Ionoacoustics for range monitoring of proton therapy

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Abstract. Proton beams exhibit favourable interaction properties for highly conformal tumour dose delivery with better sparing of surrounding healthy tissue and critical structures in comparison to widely established photon beams. However, full clinical exploitation of these advantages is still hampered by treatment uncertainties, particularly related to the stopping position of protons in tissue, determining the so called Bragg peak, where protons release most of their energy. Hence, several approaches are currently investigated to enable an in-vivo, ideally real-time verification of the proton beam range in the patient. While most of the considered techniques aim at exploiting secondary emissions from nuclear interactions, interest is being regained for alternative, cost-effective solutions exploiting acoustic emissions originating from ion interaction in tissue. This contribution will thus address the basics and recent experiments of this so called “ionoacoustics” for pre-clinical and clinical beam energies.

1. Introduction
Proton therapy is an emerging treatment modality exploiting the favourable interaction properties of swift ions in matter. Along with advanced scanning delivery methods, proton therapy can enable very good targeting of the dose to the tumour with excellent sparing of surrounding healthy tissue and critical structures compared to widely established external photon beam therapy. However, full clinical exploitation of the promised advantages in the clinical practice is still hampered by the main issue of range uncertainties, i.e., uncertainties in the position of the well localized dose deposition of individual pencil beams in the so-called Bragg peak (BP). To this end, most of the currently investigated techniques aim at exploiting secondary emissions from nuclear interactions less obviously correlated to the dose deposition, such as positron emission tomography and prompt gamma imaging [1]. Here, we present an alternative approach exploiting acoustic emissions originating from ion interaction in tissue, so called “ionoacoustics” [2]. This method has recently been revisited at two medical facilities in USA [3] and France [4]. After reviewing the basic principles, initial experience at the two facilities along with systematic measurements at low proton beam energies are presented and compared.

2. Material and methods
When penetrating a medium, protons mainly lose energy in electronic collisions, resulting in localized heating and a thermal expansion, which generates thermoacoustic emissions detectable with acoustic transducers. However, only spatial and temporal gradients can produce a pressure wave in such adiabatic heating. These gradients are generated temporally by pulsed beams with steep rise times, and spatially by locally confined energy deposition as in the Bragg peak. Under these conditions different spatial source locations can be identified for pencil-like beams depending on the detector position and
proton range. For short ranges (e.g. 4.1 mm for 20 MeV protons as shown in figure 1) a so called direct signal expanding spherically around the BP can be measured, along with a signal generated at the entrance in water and a reflection of the direct signal at the water/air interface [1]. By placing a suitable transducer, e.g., axially and distal to the BP, the range of protons can be directly calculated from the time difference between the entrance or the reflection signal and the direct signal knowing the water temperature (for accurate speed of sound determination) [1]. For higher proton energies and longer ranges, an additional signal can be seen from the cylindrical ultrasound wave expanding only laterally from the beam axis. A full theoretical description can be found for example in [5].

To better understand the complex dependence of the ionoacoustic signal strength and shape on the spatial and temporal distribution of the dose deposition, we performed a large series of measurements of ionoacoustic emissions from pulsed proton beams (~ns for pre-clinical energies, ~ns for clinical energies) in water, varying possible beam parameters (e.g., pulse length/intensity) that influence the signal amplitude. Since the properties of the used hydrophone in sensitivity and size are also important, comparative measurements between currently used detectors are shown. The presented data in water are from a 20 MeV proton beam studied at the MLL Tandem accelerator in Garching near Munich, Germany [1], a ≥ 200 MeV clinical beam from a superconducting synchrocyclotron at the Centre Antoine Lacassagne (CAL) in Nice, France [3], and a comparative measurement conducted at the Roberts Proton Therapy Centre located at the university of Pennsylvania (UPENN) in Philadelphia, USA, with a 230 MeV proton beam.

3. Results and discussion

The linear dependency of the signal amplitude with the deposited energy was confirmed with a 20 MeV proton beam and a pulse width of 473 ns, varying the particle number per pulse from ca. $10^5$ to $10^7$ protons/pulse. A polynomial fit of the data showed a linear relation with a detection limit for this setup of about $10^5$ particles/pulse with averaging of 16 events, corresponding to a dose deposition of about 1.6 Gy in the Bragg peak region [1]. A similar study was then conducted with 200 MeV proton and a 3.7 µs pulse width at CAL. Since the signal amplitude at these higher beam energies is significantly lower, averages up to 1000 pulses were required. In a study with 5000 consecutive single pulses, the amount of averages was successively reduced and the resulting precision in time-of-flight (TOF) range determination is shown in figure 3, demonstrating that an averaged dose of 2.8 Gy is...
required for a range retrieval precision of ±1 mm [4]. Here, doses were averaged in a cylindrical volume around the Bragg peak with dimensions deduced from radiochromic film measurements.

The frequency spectrum of the ionoacoustic signal is, amongst others, determined by the heating spatial distribution, hence depending on the initial proton kinetic energy and energy dependent lateral and range straggling. While for the 20 MeV proton beams the FWHM of the Bragg peak was about 300 µm, providing a central frequency of ~2.5 MHz, the FWHM of a 230 MeV proton beam increases to ~28 mm, thus decreasing the central frequency of the ionoacoustic signal to ~10 kHz. Results presented in [3] and figure 2 show that range determination with > 200 MeV proton beams with sub-millimetre resolution is possible and hence not limited by the low central frequency of the ionoacoustic signal. The challenge arising from these broad heat distributions is the choice of a proper detector matched to the signal frequency. Additionally, with longer proton ranges the TOF for reflection of the direct signal increases (figure 1) and the amplitude of window and reflection signals is significantly lower than for the direct signal, thus challenging their detection.

Another very important parameter is the pulse width. Two important time scales are commonly given for two regimes: thermal and stress confinement. The first one is the time limit for adiabatic heating, usually in the order of milliseconds. For pulse length below the thermal confinement, heat diffusion can be neglected. Stress confinement is fulfilled, if the pulse width is shorter than the flight time of the generated acoustic signal through a characteristic volume, in this case the Bragg peak. When stress confinement is fulfilled, the temporal profile can be considered as a delta spike excitation providing optimal condition for pressure generation with highest amplitudes. In this case, the resulting acoustic signal is mainly defined by the spatial heating distribution. The stress confinement for a 230 MeV proton beam is a pulse width of 18.5 µs. At the isochronous cyclotron at UPENN, this stress confinement was achieved with a pulse width of 17 µs [3] by pulsing the arc current. However, better conditions are provided by the synchrocyclotron at CAL, with inherently pulsed proton beams with a width of 3.7 µs [4]. Along with the higher pulse intensity of 2 pC per pulse, this synchrocyclotron provides optimal conditions for ionoacoustic measurements, translating in better precision and accuracy for proton range determination. Here, we measured for the first time the ionoacoustic signal with a bidirectional, flat Cetacean C305x hydrophone, simultaneously using a scintillator to define the start of the TOF measurement from the proton entering the water phantom to the arrival time of the highest pressure wave carrying the signal from the Bragg peak [4]. With a precise levelling of the hydrophone to the water surface, this distance was subtracted from the total depth of the hydrophone, yielding the range of the proton in water. From the comparison with ionization chamber (IC) depth measurements done directly following the ionoacoustic measurements with the same energy settings, as well as from previous commissioning measurements, a sub-millimeter range accuracy and precision could be confirmed for sufficient signal strength, i.e., deposited dose (figures 2 and 3).

Finally, comparative measurements were conducted at UPENN, comparing our C305x hydrophone with their omnidirectional calibrated Brüel & Kjaer 8105, used for the results reported in [3]. To this end, the hydrophones were placed axially to an artificially pulsed 230 MeV proton beam in a water phantom, as in [3]. The position of the hydrophones was fixed and the proton beam range was reduced by introducing additional plates of solid water into the beam path. The increased distance of the Bragg peak from the two hydrophones is shown in dependence of the introduced additional absorbers in figure 4. The intended shift is shown by the black dashed line. In general, both hydrophones were able to follow the intended BP shift, with a slight underestimation for the 8105 model. However, this latter hydrophone was found less sensitive to noise and distortion, so that its precision is better compared to the fluctuation observed in the results from the C305x.
Figure 3. Compilation of ionoacoustic-deduced ranges in water, compared to a fit of reference IC measurements at CAL ([4], https://doi.org/10.1088/1361-6560/aa81f8. (© Institute of Physics and Engineering in Medicine. Reproduced by permission of IOP Publishing. All rights reserved).

Figure 4. Comparative measurement of relative range shifts induced by additional plates of solid water, measured with two different hydrophones at UPENN. The dashed black line indicates the intended shift of the Bragg peak.

4. Conclusions
Recent systematic TOF measurements in water revealed the potential of (sub)millimetre accuracy and precision of ionoacoustics for range monitoring, provided that sufficient signal is collected, e.g., by averaging over more proton pulses for total doses up to 10 Gy [3,4]. While the considered low beam energies of ~20 MeV generate high frequency acoustic waves detectable with typical ultrasound transducers operating in the MHz range, clinical beam energies delivered by intrinsically or artificially pulsed (synchro)cyclotrons demand the usage of broadband, low-frequency (kHz) hydrophones. Although millimetre range monitoring based on ionoacoustics still demands relatively high fraction doses of a few Gy and is challenged by increased absorption and scattering in patient-like heterogeneous tissue compared to water, the reported results encourage ongoing efforts of several groups to improve the detection efficiency and to account for tissue heterogeneities with proper simulation and image reconstruction methods [6,7]. Ultimately, ionoacoustics could offer a compact and cost-effective modality for real-time in-vivo verification of the beam range (and possibly also anatomy with additional co-registered ultrasound imaging), at least for suitable clinical tumour indications of easy sonic access such as prostate, breast, liver [1].

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