signals from a pulsed proton beam (about 5 pC/pulse, 6 µs FWHM) and detector shifts down to 2 mm. The measured relative shifts of the Bragg peak position of 2.3 mm for 1 MeV energy change and 173.25 mm for 82 MeV are in perfect agreement with Geant4 predictions. However, the low signal amplitude below 1 mV required an averaging with 1024 acquisitions.
Conclusion: Measuring the ionoacoustic signal at the IBA synchro-cyclotron, the detectability of 2 mm range shifts could be demonstrated. Experimental upgrades will be discussed, from which we reasonably assume to improve the resolution to 1 mm and below. In order to determine an absolute ion range in water in future ionoacoustic experiments, a method using an additional ultrasound transducer to measure the distance of the hydrophone to the water surface was developed. Remaining challenges on signal detectability for clinical dose rates as well as perspectives of future setup improvements will be discussed.
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Keywords: Ionoacoustics, Range Verification, Ultrasound

References:
[1] Hayakawa, Y., et al., Acoustic pulse generated in a patient during treatment by pulsed proton radiation beam. Radiation Oncology Investigations, 1995. 3(1): p. 42-45.
[2] Sulak, L., et al., Experimental Studies of the Acoustic Signature of Proton-Beams Traversing Fluid Media. Nuclear Instruments & Methods, 1979. 161(2): p. 203-217.
[3] Albul, V.I., et al., Acoustic field generated by a beam of protons stopping in a water medium. Acoustical Physics, 2005. 51(1): p. 33-37.
[4] Alsanea, F., V. Moskvin, and K.M. Stantz, Feasibility of RACT for 3D dose measurement and range verification in a water phantom. Med Phys, 2015. 42(2): p. 937-46.
[5] Jones, K.C., et al., Proton beam characterization by proton-induced acoustic emission: simulation studies. Phys Med Biol, 2014. 59(21): p. 6549-63.
[6] Assmann, W., et al., Ionoacoustic characterization of the proton Bragg peak with submillimeter accuracy. Med Phys, 2015. 42(2): p. 567-74.

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Monte Carlo simulation of prompt-γ emission in proton therapy using a track length estimator
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Purpose: Online in vivo control of the ion range in a patient during proton therapy is a major challenge for quality assurance of treatments. After measurements showed that prompt-γ emission is correlated to the ion range (Min *et al* 2006, Testa *et al* 2008), prompt-γ imaging emerged as a promising method (Verburg *et al* 2013). Fast methods are required to compute accurate prompt-γ emission maps to design and predict the camera response from treatment plans. An analytic computation method based on the structure of the dose calculation engines in treatment planning system has recently been proposed (Sterpin *et al* 2015). An alternative technique based on variance reduction in Monte Carlo (MC) calculations is developed here for computing prompt-γ emission maps in proton therapy.
Materials/Methods: The track length estimator (TLE) method is a standard variance reduction technique in voxel-based dose computation in the kerma approximation (Williamson 1987), and similar approaches have also been developed for positron emitter distributions in proton therapy (Parodi *et al* 2007). A specific track length estimator has been developed here to design a continuous process along the proton track that locally deposits the expected value of the prompt-γ emission (induced by proton inelastic scattering) that would have occurred if a large number of protons with the same incident energy had followed the same step (i.e. track element). First an elemental database of prompt-γ emission spectra is established in the clinical energy range of incident protons for all elements in the composition of human tissues. This database of the prompt-γ spectra is built offline with high statistics. Regarding the implementation of the prompt-γ TLE MC tally, each proton deposits along its track the expectation of the prompt-γ spectra from the database according to the proton kinetic energy and the local material density and composition. All software developments have been carried out with the Gate/Geant4 toolkit.
Results: A detailed statistical analysis is reported to characterize the dependency of the variance reduction on the geometrical (track length distribution) and physical (linear prompt-γ spectrum database) parameters. Benchmarking of the proposed technique with respect to an analogous MC technique is carried out. A large relative efficiency gain is reported, ca. 10^5. Such an efficiency gain could reduce the MC computing time of a full treatment from some weeks to less than one hour. Implementation issues are also addressed.
Conclusions: This MC-based technique makes it possible to deal with complex situations such as heterogeneities for which proton straggling and secondary protons may have a decisive contribution. When considering translation to clinic, measurements for the prompt-γ spectrum database, or at least a sound calibration protocol of the simulated prompt-γ spectra, will have to be carried out.

Keywords: prompt-γ imaging, Monte Carlo simulation, variance reduction

References:
[1] Min *et al* (2006) App Phys Lett 89 183517
[2] Parodi *et al* (2007) Phys Med Biol 52 778–86
[3] Sterpin *et al* (2015) Phys Med Biol 60 4915
[4] Testa *et al* (2008) App Phys Lett 93 093506
[5] Verburg *et al* (2013) Phys Med Biol 58 L37-49
[6]Williamson (1987) Med Phys 14 567-76

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Preclinical imaging and radiotherapy of prostate cancer using the theranostic twins(^{68}Ga/^{177}Lu)-radiolabeled peptides
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Since the gastrin-releasing peptide receptor(GRPR) has been shown to be overexpressed in prostate cancer, bombesin which is the ligand of GRPR has been investigated to be a successful candidate for the peptide receptor radiotherapy(PRRT)[1]. The present study describes the imaging and therapeutic efficacy of the theranostic twins(^{68}Ga/^{177}Lu)-labeled bombesin derivatives for the PRRT of GRPR-overexpressing prostate tumors.
A series of DOTA-conjugated bombesin derivatives were synthesized using a solid-phase synthesis. Competitive binding studies were performed for selecting a GRPR-targeting peptide with high affinity. The selected peptide was labeled with ^{68}Ga using the NaCl method for imaging[2], and labeled with ^{177}Lu which was produced by the HANARO research reactor (thermal neutron flux of 1.8×10^{14} n·cm^{-2}·s^{-1}) for therapy. The labeling yield was evaluated by iTLC-SG, and the PET/CT imaging and therapeutic efficacy of the radiolabeled peptides were evaluated using nude mice bearing PC-3 human prostate carcinoma xenograft.
Hydrophilic-modified bombesin derivative showed a nanomolar binding affinity for GRPR. The peptide was labeled with the both radionuclides in high incorporation yields(>98%). ^{68}Ga-labeled peptide was quickly cleared from the blood and clearly visualized in PC-3 tumors at 1 hr p.i. ^{177}Lu-labeled peptide were also rapidly accumulated in a PC-3 tumor, and the % ID/g of the tumor was 12.42 ± 2.15 1 hr p.i. The radio-peptide significantly inhibited the tumor growth

(P<0.05), and treatment-related toxicity was not observed in the pancreas and kidneys while slight glomerulopathy was detected.
The pharmacokinetic, imaging, and therapy studies suggest that the theranostic twins(^{68}Ga/^{177}Lu)-labeled bombesin derivatives have promising characteristics for application in nuclear medicine, namely, for the diagnosis and treatment of GRPR-overexpressing prostate tumors.

Keywords: Theranosis, Prostate cancer, Bombesin, Radionuclide

References:
[1] Cescato, R., et al., Bombesin receptor antagonists may be preferable to agonists for tumor targeting. J Nucl Med, 2008. 49(2): p. 318-26.
[2] Mueller, D., et al., Simplified NaCl based (68)Ga concentration and labeling procedure for rapid synthesis of (68)Ga radiopharmaceuticals in high radiochemical purity. Bioconjug Chem, 2012. 23(8): p. 1712-7.

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The role of adipose stromal cells for reversal of radiation fibrosis
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Hypothesis: Radiation fibrosis (RF) effects up to 70% of patients who have undergone radiotherapy. It is characterized by irreversible scarring of normal tissue resulting in functional morbidity and increased risk of surgical complications. Adipose-derived stromal cells (ADSCs) are a subcategory of mesenchymal stromal cell. Much of the therapeutic benefit of ADSCs has been attributed to secretion of cytokines and growth factors involved in immunomodulation, cell survival, and metabolism. We hypothesize that ADSCs may be therapeutically effective for RF through reversal of metabolic aberrations.
Methods: A mouse model of RF was developed and ADSC isolation was confirmed by surface marker expression and by differentiation capacity down the mesenchymal lineage. GFP and luciferase labelled ADSCs were used to assess biodistribution and cell survival after transplantation. To determine the therapeutic effect of ADSC transplantation for RF, we assessed functional changes to tissue elasticity using a leg contracture measurement tool and to collagen deposition using trichrome blue staining. To determine the mechanism of ADSC-mediated fibrosis reversal, we assessed transcriptomic changes to RF tissue.
Results: A RF model was created by radiating the hind limb of C3H mice. This model showed a dose dependent leg contracture and histological findings of fibrosis. We confirmed the immunophenotype of isolated ADSC and their ability to differentiate into adipogenic, chondrogenic, and osteogenic lineages. ADSC transplantation showed a statistically significant trend towards improved leg contracture (2-way ANOVA, p<0.05) and reduced collagen deposition. Biodistribution studies confirmed the presence of ADSCs in the subdermis of RF tissue with persistence for at least 18 days post-transplantation. Preliminary RNA-seq over-representation pathway analysis showed that lipid metabolism and PPARG signaling were among the top pathways down regulated in radiation fibrosis and was partially reversed with ADSC treatment. ADSCs directly reversed alterations to lipid metabolism in radiated fibroblasts through indirect co-culture.
Conclusions: ADSC transplantation may be an effective treatment for the reversal of radiation fibrosis through metabolic reprogramming. As cancer survivorship increases, the prevalence of radiation fibrosis will rise and necessitate increased focus on effective treatment strategies for this condition.

Keywords: Adipose Derived Stromal Cells, Radiation Fibrosis, Cancer Survivorship

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Characterization and test beam results of a $LaBr_3$ Compton Telescope for treatment monitoring.
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Purpose: The detection of gamma rays for monitoring purposes can overcome some of the limitations of PET, since they are more abundant than positron emitters and are produced within nanoseconds after irradiations. However, their continuous emission spectrum up to high energies (more than 10 MeV) make their detection challenging [1]. Collimated systems and Compton cameras are being developed for this application.
The IRIS group of the Instituto de Fisica Corpuscular (IFIC-CSIC/UVEG, Valencia) has developed a three-layer Compton telescope based on $LaBr_3$ scintillator crystals for hadron therapy monitoring within the ENVISION project.
Materials and Methods: The telescope consists of three planes of $LaBr_3$ crystals, which provide high energy resolution and fast response, coupled to silicon photomultiplier arrays. A custom made data acquisition system has been developed to read out the detectors and operate them in time coincidence, employing the VATA64HDR16 ASIC[2]. The system aims at combining two- and three-layer events in order to profit from the high efficiency of the former and the high precision of the latter. The functionality of the device has been tested in the laboratory with radioactive sources, and also in beam tests. A dedicated image reconstruction ML-EM code has also been developed for both types of events.
Results: The system has been characterized in the laboratory acquiring data with radioactive sources of different energies. The detector response in terms of linearity, uniformity and spatial, energy and timing resolution has been obtained for the three layers, improving the results of the first tests. In addition, images of a point-like Na-22 source have been reconstructed with two and three-layer systems. The preliminary spatial resolution obtained is 7.3 mm FWHM with the two-layer system and 8.6 mm FWHM with the three-layer system.
The two-layer system has also been tested in a proton beam at KVI-CART, Groningen. Data were taken with a 150 MeV proton beam with an intensity of about 10^8 protons/s and a lateral beam spread of 5.3 mm impinging on a PMMA phantom. The PMMA target was placed in two different positions along the beam separated by 10 mm. The data analysis and image reconstruction of the data have shown a difference in the reconstructed profile consistent with the phantom position [3].
Conclusions: The laboratory tests carried out assess the correct functioning of the device. In-beam results show the capability of detecting range shifts. Current work is focused on performance improvement of the system and on simultaneous operation of two and three detector layers. Further tests in beam are planned at HZDR Dresden for December 2015.

Keywords: Compton Telescope, Hadron therapy, treatment monitoring.

References:
[1] Roellinghoff, F. et al. Design of a compton camera for 3d prompt-imaging during ion beam therapy. Nuclear Instruments and Methods A 648, S20–S23.
[2] Trovato, M., Solevi, P., Torres-Espallardo, I., Gillam, J., Lacasta, C., Rafecas, M., et al. A three layer compton telescope for dose monitoring in hadron therapy. 2014 IEEE NSS MIC.