Ultra-sensitive optoacoustic sensor for dosimetry in proton therapy - OMUS4PT

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ABSTRACT

Proton therapy is a promising cancer treatment modality able to concentrate dose in a localized region (Bragg peak, BP) in the tumor while well sparing surrounding tissue. Yet, uncertainties in beam range and patient anatomy restrict the BP localization accuracy to ≈ 0.5-1.0 cm. To overcome this, real-time dosimetry could enable accurate dose deposition within ~1 mm, thereby improving clinical outcome for irregularly shaped tumors near vital organs and in moving anatomies.

Our objective is to develop an innovative ultra-sensitive Optical Micromachined Ultrasound Sensor (OMUS) for real-time accurate BP localization exploiting thermoacoustic waves emitted at the BP during pulsed proton irradiation.

Keywords: proton therapy; ionoacoustics; integrated photonics; sensitivity; ultrasonic sensor

1. INTRODUCTION

Cancer is a major public health problem, with an incidence of 1.37 million cases in 2018 and a mortality of 548.355 people in Western Europe [1]. Approximately 50% of the patients are treated with radiation therapy (X-rays). Its drawback is collateral damage to healthy tissue, due to the penetrating nature of X-rays. Proton therapy (PT) overcomes this issue because most of proton energy is deposited in a sharply defined region (the Bragg peak, BP), enabling the precise delivery of dose to the tumor while minimizing collateral damage (Fig. 1). PT is therefore especially suited for cancer treatment in close proximity to vital organs or in patients with a long life expectancy.

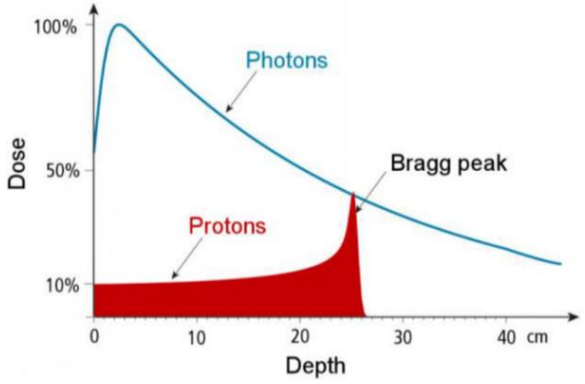

Fig. 1. The energy deposition of a proton beam versus an optical (x-ray) beam – from [2].

Treatment planning for PT is calculated from high-quality and quantitative CT (computed tomography) images of the tumor and surrounding tissues, possibly complemented with e.g. magnetic resonance imaging (MRI) or positron emission tomography (PET) data.

These calculations are based on the knowledge of unknown tissue properties (stopping power), which makes PT prone to errors, resulting in overdosing of healthy tissues and underdosing of tumors.

To exploit the full potential of high precision PT, the real-time dose delivery combined with anatomical imaging should be monitored during treatment: an hitherto unmet challenge. Currently, two main concepts are investigated for real-time monitoring of proton dosimetry. The first one uses prompt gamma radiation emitted by nuclear de-excitation of oxygen and carbon nuclei excited by the protons. Its main drawbacks are the fundamental difference in tissue interaction, the required bulky and expensive instrumentation and the limited number of measured prompt gamma rays leading to a low signal-to-noise-ratio (SNR). The second concept is based on ionoacoustics, which uses the conversion of the proton kinetic energy into heat, leading to tissue expansion and acoustic waves. However, under clinical relevant conditions, the acoustic waves have low frequencies (≈ 100 kHz) and low amplitudes (≈10mPa) [3-5]. These amplitudes are 1–2 orders below the noise threshold of conventional ultrasound transducers.

In this Attract project, we present a sensing concept for the accurate localization of the BP during PT based on opto-acoustic sensors with an up to 2 orders of magnitude lower noise threshold. The following innovations were performed:

(i) The relevant PT physics and induced pressure waves were modeled.
(ii) Algorithms to acoustically localize the BP were developed.
(iii) Opto-acoustic sensors were adapted to PT (OMUS4PT) and designed.
(iv) OMUS4PT prototypes were constructed and will be experimentally tested.

2. STATE OF THE ART

In this work the BP is detected and localized through direct detection of the ionoacoustic signal, i.e., the acoustic pressure wave generated by the expansion of the volume in which the protons rapidly lose energy [3-5]. The pressures and frequencies associated with the ionoacoustic signals are low and vary as a function of the treatment depth (proton beam energy). Typically, the acoustic signal produced by a proton beam at the surface of the body is in the order of 1 Pa at 1 MHz. This reduces to 10 mPa at 20 kHz at 30 cm treatment depth [5].

The current state-of-the-art medical ultrasound transducer technology based on piezomaterials has a number of fundamental limitations. Firstly, transducers with resonance frequencies <100 kHz are needed when tumors at larger depths (>10 cm) are treated. Due to the inverse relation of the piezomaterial thickness with its center frequency [6] the transducer size would increase prohibitively at these frequencies (e.g. 9 cm for a 20 kHz resonance frequency). The entire ultrasonic sensor, including matching layers and backing would be far too large for practical usage. Secondly, in order to treat many tumors, a large range of treatment depths have to be covered, resulting in the usage of different beam energies producing ionoacoustic emissions of different frequency content. This consequently requires a sensitivity over a very large frequency bandwidth – much larger than is possible using traditional transducer technology. Several transducers would be needed to cover the entire frequency range associated with the axial ranges used in PT. Thirdly, to achieve a BP location error below 1 mm at low frequencies, the noise-equivalent-pressure (NEP) of the ultrasound system including the transducer should be one to two orders of magnitude better than the acoustic pressures produced by the ionoacoustic effect.

3. BREAKTHROUGH CHARACTER OF THE PROJECT

We aim to solve the challenges mentioned above through the development of a novel opto-acoustic sensor. Opto-acoustical sensors (OMUS) consist of a thin micro-machined membrane, which deflects under the influence of incoming pressure waves. The deflection is detected by an optical circuit integrated on top of the membrane. If the optical circuit is a ring resonator (see Fig. 2), the wavelength dependent optical transfer function of the device is affected by the mechanical stress and strain induced by the membrane deflection due to the acoustic wave. In the case the optical circuit forms an interferometric detector the phase difference between an optical path over the membrane and an optical path outside the membrane is detected. This phase difference is caused by deformation (elongation) of the waveguide and/or refractive index change of the optical path traveling over the membrane induced by the impinging acoustic wave.

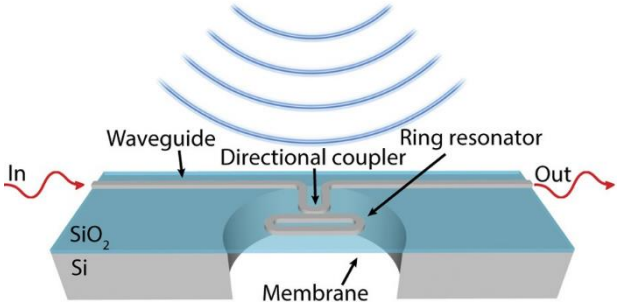

Fig. 2. Schematic of a ring resonator based opto-acoustic sensor -from [7].

Recently we have demonstrated a first prototype single opto-acoustical ultrasound sensors with a NEP of 0.4 Pa at 0.8 MHz [7,8]. Although that is similar to the NEP of state-of-the-art piezoelectric ultrasound transducers, the revolutionary aspect of this sensor is that its diameter is only 120 µm. From practical perspective, this makes the optical chip very suitable for ionoacoustics - even for low frequencies, especially compared to the large dimensions of current piezoelectric sensors.

Because of the small footprint of the opto-acoustic sensor it can be massively parallelized – 100s-1000s of opto-acoustic sensors will fit on the surface area of a regular state-of-the-art piezoelectric sensor. This matrix of optoacoustic sensors can be used to lower the NEP by more than one order of magnitude, or to massively increase the effective sensor bandwidth by varying the resonance frequency of the membrane and/or optical resonator. The noise in regular piezoelectric medical ultrasound transducers is limited by Johnson thermal noise caused by the electrical resistance of the piezo material. Although new materials have been developed over the last 50 years, progress and the associated improvements have been slow. In contrast, the noise floor in the opto-acoustic sensor is limited by the thermo-acoustical noise from random motion of the particles in the tissue and the membrane. This thermo-acoustical noise is typically much lower than the thermal noise in piezomaterials [7,8].

Next to parallelization, the sensitivity and NEP of the opto-acoustic sensors can further be improved by optimizing both membrane and waveguide on the membrane to maximize stress and strain sensitivity.

4. PROJECT RESULTS

Numerical modelling (i)

The ionoacoustic responses of pulsed pencil beams for PT were simulated in MATLAB. The proton energy of the protons delivered in a watery medium is based on the work of Bortfeld, Jones, Esra and Ahmad [9-12]. Clinical relevant pulsed pencil beams use $N_p = 2{\cdot}10^6$ - $10{\cdot}10^6$ protons/pulse, energy range of 50-200 MeV and temporal pulse lengths of 2-10 µs. For these clinical relevant doses, temperature rises are in the order of ΔT = 1-5 µK and acoustic pressure waves at the BP in the order of 0.5-2.5 Pa can be created for ionoacoustics [3-5] (Fig 3).

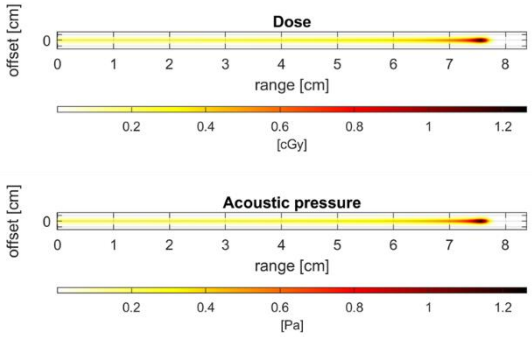

Fig. 3. Example of a dose distribution of a proton pencil beam (top) and the corresponding induced acoustic pressure (bottom). Proton energy = 100 MeV, Np=4·106 protons/pulse and a 2 µs Gaussian pulse length.

The pressure waves generated by a single pencil beam propagate in the body and can be detected by an array of ultrasonic detectors located outside of the body. As an example, we simulated an array of detectors circularly distributed at 25 cm around the BP in an aqueous medium (with α=0.3 dB/MHz/cm) for Gaussian pulses with lengths of 2 µs to 10 µs (Fig. 4 and Fig 5). Typical acoustic pressures of several mPa can be detected (Fig. 5). The detected signal reveals both the entry point of the pencil beam in the body and the location of the BP.

If sensors are able to detect acoustic pressures at the mPa range and the proton delivery system is able to deliver very short pulsed pencil beams, the measured ionoacoustic responses can be used for localization of the BP and range verification.

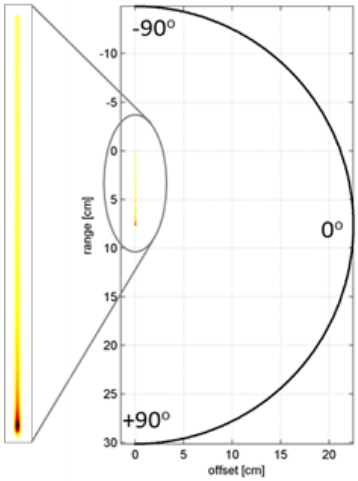

Fig. 4. Geometry of the OMUS detectors. The detectors are distributed along a half circle in the *x*-*z* plane, 25 cm from the location of the BP. The first detector is located at the top (-90 degrees) and the last at the bottom (+90 degrees).

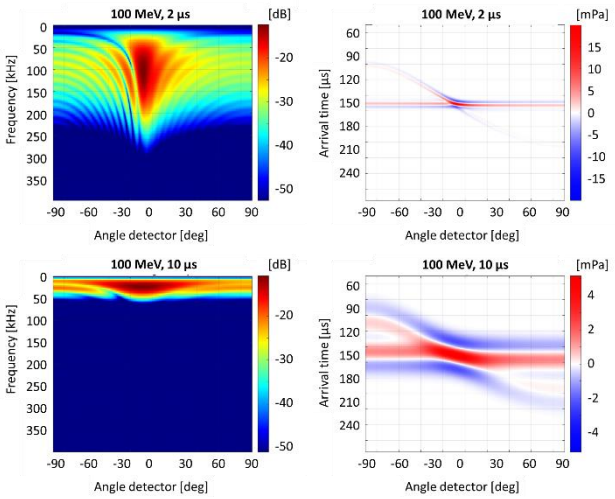

Fig. 5. Simulated ultrasonic responses; top 2 µs pulse length, bottom 10 µs pulse length. Left the spectral response and right the temporal response.

Signal processing for localization (ii)

A study was performed looking into different algorithms to acoustically localize the BP. A multilateration technique was opted for [13-15]. This algorithm determines the location of the sound source based on the arrival time differences between the receivers. Therefore, no trigger/time synchronization with the proton beam is necessary. The time differences were determined using cross-correlation. The pulse-detection, filtering and windowing was fully automated. The algorithm was implemented in MATLAB. Furthermore, a

simulation algorithm was written to simulate the propagation of the pressure waves induced by proton beams, which also allowed for varying the receiver geometry and SNR. A receiver geometry with 7 separate receivers in an aqueous medium mounted in a grid of 5 cm × 5 cm was chosen. Assuming an SNR of 20 dB (intensity dB's) an accuracy of <0.7 mm was achieved for an incoming pressure wave with a center frequency of 50 kHz produced by a BP measured at 15 cm distance (Fig. 6). This results is promising to reach the required 1 mm accuracy for PT.

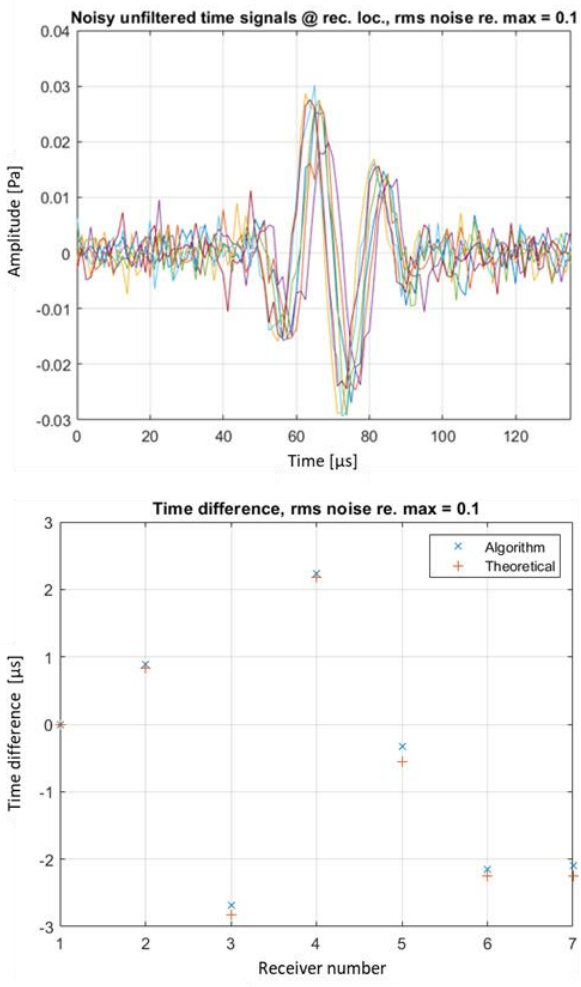

Fig. 6. Top graph: time signals picked up by the 7 receivers using an SNR of 20 dB. Bottom graph: Time differences between receiver N and receiver 1 from theory (red pluses) and as obtained by the implemented algorithm (blue crosses).

Chip design (iii+iv)

We have designed and fabricated a series of waveguide-based optoacoustic sensor chips, using the waveguide cross section as depicted in Fig. 7. It consists of a stack of two waveguiding Si_3N_4 layers, separated by SiO_2 layers. The layer stack is designed for a wavelength of 1550 nm. Simulations have shown that the optical absorption due to water is acceptable for the device performance.

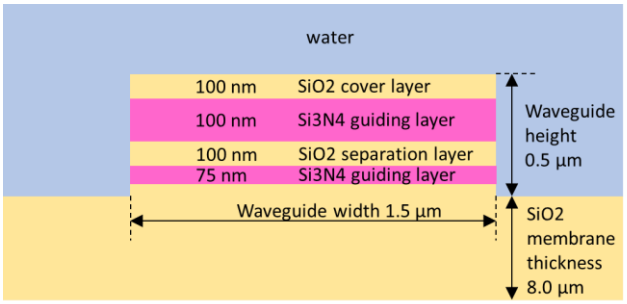

Fig. 7: Waveguide cross section.

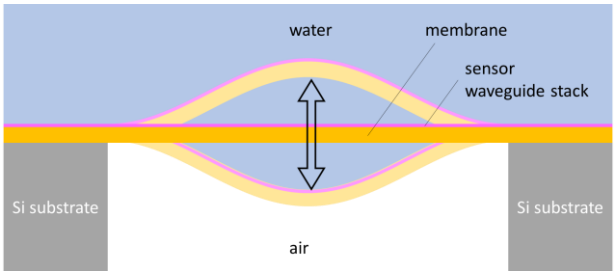

Fig. 8: Waveguide-based photonic integrated circuit on a membrane.

The layer stack sits on the 8 µm thick membrane (Fig. 8), which is created by locally etching the silicon substrate below the waveguide layers. An acoustic signal deforms the membrane, causing a change in the physical dimensions of the waveguides on the membrane (length and cross section), as well as a change in the material refractive indices due to mechanical strain. The resulting changes in the waveguide effective refractive index are detected by means of a ring resonator [7,8] or an interferometer [16] on the membrane. We extensively investigated different circuit concepts and varied design parameters to come to our final design, resulting in a total of 11 different chips, each containing several sensors. At the time of writing, fabrication of chips with membranes is in progress, optical characterization of reference chips without membranes has started.

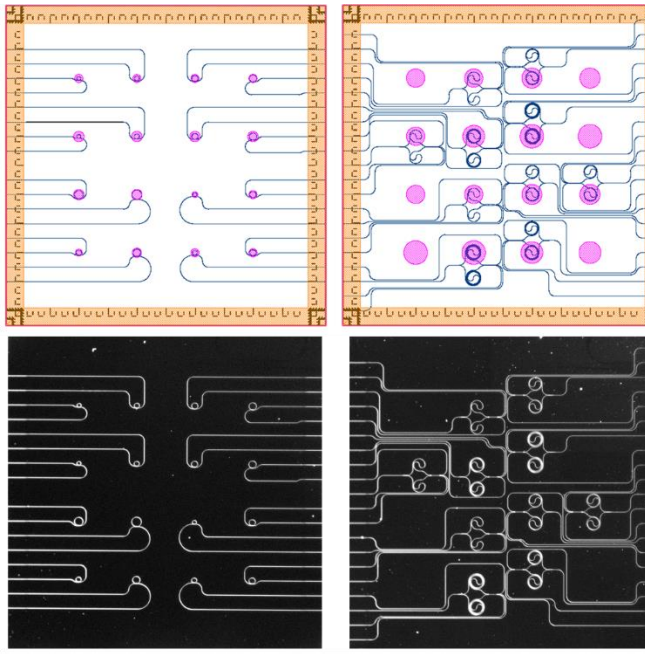

Fig. 9: Design of optoacoustic sensor chips with ring resonators (top left) and interferometers (top right), and fabricated chips without membranes (bottom left and right).

5. FUTURE PROJECT VISION

5.1. Technology Scaling

The technology development required to advance in TRL-level is divided in 5 main activities:

- **WP1 Further optimization of the OMUS4PT sensor**. Improvements of the sensor sensitivity and bandwidth together with robustness and manufacturability are needed. Integration of several promising technologies under development in other Attract projects, such as different lithographic processes and optical detection techniques e.g. photonic crystals are planned.
- **WP2 Development of an efficient read-out system**. Advanced optical read-out systems such as interferometers - and interrogators on chip are very promising will be developed, especially with respect to SNR and parallelization. The read-out system together with signal processing must accurately determine the location of the entry point and the Bragg peak.
- **WP3 Integration of the OMUS4PT sensor in an ultrasound system** to provide the radiotherapist with localization and a real-time overlay image of the BP with respect to tumor.
- **WP4 Impact to proton delivery systems**. Ionoacoustics require a short pulsed pencil beam. Solutions will be explored to enable ionoacoustics while safeguarding accurate dosimetry. Involvement of PT centers and proton delivery vendors will enhance the uptake and thus the societal impact.
- **WP5 validation**. All the elements of OMUS4PT will be integrated for technical and pre-clinical validation to demonstrate TRL5-7.

5.2. Project Synergies and Outreach

In order to ensure the development of relevant technology with impact, all relevant stakeholders will participate in Attract phase 2:

- Academic/industrial partners with expertise to improve and realize the OMUS4PT sensor and the development of read-out systems.
- Partners with expertise in medical ultrasound and real-time image processing to enable real time visualization of the Bragg peak in an ultrasonic image.
- Partners with expertise in quality assurance, phantoms and dosimetry for PT for validation of the sensors under clinical relevant conditions
- Vendor of proton delivery systems for implementation of the sensors.

- A medical device manufacturer who can bring the systems to the market.
- Proton therapy centers for the technical validation, characterization and the first clinical validation experiments.
- A steering committee will include end-users (patient and care professional federations together with health insurance companies) to define a solid business case.

5.3. Technology application and demonstration cases

OMUS4PT is dedicated to implement ionoacoustics in high precision proton therapy, to enable precise tumor treatment with minimum collateral damage to adjacent organs. Especially crucial for vital organs in close proximity to the tumor, high precision proton therapy will strongly improve the quality of life of patients after treatment (see 5.4).

5.4. Technology commercialization

The OMUS4PT technology aims to advance high precision PT at multiple levels. Three different products for commercialization of the OMUS4PT sensor are foreseen (with increasing complexity):

- A first minimum viable product is a range verification system, which only verifies the depth of the BP in the tissue.
- Range verification can be extended to full on-line 3D localization of the BP and of the entry point in the body. This enables a more sophisticated method to verify treatment planning, or a tool for quality assurance.
- A third interesting product is the integration of the OMUS4PT sensor in an ultrasound imaging system. This enables real-time visualization of both the BP and the location of the tumor during treatment and provides the real time information to direct the pencil beam to exactly hit the tumor.

To maximize societal impact, as many as possible cancer patients should benefit from the future OMUS4PT system. Therefore, these systems should be accessible to all proton therapy clinics. We therefore strive for a future situation wherein the OMUS4PT technology will be marketed by a dedicated medical device manufacturer (or start-up company). This medical device manufacturer should be closely involved in further prototype development and take responsibility for final product engineering. To ensure the successful commercialization of these products, participation of the end-users will be essential.

Other applications

Europe has a high tech leading ecosystem for the realization of integrated optical devices (SmartPhotonics, Lionix, IMEC, LETI, VTT, Ligentec, etc.). OMUS is a generic integrated photonic ultrasound sensor platform. Besides the proton beam applications, we will also separately explore valorization of the integrated nanophotonics opto-acoustic sensor for other applications. Utilization will be explored for MRI compatible all-optical-ultrasound systems for intravascular (IVUS) and intracardiac (ICE) applications and utilization in other domains such as the acoustic detection of neutrinos (KM3-net), detection of heavy ion beams, and applications in the sonar or oil and gas market.

5.5. Envisioned risks

The main envisioned risks are given in the table below:

Tab. 1. Envisioned risks for OMUS4PT

Risk	Mitigation strategy
Sensitivity of the OMUS sensor to reach accurate localization	First iteration will be analyzed shortly after Attract phase 1. Alternative optical sensing techniques will be explored (WP1).
Robustness of the OMUS sensor	Packaging of the sensor in a sensor head (WP1-WP2).
Manufacturability of the OMUS sensor	The sensor will be further developed in close collaboration with foundry industry partners (WP1, WP2).
Uptake in PT; Embedding in the proton delivery systems, acceptance by the radiotherapists	WP3 and WP4 are dedicated to integrate OMUS4PT in a proton delivery system WP4 and WP5 are planned to ensure accurate dosimetry and to validate and demonstrate OMUS4PT.

5.6. Liaison with Student Teams and Socio-Economic Study

We foresee multiple student projects (BSc, MSc as well as PhD students) to focus on specific aspects of the sensor technology, as well as demonstration to the high precision PT use-case. The OMUS concept was already used for the CERN IdeaSquare 2020 by a team of Dutch Students following the Honour program of TUDelft and NIKHEF.

In order to achieve societal impact, during the project we will stimulate entrepreneurship and explore the routes for commercialization.

6. ACKNOWLEDGEMENT

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7. REFERENCES

[1] Globocan 2018: https://gco.iarc.fr/today/data/factsheets/cancers/39-All-cancers-fact-sheet.pdf

[2] Studenski, M. T., & Xiao, Y. (2010). Proton therapy dosimetry using positron emission tomography. World journal of radiology, 2(4), 135–142. https://doi.org/10.4329/wjr.v2.i4.135

[3] K.C. Jones, F. Vander Stappen, C.R. Bawiec, G. Janssens, P.A. Lewin, D. Prieels, S. Avery. Experimental observation of acoustic emissions generated by a pulsed proton beam from a hospital-based clinical cyclotron. Medical physics, 42(12), 7090-7097, 2015.

[4] S. Kellnberger, W. Assmann, S. Lehrack, S. Reinhardt, P. Thirolf, D. Queirós, V. Ntziachristos. Ionoacoustic tomography of the proton Bragg peak in combination with ultrasound and optoacoustic imaging. Scientific reports, 6, 29305, 2016.

[5] S. Lehrack, W. Assmann, D. Bertrand, S. Henrotin, J. Herault, V. Heymans, J. Van de Walle. Submillimeter ionoacoustic range determination for protons in water at a clinical synchrocyclotron. Physics in Medicine & Biology, 62(17), L20, 2017.

[6] R.S.C. Cobbold. Foundations of Biomedical Ultrasound. Oxford University Press, Inc., Oxford, New York, 2007.

[7] S.M. Leinders, W.J. Westerveld, J. Pozo, P.L.M.J. van Neer, B. Snyder, P. O'Brien, H.P. Urbach, N. de Jong, M.D. Verweij. A sensitive optical micro-machined ultrasound sensor (OMUS) based on a silicon photonic ring resonator on an acoustical membrane. Scientific Reports 5, article id. 14328, 2015.

[8] S. Leinders. Characterization of a novel Optical Micro-machined Ultrasound Transducer. PhD thesis, 2017.

[9] Thomas Bortfeld An analytical approximation of the Bragg curve for therapeutic proton beams. Med. Phys. 24(12), 2024-2033, 1997.

[10] K C Jones et al: Proton beam characterization by proton-induced acoustic emission: simulation studies. 2014 Phys. Med. Biol. 59 6549

[11] Esra Aytac Kipergil et al An analysis of beam parameters on protonacoustic waves through an analytic approach. 2017 Phys. Med. Biol. 62 4694

[12] Ahmad, M., Xiang, L., Yousefi, S. and Xing, L. (2015), Theoretical detection threshold of the proton-acoustic range verification technique. Med. Phys., 42: 5735-5744. doi:10.1118/1.4929939

[13] S. Bancroft. An Algebraic Solution of the GPS Equations, IEEE Transactions on Aerospace and Electronic Systems, AES-21(1): 56–59, 1985.

[14] L.O. Krause. A direct solution to GPS-type navigation equations, IEEE Transactions on Aerospace and Electronic Systems, AES-23(2): 225–232, 1987.

[15] B. T. Fang. Simple Solutions for Hyperbolic and Related Position Fixes, IEEE Transactions on Aerospace and Electronic Systems, 26(5): 748–753, 1990.

[16] W. J. Westerveld et al., "Optical micro-machined ultrasound sensors with a silicon photonic resonator in a buckled acoustical membrane," 2019 20th International Conference on Thermal, Mechanical and Multi-Physics Simulation and Experiments in Microelectronics and Microsystems (EuroSimE), Hannover, Germany, 2019, pp. 1-7, doi: 10.1109/EuroSimE.2019.8724528.