Nanometer-scale Monte Carlo simulations

MASSACHUSETTS GENERAL HOSPITAL

Jan Schuemann

AAPM Annual Meeting
Washington
07/03/2016

What is "Monte Carlo"

- Part of a nuclear weapons research project at Los Alamos during World War II
- Code name "Monte Carlo", after the city in Monaco, because of a roulette, a simple random number generator

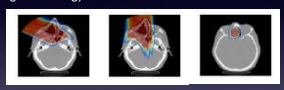
Monte Carlo methods refers to any procedures which involve sampling from random numbers

Monte Carlo Applications in Biomedicine

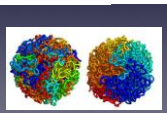
- Diagnostic Radiology / Nuclear Medicine
  - Detectors
  - Imaging correction techniques
  - Determination of physical quantities (e.g. scattering)
  - Radiation protection

Radiotherapy
- Dosimetry equipment
- Phantom simulations
- Beamline design

Treatment planning (dose calulations, optimization)



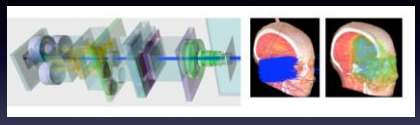
- Radiation protection

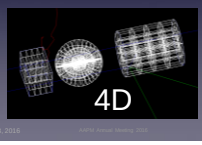


- Applications based on microscopic MC techniques
  - Track structure and microdosimetry

TOPAS

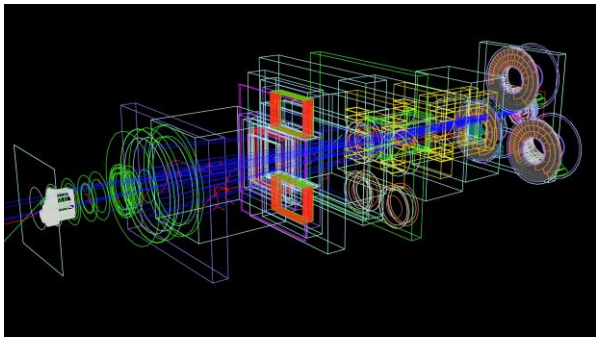
Tool for Particle Simulation





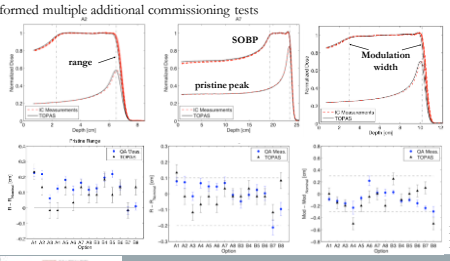
TOPAS:
Wrap Geant4 for Particle Therapy

Joseph Perl - SLAC National Accelerator Laboratory
Bruce Faddegon, Jose Ramos - University of California San Francisco
Jungwook Shin – St Jude Children's Research Hospital
Harald Paganetti, Aimee McNamara, Jan Schuemann - Massachusetts General Hospital



FHBPTC Commissioning

- ★ Range and Modulation width of SOBPs for both Gantries
- ★ Performed multiple additional commissioning tests

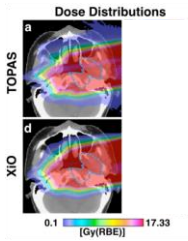


M. Testa et. al, Med. Phys. 2013

Sample Patient study, dose, range, TCP, NTCP

J. Schuemann et. al. PMB. 2014

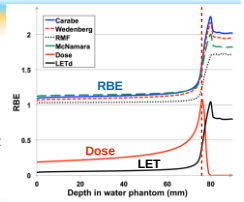
- ★ Comparing Monte Carlo to TPS
- ★ Effects of high density interfaces parallel to beam on analytical calculations clearly visible
- ★ Various studies have compared TPS to Monte Carlo
- ★ D50, D90, R90, EUD, TCP, NTCP, …

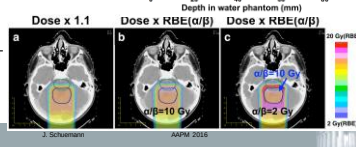


Including Biology

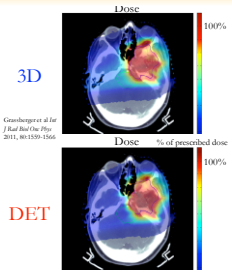
- ★ Clinical endpoint of interest: **Biological effect**
- ★ There is a large gap between physics events and biological outcome (and physics/biology research)
- ★ Concept of Relative Biological Effectiveness (RBE):
  - ★ RBE assigns a biological effectiveness to radiation
  - ★ Protons assumed10% more effective than photons: Clinically used RBE = 1.1
  - ★ RBE depends on multiple things:
    - ★ dose, tissue, endpoint, etc.
    - ★ the modeling approach
    - ★ Linear energy transfer, LET

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



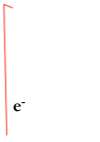


The effect of LET for biological optimization



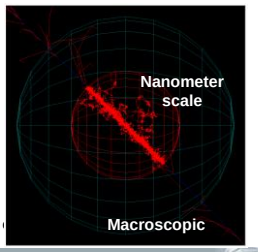
Why do we need more?

Standard Monte Carlo simulation



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
- ★ The goal is to study:
  - ★ cell structure effects
  - ★ track structure effect
  - ★ single track effects (out-of-field, SPE, GCR)
  - ★ new ideas (i.e. sub-cellular targets, GNPs,



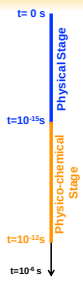
The Simulation Stages

Physical Stage:

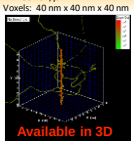
- ★ first femtoseconds, low-E physics processes (ionization, excitation, scattering, etc)
- ★ most track structure codes only work in water
- ★ cross sections for DNA coming

Physico-chemical Stage:

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



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	$H_2O^+ + {}^\bullet OH$
Excitation state A_1B_1: $(1b_1) \rightarrow (4a_1^*/3s)$	${}^\bullet OH + H^\bullet$ $H_2O + DE$
Excitation state B_1A_1: $(1a_1) \rightarrow (4a_1^*/3s)$	$H_2O^+ + {}^\bullet OH + e^-_{th}$ (Al) ${}^\bullet OH + {}^\bullet OH + H_2$ $H_2O + DE$
Excitation state: Rydberg, diffusion bands	$H_2O^+ + {}^\bullet OH + e^-_{th}$ (Al) $H_2O + DE$

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

Chemical Stage

Chemical Stage:

t=0s — t=10⁻¹⁵s — t=10⁻¹²s — t=10⁻⁶s

★ Recombinations to form new chemical species

★ combine tracks for inter-track effects

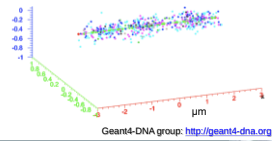
★ Greens function, Brownian motion, Smoluchowski, etc.

1 microsecond

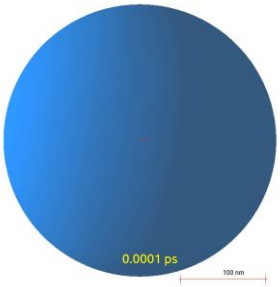
Knipl et al, 2015

Species	Diffusion coefficient D (10^{-9} m² s⁻¹)
H_2O^+	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)
$H_2O^+ + OH^- \rightarrow 2\,H_2O$	14.1
$^\bullet OH + e^-_{aq} \rightarrow OH^-$	2.95
$H^+ + e^-_{aq} + H_2O \rightarrow OH^- + H_2$	2.65
$H_2O^+ + e^-_{aq} \rightarrow H^\bullet + H_2O$	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
$e^-_{aq} + e^-_{aq} + 2\,H_2O \rightarrow 2\,OH^- + H_2$	0.50
$^\bullet OH + {}^\bullet OH \rightarrow H_2O_2$	0.44



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



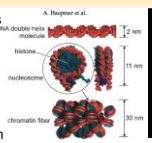
Geometric modeling

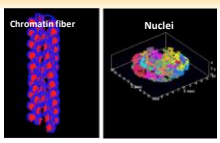
★ Get effect from energy depositions

★ Two basic approaches:
- ★ Geometry overlay
- ★ Simulation with geometry

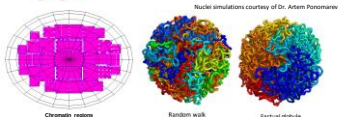
★ Simulate nucleus:
- ★ Better understand formation of DSBs
- ★ Use' building blocks"

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





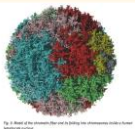
Nuclei simulations courtesy of Dr. Artem Ponomarev

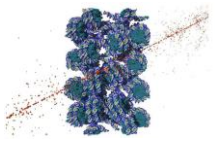


More about geometries in TOPAS-nBio: Aimee McNamara, 17:00 Ballroom A

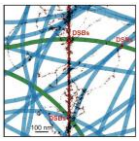
From Energy Depositions to DSBs

- ★ To obtain DNA damage, zoom in to 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

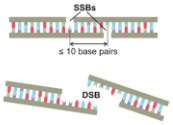




Hauptner et al MFMS2



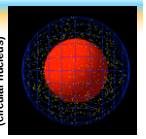
The projection of a 100 MeV 16O ion track structure is overlaid on a simple model for a cell nucleus containing homogeneously distributed chromatin fibers.



Ways to model nuclear / DNA damage

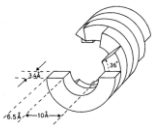
- ★ Use the appropriate model depending on the question
- ★ possible to combine geometries

Simplistic (circular nucleus)

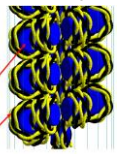


Charlton DNA (cylinder sectisons)

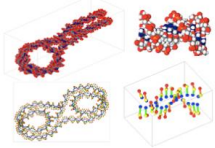
D. E. Charlton et al.



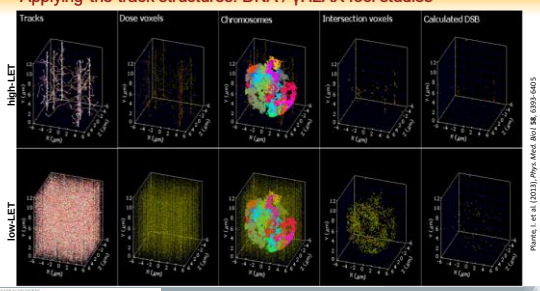
Basepair / histone modeling



Atomistic DNA model



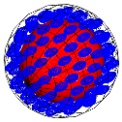
Applying the track structures: DNA / γH2AX foci studies

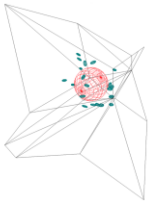


Plante I. et al. (2013). Phys. Med. Biol. 58, 6393-6405

Other geometries

★ Cells consist of multiple components (membranes, liposomes, etc)
★ Can be used to study non-nuclear (secondary?) effects
★ study proteins (PDB), viruses, etc.
★ potential target for drugs/nanoparticles



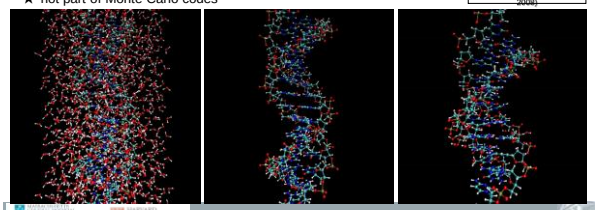


Trung Pham PhD thesis
http://pdbq4na-inspg.fr
http://geant4-dna.org

Molecular Dynamics

★ Molecular dynamics model of DNA and surrounding water molecules
★ complex inter-molecule behavior
★ 2.6 nm x 2.6 nm x 6 nm
★ not part of Monte Carlo codes

video courtesy of R. Abolfath
arXiv:1309.0426v1
MD with ReaxFF
(van Duin 2001, Chenoweth 2008)

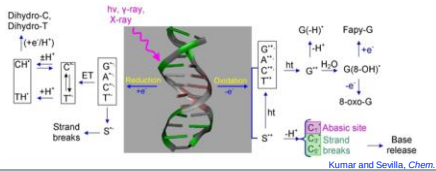


What happens after the initial DNA damage?

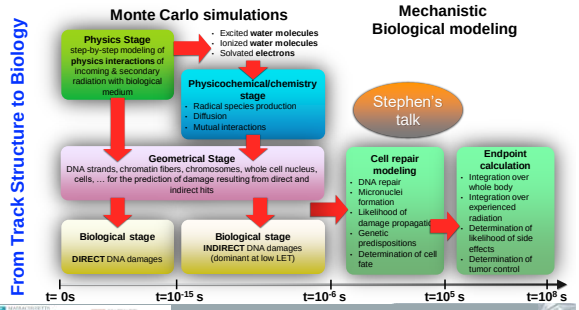
0 - 10^{-15} s	**Physics interactions**
10^{-12} - 10^{-6} s	**Chemistry- radical reactions, protonation, deprotonations**
10^{-6} - 10^{10} s	**Biochemistry & biology**

Radiation Chemistry - extended

- ★ What happens to DNA after ionization
- ★ Charge transport along the DNA strand
- ★ Based on stepwise optimization of a dA cation
- ★ Not included in any MC yet

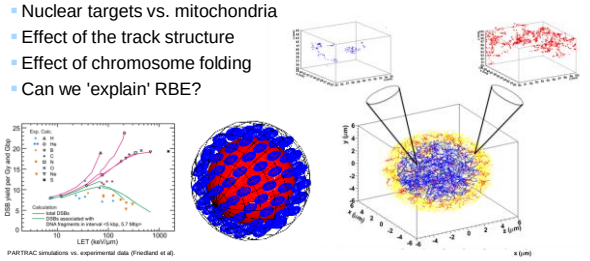


Kumar and Sevilla, *Chem. Rev.* 2010



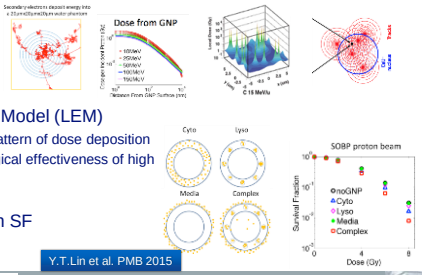
What can we do: Studying effects on sub-cellular structures

- Nuclear targets vs. mitochondria
- Effect of the track structure
- Effect of chromosome folding
- Can we 'explain' RBE?



What can we do: Modeling of Gold Nano Particle Effect

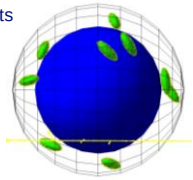
- GNPs
- Get radial dose distribution
- used Local Effect Model (LEM)
  - Account for spatial pattern of dose deposition
  - Used to model biological effectiveness of high LET radiation
- study the effect on SF

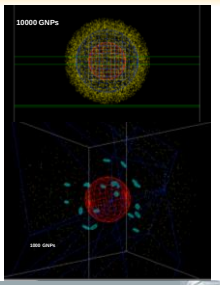


Y.T.Lin et al. PMB 2015

What can we do: Full Track Structure GNP simulations

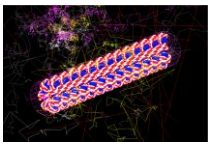
- But: Dose is not radially symmetric
- Most GNPs don't even interact
- Only full track structure simulations can capture real effects
- Similar considerations hold for other scenarios





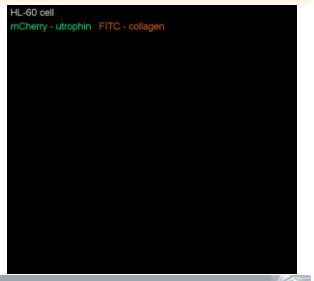
Summary

- 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 both sides



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



Credit: Betzig Lab, HHMI/Janelia Research Campus, Mullins Lab, HHMI/University of California, San Francisco; 10/24/14 issue of the journal Science

Acknowledgements

- Aimee McNamara
- Wonmo Sung
- Yuting Lin
- Clemens Grassberger
- Ramin Abolfath
- Ianik Plante
- Michael Sevilla
- Harald Paganetti

TOPAS collaboration

- and many more.