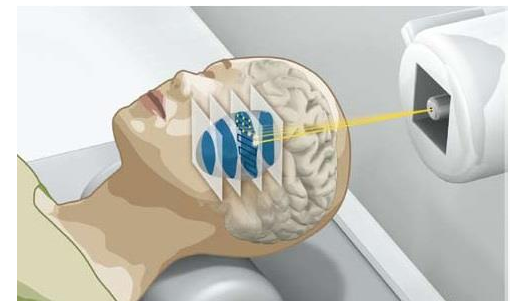
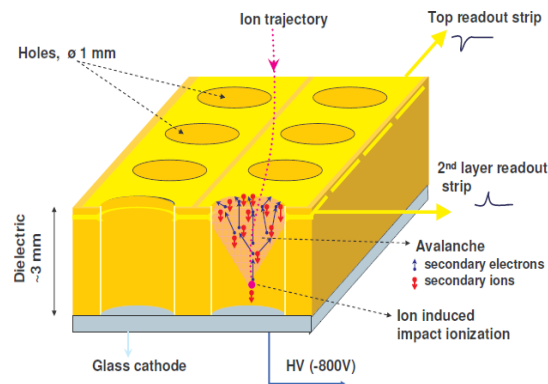
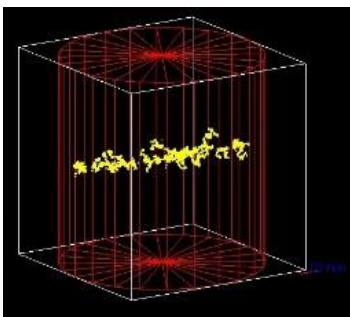


A Novel Approach to Particle Therapy Radiation Metrology Based on Nanodosimetry - Concepts and First Results

Reinhard W. Schulte, Professor of Radiation Medicine
Loma Linda University, California, USA



Acknowledgements

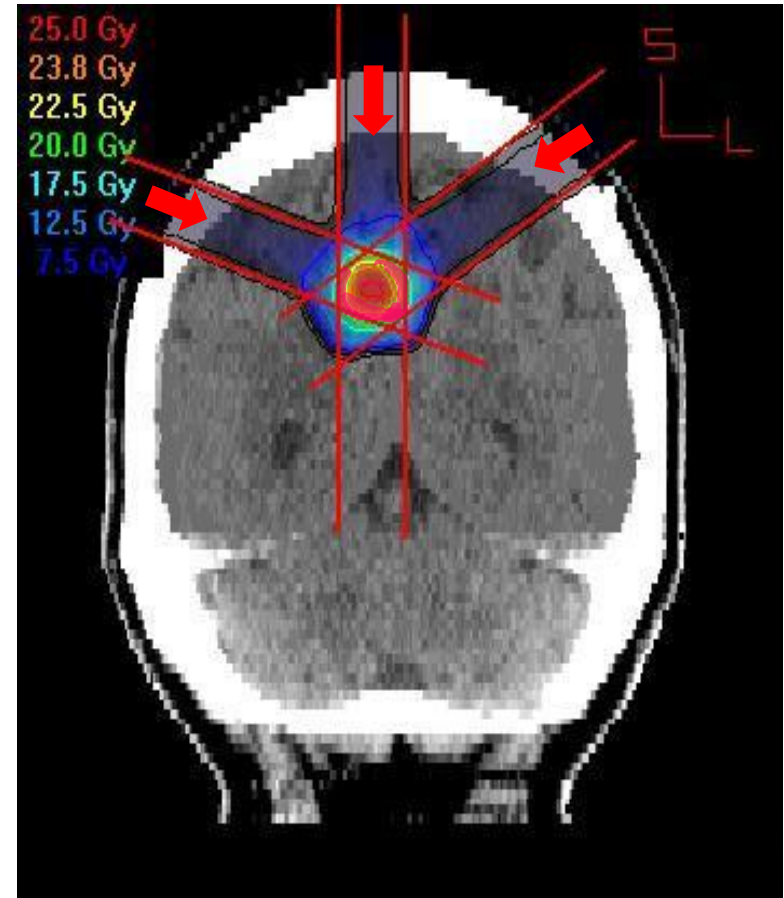
- **Team:** Vladimir Bashkirov & Ford Hurley LLU, Ana Belchior, IST/ITN Portugal, Margherita Casiraghi, Roger Haelg, & Tony Lomax PSI, Switzerland; Anatoly Rozenfeld & Susanna Guatelli, UoW,
- **Funding:** ANDANTE Project (European Commission (LLU, PSI); EMRP/BioQuaRT (R. Schulte, advisor); EMRP Researcher Excellence Grant (A. Belchior)

Outline

- Motivation: The Problem with RBE
- Nanodosimetry - Concepts and Devices
- Nanodosimetry - Biological Rationale
- Nanodosimetry - Treatment Plan Optimization
- Nanodosimetry - Open Questions
- Summary & Outlook

Room for Improvement: Relative Biological Effectiveness (RBE) a Flawed Concept

- Protons and ions have a depth-dependent biological effect profile
- Current concept of $D_{RBE} = RBE \times D$, has limitations:
 - RBE is depth-, dose-, and tissue- (or endpoint) -dependent
 - In proton therapy, $RBE = 1.1 = \text{const}$ is assumed, which was recently endorsed by ICRU report 78, but we know that it is not correct
 - There is higher biologically effective dose in the distal third of the SOBP
- Nanodosimetry-based treatment planning may be able address some of these issues



The biological dose is higher in the distal regions of each beam

SECTION I

NANODOSIMETRY CONCEPTS AND DEVICES

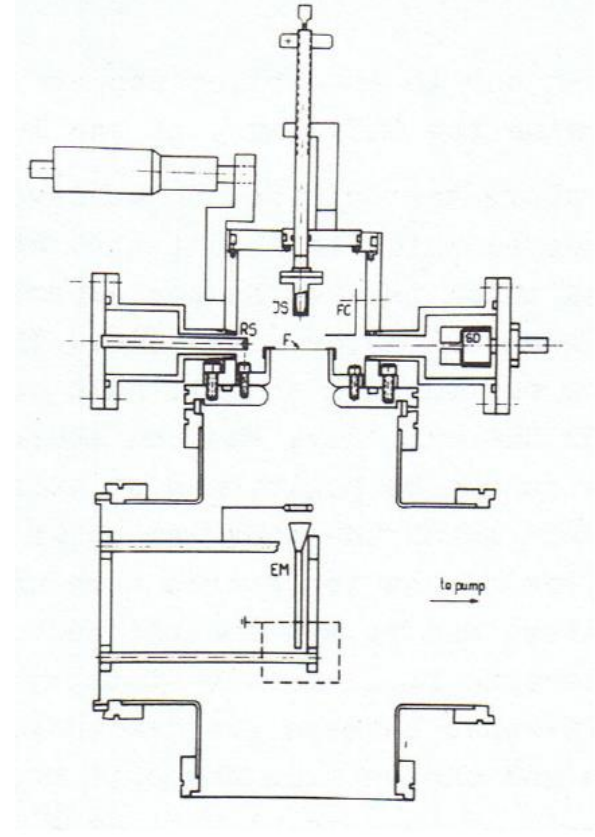
Origins of Nanodosimetry

1. Pszona S. *Studies for nanometer microdosimetry*. Annual report on research project COO 3243-2. USAEC, New York, pp 102-107 (1973)
2. Chmelewski D, Parmentier N, Le Grand J. *Dispositive experimental en vu d'étude dosimétriques au niveau du nanometre*. In: Proc 4th Symp on Microdosimetry. (Report EUR 5122) Commission of the European Communities, Luxembourg, pp 869-885 (1974).
3. Pszona S. *A track ion counter*. In: Booz, J, Ebert HG, Smith BGR (eds) Proc 5th Symp on Microdosimetry. (Report EUR 3452) Commission of the European Communities, Luxembourg, pp 1107-1121 (1976).

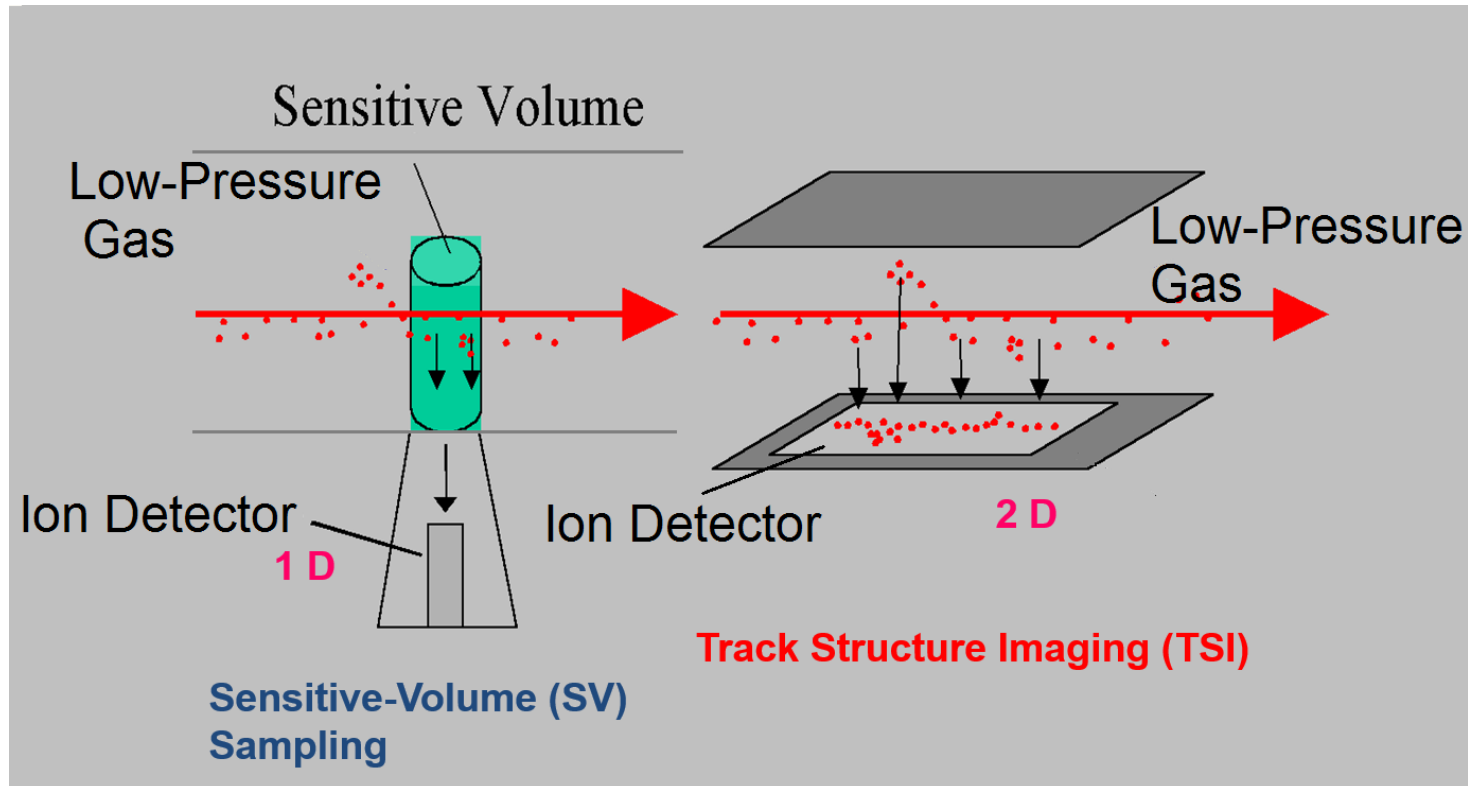
The Origins of Ion-Counting ND

Abstract

A method to measure the frequency of production of various number of ions in a gas domain is described. The characteristics of a device, which is termed a "track ion counter," are presented. The counter consists of two cylindrical volumes separated by a diaphragm with 500 μ m dia. orifice. The device is connected to an oil diffusion pump with high pumping speed. The gas flow through the orifice determines the pressure in the upper and the lower volumes of the device. The positive ions produced in a cylindrical volume above an orifice by charged particles traversing that volume move in a constant electric field. Some of these ions pass through the orifice are accelerated and detected by an electron multiplier. The absolute efficiency of ions detection from the domain above the orifice as well as the extension the domain from which ions are collected have determined. The measurements were carried out for single charged ions of N_2 , H_2 , CH_4 , CO_2 . The preliminary measurements of the frequency of various number of ions created within cylindrical gas domain equivalent to 0.15 nm dia. and 7.6 nm height tissue cylinder are reported.



Principle Approaches to Ion Counting Nanodosimetry

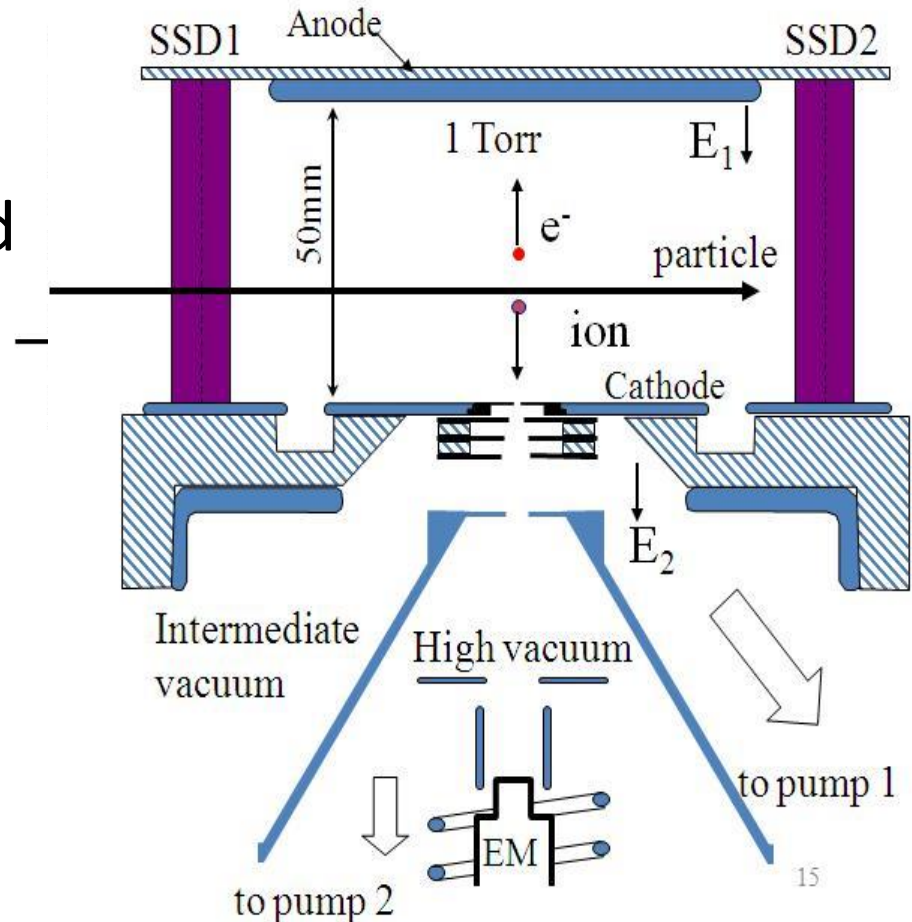


R Schulte et al. Australas. Phys. Eng. Sci. Med., 26(4), 149-55, 2003

Ion Counting Nanodosimeter with Particle Tracking

Weizmann Institute, LLUMC, UCSC, PTB

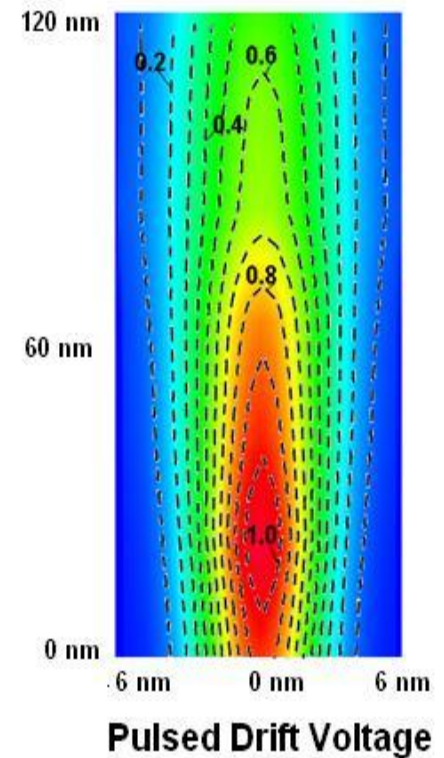
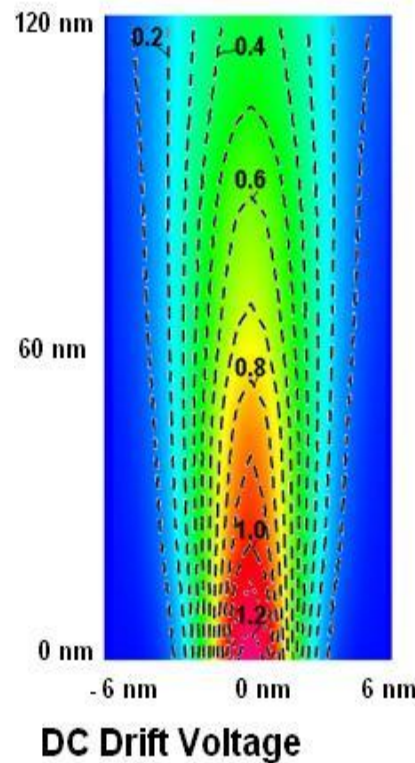
- Propane based (1.3 mbar)
- Operating in DC or pulsed mode
- Electron multiplier (EM) for ion counting
- Particle tracking system (4 silicon strip detectors) developed by SCIPP @ UCSC



G Garty et al., Nucl. Instr. and Meth. A 491, 212-235, 2002.

Sensitive Volume Maps

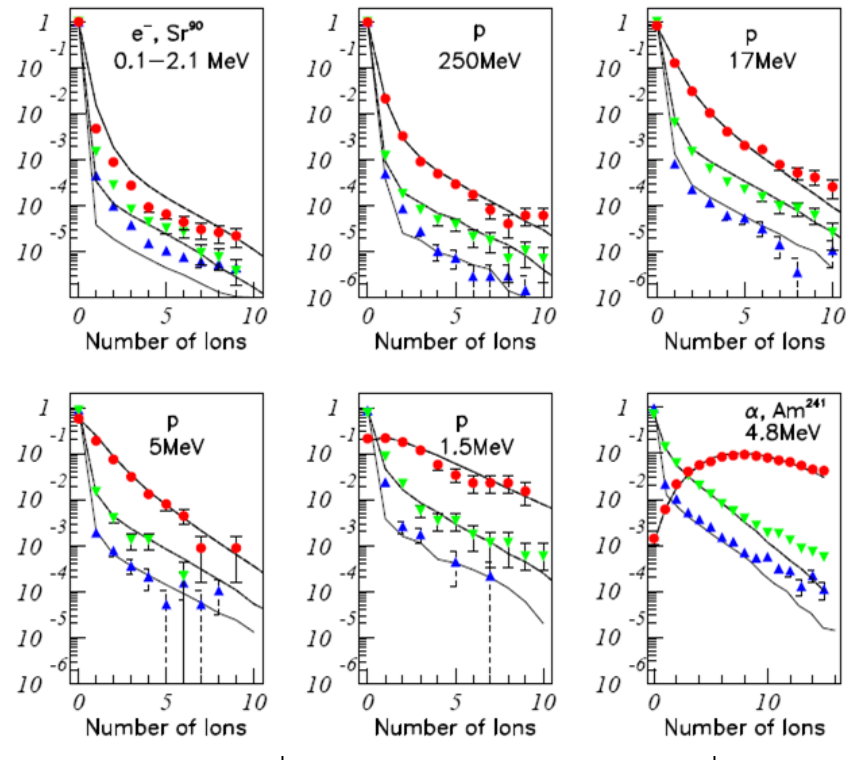
- Pulsed drift voltage operation is important to suppress charge multiplication
- Sensitive volume transverse diameter matches that of DNA molecule
- Penumbra simulates probability of ionization causing DNA damage via indirect effect



R Schulte et al. J Instrum.
2006

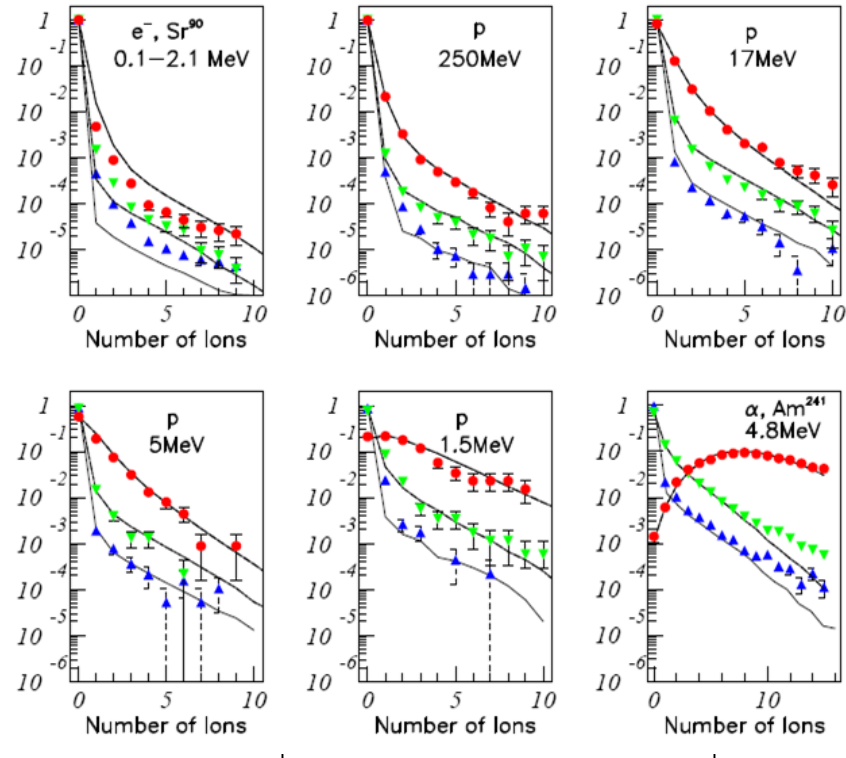
Ionization Clustering of Protons Varies with Depth

- We measured and simulated (with the PTB code) the clustering statistics of proton-generated ions in propane gas volumes of nanometer-equivalent size
- The rel. frequency of large clusters increases with decreasing energy and thus depth



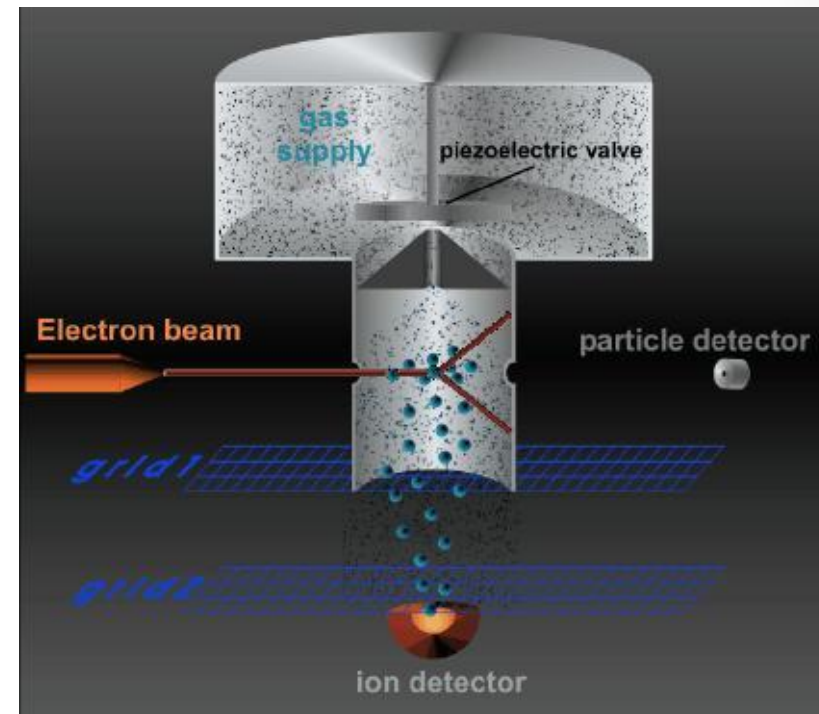
Ionization Clustering of Protons Varies with Depth

- We have measured and simulated the clustering statistics of protons, electrons and alphas in propane gas volumes of nanometer-equivalent size
- The rel. frequency of large clusters increases with decreasing proton energy and thus depth



Jet Counter (JC) Nanodosimetry

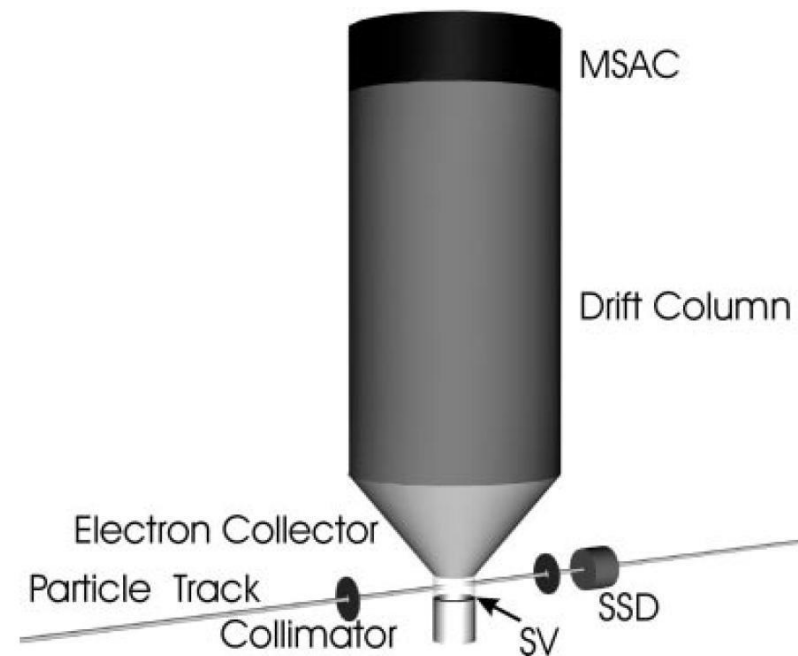
- Developed by Pszona et al at the Soltan Inst. for Nucl. Studies., Poland
- Periodic short pulses ($\sim 100 \mu\text{s}$, 1 Hz) of expanding gas jet (nitrogen, propane) into vacuum chamber
- Dynamic density measured with electron transmission (Beer's law)
- Equivalent cylindrical sensitive volume: 2.3 nm x 2.3 nm
- Gated ion collection ($100 \mu\text{s}$ interval) timed with particle traversal (1 particle/ $1 \mu\text{s}$ on average)



Courtesy Stan Pszona

STARTRACK Electron-Counting Nanodosimetry

- Developed at the INFN Laboratori Nazionali di Legnaro, Italy
- Low-intensity, focused particle beam crosses cylindrical sensitive volume (20nm x 20nm), filled with low-pressure propane (3mb)
- Ionization electrons drift through aperture into drift column
- Electrons are slowed down to be separated in time (>20 ns) and are counted in multi-step avalanche chamber (MSAC)
- Sensitive volume can be transversely moved to different impact parameters d from the ion track to measure the cluster event size of the track penumbra,



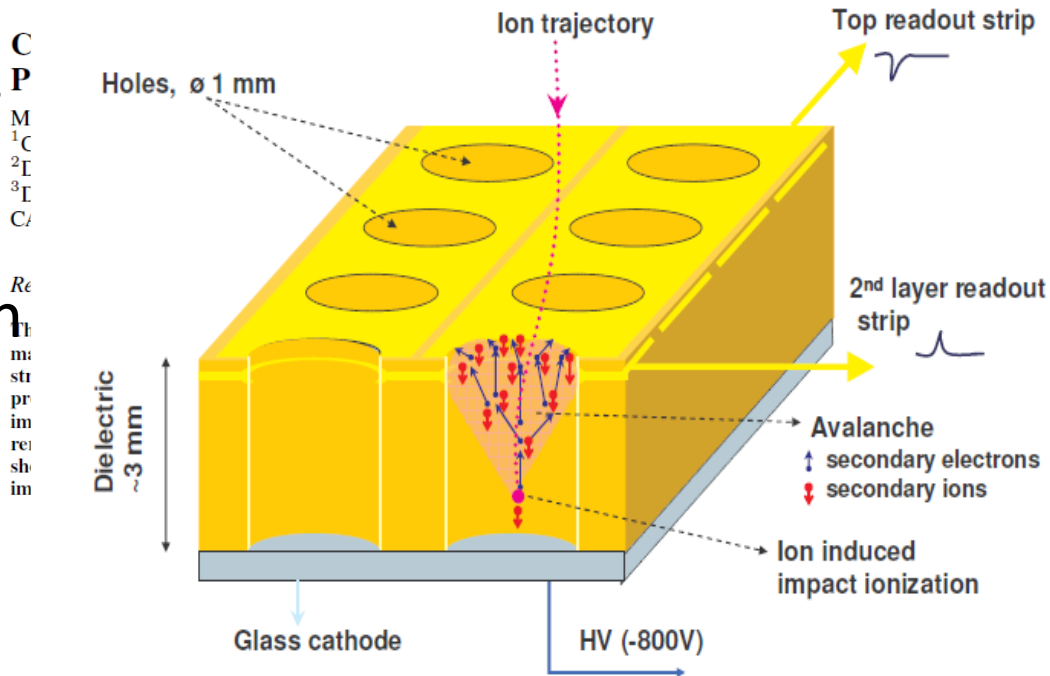
L De Nardo et al, Radiat Prot Dosimetry
122 (1-4): 427-431, 2006

A Novel Detector for 2D Ion Detection in Low-Pressure Gas

- Novel 2D ion detector developed in the LLU Radiation Research Labs
- Principle proven and presented in 2009
- Can be applied to proton and ion track structure studies
- Currently developed in our Radiation Physics Research lab

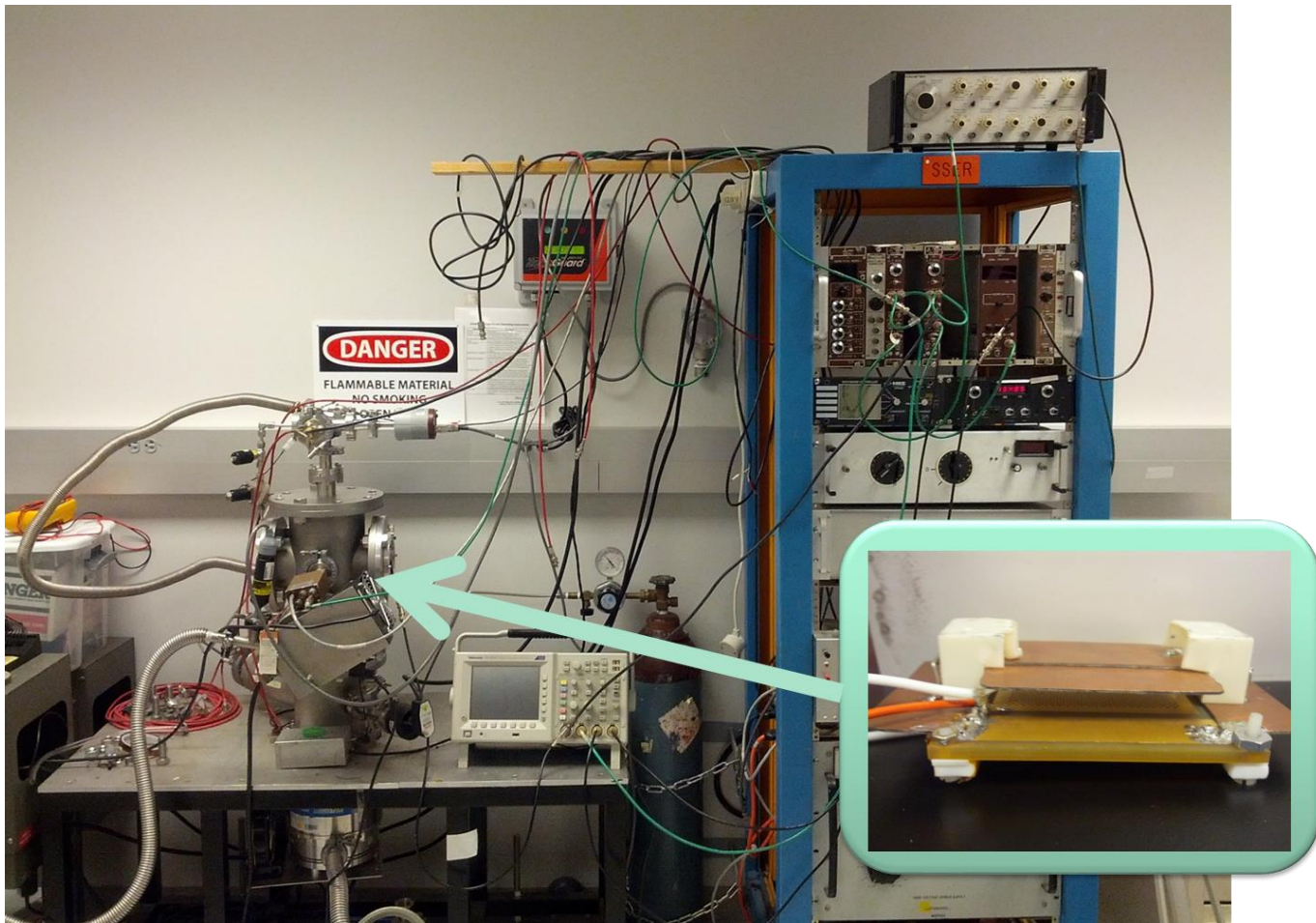
Radiation Protection Dosimetry (2013), Vol. 0, No. 0, pp. 1-4
DOI: 10.1003/rpd/111111

SECTION TITLE



V. Bashkirov, 15th International Symposium on Microdosimetry (MICROS 2009), October 25-30, 2009, Verona, Italy

Experimental Setup for the TIDE

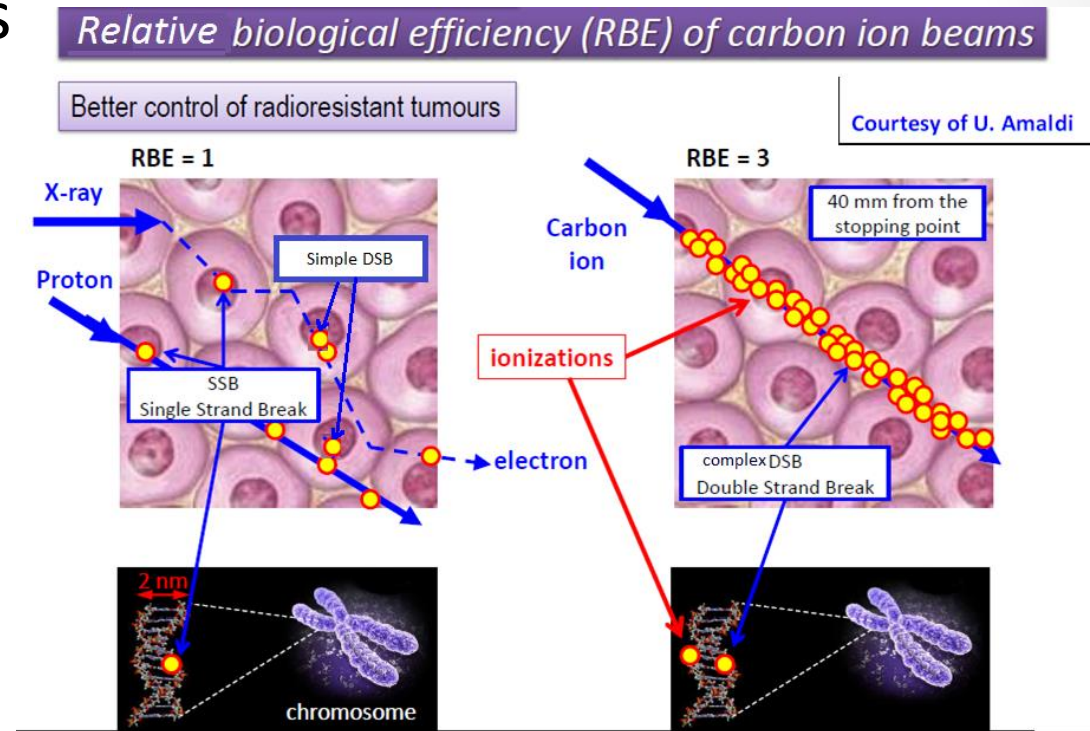


SECTION II

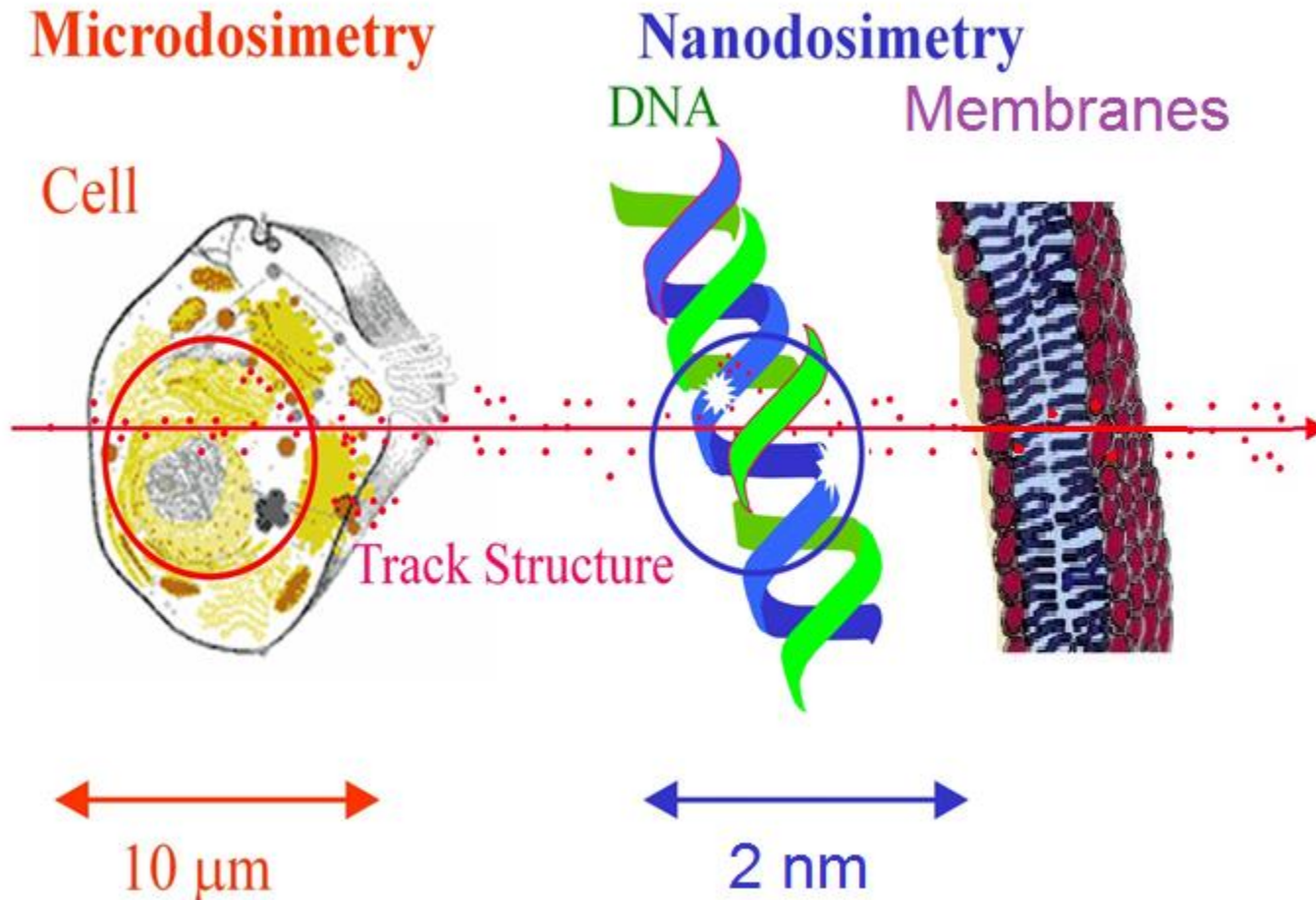
NANODOSIMETRY – RADIOBIOLOGICAL RATIONALE

What is Different between Protons and Carbon Ions

- Protons and carbon ions both have excellent dose-localization properties
- Compared to protons, carbon ions are characterized by larger regional (chromosomal) and local (DNA, membranes) clustering of ionizations

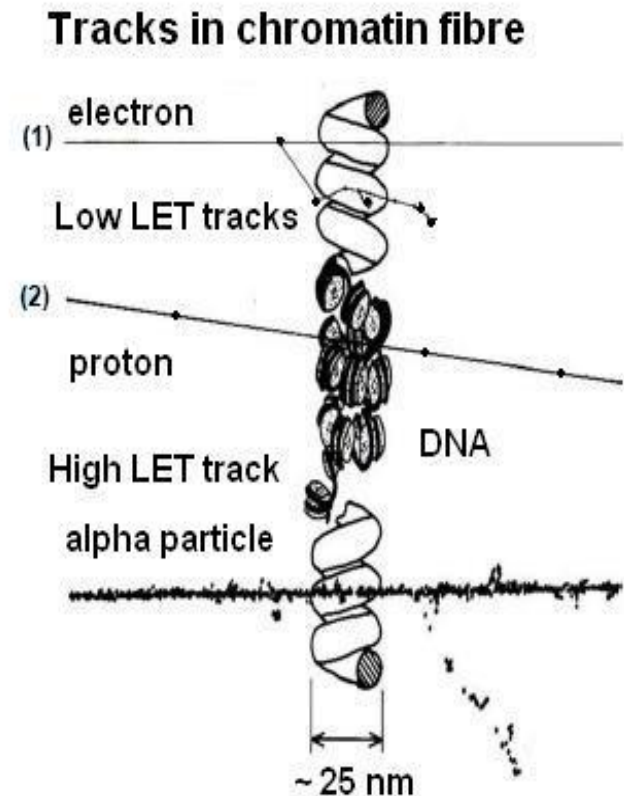


Radiation Quality – Micro- vs. Nanodosimetry



Monte Carlo Track Structure Simulations: Lessons Learned

- All particle tracks are highly structured on the nanoscopic scale
- Low-energy electrons can also produce rel. large ionization clusters on the DNA scale
- Mean free path length comparable to diameter of DNA molecule (~2 nm) for most effective high-LET radiation



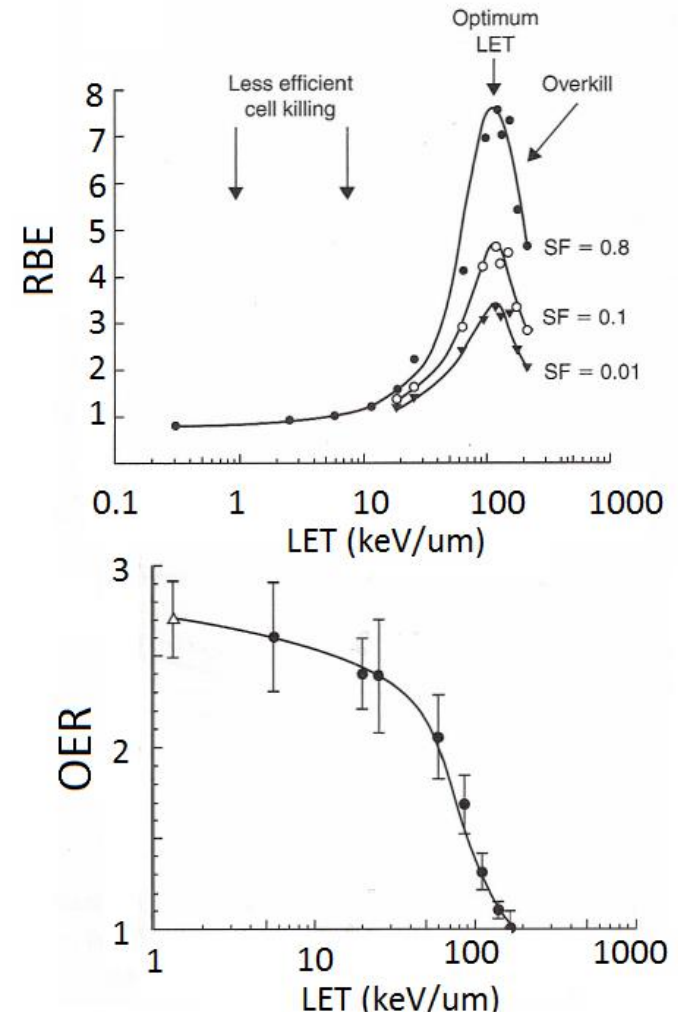
Courtesy D. T. Goodhead

Radiobiological Evidence for the Importance of Clustered Ionizations of Nanometer Size

- There is indirect evidence that clustering of ionizations over dimensions over 2-10 nm distances is an important quality parameter for larger biological effectiveness at the same absorbed dose level
- Ultrasoft x-rays (0.1- 10 keV), which produce more electron track ends (~30% dose contribution), appear to be biologically more effective compared to low-LET radiation, although, one has to take into account the dose non-uniformity in RBE calculations
- Low-energy beta emitting radionuclides that associate with DNA are about 2 times more effective per unit dose delivered compared to low-LET radiation

Biological Optimization: What should we optimize?

- Optimization of RBE within a gross tumor volume (GTV) is flawed, because RBE depends on cell type, oxygen status, and dose/fx size
- A more promising approach may be to optimize the yield (per particle fluence) of large ionization clusters in the tumor and minimizing their yield in critical normal tissues (based on low-LET accumulated experience)
- In order to create uniform cell kill in a uniform target, the yield of large, e.g., (4-10) and small (2-10) ionization clusters should be made uniform as well
- In case of hypoxic regions, the number of small ionization clusters should be enhanced by the low-LET OER (~ 2.7) for uniform cell kill



SECTION III

NANODOSIMETRY – TREATMENT PLAN OPTIMIZATION FOR PROTONS

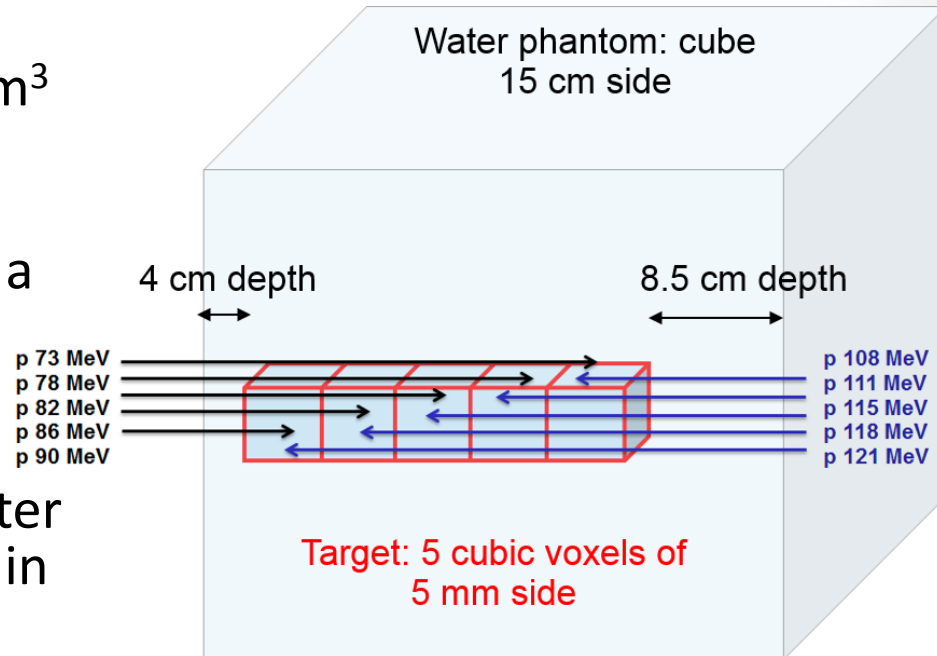
By Margherita Casiraghi, M.S.

Simulations and Optimization of Ionization Cluster Yield for Proton Therapy

- **Aim:** optimization of a simplified proton treatment plan with the goal to obtain a uniform distribution of large ionization clusters (4-10 ionizations) and, if possible, small clusters (2-3 ionizations) capable of producing clustered lesions DNA
- **Simulations** were performed with the Geant4 toolkit combining standard physics, low energy physics (Livermore) and very low energy physics (Geant4 DNA) models

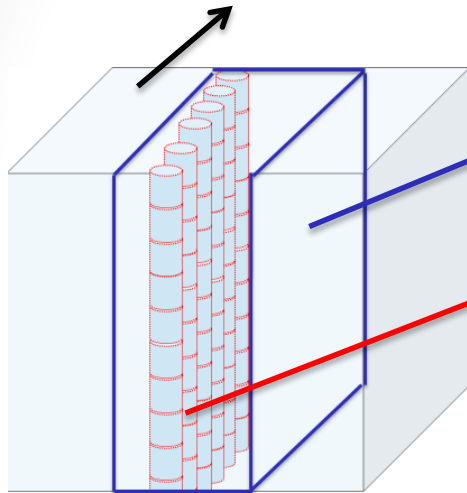
Simulation Geometry and Strategy

- The planning target volume consisted of 5 voxels $5 \times 5 \times 5 \text{ mm}^3$ embedded in a water cube of 15 cm side length
- The PTV was treated with either a single or two opposing beams consisting of a stacks of equally spaced 3-mm p-pencil beams
- The simulation of ionization cluster size (ICS) distributions was done in three conseq. steps:
 - **1st step:** macroscopic level
 - **2nd step:** nanoscopic level
 - **3rd step:** random sampling with nanometer sensitive volumes



Simulation Step 2: Collection of Tracks for Nanodosimetric Sampling

Voxel: activation of **Livermore EM** models (e- down to 250 eV)

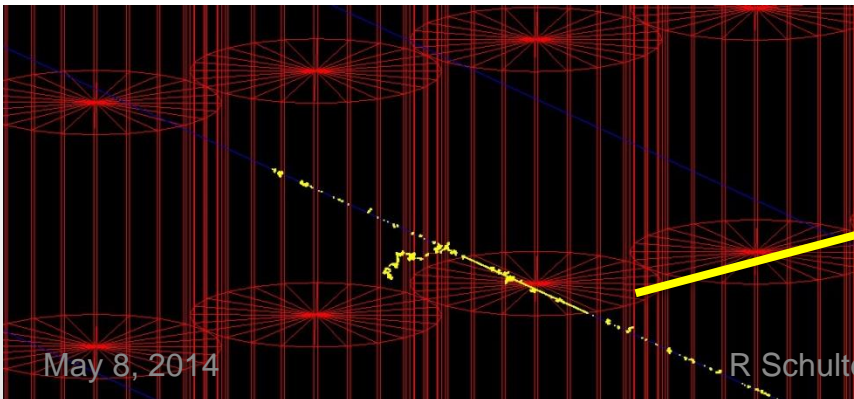
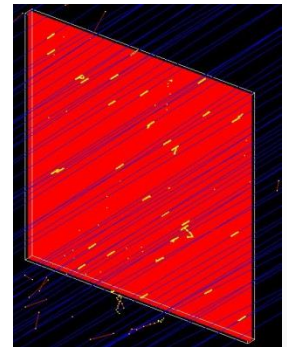


2 μm thick slab placed in the center of the voxel:
activation of **DNA physics** (e- down to 0 eV)

2D array of nanometric sensitive volumes (SV):
Cylinders of 500 nm diameter and 500 nm height placed at the center of the slab.

- In order to increase the chance of scoring a SV affected by a single proton track or a secondary, the SV was replicated $10^4 \times 10^4$ times in the 2D plane at the center of the slab

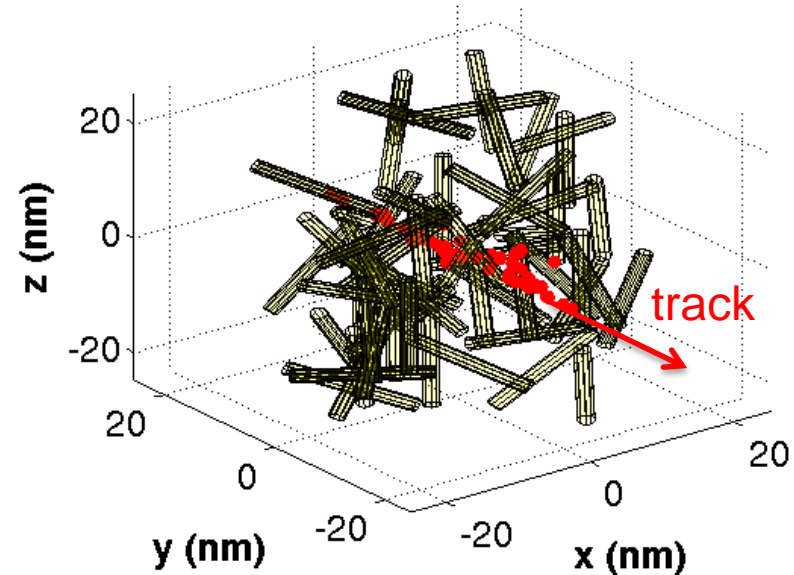
- In a single affected SV affected, the tracks produced by protons and their secondaries were simulated



Simulation output: coordinates of all the ionization events produced in the nanometric SV per proton entering the macroscopic phantom

Simulation Step 3: Nanodosimetric Sampling

- Geant4-simulated tracks were sampled with 100k cylindrical volumes of 2 nm diameter and 16 nm length randomly distributed throughout the larger SV
- In each sampling SV, the number of ionizations was scored
- Composite ionizations cluster size distributions (absolute and conditional) were calculated for unit- and weighted pencil beam fluences



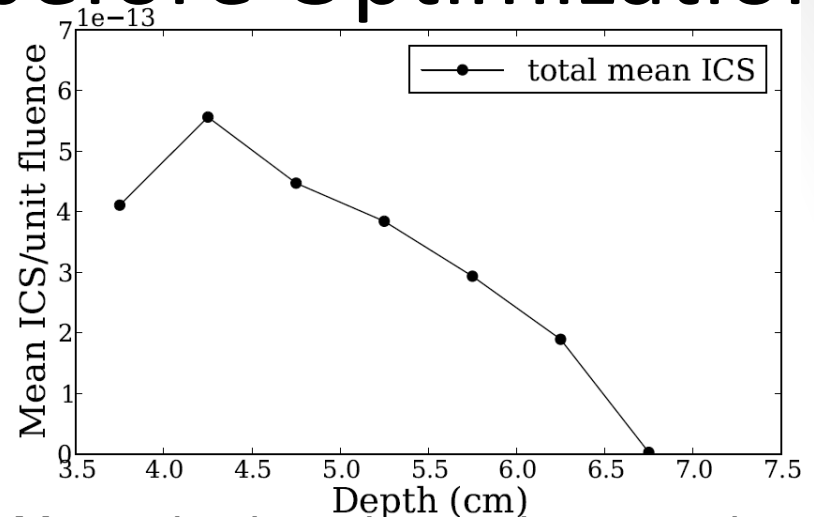
Nanodosimetric Optimization Strategy

- Different optimization strategies were tried and compared with the non-optimized case:
 - No optimization: all pencil beams had unit fluence
 - Mean cluster size optimization: The beam fluence was weighted to achieve a uniform mean ICS (first moment of the absolute ICS distributions)
 - Uniform small ICS yield per total fluence (2-3 ionizations) assumed responsible for simple DSBs
 - Uniform large ICS yield (4-10 ionizations) assumed responsible for complex DSBs
- A least squares routine with positive weight constraints implemented in Matlab was used to find the optimized fluences for each pencil beam

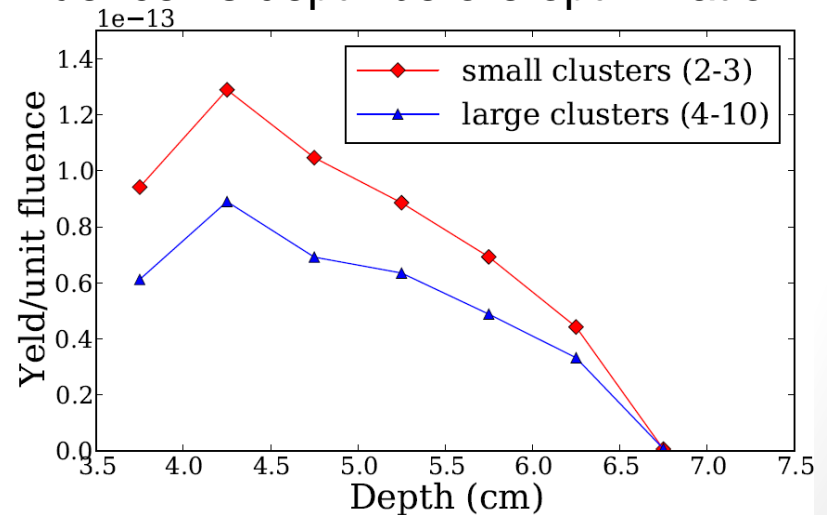
Single-Beam ICSDs before Optimization



- For non-optimized (unit) fluence of each pencil beam, the mean absolute cluster size reduces with depth
- The same holds for small and large ionization clusters



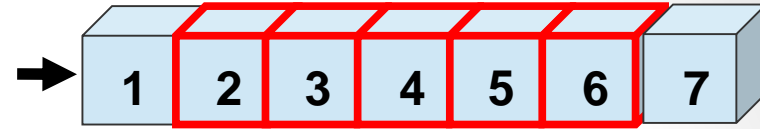
Mean absolute cluster size per unit fluence vs depth before optimization



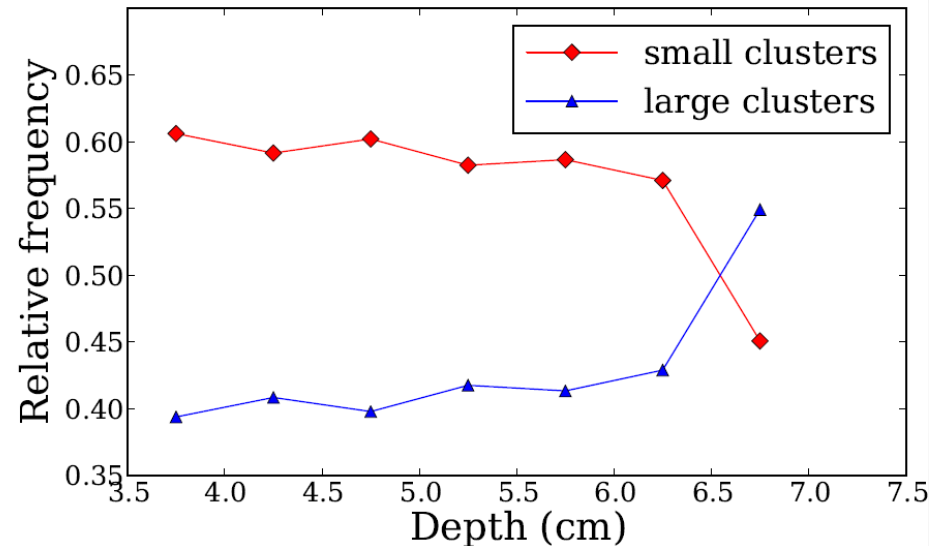
Yield of **small** and **large** clusters

Radiation Quality vs. Depth for a Single

SOBP

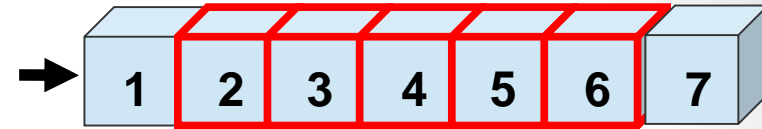


- The relative frequency of small clusters reduces towards the distal end of a single spread-out Bragg peak (SOBP)
- Correspondingly, the relative frequency of large clusters increases with depth
- There are only stopping protons in the last voxel

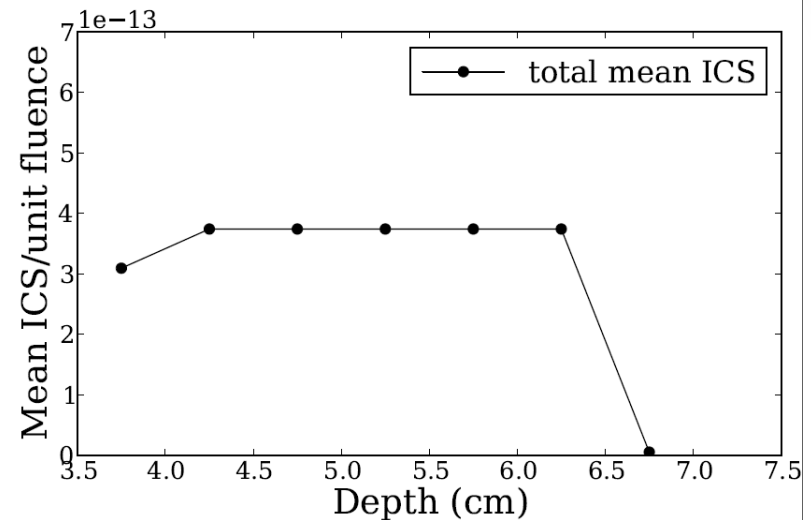


Relative yield of **small** and **large** clusters

Optimization of Dose for Single SOBP

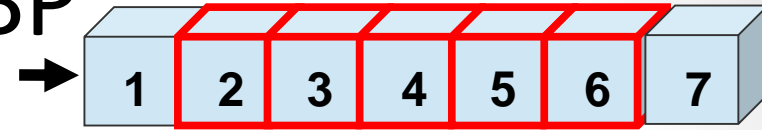


- After optimizing the individual pencil beam fluence of a single SOBP, the mean absolute ICS is constant throughout the PTV
- This means, the absorbed dose is also uniform
- The first and last point are outside the PTV

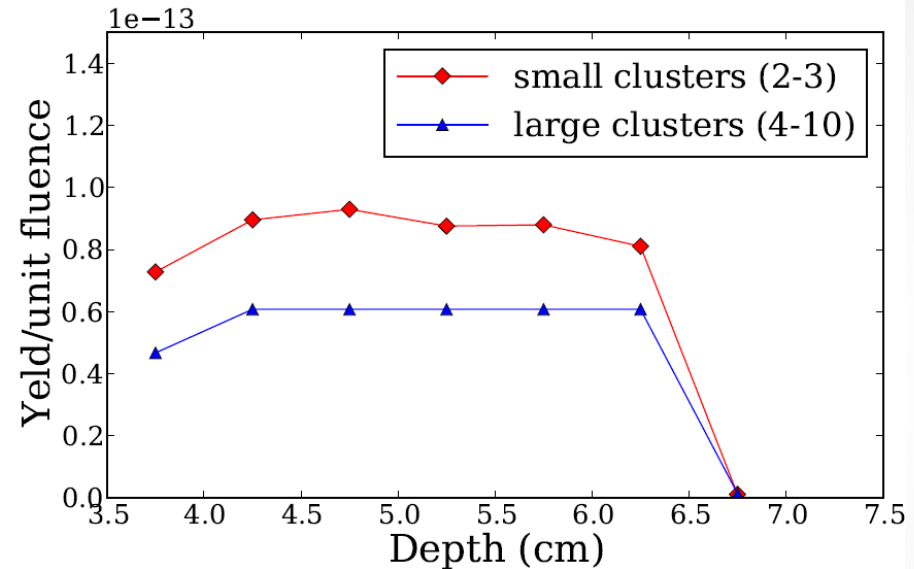


Mean absolute cluster size per unit fluence vs depth after optimization

Optimization of Large Cluster Yield for Single SOBP

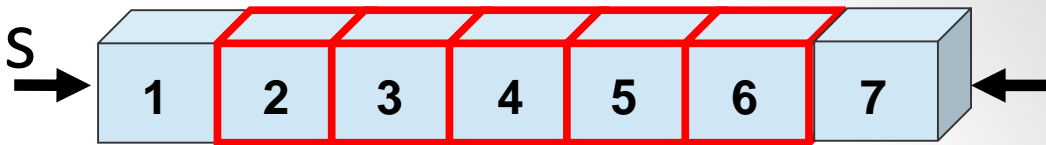


- After optimizing the yield of large ionization clusters, its yield becomes uniform in the PTV
- However, the yield of small clusters reduces towards the last voxel
- A uniform biological effectiveness can, thus, not be assumed

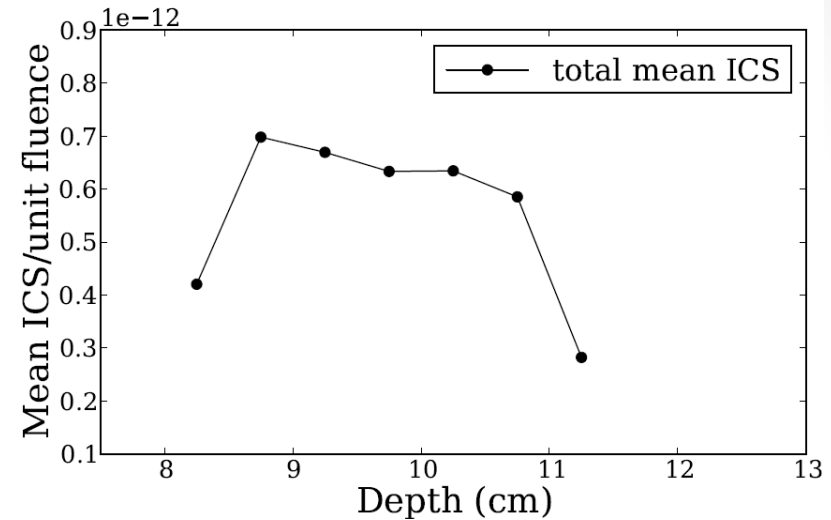


Yield of **small** and **large** clusters

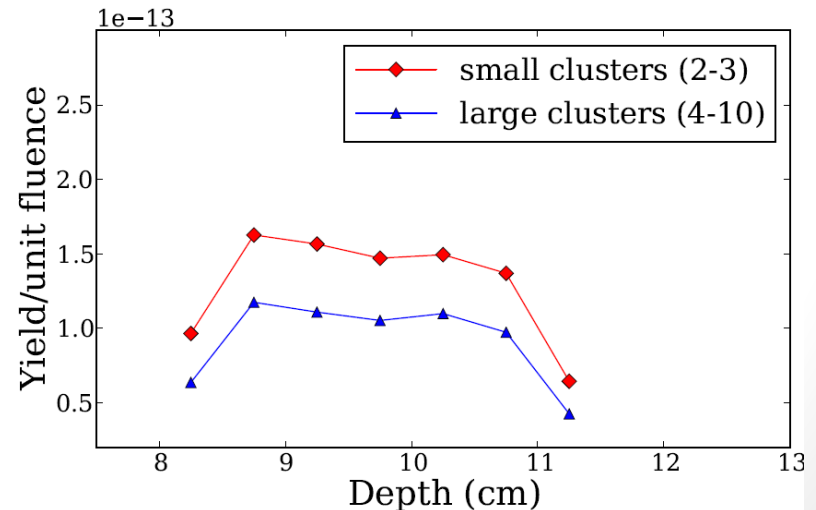
Opposing-Beam ICSDs before Optimization



- For non-optimized (unit) fluence of each pencil beam, the mean absolute cluster size reduces with depth, but less compared to the single SOBP
- The same holds for small and large ionization clusters

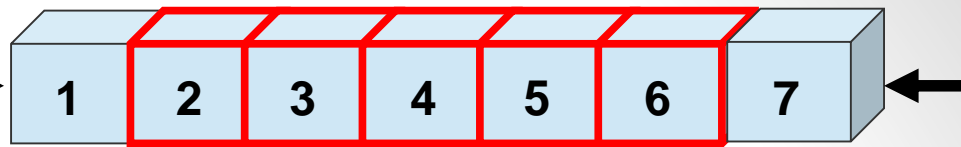


Mean absolute cluster size per unit fluence vs depth before optimization

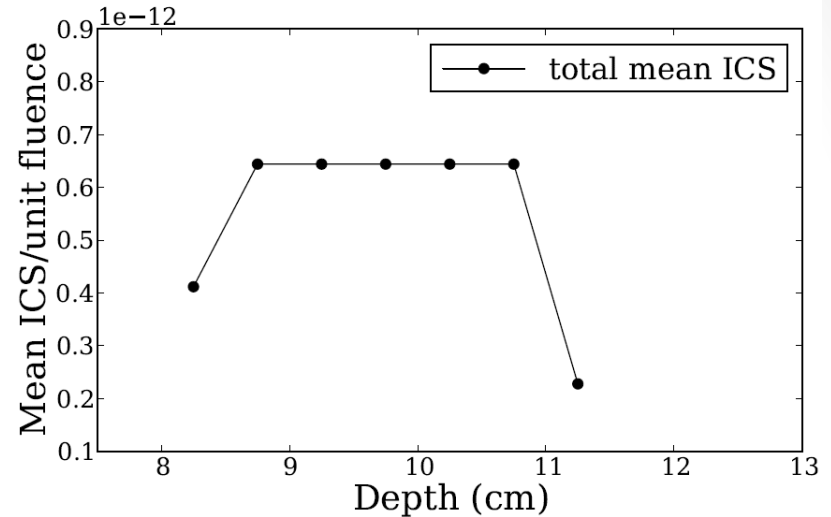


Yield of **small** and **large** clusters

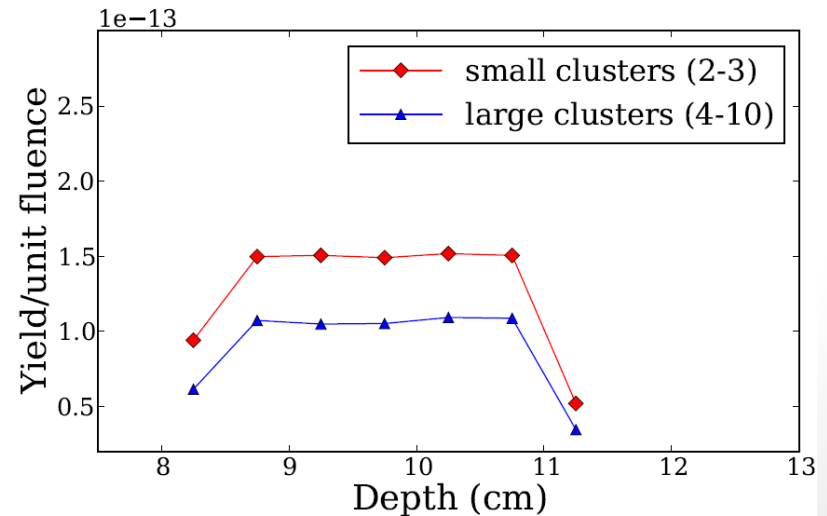
Optimization of Dose and ICS for Opposing SOBPs



- After optimizing the individual pencil beams of the opposing SOBPs, the mean absolute ICS is constant throughout the PTV
- The optimization goal of the same yield of small and large clusters is also achieved that way
- This should mean, equal biological effectiveness in the target if it is biologically uniform



Mean absolute cluster size per unit fluence vs depth after optimization of two opposing SOBPs



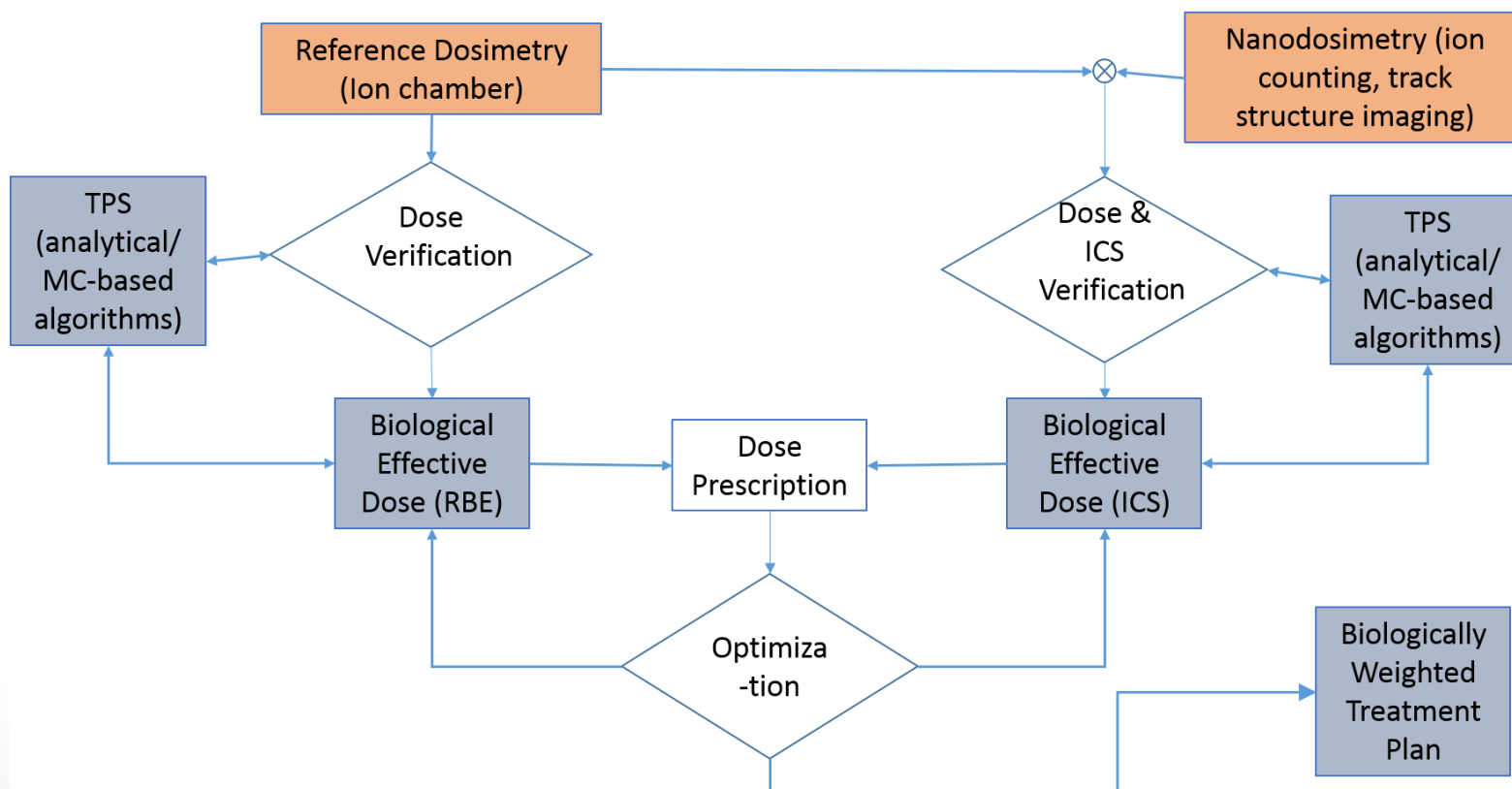
Open Questions

- What is the most relevant sampling (sensitive) volume to score nanodosimetric ionization cluster size distributions for bio-effectiveness? (here 2 nm x 16 nm was assumed)
- What is the upper limit of cluster size that should be considered? (here size 10 was assumed)
- What are the tolerance limits of large clusters (>3 ionizations per SV) for normal tissues?
- How important is the influence of regional spacing of ionization clusters for bio-effectiveness

Proposed Scheme of ND-Based Particle Radiation Therapy Metrology

Absorbed Dose to Water Based
Dosimetry (IAEA Tech Report 398)

Nanodosimetry/Track Structure
Based Approach



Summary and Outlook

- Particle (proton and ion) beams not only have an increased dose (Bragg peak) near their stopping point, but also an increase in biological effectiveness per unit dose towards the distal edge
- Future optimization of particle (proton and ion) therapy should aim at **optimizing biologically-weighted dose** rather than physical dose
- Equivalence of ND ionization cluster size distributions appears to be a useful parameter for biological effect uniformity optimization, but needs to be experimentally confirmed

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