Introduction to Monte Carlo simulations at the (sub-)cellular scale: Concept and current status

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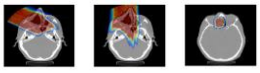
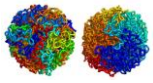
Monte Carlo Applications in Biomedicine

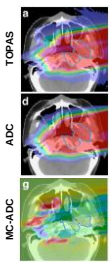
- Diagnostic Radiology / Nuclear Medicine
  - Detectors
  - Imaging correction techniques
  - Determination of physical quantities (e.g. scattering)
  - Radiation protection
- **Radiotherapy**
  - Dosimetry equipment
  - **Phantom simulations**
  - Beamline design
  - **Treatment planning (dose calulations, optimization)**
- Radiation protection
- **Applications based on microscopic MC techniques:**
  - **Track structure and microdosimetry**



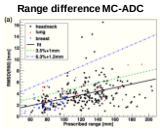


Sample Patient study, dose, range, TCP, NTCP

- ★ MC consider gold standard
- ★ Comparing Monte Carlo to TPS
- ★ Effects of high density interfaces parallel to beam on analytical calculations clearly visible
- ★ Various studies have compared TPS to Monte Carlo
- ★ D50, D90, R90, EUD, TCP, NTCP, …

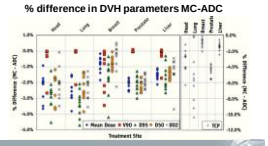


Range difference MC-ADC



J. Schuemann et. al, PMB. 2014, IJROBP 2015

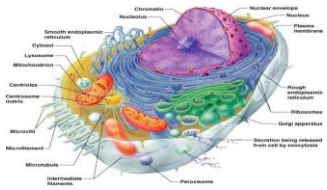
% difference in DVH parameters MC-ADC



Including Biology

★ Clinical endpoint of interest: **Biological effect**

Structure of a Generalized Cell

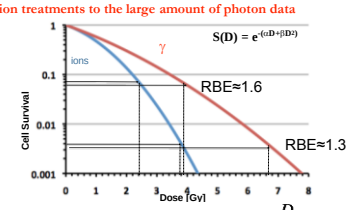


+ inter-cell interactions

It's complicated!

Including Biology: Relative Biological Effect - RBE

RBE is a concept to relate radiation effectiveness of proton and ion treatments to the large amount of photon data

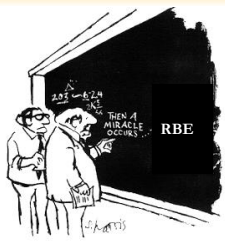


$$\text{RBE} = \text{Relative Biological Effect} = \frac{D_{\gamma}}{D_{protons}}\langle effect \rangle$$

RBE dependences

RBE depends on

- tissue
- radiation type
- dose
- energy/LET
- endpoint
- fractionation
- etc.

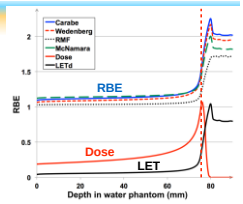


"I think you should be more explicit here in step two."

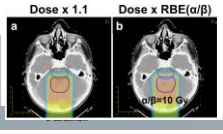
Including Biology

★ There is a large gap between physics events and biological outcome (and physics/biology research)
★ Protons assumed10% more effective than photons: Clinically used RBE = 1.1

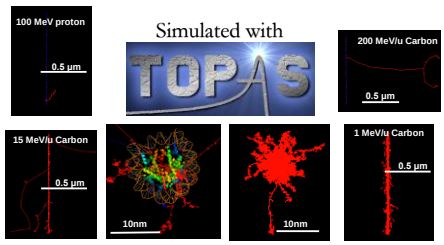
★ Examples for RBE dependence:
- ★ the modeling approach
- ★ α/β ratio
- ★ LET



Why do we focus on LET?
It is factor we can influence
It's physics
Independent of the model



The reason for increasing RBE with increasing LET

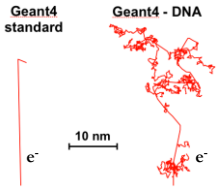


Radiation is more effective when energy depositions are more concentrated in space

Nanometer scale Monte Carlo track structure codes

★ Provide MC simulations at the nanometer scale
★ No approximations in physics descriptions*
★ Includes very low energy processes

★ Track structure goals:
- ★ Investigate effects of (single) track structures
- ★ Space radiation effects (out-of-field, SPE, GCR)
- ★ Electronics etc.

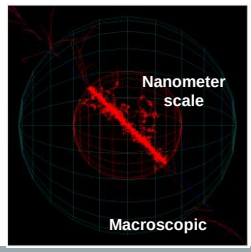


* no condensed histories, but our physics knowledge is limited.

Applicability

★ Track structure simulations are very time consuming!
★ Not feasible for whole patient treatment plan
★ Pick the region of interest:
  ★ Select cells across tumor
  ★ Cells in healthy tissue

★ Biological modeling goals, study:
  ★ cell structure effects
  ★ (single) cell response to radiation
  ★ new ideas (i.e. GNP)

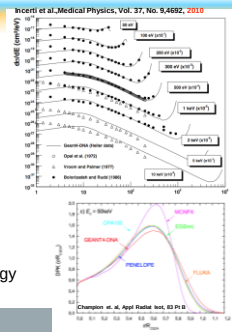


Cross sections and experimental data

★ Dosimetry at nanometer scale is non-trivial
  ★ water cross sections extrapolated from gas form
  ★ use density scaling → micrometer scale dosimetry
  ★ but gas ≠ water

★ most MC physics only valid for water
  ★ most experimental data available for water
  ★ majority of the cell is water

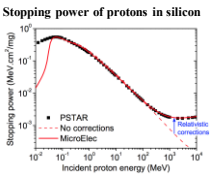
★ uncertainties even for water high in low Energy region



Water vs. other materials

★ Biological systems consist mostly of water
★ Most important radiation target: DNA
  ★ not the same as H_2O
  ★ varying density with cell cycle stage
  ★ base-pair wrapping, interactions, etc.

★ Other materials necessary for
  ★ Gold nanoparticles
  ★ Silicon (space radiation effects on electronics)
  ★ etc.

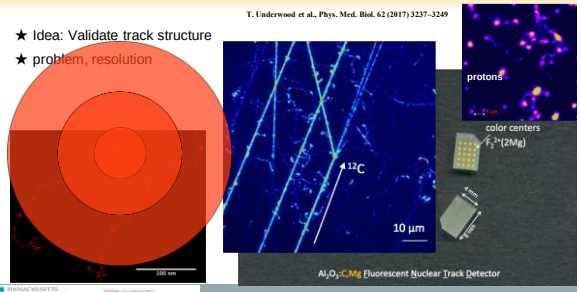


M. Raine et al. / Nuclear Instruments and Methods in Physics Research B 325 (2014) 97–100

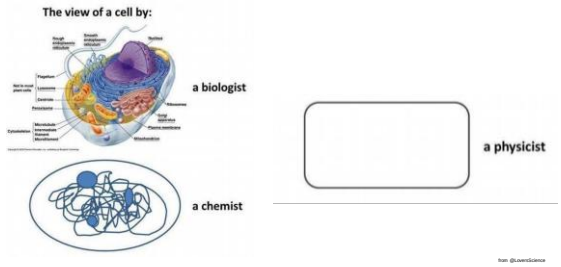
Problem - Validation: Fluorescent Nuclear Track Detectors

T. Underwood et al., Phys. Med. Biol. 62 (2017) 3237–3249

★ Idea: Validate track structure
★ problem, resolution



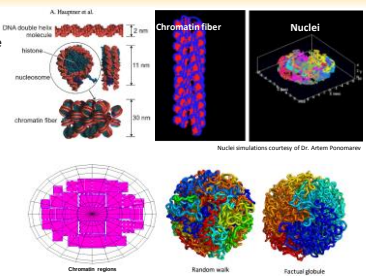
Next step: Modeling of cell geometry



Geometric modeling

★ Geometry determines cell response
★ Three basic approaches:
  ★ Clustering of energy depositions
  ★ Geometry overlay
  ★ Simulation with geometry

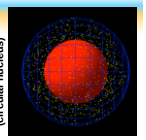
★ Some available codes:
  ★ PARTRAC
  ★ RITRACK
  ★ Geant4-DNA / TOPAS-nBio



Ways to model nuclear / DNA damage

★ Use the appropriate model depending on the question
★ possible to combine geometries

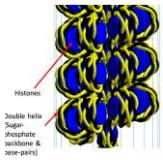
Simplistic (circular nucleus)

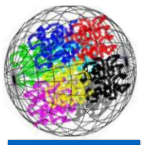


Charlton DNA (cylinder sectisons)

D. E. Charlton et al.

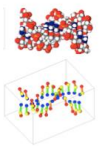
Basepair / histone modeling





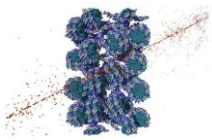
work by Aimee McNamara

Atomistic DNA model

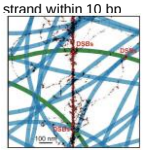


From Energy Depositions to DSBs

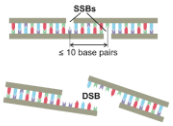
★ To obtain DNA damage, use single fibers or double helix stands
★ categorize damages:
  ★ SSB: 1 damage on 1 strand
  ★ SSE: 2 damages on same strand (<10 base paris)
  ★ DSB: 1 damage on each strand within 10 bp



Hauptner et al MFM52



The projection of a 100 MeV 16O ion track structure is overlaid on a simple model for a cell nucleus containing homogeneously distributed chromatin fibers.



What happens after the initial DNA damage?

10^{-10} 10^{-6} s **Chemistry- radical reactions, protonation, deprotonations**

10^{-6} 10^{10} s **Biochemistry & biology**

The Simulation Stages

Physical Stage:

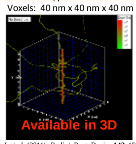
- ★ first femtoseconds, low-E physics processes (ionization, excitation, scattering, etc)
- ★ most track structure codes only work in water
- ★ cross sections for DNA coming

Physico-chemical Stage:

- ★ Water Radiolysis: creation and interaction of oxidative species
- ★ Water molecules
  - ★ dissociate if ionized
  - ★ relax or dissociate if excited

t= 0 s — Physical Stage — $t=10^{-15}$s — Physico-chemical Stage — $t=10^{-12}$s — $t=10^{-6}$ s

1 GeV/amu $^{56}Fe^{26+}$ ion
LET150 keV/µm
Voxels: 40 nm x 40 nm x 40 nm



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

Electronic state	Dissociation channels
All ionization states	$H_3O^+ + \bullet OH$
Excitation state A1B1: (1b1) → (4a1/3s)	$\bullet OH + H\bullet$ $H_2O + DE$
Excitation state B1A1: (3a1) → (4a1/3s)	$H_3O^+ + \bullet OH + e^-_{aq}$ (AI) $\bullet OH + \bullet OH + H_2$ $H_2O + DE$
Excitation state: Rydberg, diffusion bands	$H_3O^+ + \bullet OH + e^-_{aq}$ (AI) $H_2O + DE$

Geant4-DNA group: http://geant4-dna.org

Chemical Stage

Chemical Stage:

t=0s — $t=10^{-15}$s — $t=10^{-12}$s — $t=10^{-6}$s

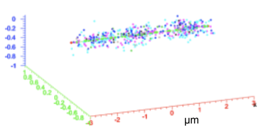
- ★ Recombinations to form new chemical species
- ★ combine tracks for **inter-track** effects
- ★ Greens function, Brownian motion, Smoluchowski, etc.

1 microsecond

Kreipl et al, 2009

Species	Diffusion coefficient D (10^{-9} m² s⁻¹)
H_3O^+	9.0
$H\bullet$	7.0
OH^-	5.0
e^-_{aq}	4.9
H_2	4.8
$\bullet OH$	2.8
H_2O_2	2.3

Reaction	Reaction rate (10^{10} M⁻¹ s⁻¹)
$H_3O^+ + OH^- \rightarrow 2\,H_2O$	14.3
$\bullet OH + e^-_{aq} \rightarrow OH^-$	2.95
$H\bullet + e^-_{aq} + H_2O \rightarrow OH^- + H_2$	2.65
$H_3O^+ + e^-_{aq} \rightarrow H\bullet + H_2O$	2.11
$H\bullet + \bullet OH \rightarrow H_2O$	1.44
$H_2O_2 + e^-_{aq} \rightarrow OH^- + \bullet OH$	1.41
$H\bullet + H\bullet \rightarrow H_2$	1.20
$e^-_{aq} + e^-_{aq} + 2H_2O \rightarrow 2\,OH^- + H_2$	0.50
$\bullet OH + \bullet OH \rightarrow H_2O_2$	0.44



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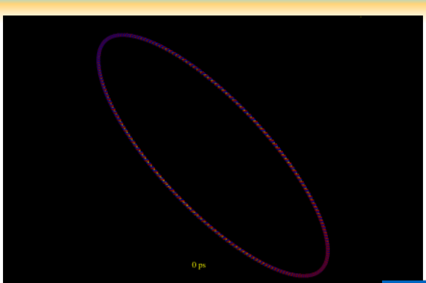
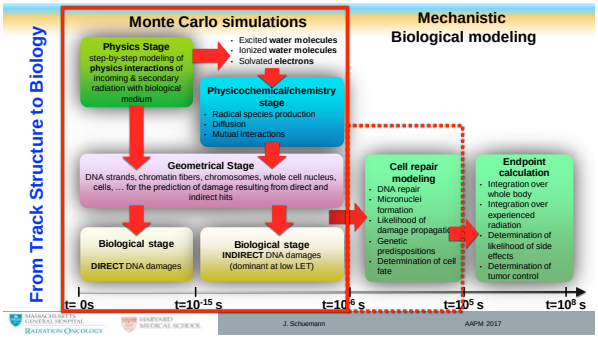


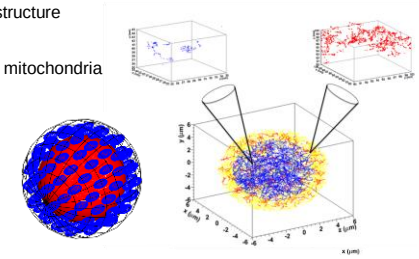
work by Jose Ramos



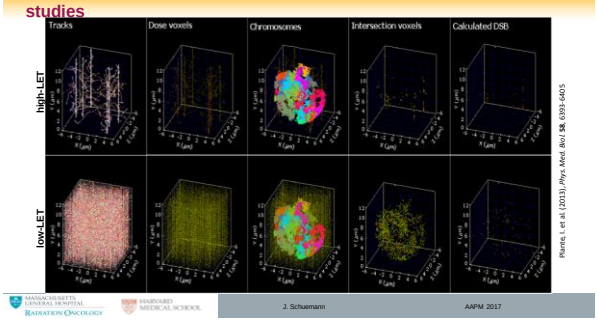
What can we do: Studying effects on sub-cellular structures

★ Effect of the track structure

★ Nuclear targets vs. mitochondria

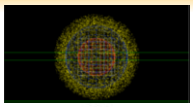


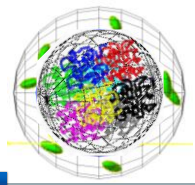
What can we do: Applying the track structures: DNA / γH2AX foci studies



What can we do: Full Track Structure GNP simulations

- ★ Use realistic GNP distributions in/around cells
- ★ Many studies use radial dose distributions around GNPs, but
  - ★ Most GNPs don't interact
  - ★ Dose not radially symmetric
  - ★ Only full track structure simulations can capture real effects
- ★ Gold cross sections recently published
- ★ Similar argument holds for other scenarios

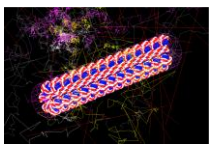




work by Aimee McNamara and Wonmo Sung

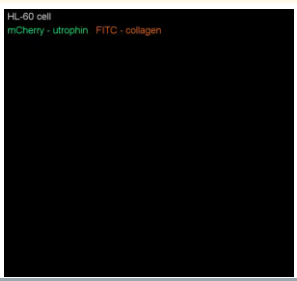
Summary

- ★ Track structure simulations can help us understand sub-cellular effects
- ★ Best use for:
  - ★ low dose (space, out of field)
  - ★ high LET radiation (less tracks, more structure)
- ★ Emerging Technology
  - ★ still very much under development
  - ★ steadily expanding
- ★ Goal: Advance understanding of radiation effects
  - ★ connect physics to biology
  - ★ close the gap from the bottom up



Is nanometer scale in 3D enough?

- ★ Two-color volume rendering of a neutrophilic HL-60 cell expressing mCherry-utrophin migrating through a 3D collagen matrix
- ★ Complex 4D behavior of cells
- ★ Not even considering inter-cell signaling
- ★ Lots left to do



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The TOPAS and TOPAS-nBio collaborations

and many more.