New modeling approaches to investigate cell signaling in radiation response

by

Ianik Plante and Francis A Cucinotta

Ionizing radiation damages individual cells and tissues leading to harmful biological effects. Among many radiation-induced lesions, DNA double-strand breaks (DSB) are considered the key precursors of most early and late effects [1] leading to direct mutation or aberrant signal transduction processes. In response to damage, a flow of information is communicated to cells not directly hit by the radiation through signal transduction pathways [2]. Non-targeted effects (NTE), which includes bystander effects and genomic instability in the progeny of irradiated cells and tissues, may be particularly important for space radiation risk assessment [1], because astronauts are exposed to a low fluence of heavy ions and only a small fraction of cells are traversed by an ion. NTE may also have important consequences clinical radiotherapy [3]. In the recent years, new simulation tools and modeling approaches have become available to study the tissue response to radiation. The simulation of signal transduction pathways require many elements such as detailed track structure calculations, a tissue or cell culture model, knowledge of biochemical pathways and Brownian Dynamics (BD) propagators of the signaling molecules in their micro-environment. Recently, the Monte-Carlo simulation code of radiation track structure RITRACKS was used for micro and nano-dosimetry calculations [4]. RITRACKS will be used to calculate the fraction of cells traversed by an ion and delta-rays and the energy deposited in cells in a tissue model. RITRACKS also simulates the formation of chemical species by the radiolysis of water [5],

notably the $^\bullet$OH radical. This molecule is implicated in DNA damage and in the activation of the transforming growth factor beta (TGFβ), a signaling molecule involved in NTE. BD algorithms for a particle near a membrane comprising receptors were also developed and will be used to simulate trajectories of signaling molecules in the micro-environment and characterize autocrine and paracrine cell communication and signal transduction.

References:
[1] Durante M and Cucinotta FA (2008) Nat Rev Cancer 8, 465-472.
[2] Barcellos-Hoff MH (2005) Br J Radiol Suppl 27, 123-127.
[3] Snyder AR (2004) Hum Exp Toxicol 23, 87-89.
[4] Plante I et al. (2011) Radiat Prot Dosim 143, 156-161.
[5] Muroya Y (2006) Radiat Res 165, 485-491.

New modeling approaches to investigate cell signaling in radiation response

Ianik Plante[1,2], Artem L. Ponomarev[1,2] and Francis A. Cucinotta[1]

[1]NASA/JSC, Houston, TX; [2]Division of Space Life Sciences, Universities Space Research Association, Houston, TX

Introduction

- Following radiation exposure, a flow of information is exchanged between cells in tissues, and cells not directly hit are also affected [1].

- These so-called non-targeted effects (NTE) may have important consequences. Therefore, several elements should be included in irradiated tissue models:

  - Stochastic track structure and dosimetry
  - Tissue or cell culture model
  - DNA damage and repair models
  - Brownian dynamics algorithms for the simulation of signaling molecules in the micro-environment
  - Cell signaling pathways

Tissue or cell culture model

- Most tissue and cell culture models are based on Voronoi tessellation (in 2D and 3D)
- A Voronoi cell is the space closest to a given point (than the other points)
- Some rules are added:
  - Diameter limits (min and max)
  - Contact energy: harmonic oscillator
- Models derived from microscopic images can also be used
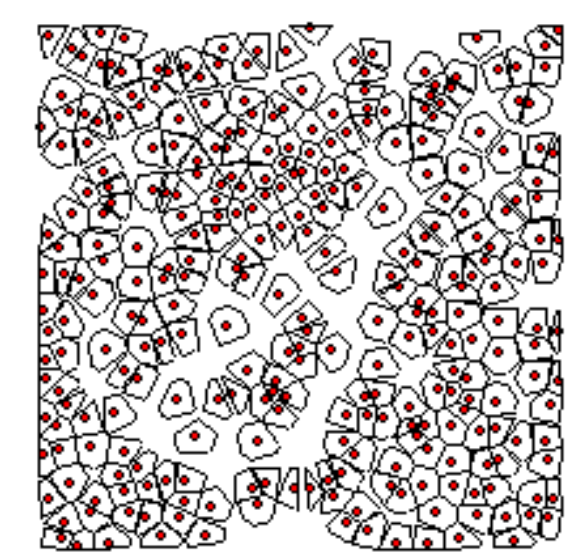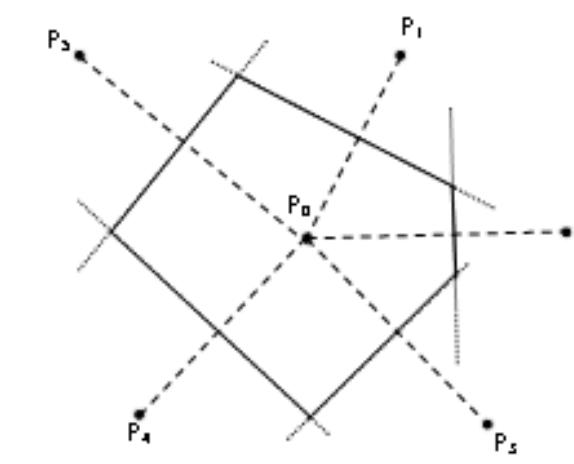
Top: a Voronoi cell in 2D
Bottom: a cell culture simulated with modified Voronoi cells

Simulation of radiation track and dose calculations

- The energy deposition by the radiation is highly dependent on the radiation type and energy and leads to the formation of the track structure.
- The radiation track structure is dependent on the radiation type and energy.
- Many radiolytic species (H·, ·OH, H_2, H_2O_2, e^-_{aq}, etc) may be formed during this process.
- The track structure is simulated using the Monte-Carlo simulation code RITRACKS [2].
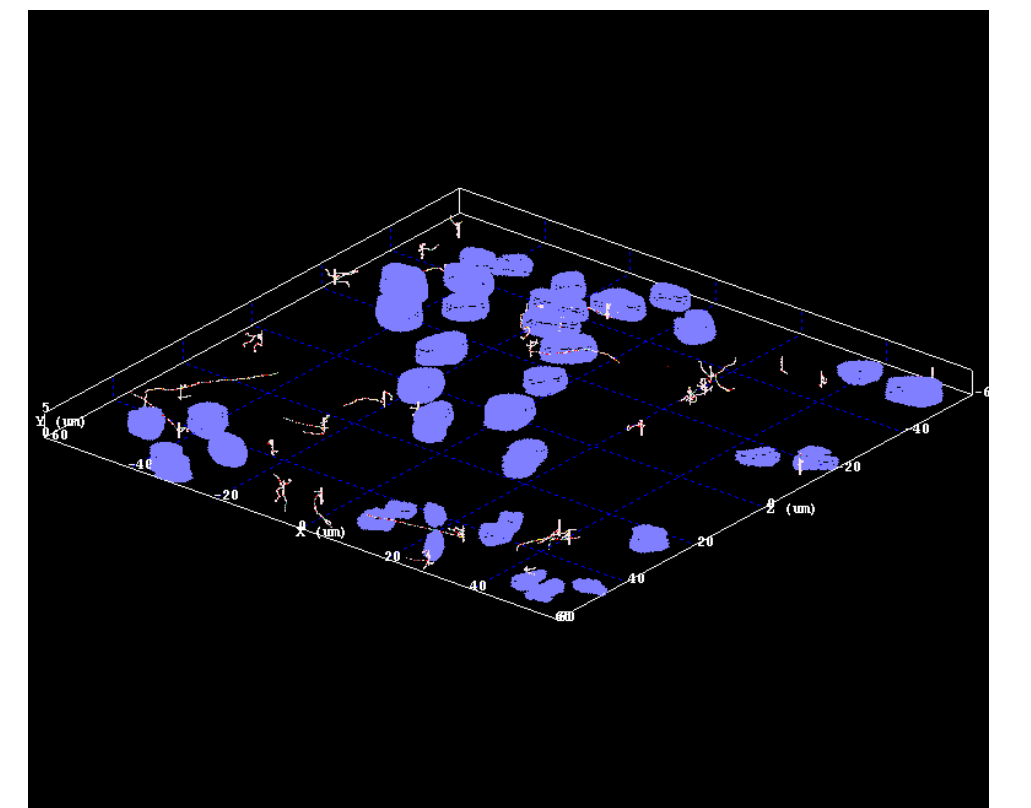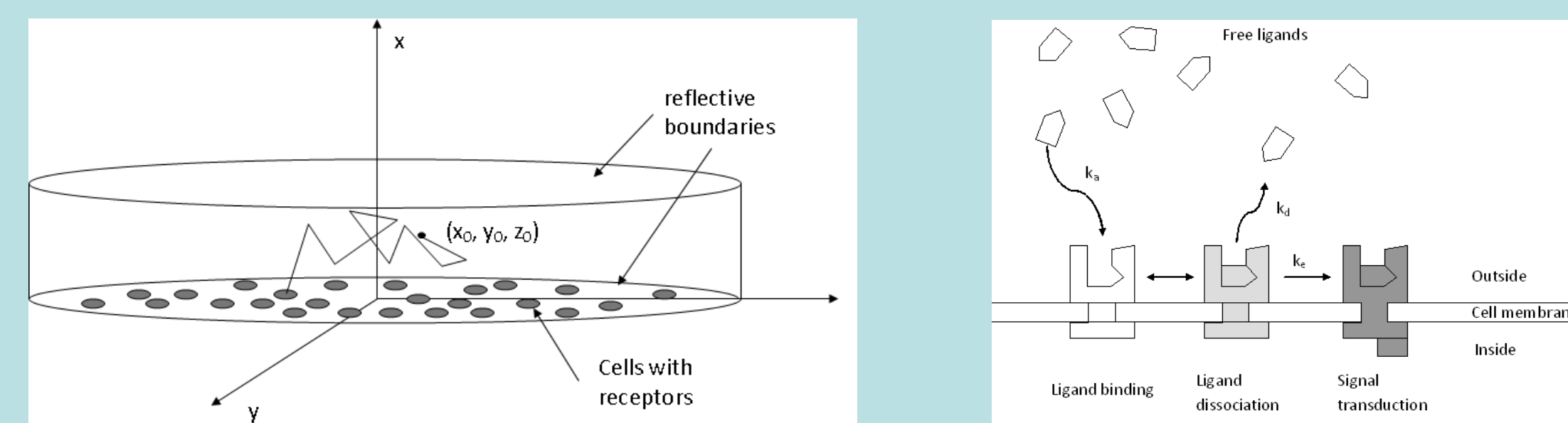
Image of a cell culture (120 μm x 120 μm) irradiated with 30 $^{56}Fe^{26+}$ ions, 1 GeV/amu, LET ~150 keV/μm. Dose: ~5 cGy

Signaling molecules: TGFβ

- Among signaling molecules involved in the response of cells to ionizing radiation, TGFβ is of particular interest
- TGFβ is secreted as an inactive form (the Large Latent Complex "LLC") [3]; it is released from the LLC by several factors, notably the ·OH radical [4].
- TGFβ binds to its receptors and initiate several actions mediated by the SMAD proteins; it has been shown to suppress apoptosis in irradiated cell culture and also to mediate cellular response to DNA damage [5].

TGFβ signaling pathways

Data for TGFβ

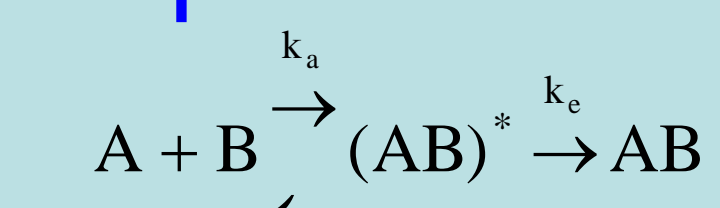| Parameter	Description	Value
D	Ligand diffusivity	2.6×10^{-7} cm^2/s
A	Culture surface	10 cm^2
h	Height of the extracellular medium	0.2 cm
k_e	Complex internalization rate constant	3 min^{-1} = 0.05 s^{-1}
k_{on}	Forward binding rate constant	$(2.3\pm0.2)\times10^7$ M^{-1}s^{-1}
k_d	Complex dissociation rate constant	$(1.5\pm0.2)\times10^{-4}$ s^{-1}
R_0	Number of receptors at cell surface	1000
R_{cell}	Radius of cells	0.0025 cm
N_{cells}	Number of cells in culture	100000

Brownian dynamics (BD) algorithms

Brownian dynamics for a particle in a cell culture near cells comprising receptors. Left: particle in the cell culture. Right: Ligand-receptor interaction near a cell membrane.

- Free diffusion in the Y and Z directions
- Reflective boundary on top
- Homogenization of the boundary at the bottom surface of culture (partially absorbing)
- Possible states for a ligand molecule
  - Free at position x_0
  - Bound in the reversible state (*)
  - Initiation of signal transduction(**)

Equations of the model
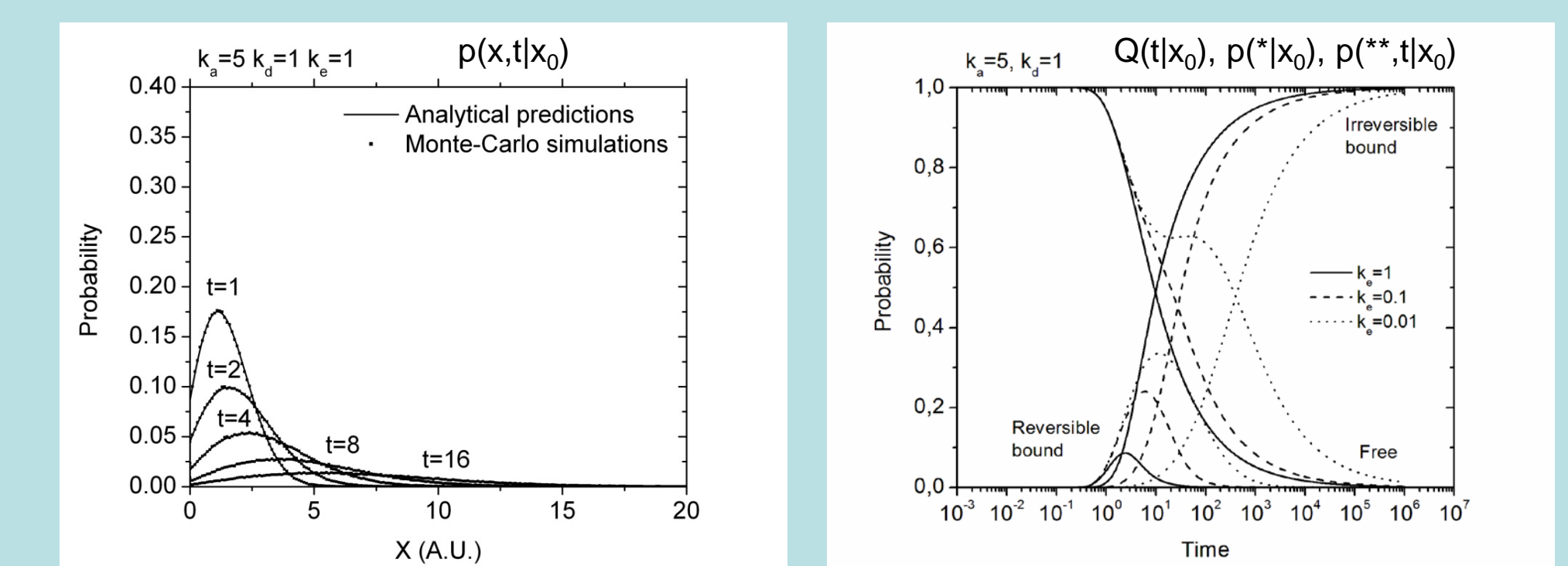
$$A + B \underset{k_b}{\overset{k_a}{\rightleftharpoons}} (AB)^* \overset{k_e}{\rightarrow} AB$$

k_a: association rate constant,
k_d: dissocation rate constant:
k_e: signal transduction rate constant.

$$\frac{\partial p(x,t \mid x_0)}{\partial t} = D \frac{\partial^2}{\partial x^2} p(x,t \mid x_0)$$

$$\frac{dp(*,t \mid x_0)}{dt} = k_a p(0,t \mid x_0) - (k_d + k_e)p(*,t \mid x_0)$$
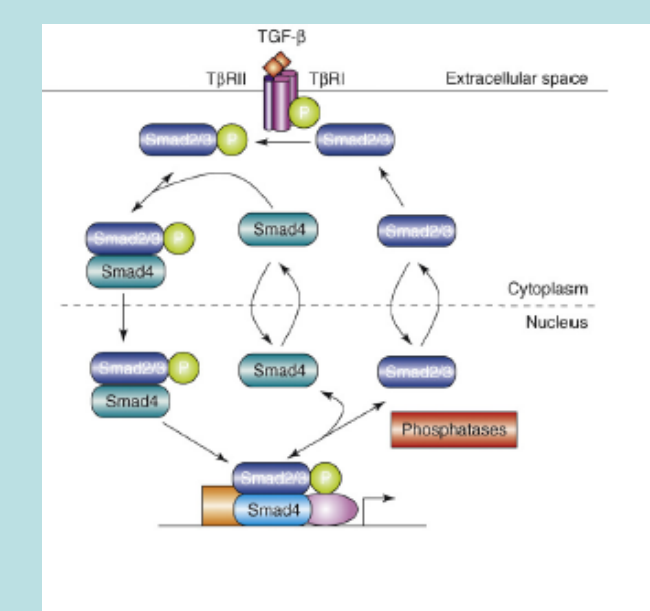
Results: 1 membrane

$k_a=5$ $k_d=1$ $k_e=1$ $p(x,t|x_0)$

Analytical predictions
Monte-Carlo simulations

$k_e=5,\ k_d=1$ $Q(t|x_0),\ p(*|x_0),\ p(**,t|x_0)$

p(x,t|x$_0$): Probability distribution of distances for free particle
Q(t|x$_0$): Survival probability
p(*,t|x$_0$): Reversible binding probability
p(**,t|x$_0$): Signal transduction probability

DNA damage models
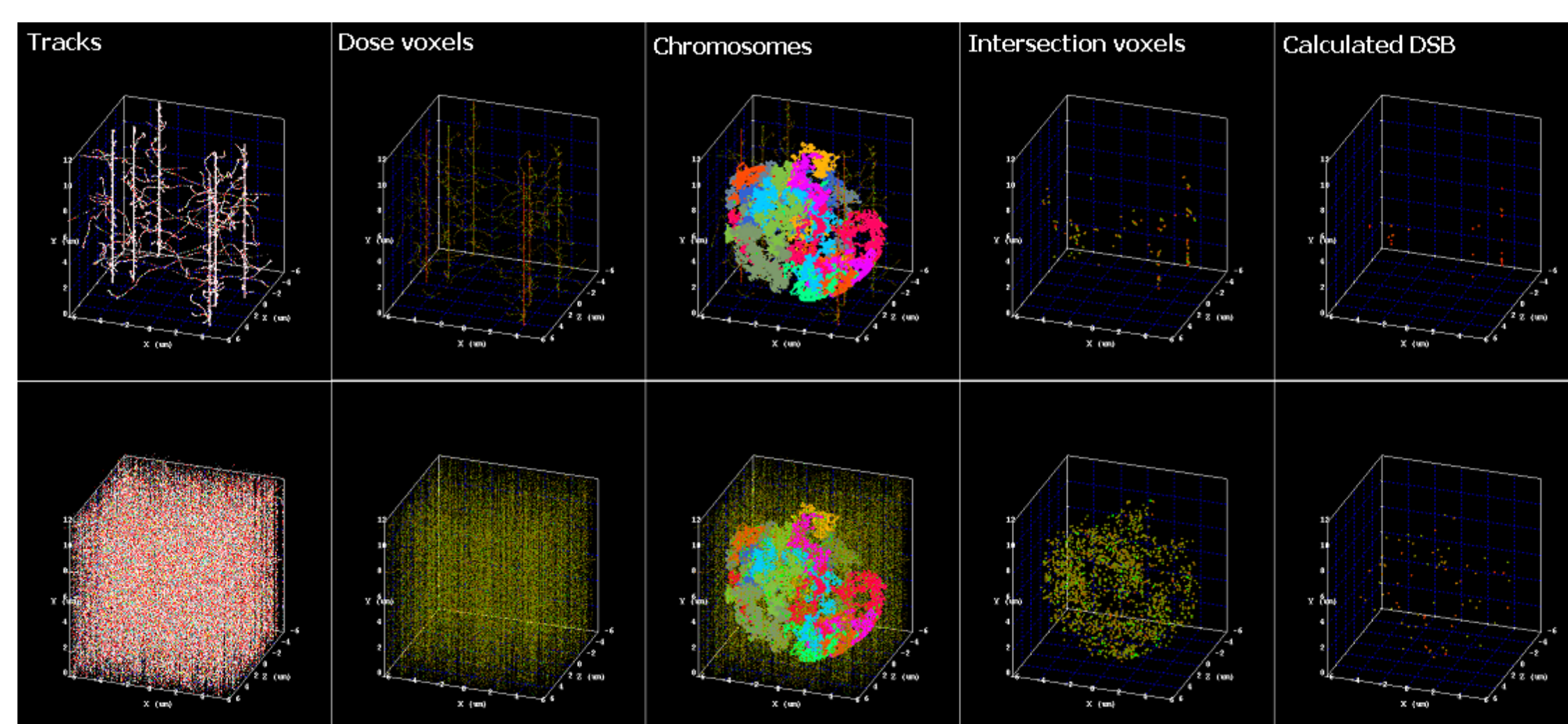
Tracks | Dose voxels | Chromosomes | Intersection voxels | Calculated DSB

Irradiation of a cubic volume of 12 μm x 12 μm x 12 μm by 6 $^{56}Fe^{26+}$ ion, 1 GeV/amu (top) and by 2700 $^1H^+$ ions, 300 MeV (bottom). In both cases, the dose deposited is ~1 Gy. From left to right: tracks, dose in 20 nm voxels, human chromosomes (only 1-10 are shown), intersection voxels, intersection voxels with probability of DSB applied.

DNA damage models

- The chromosomes are simulated by random walk
- The dose to the nucleus is calculated with the code RITRACKS
- The intersection voxels with energy deposited and chromosomes are obtained
- The probability of DSB is obtained by applying the equation

$$\psi = 1 - e^{-QD}$$

where D is the dose in a voxel, and Q is a parameter which may depend on the radiation type [6]

Discussion

- We are working on a model combining stochastic radiation track simulations, cell culture or tissue models, DNA damage and repair models, cell signalling pathways and BD algorithms.

- These models and simulations should help understand the role of cell signalling in the response to ionizing radiation

References

[1] Mothersill, C. and Seymour, C.B. Nat. Rev. Cancer **4**, 158–164 (2004).
[2] Plante, I. and Cucinotta, F.A. New J. Phys. **10**, 125020 (2008).
[3] Annes, J. P. et al. J. Cell Science **116**, 217-224 (2003).
[4] Jobling, M. F. et al. Radiat. Res. **166**, 839-848 (2006).
[5] Ewan, K. B. et al. Cancer Res. 62, 5627-5631 (2002).
[6] Plante, I. et al. Submitted