DE for the propagation of particles A and B

$$\partial p(\mathbf{r_A}, \mathbf{r_B}, t \mid \mathbf{r_{A0}}, \mathbf{r_{B0}}, t_0)/\partial t$$
$$= \left[D_A \nabla_{\mathbf{A}}^{\,2} + D_B \nabla_{\mathbf{B}}^{\,2}\right] p(\mathbf{r_A}, \mathbf{r_B}, t \mid \mathbf{r_{A0}}, \mathbf{r_{B0}}, t_0)$$

$p(\mathbf{r_A},\mathbf{r_B},t|\mathbf{r_{A0}},\mathbf{r_{B0}},t_0)$: probability of particles A and B to be at positions $\mathbf{r_A}$ and $\mathbf{r_B}$ at time t, given that they were at $\mathbf{r_{A0}}$ and $\mathbf{r_{B0}}$ at t_0

D_A, D_B: Diffusion coefficients

❑ Transformation of variables

$$\mathbf{R} = (D_B \mathbf{r_A} + D_A \mathbf{r_B})/(D_A + D_B) \qquad \nabla_{\mathbf{R}} = \partial / \partial \mathbf{R}$$

$$\mathbf{r} = \mathbf{r_B} - \mathbf{r_A} \qquad \nabla_{\mathbf{r}} = \partial / \partial \mathbf{r}$$

$$\partial p(\mathbf{R}, \mathbf{r}, t \mid \mathbf{R_0}, \mathbf{r_0}, t_0)/\partial t = (D_A + D_B)\left[\nabla_{\mathbf{R}}^{\,2} + \nabla_{\mathbf{r}}^{2}\right] p(\mathbf{R}, \mathbf{r}, t \mid \mathbf{R_0}, \mathbf{r_0}, t_0)$$

$$p(\mathbf{R}, \mathbf{r}, t \mid \mathbf{R_0}, \mathbf{r_0}, t_0) = p^{\mathbf{R}}(\mathbf{R}, t \mid \mathbf{R_0}, t_0)\, p^{\mathbf{r}}(\mathbf{r}, t \mid, \mathbf{r_0}, t_0)$$

$$\partial p^{\mathbf{R}}(\mathbf{R}, t \mid \mathbf{R_0}, t_0)/\partial t = (D_A + D_B)\nabla_{\mathbf{R}}^{\,2} p^{\mathbf{R}}(\mathbf{R}, t \mid \mathbf{R_0}, t_0)$$

$$\partial p^{\mathbf{r}}(\mathbf{r}, t \mid \mathbf{r_0}, t_0)/\partial t = (D_A + D_B)\nabla_{\mathbf{r}}^{2} p^{\mathbf{r}}(\mathbf{r}, t \mid \mathbf{r_0}, t_0)$$

Uncoupled equations

in **r** and **R**

Van Zon, J. S. et al. (2005) *J. Chem. Phys.* **123**, 234910

Bimolecular reactions

❑ Free diffusive motion of the coordinate R

$$\partial p^{\mathbf{R}}(\mathbf{R},t\,|\,\mathbf{R_0},t_0)/\partial t = D\nabla_{\mathbf{R}}{}^2 p^{\mathbf{R}}(\mathbf{R},t\,|\,\mathbf{R_0},t_0) \qquad \text{(DE)}$$

$$p^{\mathbf{R}}(\mathbf{R},t\,|\,\mathbf{R_0},t_0) = \delta(\mathbf{R}-\mathbf{R_0}) \qquad \text{(Initial condition)}$$

$$p^{\mathbf{R}}(|\,\mathbf{R}\,|\to\infty,t\,|\,\mathbf{R_0},t_0) = 0 \qquad \text{(Boundary condition)}$$

$$p^{\mathbf{R}}(\mathbf{R},t\,|\,\mathbf{R_0},t_0) = \frac{1}{[4\pi D(t-t_0)]^{3/2}}\exp\left[\frac{(\mathbf{R}-\mathbf{R}_0)^2}{4D(t-t_0)}\right] \qquad \text{(Solution)}$$

$p^{\mathbf{R}}(\mathbf{R},t|\mathbf{R_0},t_0)$: probability distribution of the vector **R** at time t, given that it was located at position $\mathbf{R_0}$ at time t_0

$D=D_A+D_B$: Sum of the diffusion coefficients

Van Zon, J. S. et al. (2005) *J. Chem. Phys.* **123**, 234910

Bimolecular reactions

- **Free diffusive motion* of the inter-particle separation vector r**

$$\frac{\partial p^{r}(\mathbf{r},t\,|\,\mathbf{r_0},t_0)}{\partial t} = D\nabla^2_{\mathbf{r}} p^{r}(\mathbf{r},t\,|\,\mathbf{r_0},t_0) \qquad \text{(DE)}$$

$$p^{r}(\mathbf{r},t\,|\,\mathbf{r_0},t_0) = \delta(\mathbf{r}-\mathbf{r_0}) \qquad \text{(Initial condition)}$$

- **For chemical reactions, we need the inter-particle distance r.**
  - Therefore, the DE is written in spherical coordinates.
  - Only the radial component will be considered (angular dependency terms are neglected). This considerably simplifies the analytical solution.

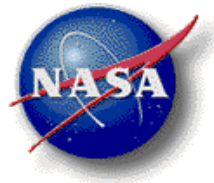
$$\frac{\partial p(r,t\,|\,r_0)}{\partial t} = \frac{D}{r^2}\frac{\partial}{\partial r}\left[r^2\frac{\partial}{\partial r}p(r,t\,|\,r_0)\right] \qquad \text{(Radial part of the DE)}$$

$$4\pi\mathbf{r}_0^2 p(r,t\,|\,r_0) = \delta(r-r_0), r \geq R \qquad \text{(Initial condition; R=reaction radius)}$$

$p(r,t|r_0,t_0)$: probability distribution of the separation distance r at time t, given that it was r_0 at time t_0

*We assume that there is no force interacting between particles. This is the case for most of the chemical reactions that we are interested in.

Bimolecular reactions



❑ Simple case: partially diffusion-controlled reaction with rate k_a and reaction radius R

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

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

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

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

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

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).

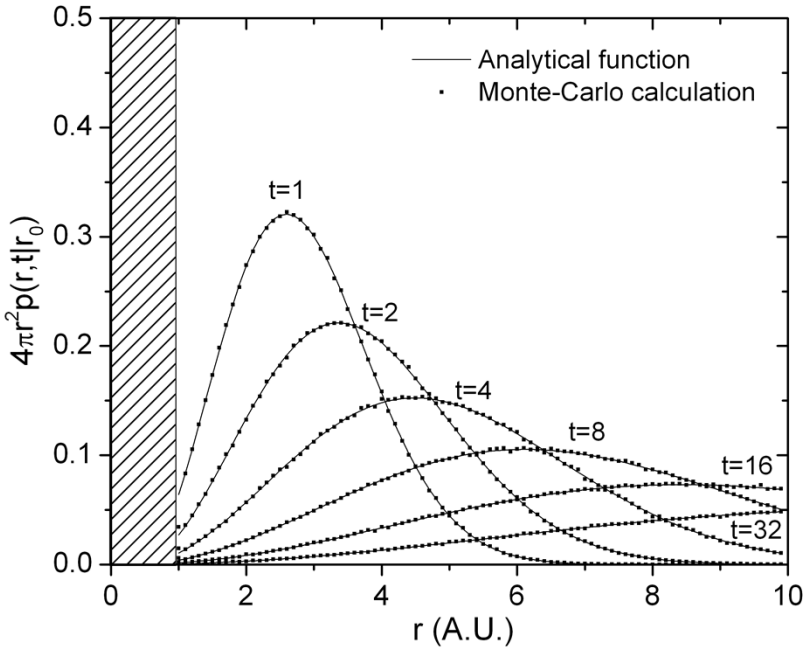
Plante, I. et al. (2013) *J. Comput. Phys.* **242**, 531-543

Green's function for radiation chemistry

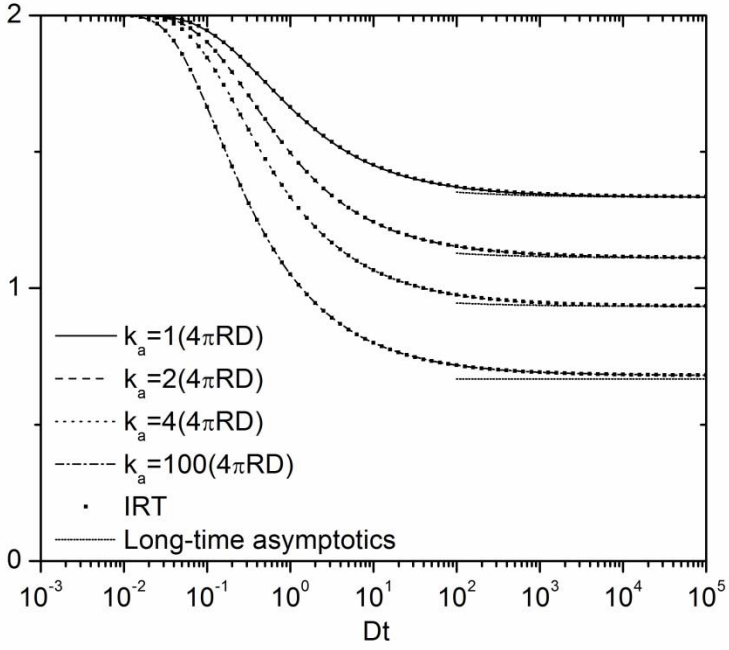
- **Simple case: partially diffusion-controlled reaction with rate k_a and reaction radius R**

$$A + B \xrightarrow{k_a} C$$

Green's functions



Survival probabilities



Plante, I. et al. (2013) *J. Comput. Phys.* **242**, 531-543

Green's functions (3D) for radiation chemistry

❑ Green's function with angular dependency (exact)

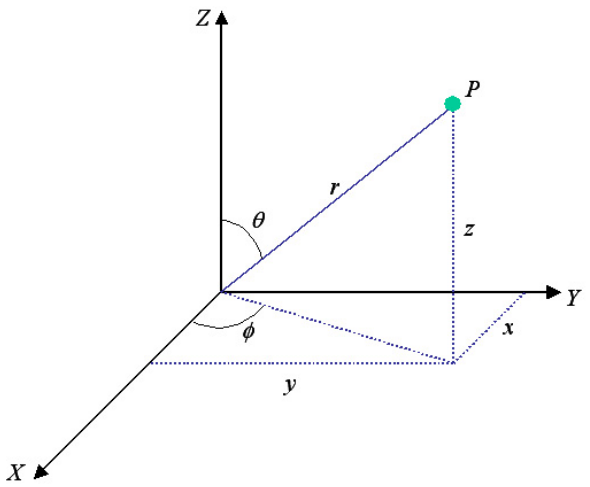
$$p(r,\theta,\phi,t \mid r_0,\theta_0,\phi_0) = \frac{1}{4\pi\sqrt{rr_0}} \sum_{n=0}^{\infty} (2n+1) P_n(\cos(\gamma)) \int_0^{\infty} e^{-u^2 Dt} u F_{n+1/2}(u,r) F_{n+1/2}(u,r_0) du$$

$$F_\nu(u,r) = \frac{(2Rk_a+1)\left[J_\nu(ur)Y_\nu(uR) - Y_\upsilon(ur)J_\upsilon(uR)\right] - 2uR\left[J_\nu(ur)Y_\nu'(uR) - Y_\nu(ur)J_\nu'(uR)\right]}{\sqrt{\left[(2Rk_a+1)J_\nu(uR) - 2uRJ_\nu'(uR)\right]^2 + \left[(2Rk_a+1)Y_\nu(uR) - 2uRY_\nu'(uR)\right]^2}}$$

$$\cos(\gamma) \equiv \cos(\theta)\cos(\theta_0) + \sin(\theta)\sin(\theta_0)\cos(\phi - \phi_0)$$

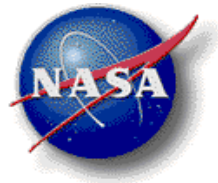
$P_n(x)$	n^{th} Legendre polynomial
$J_n(x)$	Bessel function of the first kind
$Y_n(x)$	Bessel function of the second kind

=> Even though this distribution is very complex, it is possible to generate the exact length and the approximate angles of the inter-particle vector from this Green's function



van Zon, J. S. and ten Wolde, P. R. (2005) *J. Chem. Phys.* **123**, 234910

Green's functions (3D) for radiation chemistry



- Limiting case: $R \rightarrow 0$, $k_a = 0$
- In principle, this should be equivalent to free diffusion

$$p(r,\theta,\phi,t \mid r_0,\theta_0,\phi_0) = \frac{1}{4\pi\sqrt{rr_0}} \sum_{n=0}^{\infty} (2n+1) P_n(\cos(\gamma)) \int_0^{\infty} e^{-u^2 Dt} u F_{n+1/2}(u,r) F_{n+1/2}(u,r_0) du$$

$$F_\nu(u,r) = \frac{\left[J_\nu(ur)Y_\nu(uR) - Y_\upsilon(ur)J_\upsilon(uR)\right] - 2uR\left[J_\nu(ur)Y_\nu'(uR) - Y_\nu(ur)J_\nu'(uR)\right]}{\sqrt{\left[J_\nu(uR) - 2uRJ_\nu'(uR)\right]^2 + \left[Y_\nu(uR) - 2uRY_\nu'(uR)\right]^2}}$$

$$\lim_{R\to 0} F_\upsilon(u,r) = J_\upsilon(ur)$$

$$p(r,\theta,\phi,t \mid r_0,\theta_0,\phi_0) = \frac{1}{4\pi\sqrt{rr_0}} \frac{1}{2Dt} e^{-(r^2+r_0^2)/4Dt} \sum_{n=0}^{\infty} (2n+1) P_n(\cos(\gamma)) I_{n+1/2}\left(\frac{rr_0}{2Dt}\right)$$ Weber's formula

$$\sqrt{\frac{\pi}{2z}} \sum_{i=0}^{\infty} (2k+1) I_{k+1/2}(z) P_k(\cos\gamma) = e^{z\cos\gamma}$$

$$p(r,\theta,\phi,t \mid r_0,\theta_0,\phi_0) = \frac{1}{(4\pi Dt)^{3/2}} e^{-(r^2+r_0^2-2rr_0\cos\gamma)/4Dt}$$ ≡ Free diffusion!

Plante, I. et al., *submitted*

Green's functions (3D) for radiation chemistry

- Radial distribution of the exact Green's function
- The radial distribution is not function of θ_0 and ϕ_0, so we use θ_0=0 and ϕ_0=0, for which cos(γ)=cos(θ)

$$p(r,t\,|\,r_0,0,0) = \int_0^{2\pi}\int_0^{\pi} r^2 p(r,\theta,\phi,t\,|\,r_0,0,0)\sin\theta\,d\theta\,d\phi = \int_0^{\pi} 2\pi r^2 p(r,\theta,\phi,t\,|\,r_0,0,0)\sin\theta\,d\theta$$

$$\int_0^{\pi}(2n+1)P_n(\cos\theta)\sin(\theta)d\theta = 2\delta_{n0}$$ Identity

$$p(r,t\,|\,r_0,0,0) = \frac{r^2}{\sqrt{rr_0}}\sum_{n=0}^{\infty}\delta_{n0}\int_0^{\infty} e^{-u^2Dt}uF_{n+1/2}(u,r)F_{n+1/2}(u,r_0)du = \frac{r^2}{\sqrt{rr_0}}\int_0^{\infty} e^{-u^2Dt}uF_{1/2}(u,r)F_{1/2}(u,r_0)du$$

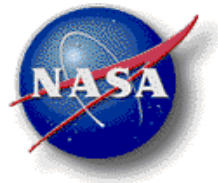
$$J_{n+1/2}(z) = \sqrt{2z/\pi}\,j_n(z) \qquad j_0(z) = \frac{\sin z}{z} \qquad Y_{n+1/2}(z) = \sqrt{2z/\pi}\,y_n(z) \qquad y_0(z) = \frac{-\cos z}{z}$$ Bessel functions

$$p(r,t\,|\,r_0,0,0) = \frac{r^2}{\sqrt{rr_0}}\int_0^{\infty} e^{-u^2Dt}u\,\frac{2(u\sigma\cos[u(r-\sigma)] + (1+k_a\sigma)\sin[u(r-\sigma])(u\sigma\cos[u(r_0-\sigma)] + (1+k_a\sigma)]\sin[u(r_0-\sigma)]}{\pi u(1+2k_a\sigma+(k_a^2+u^2)\sigma^2)}du$$ Substituting

$$p(r,t\,|\,r_0,0,0) = \frac{r}{r_0\sqrt{4\pi Dt}}\left\{\exp\left[-\frac{(r-r_0)^2}{4Dt}\right] + \exp\left[-\frac{(r+r_0-2\sigma)^2}{4Dt}\right]\right\} + \alpha W\left(\frac{r+r_0-2\sigma}{\sqrt{4Dt}}, -\alpha\sqrt{Dt}\right) \equiv 4\pi r^2 p_{rad}(r,t\,|\,r_0)$$ ≡ Radial GF!

Plante, I. et al., *submitted*

Green's functions (3D) for radiation chemistry



- The sampling algorithms for chemical reactions yields values of r, θ and ϕ
- Therefore, we need to work with the distributions $p(r,t|r_0,\theta_0,\phi_0)$, $p(\theta,t|r_0,\theta_0,\phi_0)$ and $p(\phi,t|r_0,\theta_0,\phi_0)$.
- These distributions are difficult to obtain for the general case ($\theta_0 \neq 0$, $\phi_0 \neq 0$) even for simple free 3D diffusion

$$p_{fr}(r,t \mid r_0,\theta_0,\phi_0) = \int_0^{2\pi}\int_0^{\pi} r^2 p_{fr}(r,\theta,\phi,t \mid r_0,\theta_0,\phi_0)\sin\theta\, d\theta\, d\phi = \frac{r}{\sqrt{\pi r_0^2 Dt}} \exp\left(-\frac{r^2+r_0^2}{4Dt}\right)\sinh\left(\frac{rr_0}{2Dt}\right)$$

$$p_{fr}(\theta,t \mid r_0,\theta_0,\phi_0) = \int_0^{\infty}\int_0^{2\pi} r^2 p_{fr}(r,\theta,\phi,t \mid r_0,\theta_0,\phi_0)\sin(\theta)\, d\phi\, dr$$

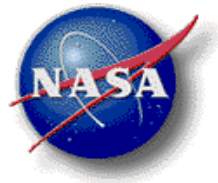
$$= \sum_{n=0}^{\infty} \frac{(2n+2)!}{(n!)^2} e^{-r_0^2(1-\cos^2\theta\cos^2\theta_0)/4Dt} i^{2(n+1)} Erfc\left(\frac{-r_0\cos\theta\cos\theta_0}{\sqrt{4Dt}}\right)\left(\frac{r_0\sin\theta\sin\theta_0}{\sqrt{4Dt}}\right)^{2n}\sin\theta$$

$$p_{fr}(\phi,t \mid r_0,\theta_0,\phi_0) = \int_0^{\infty}\int_0^{\pi} r^2 p_{fr}(r,\theta,\phi,t \mid r_0,\theta_0,\phi_0)\sin(\theta)\, d\theta\, dr = \frac{1}{2\sqrt{\pi}} e^{-r_0^2\sin^2(\phi-\phi_0)\sin^2\theta_0/4Dt} iErfc\left(-\frac{r_0\cos(\phi-\phi_0)\sin\theta_0}{\sqrt{4Dt}}\right)$$

$$i^n Erfc(z) = \int_z^{\infty} i^{n-1} Erfc(t)\, dt$$

Plante, I. et al., *submitted*

Green's functions (3D) for radiation chemistry



- The sampling algorithms for chemical reactions yields distributions of r, θ and ϕ
- The analytical distributions $p(r,t|r_0,\theta_0,\phi_0)$, $p(\theta,t|r_0,\theta_0,\phi_0)$ and $p(\phi,t|r_0,\theta_0,\phi_0)$ are difficult to obtain for the general case ($\theta_0 \neq 0$, $\phi_0 \neq 0$) even for simple free diffusion
- The case $\theta_0=0$, $\phi_0=0$ is much simpler since ϕ is uniformly distributed between 0 and 2π.
- It is possible to sample the distributions in a referential aligned with the z axis and then perform two rotations to get the sampled values for the general case

$$\begin{bmatrix} x \\ y \\ z \end{bmatrix} = \begin{bmatrix} \cos\phi_0 & -\sin\phi_0 & 0 \\ \sin\phi_0 & \cos\phi_0 & 0 \\ 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} \cos\theta_0 & 0 & \sin\theta_0 \\ 0 & 1 & 0 \\ -\sin\theta_0 & 0 & \cos\theta_0 \end{bmatrix} \begin{bmatrix} x'' \\ y'' \\ z'' \end{bmatrix}$$

Plante, I. et al., *submitted*

Green's functions (3D) for radiation chemistry

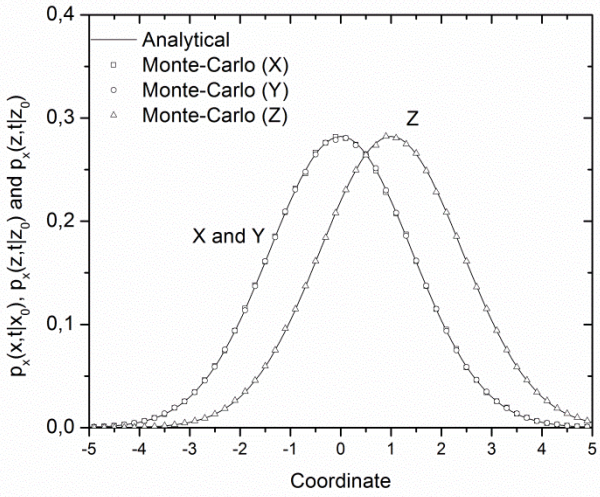
- Free diffusion for the case $\theta_0=0$, $\phi_0=0$
- The distributions in Cartesian coordinates are Gaussians. Their equivalents in spherical coordinates are given by

$$p_{fr}(r,t\,|\,r_0,0,0)=\frac{r}{\sqrt{\pi r_0^2 Dt}}\exp\left(-\frac{r^2+r_0^2}{4Dt}\right)\sinh\left(\frac{rr_0}{2Dt}\right)$$

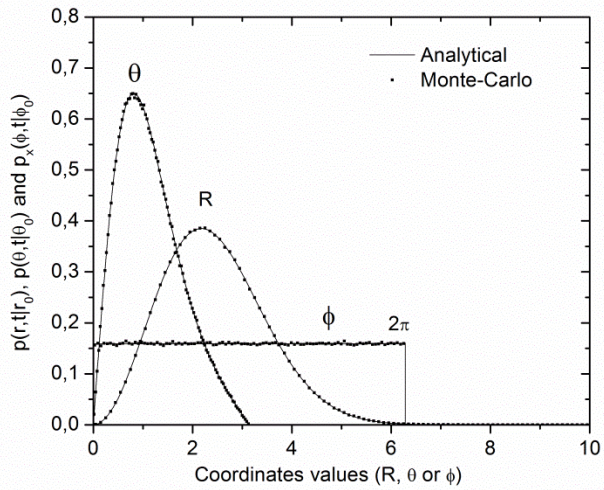
$$p_{fr}(\theta,t\,|\,r_0,0,0)=2(\sin\theta)e^{-r_0^2\sin^2\theta/4Dt}i^2Erfc\left(-\frac{r_0\cos\theta}{2\sqrt{Dt}}\right)$$

$$p_{fr}(\phi,t\,|\,r_0,0,0)=\frac{1}{2\pi}$$

Cartesian coordinates

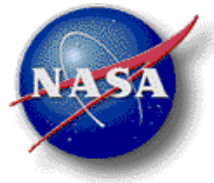


Spherical coordinates



Plante, I. et al., *submitted*

Green's functions (3D) for radiation chemistry



- We know how to sample $p(r,t|r_0,\theta_0,\phi_0)$.
- The exact Green's function is difficult to evaluate numerically.
- To calculate it we write $p(r,\theta,\phi,t|r_0,\theta_0,\phi_0)$ as the sum of free diffusion and correction terms (van Zon and ten Wolde, 2005)
- This approach reduces the number of terms necessary for convergence

$$\mathrm{p_{ex}}(\mathrm{r},\theta,\phi,\mathrm{t}\,|\,\mathrm{r_0},\theta_0,\phi_0) = \mathrm{p_{fr}}(\mathrm{r},\theta,\phi,\mathrm{t}\,|\,\mathrm{r_0},\theta_0,\phi_0) + \mathrm{p_{corr}}(\mathrm{r},\theta,\phi,\mathrm{t}\,|\,\mathrm{r_0},\theta_0,\phi_0)$$

$$\mathrm{p_{corr}}(\mathrm{r},\theta,\phi,\mathrm{t}\,|\,\mathrm{r_0},\theta_0,\phi_0) = -\frac{1}{4\pi\sqrt{\mathrm{r}\mathrm{r_0}}}\sum_{n=0}^{n_{\max}}(2\mathrm{n}+1)\mathrm{P_n}(\cos\theta)\int_0^\infty \mathrm{e}^{-\mathrm{u}^2\mathrm{Dt}}\,\frac{\mathrm{R_1}}{\mathrm{R_1^2}+R_2^2}(\mathrm{R_1G_1}+\mathrm{R_2G_2})\mathrm{udu}$$

$$R_1 = (2\sigma k_a + 1)J_{n+1/2}(u\sigma) - 2u\sigma J'_{n+1/2}(u\sigma)$$

$$R_2 = (2\sigma k_a + 1)Y_{n+1/2}(u\sigma) - 2u\sigma Y'_{n+1/2}(u\sigma)$$

$$G_1 = J_{n+1/2}(ur)J_{n+1/2}(ur_0) - Y_{n+1/2}(ur)Y_{n+1/2}(ur_0)$$

$$G_2 = J_{n+1/2}(ur)Y_{n+1/2}(ur_0) + Y_{n+1/2}(ur)J_{n+1/2}(ur_0)$$

van Zon, J. S. and ten Wolde, P. R. (2005) *J. Chem. Phys.* **123**, 234910

Green's functions (3D) for radiation chemistry

- To sample θ and ϕ, we generate values for θ_0=0, ϕ_0=0 and perform the necessary rotations. In this system, ϕ is uniformly distributed between 0 and 2π
- Use the algorithm from Clifford et al. to generate the angle θ and ϕ

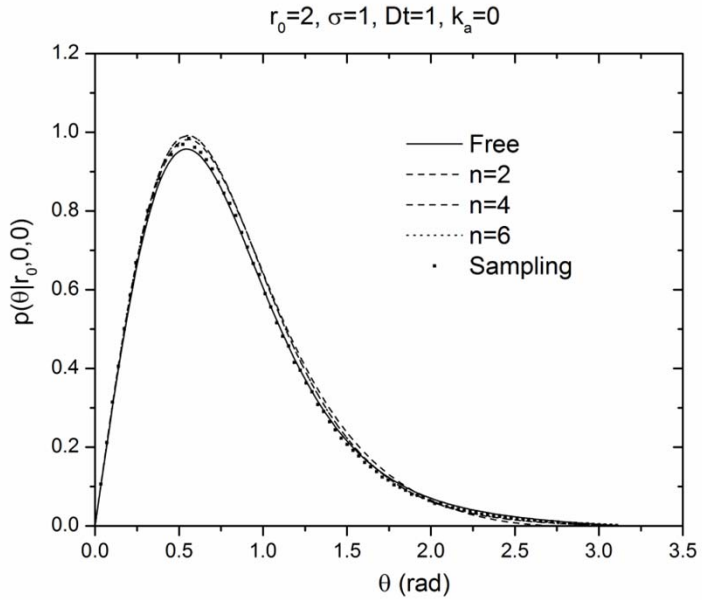
$\vartheta = 2\pi U_1$

$$\Theta = \mathrm{Cos}^{-1}\left\{1 + \frac{1}{\alpha}\ln\left[1 - U_2\left(1 - \exp(-2\alpha)\right)\right]\right\}$$

where U_1 and U_2 are random numbers uniformly distributed [0,1]

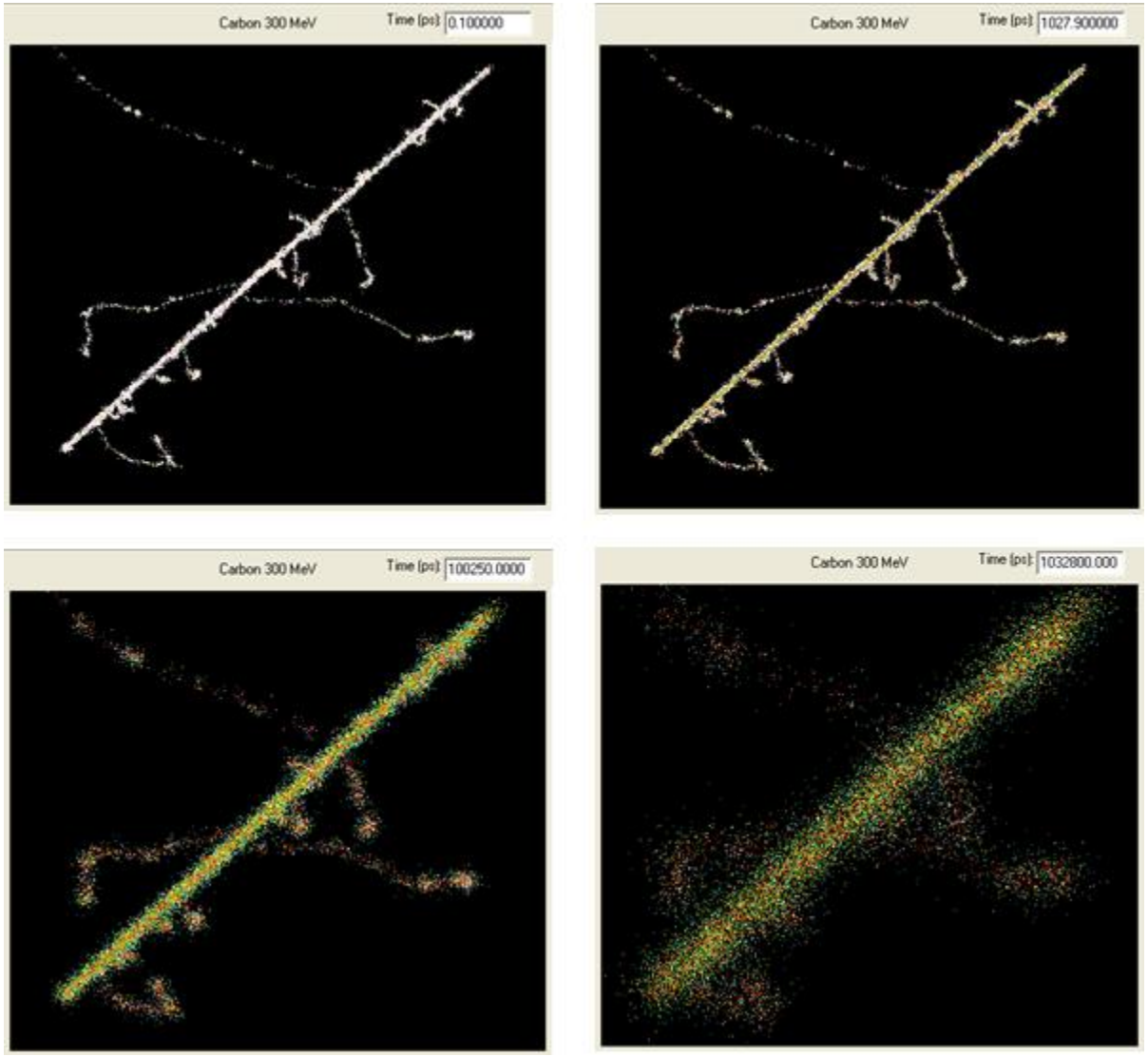
$\alpha = rr_0/2Dt$

r_0 and r are the inter-particle distances before and after the time step



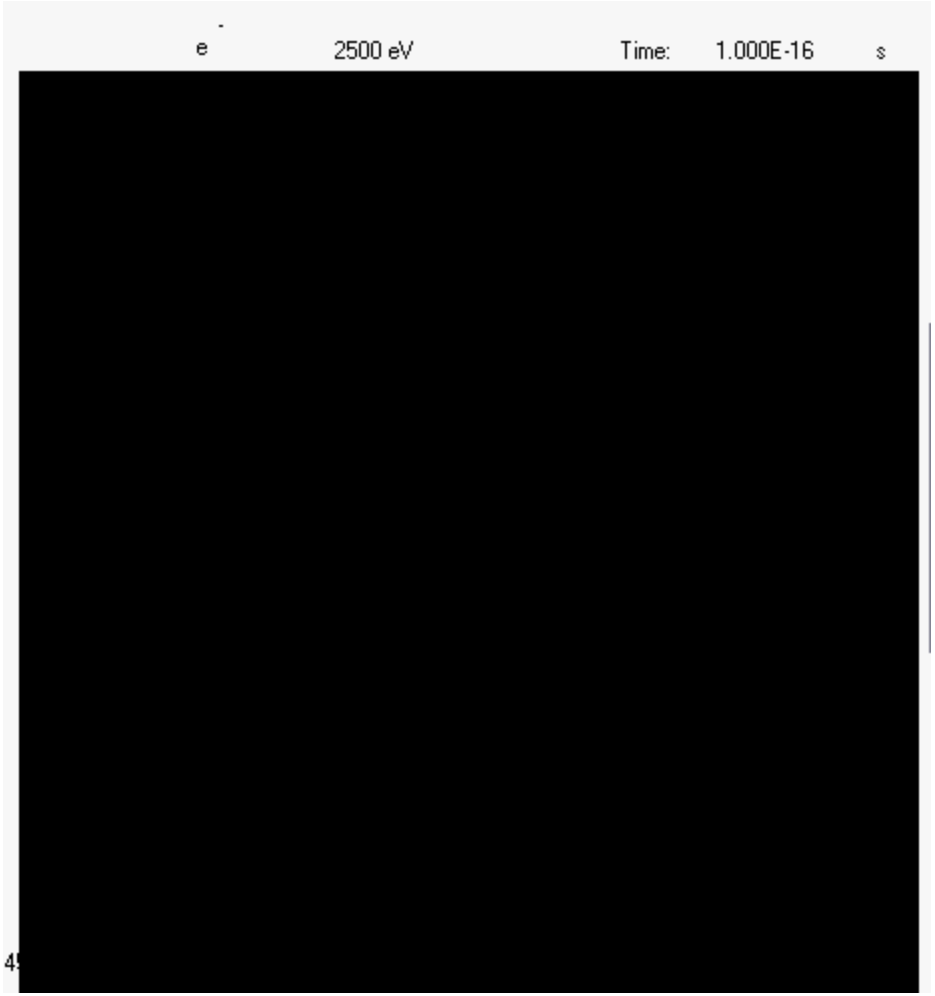
Plante, I. et al., *submitted*

Radiation chemistry



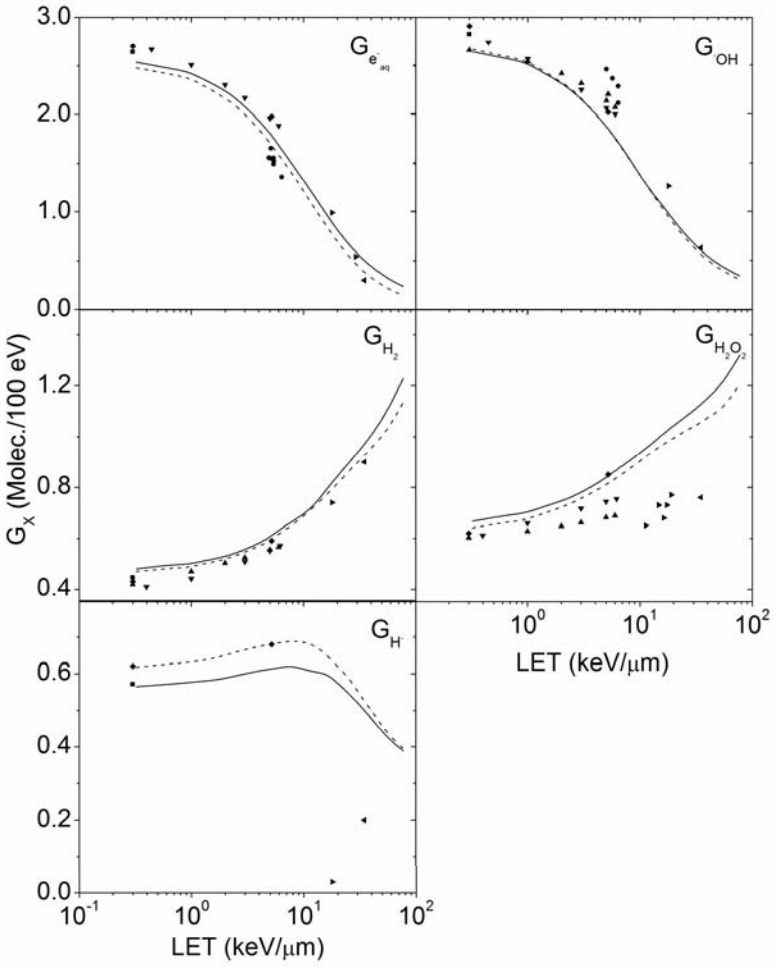
Plante, I. (2009) Ph.D. Thesis, University of Sherbrooke

Radiation chemistry



Radiation chemistry

Primary yields of e^-_{aq}, $\cdot OH$, $H^\cdot$, H_2 and H_2O_2 as a function of the LET



Irradiation by 300-0.1 MeV protons

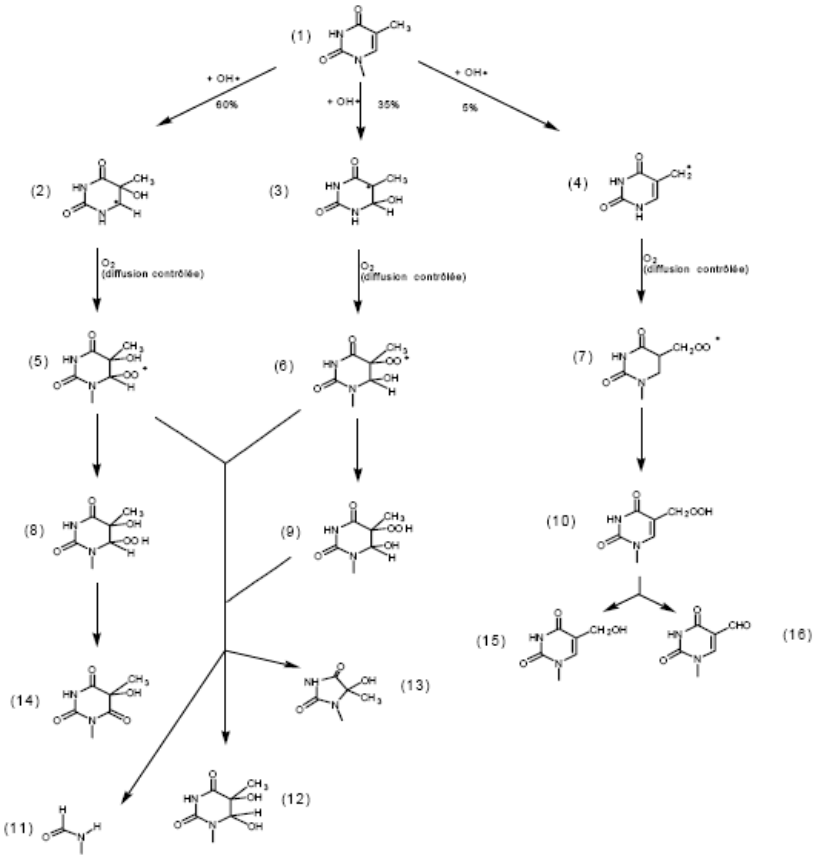
LET: ~0.3-85 keV/μm

Note: the *primary yields* (noted G_X) are the yields at the end of spur expansion (~10^{-6} s)

Plante, I. (2011), *Radiat. Env. Biophys.* **50**, 405-415

Radiation chemistry (DNA)

- The radiation chemistry of DNA is very complex
- Many reaction rate constants are known

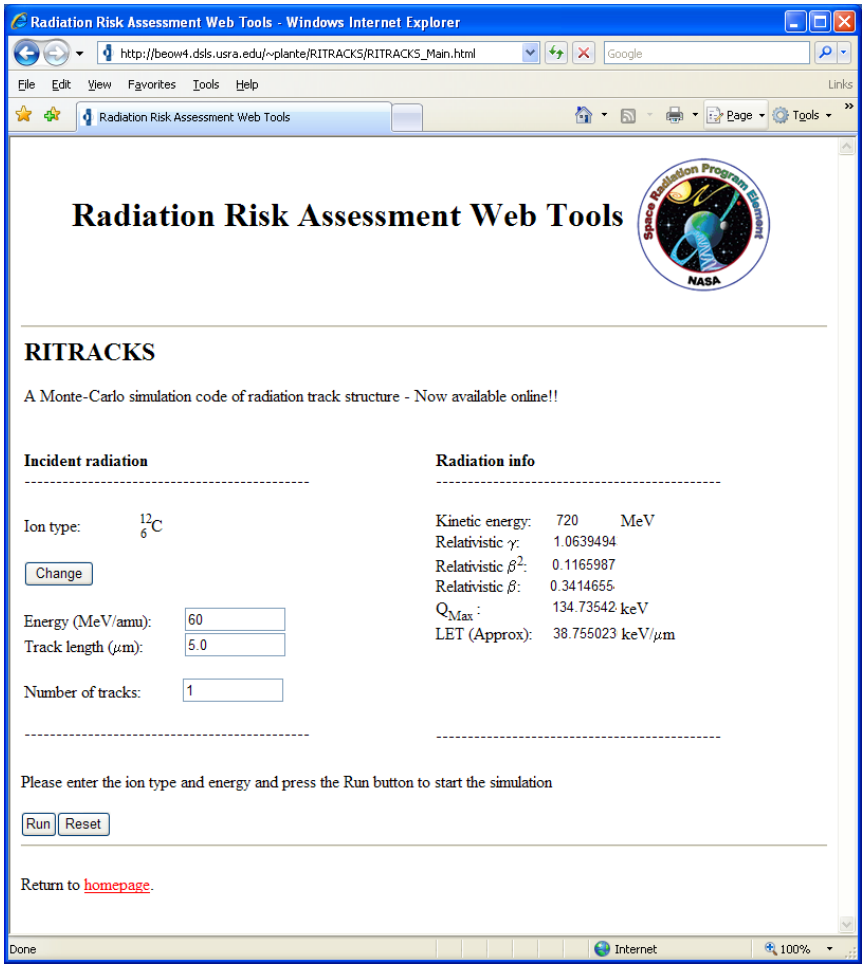


Reaction	k ($dm^3.mol^{-1}.s^{-1}$)	Radius (Å)
e^-_{aq}+Thymine→Thy(+e)	$1.79x10^{10}$	5.287
·OH + Thymine → TC5OH·+TC6OH·+TUCH2·	$6.4x10^9$	3.02
H.+Thymine→Thymine*	$5.7x10^8$	0.11

Cadet, J. et al. (1997) *Reviews in Physiology, Biochemistry and Pharmacology* **31**, 1-87

Release history

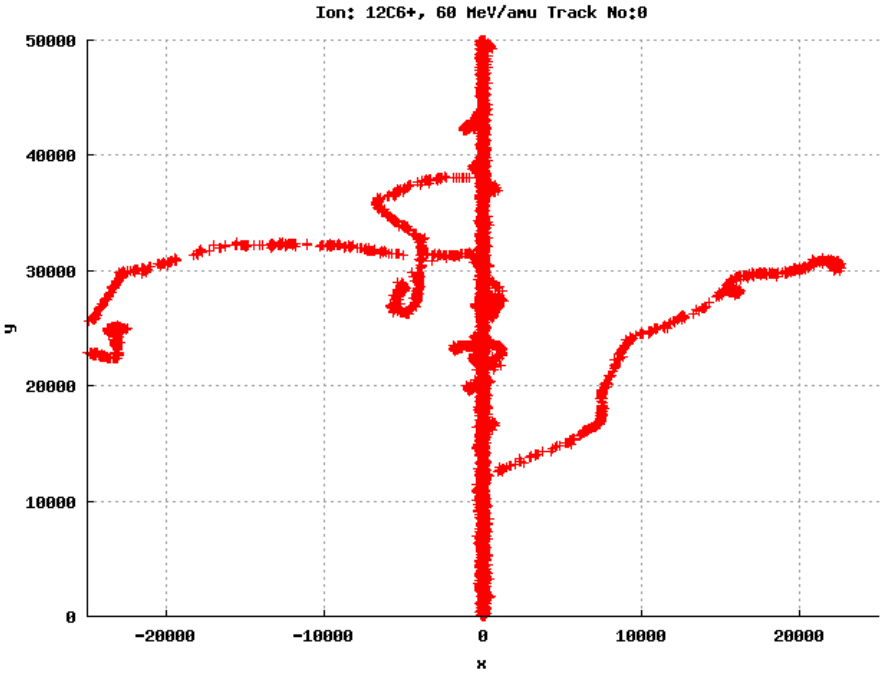
- RITRACKS was used by the students at the NASA Space Radiation Summer School at the Brookhaven National Laboratory, Upton, New York (June 6-24, 2011, May 28 - June 15, 2012, MIT ICED June 2012)(over 40 users)
- The release to international partners was approved in 2011
- RITRACKS was released to NASA space radiation community with over 20 users
- The software is now available for download on the web site http://spaceradiation.usra.edu/irModels/ (ITAR, authentication and password required)

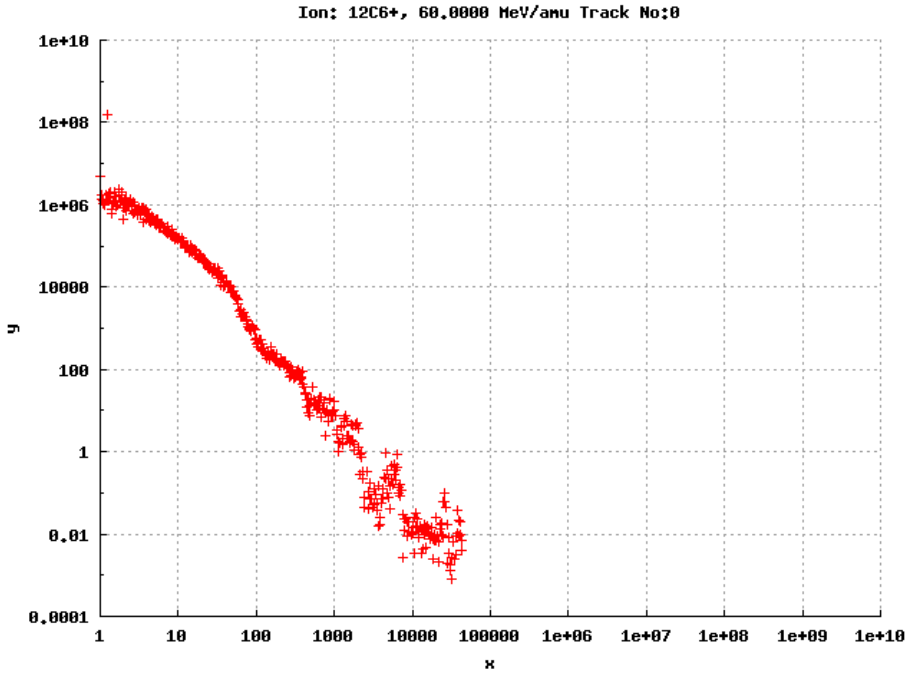


http://spaceradiation.usra.edu

Release history

- **An online version of RITRACKS will be available soon!**



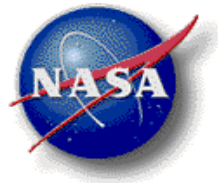


Left: Simulation of a $^{12}C^{6+}$, 60 MeV/amu, on the projected RRAW site.

Right: Calculation of the radial dose for the track depicted on the left

The track structure data and the radial dose are available for download after calculation

Future plans for development and use



- Implementation of the non-homogeneous chemistry
- Predictions of clustered and complex DNA damage yields in human cells for improving the understanding of DNA repair and signal transduction
- Use with chromosome models to study double-strand breaks (DSB) in relation to cancer risks from space radiation
- Web-based version
- New GPU-CPU version to improve computational speeds by several orders of magnitude.

Future plans for development and use

- **Android/iPhone version**
- **For ions:**
  - LET
  - Relativistic β and γ
  - Z_{eff} and Z_{eff}^2/β^2
  - Maximum energy transfer to an electron
  - Dose and fluence
  - Radial dose
  - Number of hits per cell in a cell culture
- **For electrons:**
  - Relativistic β and γ
  - Range

Future plans for development and use

- **Android/iPhone version**
- **For ions:**
  - LET
  - Relativistic β and γ
  - Z_{eff} and Z_{eff}^2/β^2
  - Maximum energy transfer to an electron
  - Dose and fluence
  - Radial dose
  - Number of hits per cell
  - in a cell culture
- **For electrons:**
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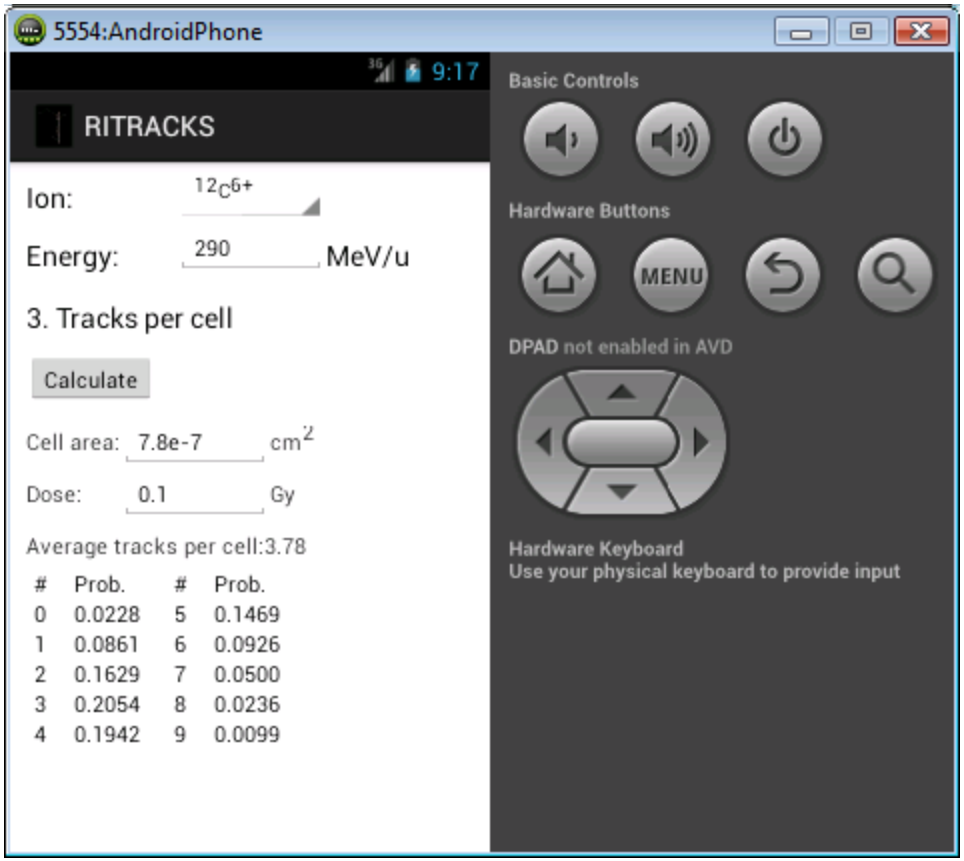
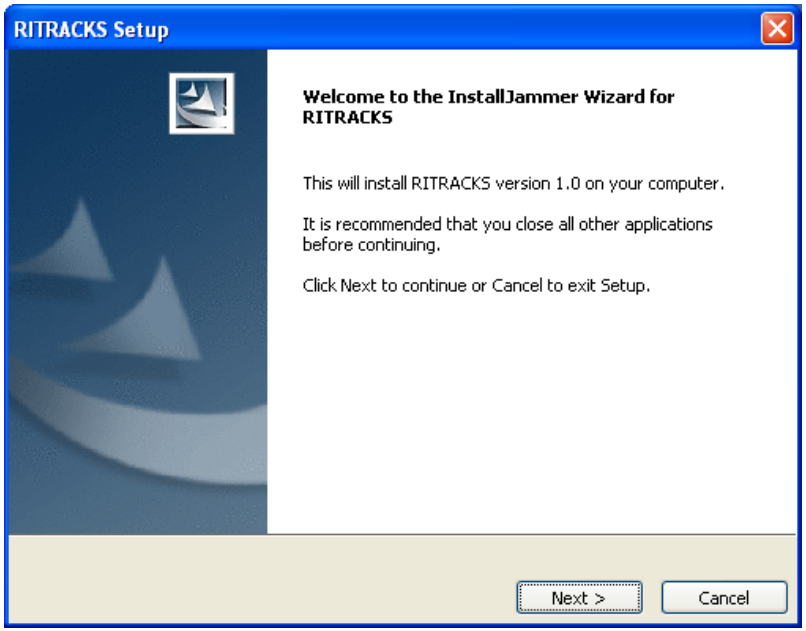
  - Range

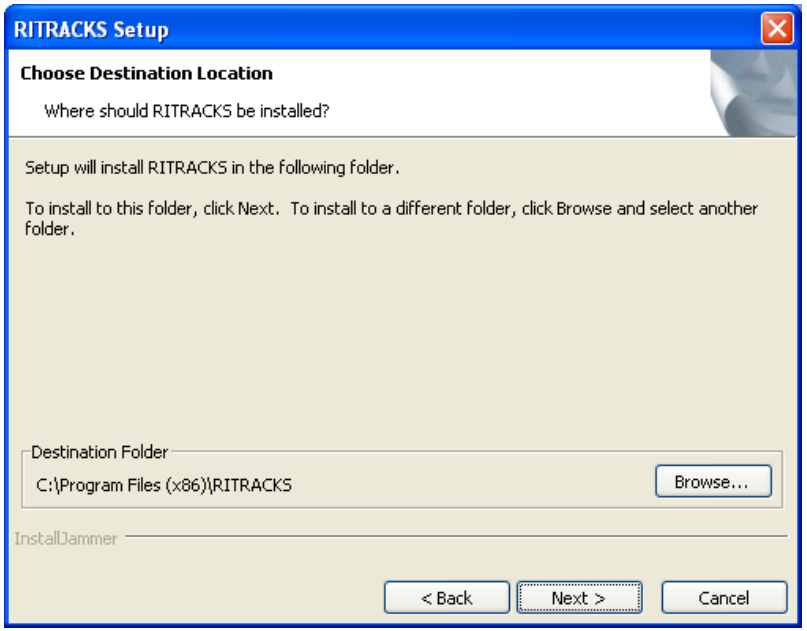


Using RITRACKS

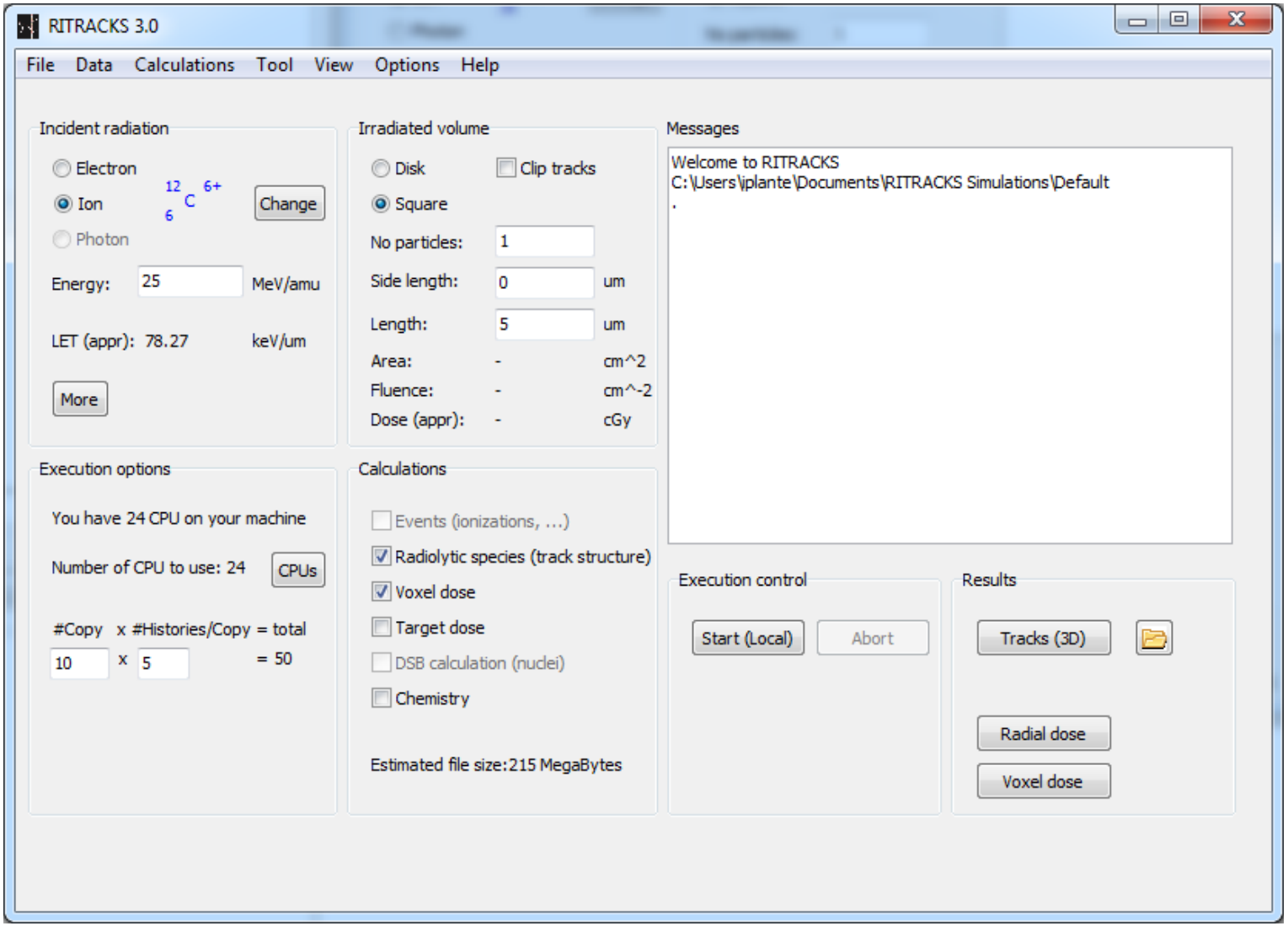
❑ The installer

- The necessary files are included in an installer created by the freeware InstallJammer
- The program is installed in the folder C:\Program Files (x86)\RITRACKS
- Simulations are stored the subfolder RITRACKS Simulations in the My Documents folder





RITRACKS main window



Radiation info window

The following information is given in this window

Rest mass energy: Mc^2

Total energy: γMc^2

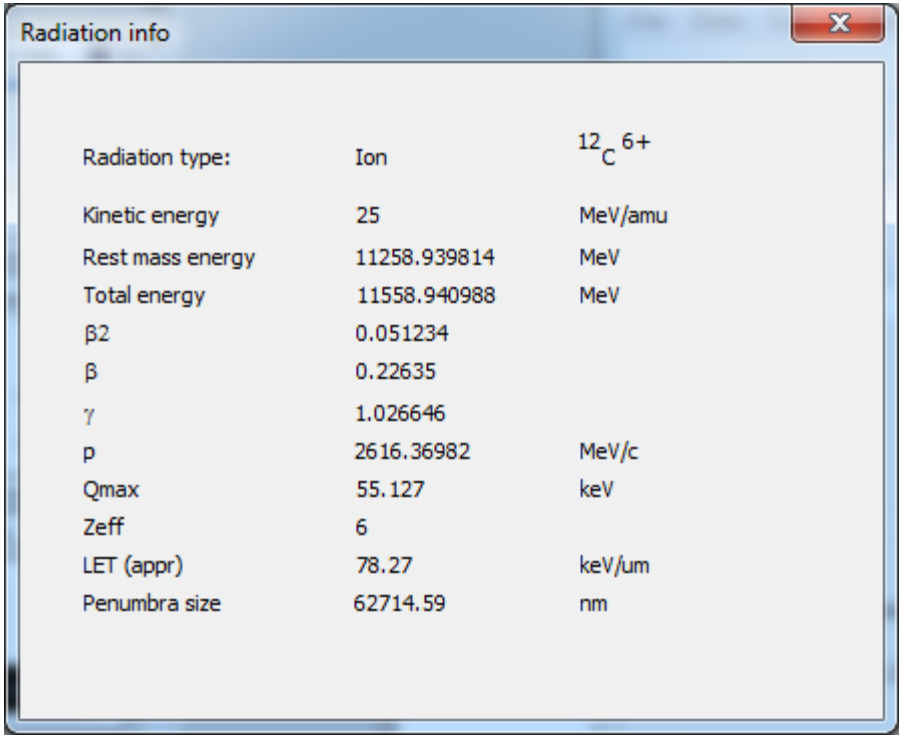
Relativistic γ: $\gamma = T / Mc^2 + 1$

Relativistic β: $\beta^2 = 1 - 1/\gamma^2$

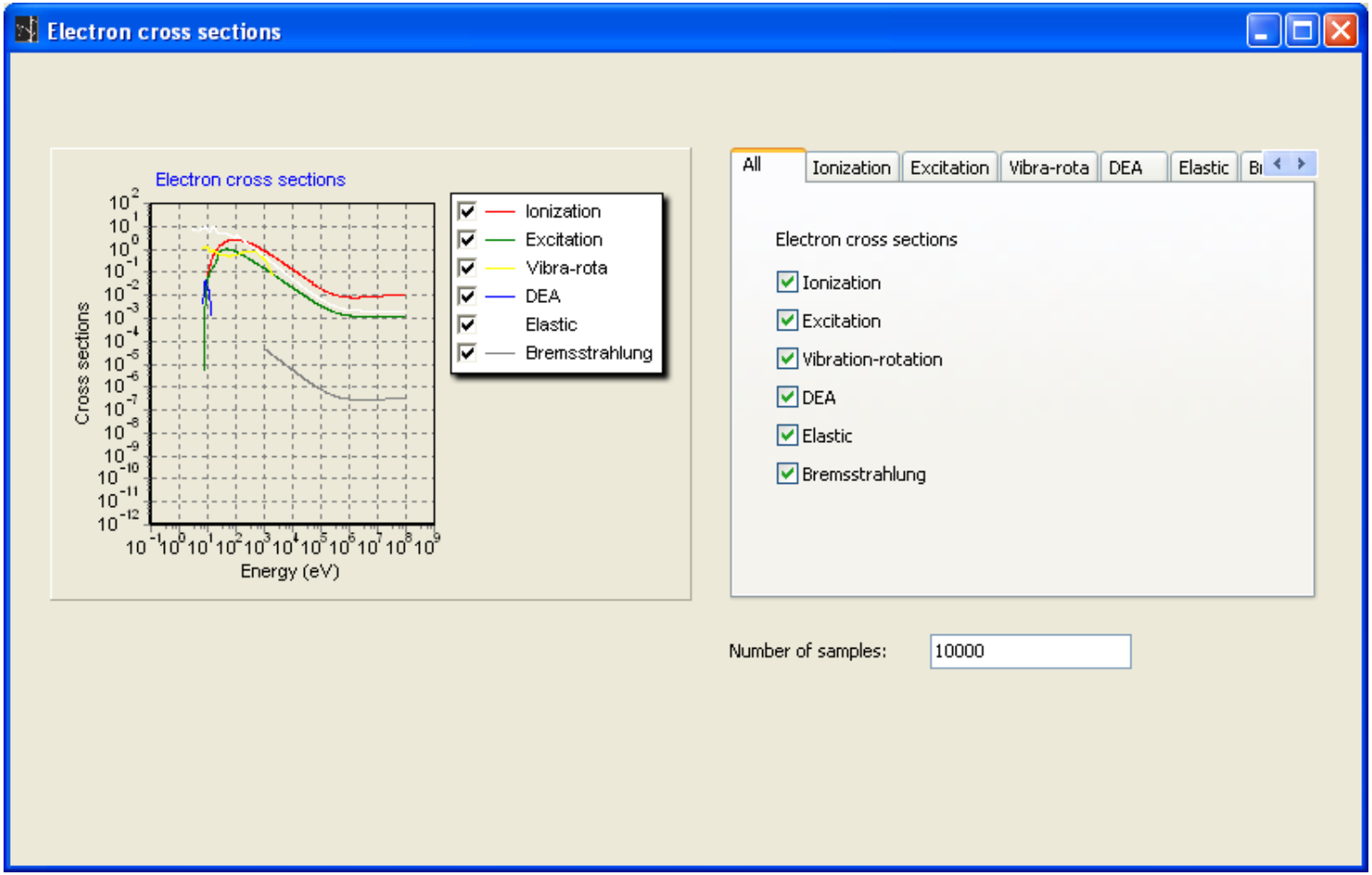
Momentum: $p = \gamma Mv$

Maximum energy Transfer to e^-: $E_{max} = \frac{2mc^2(\gamma^2 - 1)}{1 + 2\gamma(m/M) + (m/M)^2}$

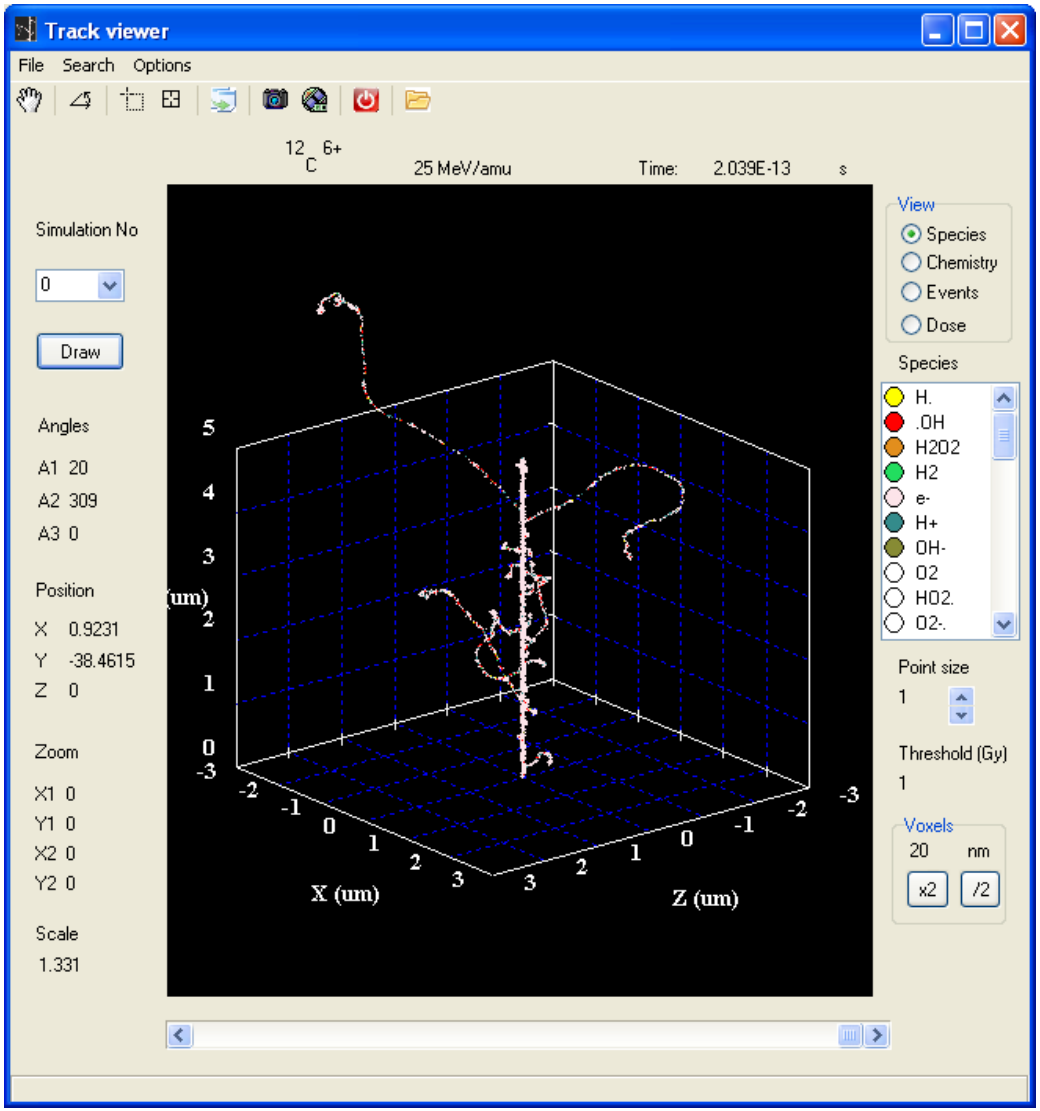
LET (MeV/cm): (Bethe) $-\frac{dE}{dx} = \frac{0.170}{\beta^2}[F(\beta) - 4.31]$ $F(\beta) = \ln\frac{1.02x10^6\beta^2}{1-\beta^2} - \beta^2$



Electron cross sections window



Visualization window



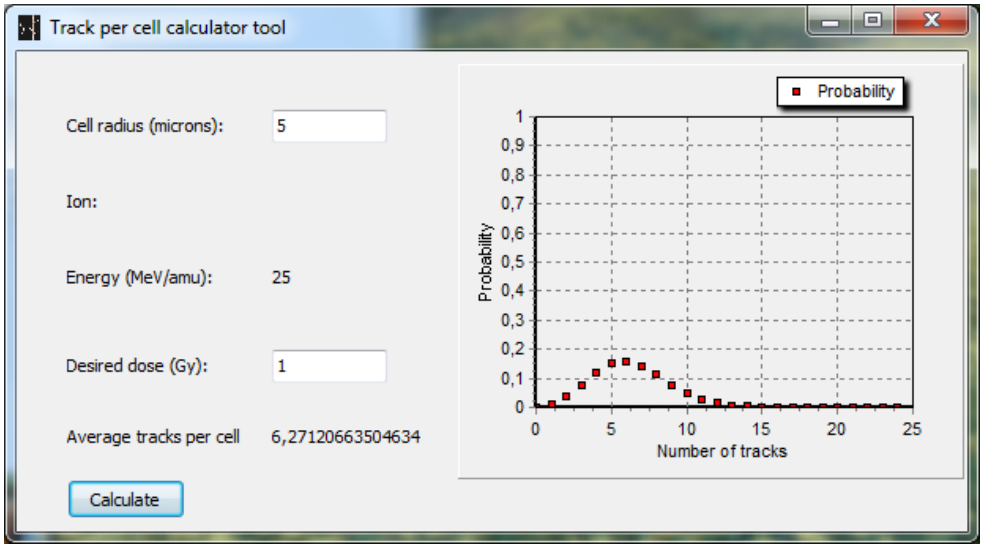
Tools:
- Rotation
- Translation
- Zoom
- Save to file
- Copy to clipboard
- Create a .avi file
- Open data folder

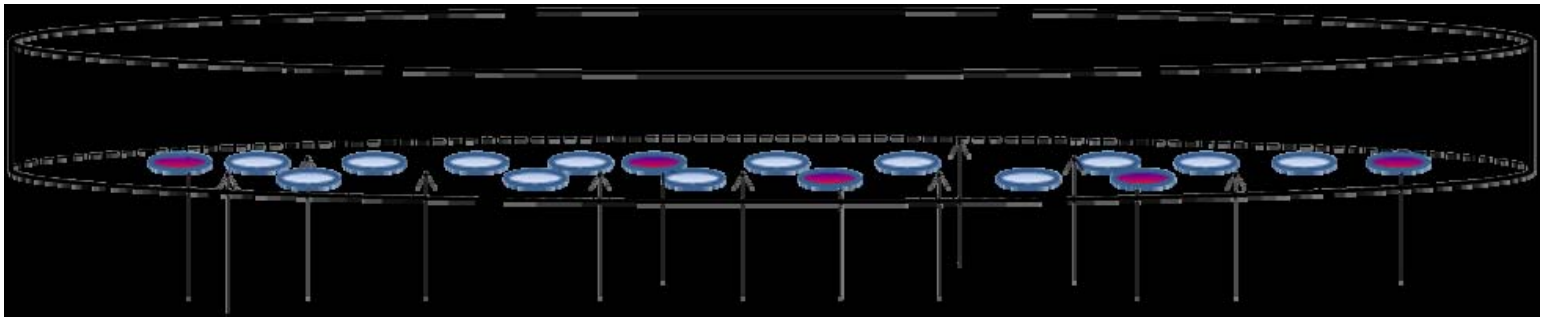
Visualization:
- Radiolytic species
- Events
- Dose (voxels)

Time evolution

RITRACKS tools

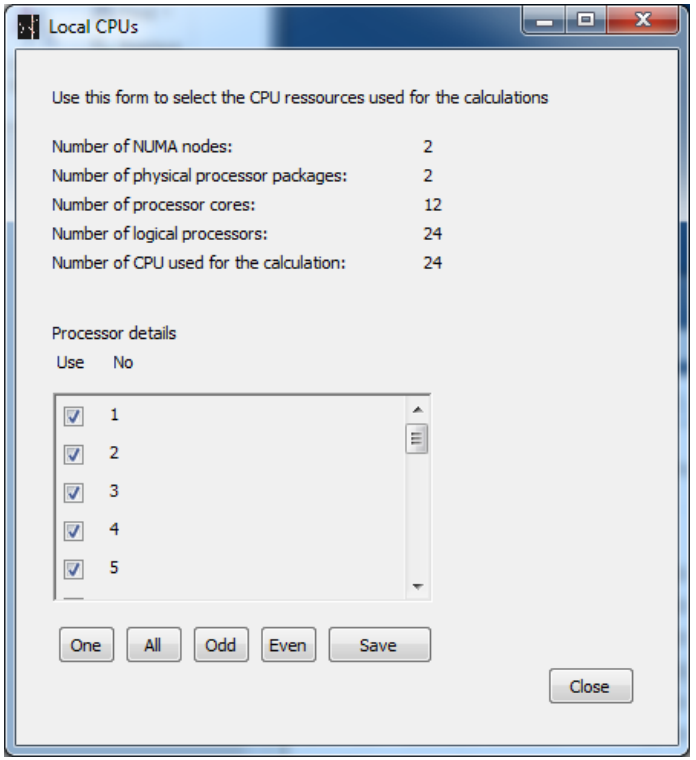
- **Calculation of tracks per cell in a cell culture for a given ion, energy and dose**

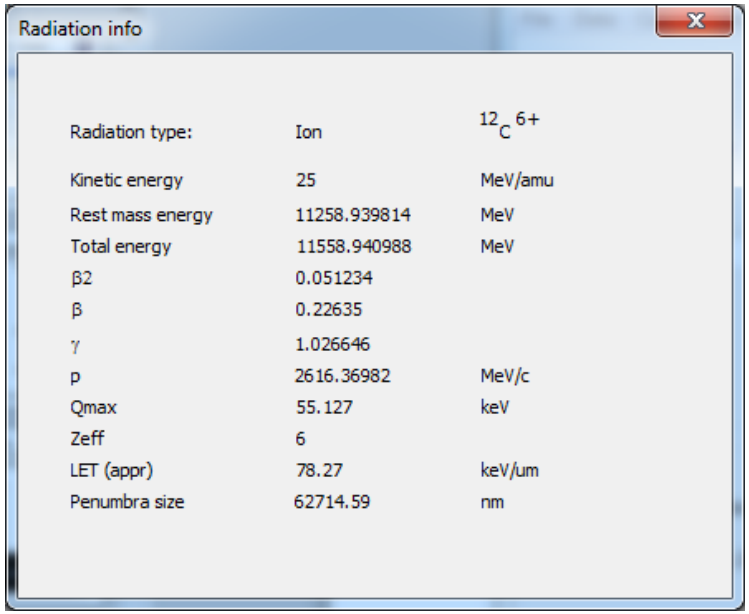




Homework

- Install RITRACKS
- Max the number of CPUs
- Click on the More button for the Radiation Info window





Homework

❑ Simulations:

- 1 ion $^{12}C^{6+}$, 25 MeV/amu, of length 5 μm. Use the following parameters:
  - ✓ #Copy = 1 and #Histories/Copy = 20
  - ✓ #Copy = 10 and #Histories/Copy = 2
  - ✓ Notice the difference in the progress window and calculation time

❑ Visualize the tracks with the 3D interface

- Use visualization tools (displace, rotate, zoom, copy to clipboard, save to file, reset parameters, open folder).
- Zoom and un-zoom (to un-zoom, draw a zoom box from the bottom right to upper left)
- Use the time evolution bar.
- Change the simulation number and click Draw.
- Create an avi file of the track. Click on the movie icon, click on Create AVI, enter a name (test.avi).

Homework

- **Visualize the tracks with the 3D interface**
  - Switch between voxel dose and track. In the voxel dose representation, vary the threshold scale (the slider located at the left of the dose scale)
  - Display the axis (go to Options->Visualization, select the tab Axis and check the boxes).
- **Display the radial dose and voxel dose (from the main interface window).**
- **Repeat the simulations with the following ions**
  - 1 ion $^{56}Fe^{26+}$, 1000 MeV/amu, of length 5 μm (10 histories)
  - Irradiation of a cube of 5 μm x 5 μm x 5 μm with 450 x 300 MeV protons (1 history)
  - Irradiation of a cube of 5 μm x 5 μm x 5 μm with 1 1000 MeV/amu $^{56}Fe^{26+}$ ions (1 history)

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