Theoretical approach based on Monte-Carlo simulations to predict the cell survival following BNCT

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Context

AB-NCT collaboration in France

A large collaboration was initiated in Grenoble (France) on Accelerator-Based Neutron Capture Therapy (AB-NCT).

➡ One objective is to realize a demonstrator for neutron beam production with an accelerator dedicated to clinical Boron Neutron Capture Therapy (BNCT), LPSC working on the design of an original rotating target with associated beam shaping assembly and on neutron directional detection ***(See oral presentation of Daniel Santos)***.

➡ Another aspect is to use modeling and experimental approaches to:
- study the local dose-effect due to the direct neutron collisions and to the high-LET fragments following neutron capture,
- characterize the cellular damages induced by AB-NCT *(apoptosis, metabolism, cell depth)*
- study the ability of AB-NCT to trigger an immunogenic cell death of tumor cells *in vitro*

Dedicated experiments will be performed on various cell lines *(melanoma, glioblastoma, lung and breast cancer)*, under very intense and clean slow neutron beams **at the research reactor ILL**, in collaboration with the team of I. Porras (Granada University).

Objectives of this modeling study

We present here a very preliminary work on BNCT Dosimetry. The approach is as follows:

➡ A full Monte Carlo calculation is used to separate all dose components and determine the corresponding physical dose fractions with a realistic clinical model.

➡ These dose fractions are then used as mixed fields to predict cell-survivals and RBE values for a specific cell-line, thanks to the radiobiological model NanOx^{TM}.

BNCT Dosimetry: convention and limitations

Dose Convention: dosimetry in BNCT is very complex due to many different dose components. Deposited doses due to these components are weighted with appropriate factors, ω, to determine the "weighted dose" as :

$$D = w_B D_B + w_{Ther} D_{Ther} + w_{Fast} D_{Fast} + w_\gamma D_\gamma$$

- D_B**: Boron dose**, $^{10}B(n,\gamma)^{7}Li$ capture,
- D_{Fast}**: Fast neutron dose,** mainly proton recoil from $^{1}H(n,n')^{1}H$,
- D_{ther}**: Thermal neutron dose,** mainly protons and ^{14}C recoils from $^{14}N(n,p)^{14}C$ captures
- **Dγ: Gamma dose**, nuclear deexitation and source contamination (main peaks from $^{10}B(n,\gamma)^{7}Li$ and $^{1}H\ (n,\gamma)^{2}H$ captures)

The weighting factors represent relative or compound biological effectiveness factors (RBE or CBE). The commonly used factors were determined experimentally by Coderre et al. on glioma cell lines (for BPA compound):

	Weighting factor	Skull	Healthy brain	tumor
CBE[1]	w_B	1.3	1.3	3.8
RBE[2]	w_t	3.2	3.2	3.2
	w_f	3.2	3.2	3.2
	w_γ	1.0	1.0	1.0

[1] Coderre et al. Rad. Res. 144(3)-1995
[2] Morris et al. Rad. & Onc. 32(3)-1994

Limitations: These factors are used as **constant values** although they can depend on many variables as delivered dose, neutron energy, target cell population and boron distribution within tumor or normal tissue cells.

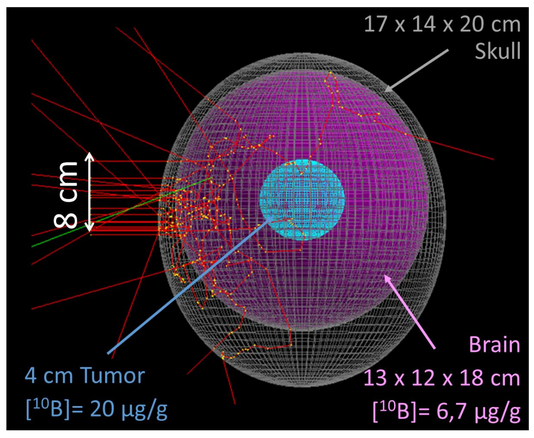
➡ Improvements in BNCT dose calculation and RBE determination are needed

Monte Carlo study and NanOx^{TM} model

Geant 4 simulation

➡ *Geant4 Physics Library*: **QGSP_BERT_HP_LIV**
adapted to neutron transport below 20 MeV and low energy electromagnetic processes

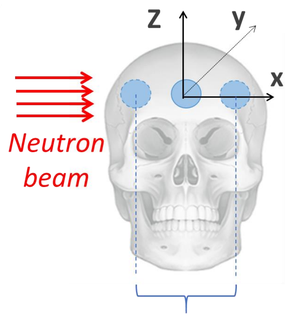
➡ *Data collection and particle sorting (*ROOT analysis*):*
- **Creation of a "Tracker"→** record all particle information at each step in tumor, brain and skull volumes.
- Dose contributions sorted per particle type, with e- and e+ contributions attributed to their parent particle.
- Main reactions of interest: **$^{10}B(n,\gamma)^{7}Li$ capture, $^{1}H(n,n')^{1}H$ collisions, $^{14}N(n,p)^{14}C$ and $^{1}H\ (n,\gamma)^{2}H$ captures**



(boron concentrations from Barth et al. 2005)

➡ *Geometry: Snyder head phantom (MIRD):*
Tissue composition ICRU 46

Neutron beam approximation:
parallel with 8 cm diameter source
monochromatic 10 keV



Tumor position from 2 to 10 cm depth (along X axis)

➡ *Dose fraction study as a function of the tumor depth:*

NanOx^{TM} model

*NanOx^{TM}: **Nano**dosimetry and **Ox**idative stress*

➡ It was originally developed to predict RBE in the context of particle therapy, takes into account the fully stochastic nature of ionizing radiation by considering dose fluctuations both at nanometric and micrometric scales, and integrates the oxidative stress.

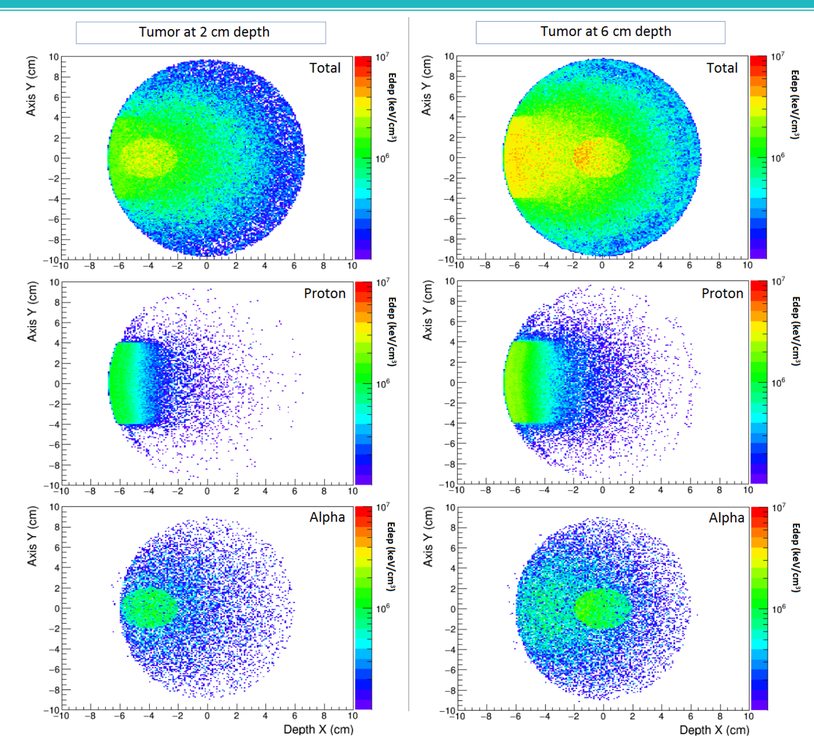
➡ NanOx^{TM} modeling of V79 cell line irradiated with photons, protons and carbon ions gave promising results in terms of the description of overkill effect and evolution of the shoulder in cell survival curves with ion LET.

➡ By estimating cell survival to mixed fields according to the Kanai approximation [3], NanOx^{TM} can be used as well for a precise determination of RBE for BNCT (taking the physical dose fractions of all the field components as input).

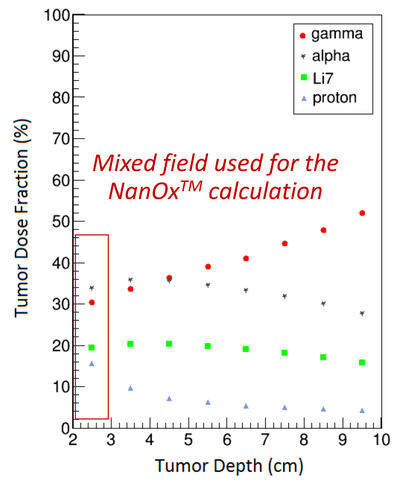
Our perspective: creation of a voxelized cartography of biological dose, integrating physical dose dependence.

[3] Kanai et al. 1997, Kanai et al. 1999

Preliminary results: Geant4 simulation with a brain tumor model

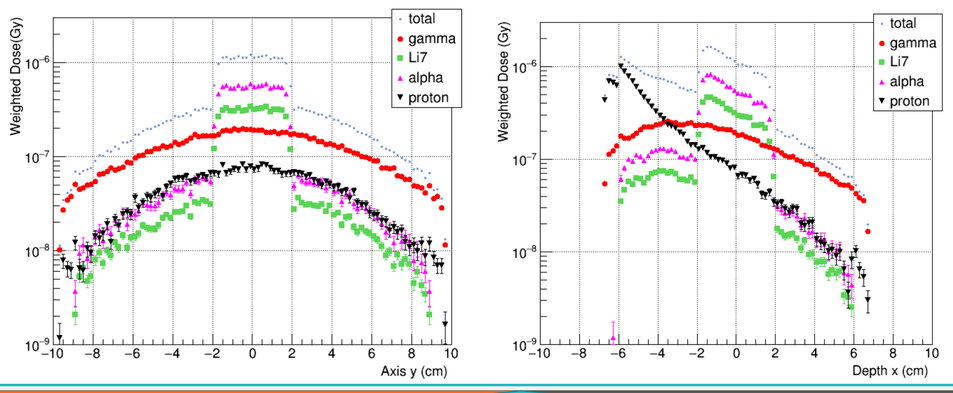


Calculated physical dose fraction to the tumor for the main components *(tumor depth : 2 - 10 cm)*



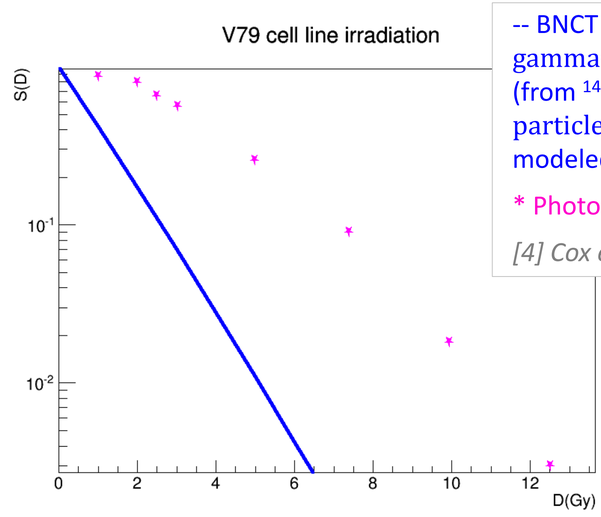
➡ Calculated total 2D maps (X,Y) of deposited energy per cm^3, with total, alpha and proton contribution. Superficial (2 cm) *versus* deep (6 cm) tumor

Weighted dose profiles using conventional weighting factors for a tumor depth of 6 cm



Preliminary results: NanOx^{TM}

Cell-survival prediction for the calculated mixed fields at 2 cm applied to V79 cell line



-- BNCT mixed field of gammas, high LET protons (from $^{14}N(n,p)^{14}C$ capture), α particles and ^{7}Li ions modeled by NanOx^{TM}

* Photons irradiation [4]

[4] Cox et al. 1977

Current limitations of the model for BNCT: recoil nuclei from neutron collisions not taken into account; Need for experimental radiobiological data to integrate the compound effect (CBE).

Conclusion and Perspectives

- **Preliminary Monte Carlo study**: we have performed a Geant4 simulation and developed an algorithm to get the BNCT contributors. Mixed fields for various tumor depths were calculated in a brain tumor model.
- **First Cell-survival calculations with NanOx^{TM}**: very promising results. Need for experimental radiobiological data to constrain the model (to be done at ILL laboratory). Improvements to come: take into account the recoiling nuclei from neutron collisions (mainly the fast neutron component) and creation of a voxelized cartography of "biological dose"
- Need for information about boron intracellular distribution (depending on the vector) to integrate the compound effect in the model.

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