Installation of a tool based on GAMOS/Geant4 with calculation of the biological effect for the planning of CUN proton therapy treatments

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Index

- The SIMPROTER project
- Dose calculation uncertainties and limitations of current commercial solutions
  - Why a full Monte Carlo instead of a TPS commercial Monte Carlo?
- Commissioning of GAMOS with CUN experimental data
- Graphical User Interface to use GAMOS at CUN
- Microdosimetric calculations and measurements
- Biological effects at protontherapy treatment planning
- Evidence of the utility of Monte Carlo calculations of biological effects in clinical protontherapy

The SIMPROTER project

SIMPROTER: Monte Carlo simulations, experimental and clinical data to improve the quality of proton therapy treatments

- **Subproject 1**: *Monte Carlo simulations for accurate dose calculations and clinical studies of biological damage in proton therapy* (PI: Pedro Arce Dubois, CIEMAT)
  - Absolute dose calibration and fine tuning of simulation parameters for proton synchrotron at CUN
  - Microdosimetric (using Geant4-DNA) and biological dose modelling in GAMOS
  - Introduce IAEA medical cross sections in GAMOS/Geant4
  - Collaboration with INFN-LNS (Catania, Italy) and IRSN-LDRI (Paris, France)
- **Subproject 2:** *Monte Carlo simulations and artificial intelligence for treatment verification and dose estimation in proton therapy by PET* (PI: Pedro Rato Mendes, CIEMAT)
  - Detailed simulations of real patient treatments, from beam interactions up to reconstructed PET images
  - Development of dose estimation and treatment verification methods based on PET images using AI
  - Development and implementation of a small TOF-PET prototype system

Duration: 4 years (09/2022 – 09/2026)

Total funding: 163.500 €

Why a full Monte Carlo instead of a TPS Monte Carlo?

- Range uncertainty is a major source of uncertainty in protontherapy
- Monte Carlo simulations is widely accepted to be the most precise method for radiotherapy dose calculation

Source of range uncertainty in the patient	Range uncertainty without Monte Carlo	Range uncertainty with Monte Carlo
Independent of dose calculation		
Measurement uncertainty in water for commissioning	± 0.3 mm	± 0.3 mm
Compensator design	± 0.2 mm	± 0.2 mm
Beam reproducibility	± 0.2 mm	± 0.2 mm
Patient setup	± 0.7 mm	± 0.7 mm
Dose calculation		
Biology (always positive) ^	+~0.8%	+~0.8%
CT imaging and calibration	± 0.5%[a]	± 0.5%[a]
CT conversion to tissue (excluding I-values)	± 0.5%[b]	± 0.2%[g]
CT grid size	± 0.3%[c]	± 0.3%[c]
Mean excitation energy (I-values) in tissues	± 1.5%[d]	± 1.5%[d]
Range degradation; complex inhomogeneities	−0.7%[e]	± 0.1%
Range degradation; local lateral inhomogeneities *	± 2.5%[f]	± 0.1%
Total (excluding *, ^)	2.7% + 1.2 mm	2.4% + 1.2 mm
Total (excluding ^)	4.6% + 1.2 mm	2.4% + 1.2 mm

Samuel España and Harald Paganetti. 'The Impact of Uncertainties in the CT Conversion Algorithm When Predicting Proton Beam Ranges in Patients from Dose and PET-Activity Distributions'. Physics in Medicine and Biology 55, no. 24 (21 December 2010): 7557–71. https://doi.org/10.1088/0031-9155/55/24/011.

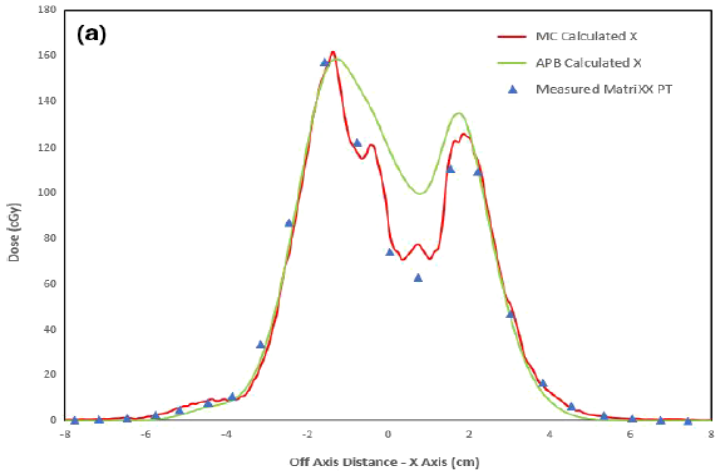
TPS commercial Monte Carlo

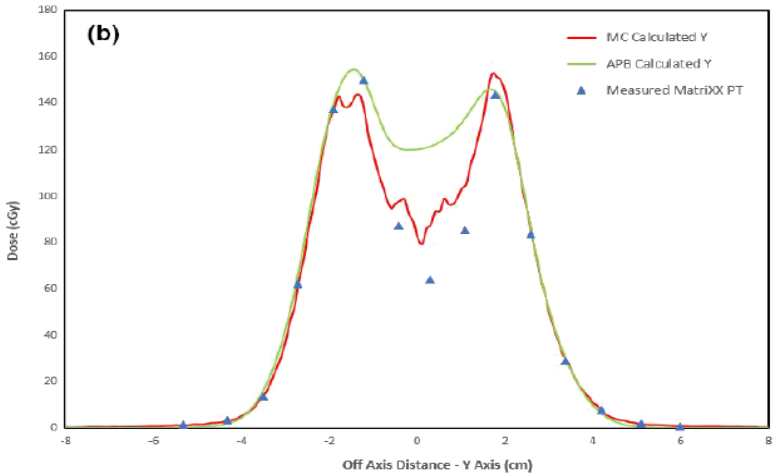
Based on the Monte Carlo technique of propagating particles in matter but **with some approximations**

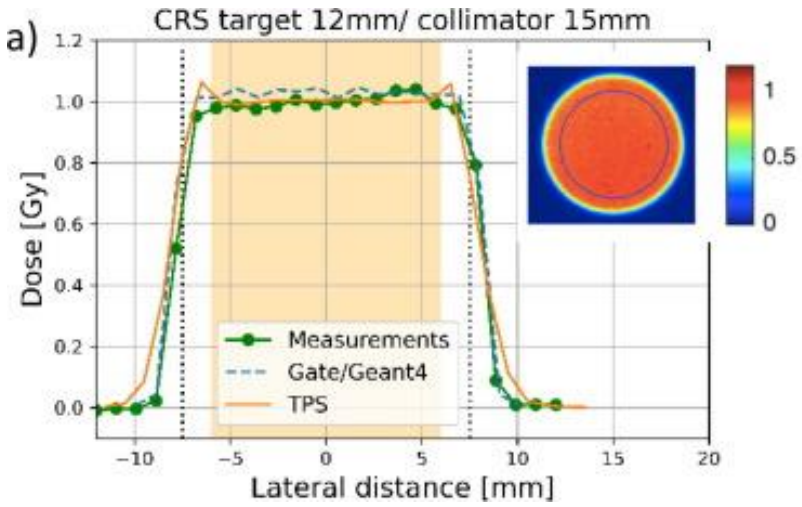
- Energy loss and straggling is computed on density and voxel specific material composition
  - **Bethe-Bloch formula to calculate absolute energy loss**
  - discretized energy spectra with adaptive energy bin sizes, which provide an accurate, within 0.2 mm, estimation of the range as predicted by the continuous slowing down approximation (CSDA)
- Elastic multiple and **plural scattering** is included through the **Goudsmit-Saunderson theory**
- Elastic proton-hydrogen scattering and inelastic nuclear reactions leading to secondary protons, deuterons, tritons and alphas particles are modelled based on voxel specific elemental compositions
  - Secondary protons are transported like primary protons
- **Heavier than proton secondaries are transported taking only energy loss into account**
- Neutral reaction products **(neutrons and gammas) are not transported**, but given fractions of the absorbed energy are considered
- **Delta electrons are not considered**
- Optimizes the beam model based on measured IDDs densities from patient CT, interaction cross-sections and correct calibration of PET detectors
- **10-100 times faster than full Monte Carlo**

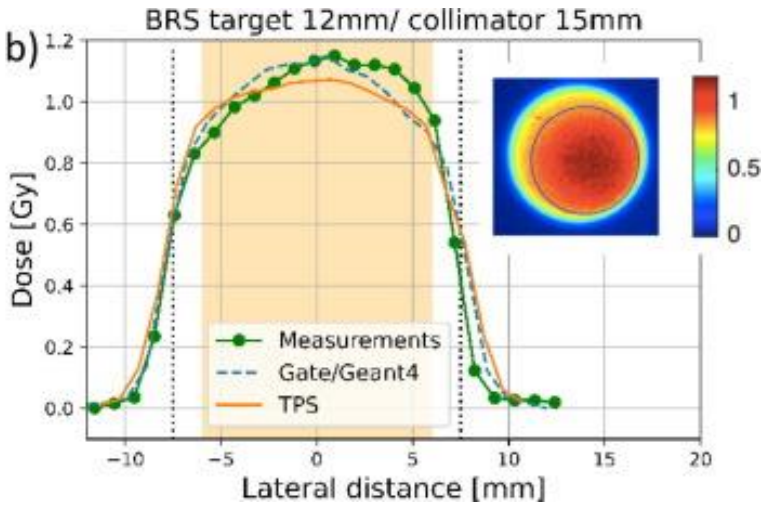
Full vs TPS Monte Carlo performance

Performance is quite good, sometimes small differences with full Monte Carlo codes





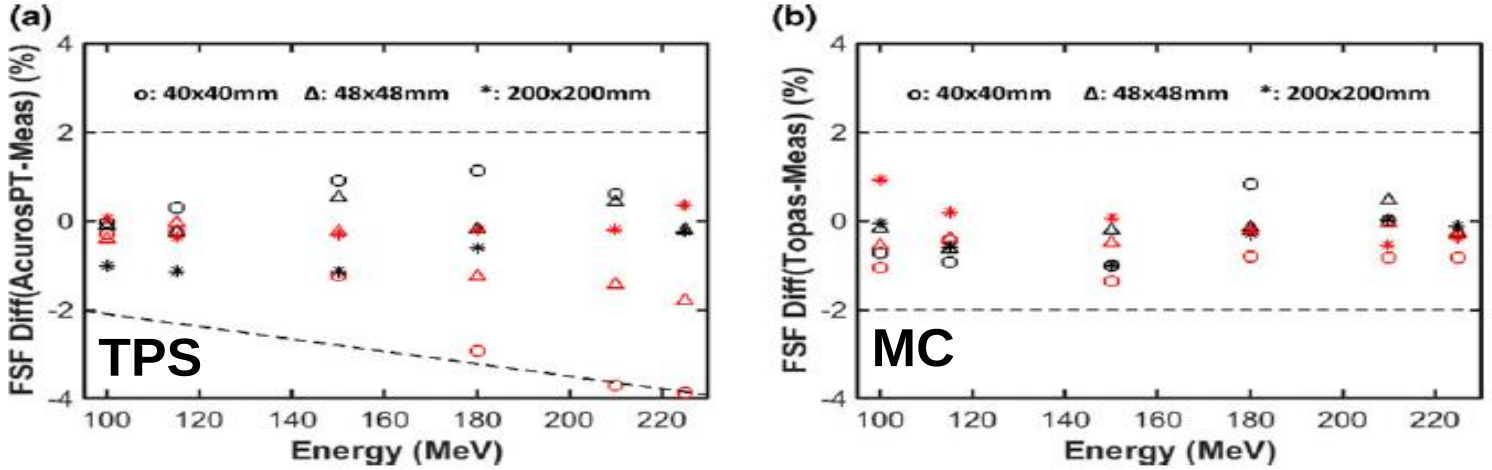




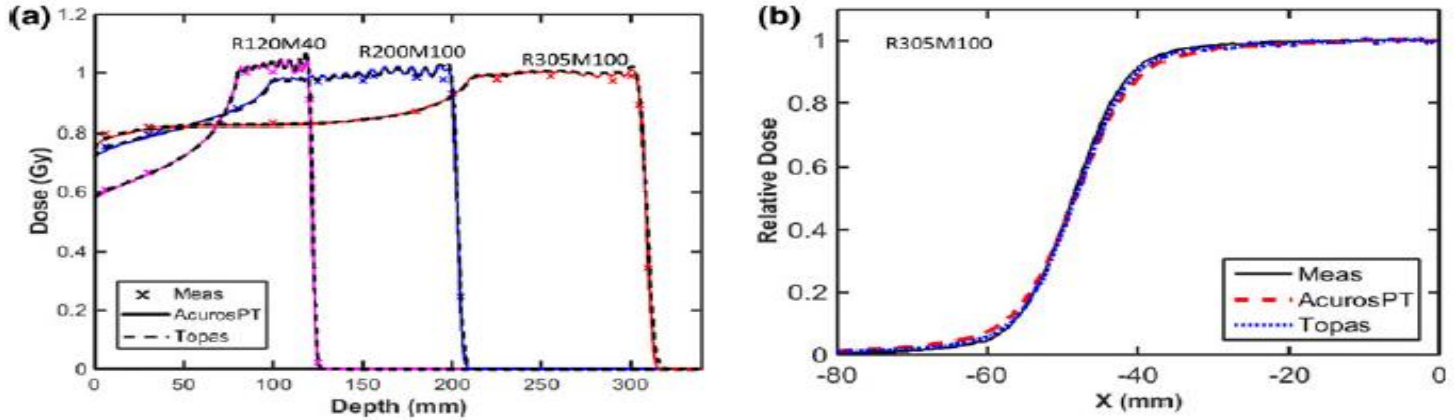
* Andries N. Schreuder et al. Validation of the RayStation Monte Carlo dose calculation algorithm using realistic animal tissue phantoms. J Appl Clin Med Phys 2019; 20:10:160–171

Full vs TPS Monte Carlo performance

Percentage differences **field size factors (**FSF) for three field sizes at two depths (black: surface, red: close to Bragg peak):



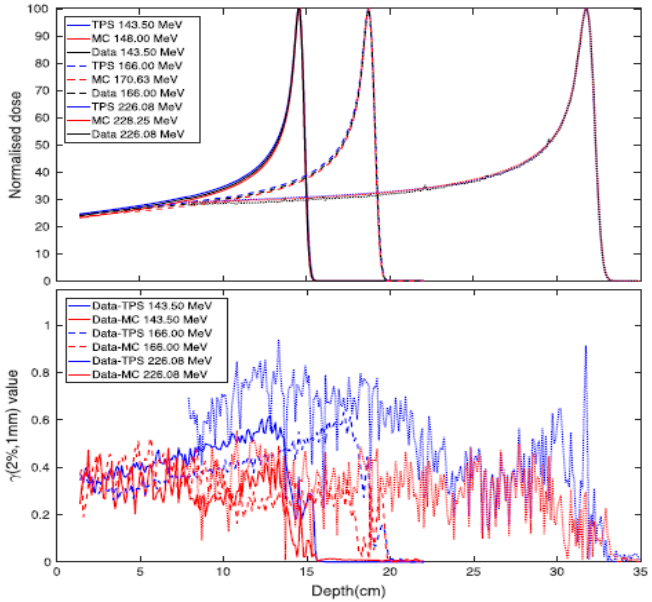
Central axis depth doses:



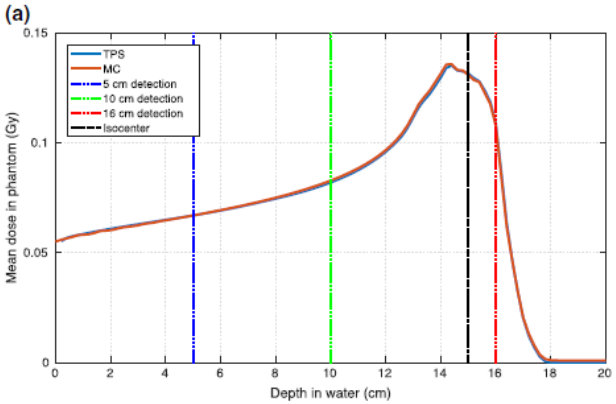
L. Lin et al. A benchmarking method to evaluate the accuracy of a commercial proton monte carlo pencil beam scanning treatment planning system. J Appl Clin Med Phys 2017; 18:2:44–49

Full vs TPS Monte Carlo performance

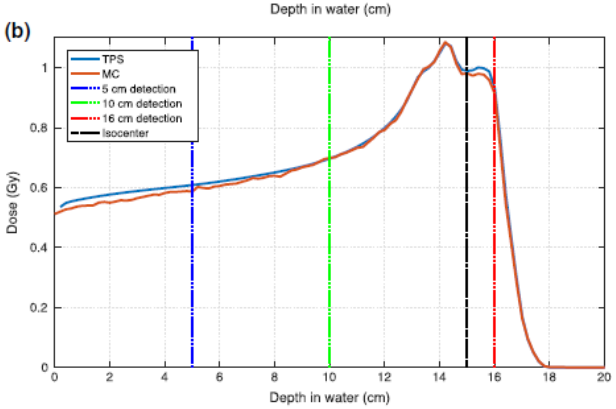
IDD Raystation MC and FLUKA vs. Exp:



Diff. w.r.t. exper.
TPS
MC



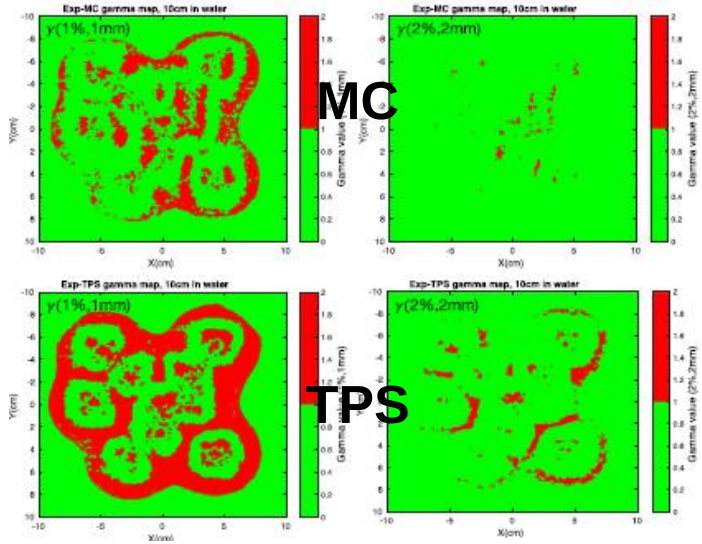
Depth dose full water phantom



Depth dose on the beam axis

Gamma index in water phantom:

Diff. w.r.t. exper



MC

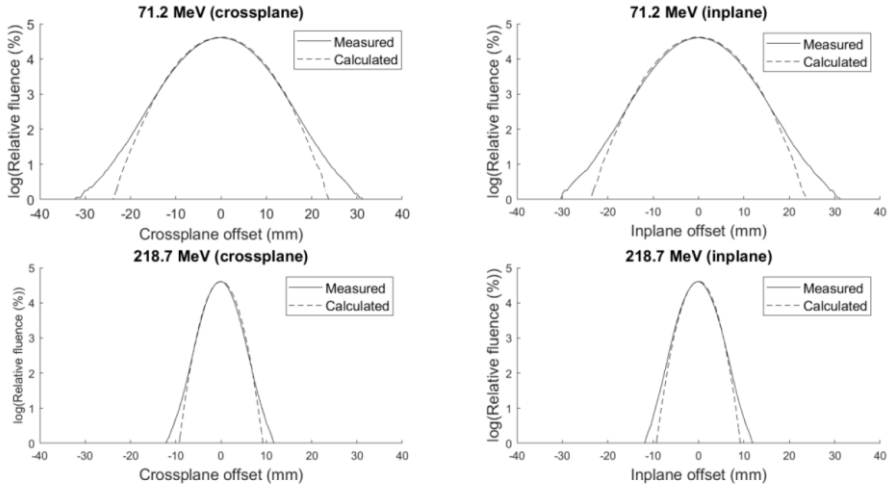
TPS

F. Fiorini at al. Technical Note: Defining cyclotron-based clinical scanning proton machines in a FLUKA Monte Carlo system. Med. Phys. 45 (2), February 2018

Commissioning of GAMOS with CUN Exper. data

1. Spot-in-air profiles:

- Exper. Measurements with Lynx, microdiamond and radiochromic film



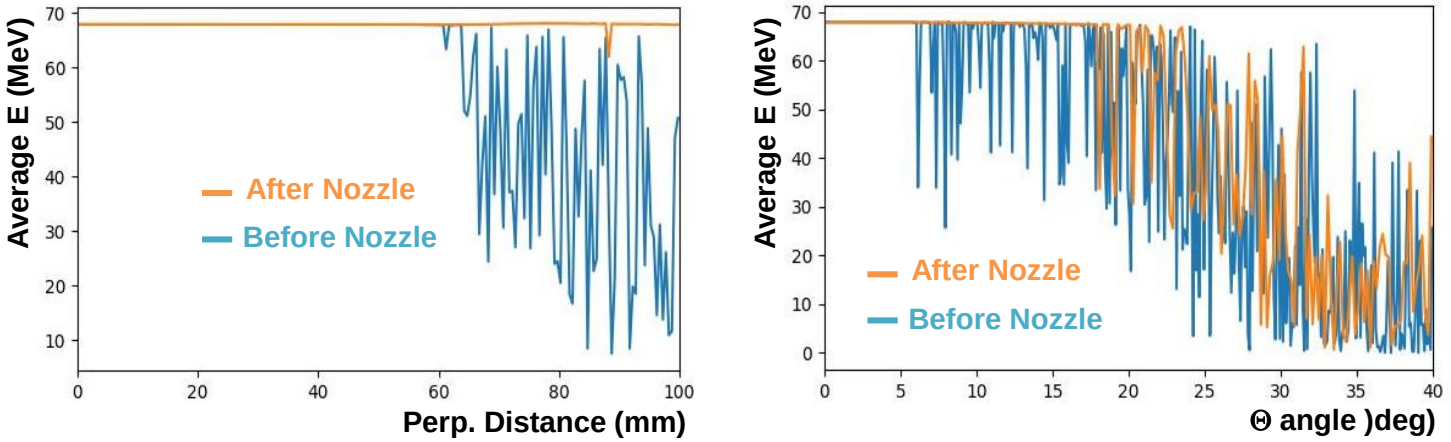
❖ **Double-Gaussian Twiss model** of beam profile XY and dispersion angles at nozzle exit

(Twiss parameters converted to σ_x, $\sigma_{\alpha x}$ and ρ_x)

- 16 parameters:

$\sigma^1_x\ \sigma^1_{\alpha x}\ \rho^1_x\ \sigma^1_y\ \sigma^1_{\alpha y}\ \rho^1_y\ \Phi^1_{xy}\ \sigma^2_x\ \sigma^2_{\alpha x}\ \rho^2_x\ \sigma^2_y\ \sigma^2_{\alpha y}\ \rho^2_y\ \Phi^2_{xy}\ \omega^{12}_x\ \omega^{12}_y$

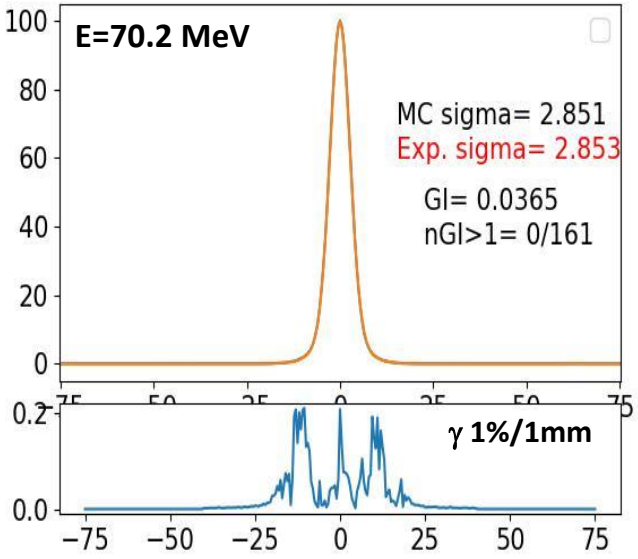
Beam is simulated after nozzle:

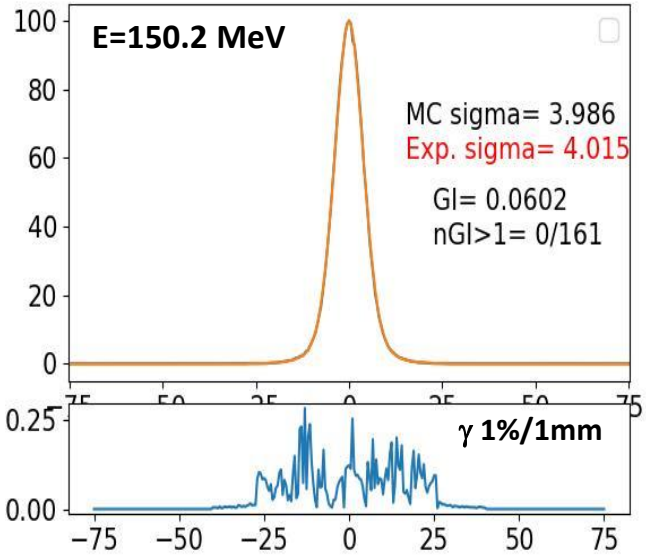


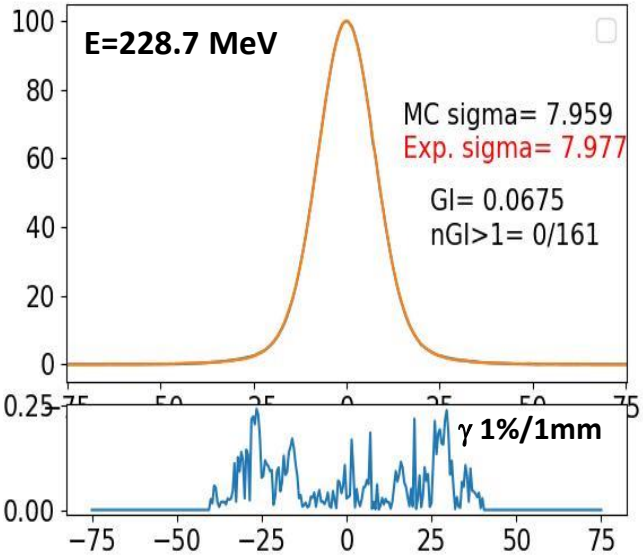
Commissioning of GAMOS with CUN Exper. data

1. Spot-in-air profiles:

- A semi-automatic method to fit the profiles for the 98 energies at 2X5 depths (-200mm to +200 mm from isocenter):







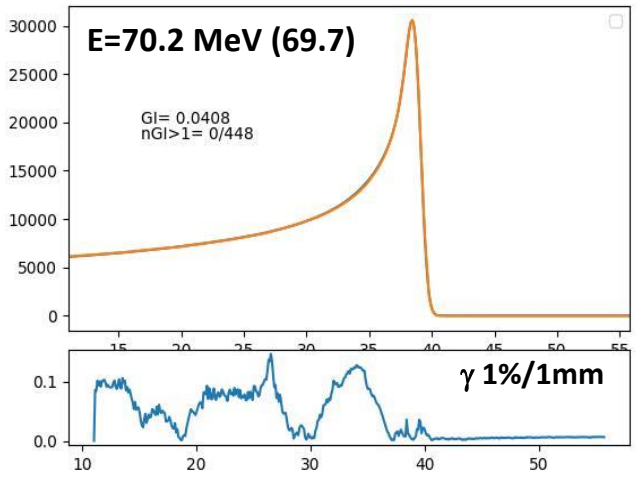
All 980 profiles fitted with Δsigma < 100 μm and γ 1%/1mm < 0.3

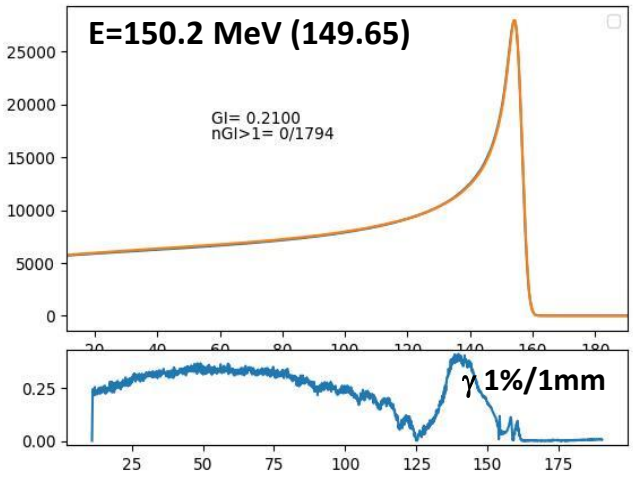
- Air profiles at 12 different gantry angles (each 30 deg) for 3 energies : 71.2, 140.8 and 218.7 MeV

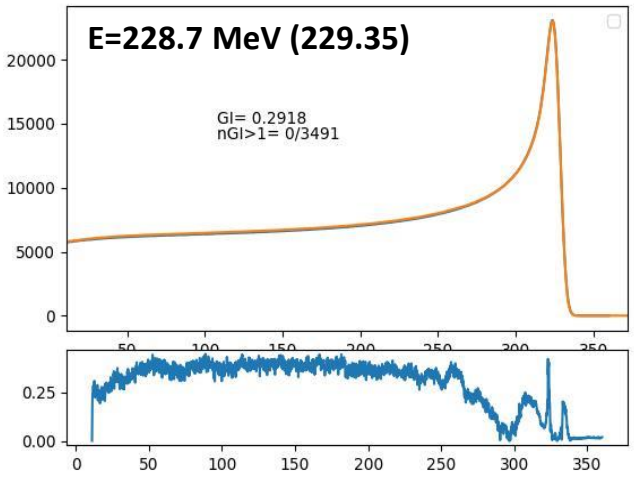
Commissioning of GAMOS with CUN Exper. data

2. Integrated Depth Dose profiles in water

- Energy is simulated before nozzle with an energy sigma 0-0.2 %
  - In a separated run the energy spectrum after the nozzle is calculated and it is used as input







All 98 IDD's with $\Delta Range_{80\%}$ < 50 μm and $peak\_width_{80\%}$ < 50 μm and γ 1%/1mm < 0.4

- Energy disagrees between -0.7 MeV and 0.6 MeV w.r.t nominal one
  - Same happens after TPS commissioning (Hitachi finds it normal)

Commissioning of GAMOS with CUN Exper. data

3. Absolute dose:

- Measurements with Advanced Markus chamber in gantry 90 degrees setup
- TRS-398 protocol

4. Profiles in water:

- Inplane and crossplane profiles for three energies:
  - 70.2 MeV: 13, 25 and 38 mm (inplane); 23.3, 31.7 and 37.5 mm (crossplane)
  - 142.5 MeV: 47, 93 and 140 mm (crossplane and inplane)
  - 228.7 MeV: 108, 216, and 324 mm (inplane); 104, 212 and 324 mm (crossplane).

5. Point dose calculations in special situations:

- **Off axis**
  - SOBP 5x5 field, at 4 corners of a 12.5 cm square
- **Oblique incidence**
  - Measuremenst at 45º in water at several depths, field 20x5 cm^2e
- **Extended distance dose**
  - TRS 398 at different depths
  - Repeated with range shifter

Commissioning of GAMOS with CUN Exper. data

6. Range shifter:

- Absolute doses using the TRS-398 protocol
- IDD for nine energies
- Spot-in-air profiles for five energies

7. SOBP fields

- Measurements with 8 field sizes and SOBP
  - SOBP between 5 and 10 cm: Depths every 1 cm between 3.5 and 10.5 cm
  - SOBP between 10 and 20 cm: Depths every 2 cm between 3 and 21 cm
  - SOBP between 15 and 20 cm: Depths of 3, 6, 9, 11, 14, 16, 17.5, 19 and 21 cm.

8. Clinical scenarios

- Several treatment plans in acrylic using radiochromic film, and the IBA Matrix 2D array (based on ionization chambers)
  - 2 Head & neck, 2 Cavum and 2 Cranial

Graphical User Interface to use GAMOS at CUN

It is mandatory to provide an easy-to-use GUI to use MC in the clinical environment, running on Windows

Several tasks:

1. Configure the variables that will take part in the simulation (use same input as TPS)
2. Specify the Monte Carlo tool execution conditions
3. Execute the simulations in a distributed manner
4. Monitor the advance of the simulation tool and stop it when required precision is reached
5. Notify when the simulations are finished and collect the output data
6. The final dose map must be in DICOM format so that it can analysed by the same tool that is daily used by the clinical personnel to analyse the dose results from the TPS

Must be trustable and robust:

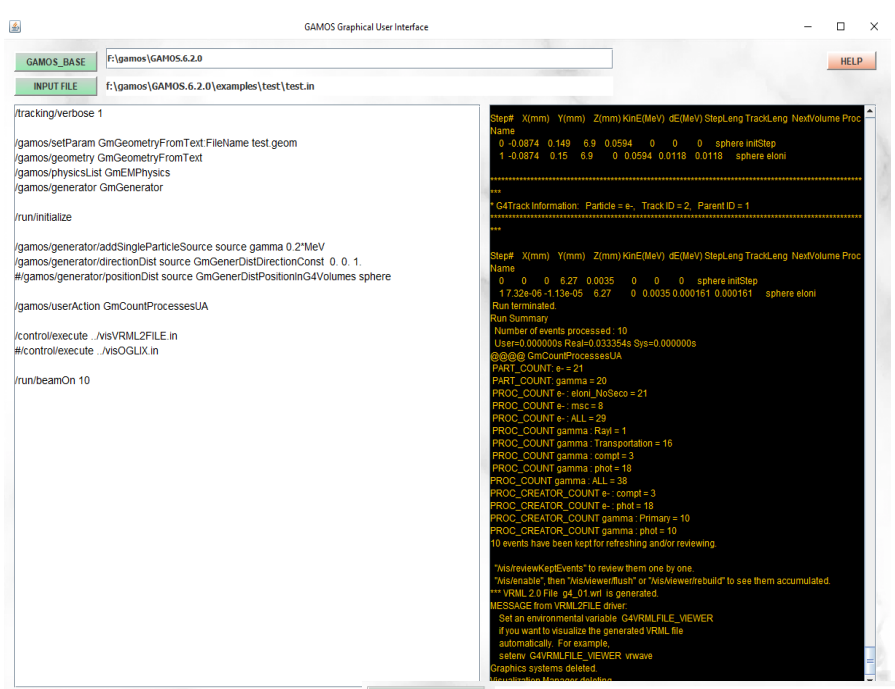
1. Test GAMOS running under stringent conditions
2. Develop a set of modules integrated on a single tool, using the latest computer technologies
   - J2EE standard for the development of the graphic interface and the programming logic
   - Control of the execution through the use of communication sockets based on TSL protocols
   - A messaging system to control the workflow
   - Output shown in a graphical manner through Java specific libraries

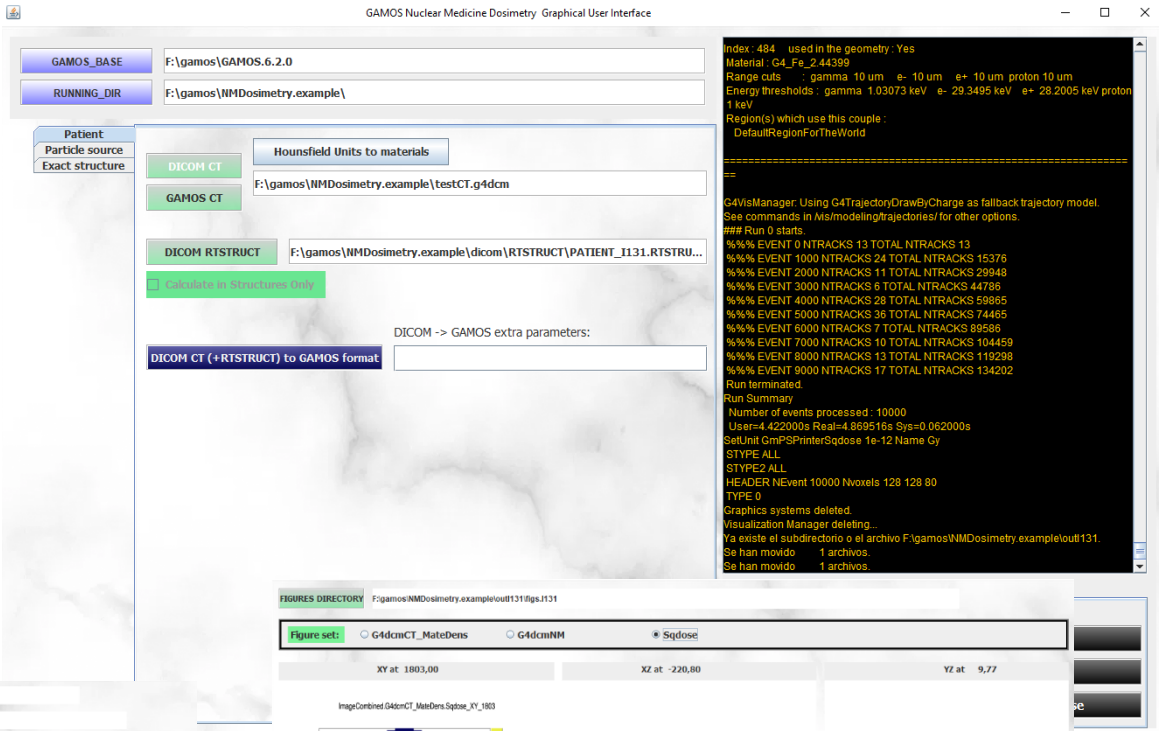
➢ We will count with the help of the Scientific Computing and the Computer Application and System Developments units of CIEMAT

Graphical User Interface to use GAMOS at CUN

At UAMRI Unit we have already the experience of developing Java GUI tools for GAMOS on Windows and Linux

- A general one and another one dedicated to Nuclear Medicine Dosimetry



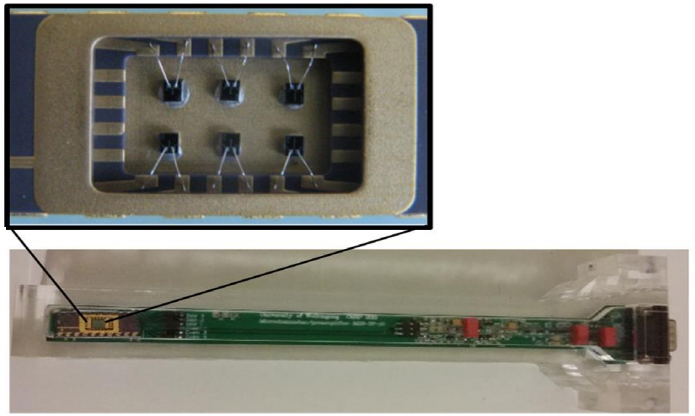


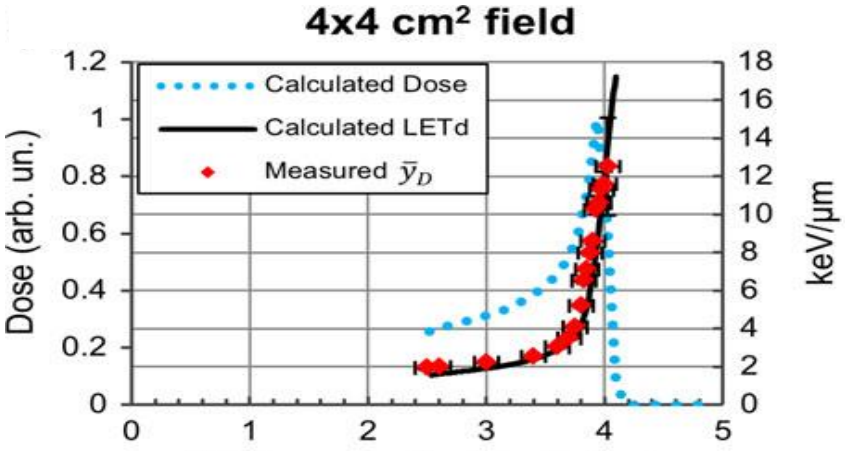
Microdosimetric calculations and measurements

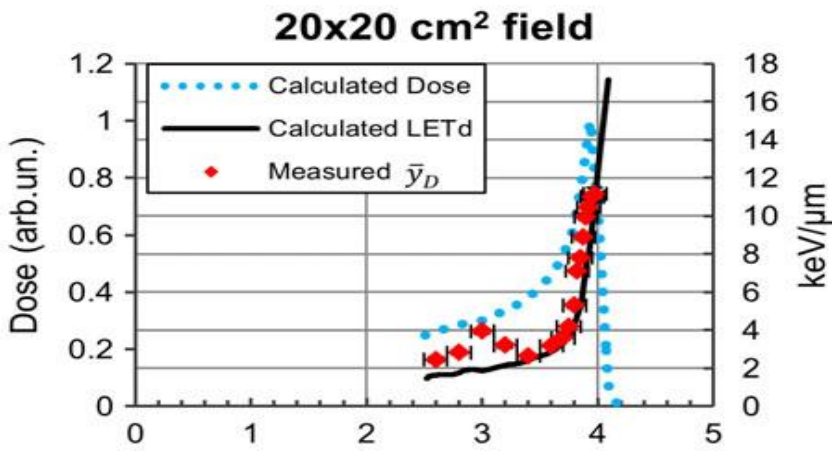
Microdosimetric measurements with a solid-state detector (by LNS-INFN group)

- **High spatial resolution** (on the order of tens of micrometers)
- Very useful in characterizing proton radiotherapy fields, particularly for making highly resolved measurements **within the Bragg peak region**
- y_D ~ LET_D : useful to **test Monte Carlo LET_D calculations** at Bragg peak region (most important area)

Measurements at Hitachi synchrotron at Mayo Clinic Rochester (same synchrotron than CUN)







Biological effects in protontherapy treatment planning

Many publications propose methods to calculate RBE in proton treatment (**biological dose = physical dose * RBE**)

- Mostly using LET_D

TPS MC and Full MC are able of calculate LET_D, and from it calculate RBE using the **phenomenological models** : RBE = f(LET)

e.g. McNamara model

$$RBE_{max} = p_0 + p_1 \frac{LET_d}{\left(\frac{\alpha}{\beta}\right)_x}$$

$$RBE_{min} = p_2 + p_3 \sqrt{\left(\frac{\alpha}{\beta}\right)_x} LET_d$$

$\left(\frac{\alpha}{\beta}\right)_x$ are the LQM parameters of a cell line under X rays

$$RBE = [Dx = \frac{1}{D_p}(\sqrt{\left(\frac{\alpha}{\beta}\right)_x{}^2 + 3Dp \left(\frac{\alpha}{\beta}\right)_x RBE_{max}{}^2 + 4RBEmin^2 D_p{}^2} - \left(\frac{\alpha}{\beta}\right)_x)$$

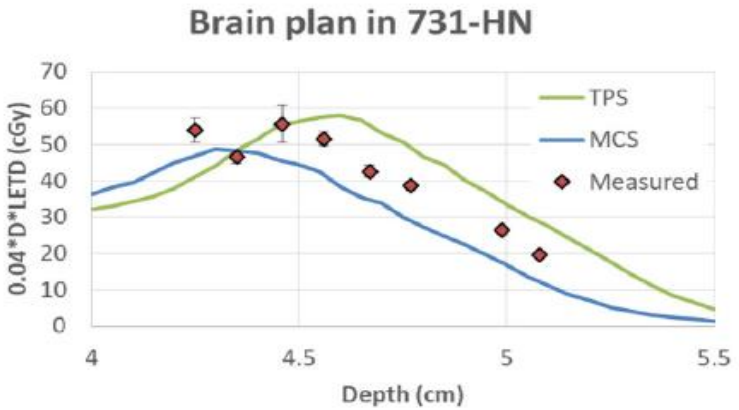
➢ difficult to extrapolate to clinical treatments

Biological effects at protontherapy treatement planning

- LET_D is a not an accurate predictor for RBE in regions with broad LET distribution as in a single SOBP or in multiple overlapping fields. The deviations are caused by the nonlinearity of the RBE(LET) relationship in the case of track segment conditions

Rebecca Grün, et al. Is the dose-averaged LET a reliable predictor for the relative biological effectiveness? Med. Phys. 46 (2), 2019

Dirk Wagenaar et al. Validation of linear energy transfer computed in a Monte Carlo dose engine of a commercial treatment planning system Phys. Med. Biol. 65 025006 (2020)



- **Mechanistic models** (LEM and MKM) are supposed to offer a better description of clinical biological dose for proton treatments (already in use for heavy ion treatments)
  - **Already in use at ion therapy centers**
  - **Calculations using these models only done with full MC**

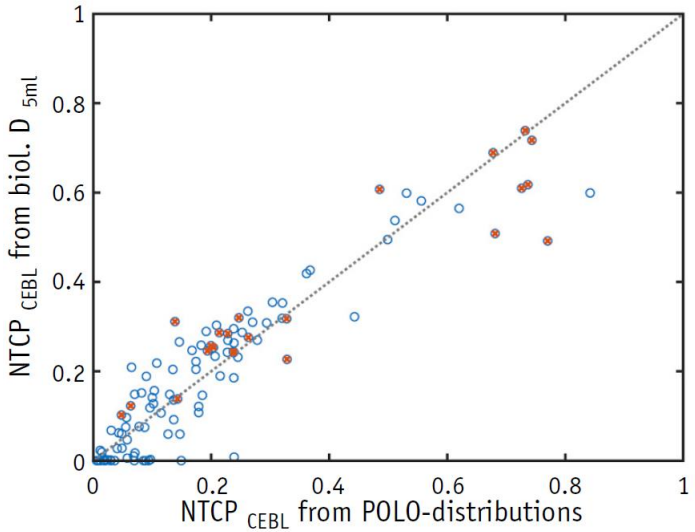
- **We plan to use the 'Survival' toolkit for the LEM and MKM models, already in use at the protontherapy center of LNS-INFN, + help LDRI-IRSN (developers of Geant4-DNA) to better understand the simulation of biological effects**

Test MC biological effects in clinical protontherapy

The final phase of the SIMPROTER-BIO project will be to do a **retrospective analysis of patient treatments** trying to correlate **post-treatment injuries with elevated RBE voxel** values

- Correlate secondary negative effects detected at post-treatment PET/MRI monitoring during > 1 year with areas where physical dose is not big, but biological dose is, as calculated by our tool

- Already several **published studies show this correlation** in the central nervous system and lung, using Monte Carlo voxel-by-voxel RBE calculations
- **Understand** use cases where the **biological effects are more important**
- Plan to **contribute to the adoption of mechanistic RBE models at protontherapy centers**



(POLO = MC voxel-wise probability of lesion origin)

- Eulitz, J., et al. "Predicting Late Magnetic Resonance Image Changes in Glioma Patients after Proton Therapy." *Acta Oncologica*, vol. 58, no. 10, Oct. 2019, pp. 1536–39
- Underwood, Tracy S. A., et al. "Asymptomatic Late-Phase Radiographic Changes Among Chest-Wall Patients Are Associated With a Proton RBE Exceeding 1.1." *International Journal of* Radiation *Oncology*Biology*Physics*, vol. 101, no. 4, 2018, pp. 809–19
- Zhang, Ying Y., et al. "Brain-Specific Relative Biological Effectiveness of Protons Based on Long-Term Outcome of Patients With Nasopharyngeal Carcinoma." *International Journal of Radiation Oncology*Biology*Physics*, vol. 110, no. 4, 2021, pp. 984–92
- Peeler, Christopher R., et al. "Clinical Evidence of Variable Proton Biological Effectiveness in Pediatric Patients Treated for Ependymoma." *Radiotherapy and Oncology*, vol. 121, no. 3, 2016, pp. 395–401
- *Late Contrast Enhancing Brain Lesions in Proton-Treated Patients With Low-Grade Glioma Clinical Evidence for Increased Periventricular Sensitivity and Variable RBE.Pdf*

Summary

- SIMPROTER project recently approved with two overlapping lines of research
  - *Monte Carlo simulations for accurate dose calculations and clinical studies of biological damage in proton therapy*
  - *Monte Carlo simulations and artificial intelligence for treatment verification and dose estimation in proton therapy by PET*
- Full Monte Carlo calculations has demonstrated its superiority vs. commercial TPS
  - More precise physical dose
  - More precise calculations of biological effects
- SIMPROTER-BIO projects stages
  - Commission GAMOS to CUN protontherapy center
  - Include biological effects using the latest mechanistic RBE models
  - Retrospective study on the correlation of higher biological dose and negative treatment effects
    - Already seen by other groups
    - Identify use cases of high importance of biological dose calculations
    - Contribute to the introduction of biological effects in routine protontherapy treatment planning

Thank you for your attention!

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Grants PID2021-127902OC-C21 and PID2021-127902OC-C22 funded by MCIN/AEI/10.13039/501100011033 and "ERDF A way of making Europe"