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Author(s)	Nakamura, Yuta; Takayanagi, Taisuke; Uesaka, Tomoki; Unlu, Mehmet Burcin; Kuriyama, Yasutoshi; Ishi, Yoshihiro; Uesugi, Tomonori; Kobayashi, Masanori; Kudo, Nobuki; Tanaka, Sodai; Umegaki, Kikuo; Tomioka, Satoshi; Matsuura, Taeko
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1 **Technical Note: Range verification of pulsed proton beams from**
2 **fixed-field alternating-gradient accelerator by means of time-of-flight**
3 **measurement of ionoacoustic waves**

4
5 **Running title:** Acoustic range verification of protons from FFA

6
7 Yuta Nakamura^{1,†}, Taisuke Takayanagi^{2,3,†}, Tomoki Uesaka², Mehmet Burcin Unlu⁴,
8 Yasutoshi Kuriyama⁵, Yoshihiro Ishi⁵, Tomonori Uesugi⁵, Masanori Kobayashi⁶, Nobuki Kudo⁷,
9 Sodai Tanaka⁸, Kikuo Umegaki^{8,9}, Satoshi Tomioka⁸, Taeko Matsuura^{8,9,*}

10
11 [†] Yuta Nakamura and Taisuke Takayanagi contributed equally to this work.

12
13 ***Corresponding author:** Dr Taeko Matsuura, Faculty of Engineering, Hokkaido University,
14 North-15 West-7, Kita-ku, Sapporo, Hokkaido, 060-8638, Japan. Tel: +81-11-706-5254; Email:
15 matsuura@med.hokudai.ac.jp

16

¹ Graduate School of Engineering, Hokkaido University, North-13 West-8, Kita-ku, Sapporo, Hokkaido, 060-8628, Japan

² Graduate School of Biomedical Science and Engineering, Hokkaido University, North-13 West-8, Kita-ku, Sapporo, Hokkaido, 060-8628, Japan

³ Hitachi Ltd., 1-1 7-chome, Omika-cho, Hitachi-shi, Ibaraki, 319-1292, Japan

⁴ Department of Physics, Bogazici University, Bebek, Istanbul, 34342, Turkey

⁵ Institute for Integrated Radiation and Nuclear Science, Kyoto University, Osaka, 590-0494, Japan

⁶ Planetary Exploration Research Institute, Chiba Institute of Technology, Chiba, 275-0016, Japan

⁷ Faculty of Information Science and Technology, Hokkaido University, North-14, West-9, Kita-ku, Sapporo, Hokkaido, 060-0814, Japan

⁸ Faculty of Engineering, Hokkaido University, North-13 West-8, Kita-ku, Sapporo, Hokkaido, 060-8628, Japan

⁹ Proton Beam Therapy Center, Hokkaido University Hospital, North-15 West-7, Kita-ku, Sapporo, Hokkaido, 060-8638, Japan

17 **Abstract**

18 **Purpose:** Ionoacoustics is one of the promising approaches to verify the beam range in proton
19 therapy. However, the weakness of the wave signal remains a main hindrance to its application
20 in clinics. Here we studied the potential use of a fixed-field alternating-gradient accelerator
21 (FFA), one of the accelerator candidates for future proton therapy. For such end, magnitude of
22 the pressure wave and range accuracy achieved by the short-pulsed beam of FFA were assessed,
23 using both simulation and experimental procedure.

24 **Methods:** A 100 MeV proton beam from the FFA was applied on a water phantom, through the
25 acrylic wall. The beam range measured by the Bragg peak (BP)-ionization chamber (BPC) was
26 77.6 mm, while the maximum dose at BP was estimated to be 0.35 Gy/pulse. A hydrophone was
27 placed 20 mm downstream of the BP, and signals were amplified and stored by a digital
28 oscilloscope, averaged, and low-pass filtered. Time-of-flight (TOF) and two relative TOF values
29 were analyzed in order to determine the beam range. Furthermore, an acoustic wave transport
30 simulation was conducted to estimate the amplitude of the pressure waves.

31 **Results:** The range calculated when using two relative TOF was 78.16 ± 0.01 and 78.14 ± 0.01
32 mm, respectively, both values being coherent with the range measured by the BPC (the
33 difference was 0.5–0.6 mm). In contrast, utilizing the direct TOF resulted in a range error of 1.8
34 mm. Five and fifty-fold averaging was required to suppress the range variation to below 1 mm
35 for TOF and relative TOF measures, respectively. The simulation suggested the magnitude of
36 pressure wave at the detector exceeded 7 Pascal.

37 **Conclusion:** A submillimeter range accuracy was attained with a pulsed beam of about 21 ns
38 from an FFA, at a clinical energy using relative TOF. To precisely quantify the range with a
39 single TOF measurement, subsequent improvement of the measuring system is required.

40

41 **Keywords:** proton therapy, range verification, ionoacoustics

42 1. Introduction

43 While proton therapy potentially allows better dose conformality compared to photon therapy
44 because of the Bragg peak (BP), the full potential of the BP is yet to be exploited because of the
45 range uncertainty.¹ Multiple sources of range uncertainty exist, including the conversion from
46 the computed tomography (CT) value to stopping power ratio, anatomical changes of the patient,
47 and organ motion, and much effort has been made to reduce this range uncertainty.² In vivo
48 range verification during or shortly after treatment is a promising approach, and three methods
49 have been proposed so far, namely prompt gamma detection (PGD),³ positron emitter
50 tomography (PET),⁴ and ionoacoustics.⁵ PGD and PET detect the gamma-ray arising from the
51 nuclear reaction between protons and nuclei along the beam path. Both are currently used in
52 clinics^{6,7} and should detect the beam range in a few millimeter accuracy.⁸

53 The method using the ionoacoustic range verification is based on acoustic waves arising from
54 a medium being hit by a pulsed proton/ion beam.⁹ Unlike PGD and PET, requiring bulky and
55 expensive gamma-ray detectors around patients, the acoustic wave detection system comprises a
56 single or an array of hydrophones, requiring smaller space, and is more affordable.¹⁰ Hayakawa
57 et al.¹¹ first applied this method to a patient in which the feasibility of monitoring the proton
58 dose distributions in patients was suggested by sensing acoustic pulses. Recently, many studies,
59 both experimental and numerical, have been conducted to exploit the ionoacoustics to reduce
60 the range uncertainty during proton therapy.¹² The experiments were performed using a
61 linac,^{13,14} a synchrotron,^{11,15,16,17} a tandem accelerator,¹⁸ a cyclotron,¹⁹ a laser-plasma
62 accelerator,²⁰ a hospital-based isochronous cyclotron,^{21,22} and a synchrocyclotron,^{23,24} all with
63 positive results. Specifically, clinically relevant energy beams were used by Jones et al. (190
64 MeV and 230 MeV beams, accelerated by a clinical cyclotron)^{21,22} and by Lehrack et al. and
65 Patch et al. (energy between 145 MeV and 227 MeV, and energy \geq 125 MeV, respectively, from
66 a clinical synchrocyclotron).^{23,24}

67 Although these results substantiate the usefulness of ionoacoustics, its clinical application has

68 been hampered by the faint signal amplitude attainable hitherto. Pressure waves are generated
69 efficiently in case thermal and stress confinement conditions are met, which is accomplished
70 when pulse duration is no more than $5 \mu\text{s}$ ²³ besides what signal amplitude is further increased if
71 the pulse duration is shortened. Jones et al. modulated a clinical cyclotron ion source current to
72 generate pulses of $17 \mu\text{s}$, which are shorter than standard treatment delivery. However, in their
73 work the wave amplitude obtained was limited to 25 mPa or below, at a maximum instantaneous
74 beam current of 790 nA, with 11.5×10^7 protons, which entailed an averaging of 1024-fold.²²
75 Even with a superconducting synchrocyclotron, which achieved the shortest pulse among
76 therapy machines ($3.7 \mu\text{s}$), Lehrack et al. reported that a dose of 10 Gy (2 pC per pulse $\times 1000$
77 average) was required to reach submillimeter range accuracy.²³ Recently, with the same
78 accelerator, Patch et al. demonstrated that the range verification is possible with the clinical
79 dosage of 0.5 Gy, however, the customized fine-tuned detectors and amplifiers were required,
80 which are not available commercially.²⁴ On the other hand, non-clinical machines such as
81 tandem accelerator,¹⁸ linac,¹⁴ and laser-plasma accelerator²⁰ produce the shortest pulses of 8 ns,
82 250 ns, and 30 fs, respectively. In the last two instances, range measurement was done with a
83 single²⁰ or 128-fold averaging,¹⁴ conversely the beam energies with all accelerators being far
84 below those that characterize therapeutic proton beams.

85 In the present study, we explored ionoacoustic range detection using a short-pulsed proton
86 beam from an FFA.^{25,26,27} The beam properties were within the range of that of clinical
87 conditions [100 MeV, 1.12×10^8 proton/pulse (0.35 Gy at BP), lateral beam size ~ 5 mm], yet
88 notably the pulse width was much smaller than that in clinical contexts ($\sigma \sim 21$ ns). Here we
89 estimate the beam range by measuring the time-of-flight (TOF) of the direct wave emitted from
90 the BP (referred to as γ -wave), as well as of the differences of TOF (referred to as relative TOF)
91 between direct wave and the ones reflected at the phantom wall. Relative TOF was also used in
92 prior studies^{14,18,19} and has the considerable advantage of not being affected neither by the
93 hydrophone positioning error nor the signal delay. The accuracy of the TOF methods was

94 assessed in comparison with the range detected by the dose measurement by the BPC. Moreover,
95 an acoustic wave transport simulation was performed to obtain the absolute amplitude of the
96 pressure waves.
97

98 2. Materials and Methods

99 2.1 Proton beam from the FFA

100 The 100 MeV proton beam accelerated by the FFA at Kyoto University^{28,29} was extracted at a
101 repetition rate of 30 Hz and incident on the DigiPhant PT water phantom (IBA Dosimetry,
102 Schwarzenbruck, Germany) through an acrylic wall of 1 cm. FFA designed for proton therapy
103 could in principle accelerate protons up to 250 MeV²⁵ or 350 MeV²⁶ but only representative
104 energy was used in this study. The pulse width was estimated at ~ 21 ns (1σ) according to the
105 measurement using an EJ-200 plastic scintillator placed at the exit of the vacuum beam duct
106 (Figure 1(B)). The scintillator coupled to a photomultiplier tube indirectly measures the beam
107 pulse shape by detecting mainly the loss protons and gamma-ray emitted by nuclei activated by
108 proton irradiation. The number of particles per pulse was measured using the Faraday cup and
109 estimated as $(1.17 \pm 0.06) \times 10^8$, which is comparable to one pulse in a clinical setting.³⁰ The
110 corresponding peak current was 0.4 mA.

111

112 2.2 Measurement of dose profiles

113 The Bragg curve shape was acquired by scanning the BPC (PTW34070, Freiburg, Germany)
114 along the beam axis (Figure 2a). Beam range was defined at the BP maximum and estimated as
115 $R_{BPC} = 77.6$ mm (mean of the two independent experiments). A transmission monitor Type
116 34014 (PTW, Freiburg, Germany) was used as the reference monitor. The lateral beam profile
117 was obtained using a radiochromic film EBT3 attached to the surface of the water phantom
118 (Figure 2b, c). The Satera MF8570Cdw (Canon Ltd.) was used as the film scanner, and at the
119 surface of the water phantom, the respective beam size (1σ) was 4.7 mm, vertically, and 5.7 mm,
120 horizontally.

121

122 2.3 Acoustic wave measurement

123 The unfocused type immersion hydrophone (V391-SU, Olympus, Waltham, USA) with a

124 central frequency of 0.5 MHz was placed 20 mm downstream of the range measured by the
 125 BPC in the water phantom. The hydrophone was positioned by aligning the detector surface to
 126 the lasers mounted on the room walls. The sensitive volume is assumed to be located at the
 127 detector surface. The water employed was deionized and degassed, with its temperature
 128 maintained at 22°C throughout the experiment, corresponding to sound speed of 1488.4 m/s. As
 129 described later, the frequency spectrum of the acoustic waves originating from the BP has its
 130 maximum at around 100 kHz. On the other hand, the peak and upper/lower -6 dB frequencies of
 131 the hydrophone were 0.48, 0.63, and 0.33 MHz, respectively, according to the datasheet
 132 provided by the manufacturer. A control signal of the beam extraction kicker of the FFA was
 133 used for triggering data acquisition, and time zero was defined at the peak of the scintillator
 134 signal. Signals were amplified using a 46 dB amplifier (SA230-F5, NF Corporation, Japan),
 135 with a flat frequency response over the bandwidth of 1 kHz~100 MHz (+0.5, -3 dB), and then
 136 stored through digital oscilloscope at a 50 MS/s sampling rate, after averaging 5–50 events. A
 137 low-pass filter with a cutoff frequency of 1 MHz was used for filtering the RF noise at 8 MHz.
 138 We investigate whether the result depends on the incident beam energy by setting additional
 139 acrylic plates of various thicknesses (4 mm–20 mm) in front of the water phantom and repeated
 140 the measurement.

141

142 2.4 TOF and relative TOF metrics

143 In the previous research, beam range estimation has predominantly relied on the absolute
 144 TOF of the compression peak of the γ -wave. Here, beyond the conventional TOF of direct
 145 γ -waves (wavelet (a) in Figure 3), we explored the relative TOF metrics,^{14,18,19} in order to avoid
 146 the bias of hydrophone positioning error (the difference between the TOF of wavelets (a) and (c)
 147 or (d) in Figure 3). Denoting the acoustic arrival time of each wavelet as $\tau^{(i)}$ ($i = a, c, d$), the
 148 beam range (R) is estimated by

$$149 \quad R = L_1 + L_2 + S_{\text{acryl}}L_{\text{wall}} - c_w \tau^{(a)},$$

150 when using the conventional TOF method, or by the expression

151
$$R = c_w \left(\frac{\tau^{(c)} - \tau^{(a)}}{2} \right) + S_{\text{acryl}} L_{\text{wall}} \text{ or } R = c_w \left\{ \left(\frac{\tau^{(d)} - \tau^{(a)}}{2} \right) - \frac{L_{\text{wall}}}{c_a} \right\} + S_{\text{acryl}} L_{\text{wall}},$$

152 if addressing relative TOF metrics. L_1 , L_2 , and L_{wall} are, respectively, the distances from the
153 wall to the BP, and from the BP to the detector position, and the acrylic wall thickness. S_{acryl}
154 represents the relative stopping power of acryl (= 1.16), while c_w and c_a are the sound speed
155 in water and acryl, respectively.

156

157 2.5 Acoustic wave simulation

158 The waveform obtained from the experiment was further explored by conducting an acoustic
159 wave simulation using a simple point-like detector with a constant frequency response and no
160 delay. The thermoacoustic wave emission and transport equation, from the energy deposition of
161 proton pulse, is described by the following expression,

162
$$\frac{1}{v^2} \frac{\partial^2 p}{\partial t^2} - \nabla^2 p = (\Gamma/v^2) E(\vec{r}) I'(t),$$

163 where $E(\vec{r})$ corresponds to the distribution of transferred energy density [J/m^3]. $I'(t)$ is the
164 time derivative of the normalized beam current [$1/\text{s}$], with the time integral of $I(t)$ over $-\infty <$
165 $t < \infty$ having been normalized to 1, and Γ and v are the dimensionless Gruneisen
166 coefficient and the sound velocity [m/s] of the medium, respectively.³¹ In this simulation, we
167 used the k-WAVE Matlab toolbox³², which solves the coupled first-order differential equations
168 for the acoustic particle velocity and density, rather than the above equivalent second-order
169 equation. The acoustic properties of the water and acryl used as the simulation input was
170 summarized in Table 1. Geant4 Monte Carlo code (ver.9.3)³³ was used to obtain $E(\vec{r})$, where
171 the input beam parameters, including the mean energy of the incident protons, energy spread,
172 and beam size were tuned to reproduce the measured Bragg curve and lateral beam profiles. For
173 simplicity, protons were assumed to have momenta parallel to the beam axis at the phantom wall.
174 The beam range, defined at the BP maximum, was $R_{\text{sim}} = 76.3$ mm, and the same number of

175 protons per pulse and the detector position as the experiment were used in the simulation. The
176 time-varying source was used in the k-WAVE simulation with the Gaussian pulse structure with
177 a sufficiently small width (250 ns (1σ)). A perfectly matched layer is applied to the boundary,
178 absorbing all outgoing acoustic waves and preventing reflection. The calculation was performed
179 in 3D with a grid of $0.3 \times 0.3 \times 0.3$ mm³. The time-step was set to 5 ns to ensure stability
180 (Courant–Friedrichs–Lewy number < 1). Due to the limited computational memory capacity, the
181 calculation volume was set as $50 \times 50 \times 100$ mm³.

182

183

184 **3. Results**

185 3.1 Range estimation from measured acoustic waveform

186 Figure 4 shows the observed acoustic waveform without additional acrylic plates in front of
187 the phantom, averaged over 50 measurements. The signal observed around time zero was the
188 electromagnetic noise emitted from the beam extraction kicker of the FFA. As explained below,
189 the hydrophone detected the four wavelets demonstrated in Figure 3.

190 Wavelet (a) shows the γ -wave from the BP. The arrival times of positive and negative peaks
191 were 13.9 and 15.3 μs , denoted as $\tau_p^{(a)}$ and $\tau_n^{(a)}$, respectively. Because the pulse width of the
192 FFA (FWHM of ~ 50 ns) is smaller than the size of BP divided by the sound speed (FWHM of
193 5.7 μs) by three orders of magnitude, the wavelet size (peak-to-peak distance of 1.4 μs), is
194 determined by the shape of the Bragg curve. The positive peak is higher than the negative peak,
195 reflecting a higher dose gradient of the distal portion of the BP compared to the proximal
196 portion.

197 Wavelet (c) and (d) are the γ -waves reflected at the water-acrylic wall and acrylic wall-air
198 boundary, respectively. Taking into account the order of acoustic impedance (acryl > water >
199 air) (Table 1), phase shift is 0° and 180° on reflection, respectively. As shown in the Appendix A,
200 in theory, the reflected waves and direct wave are related by $p_{\text{reflected}}(t) \propto -\lambda p_{\text{direct}}(-t +$
201 $\Delta t)$ where λ and Δt indicate the phase shift and the distance from the detector to its mirrored
202 image reflected at the interface. The λ and Δt are +1 and $\frac{2(L_1+L_2)}{c_w}$ for wavelet (c) and -1 and
203 $\frac{2(L_1+L_2)}{c_w} + \frac{2L_{\text{wall}}}{c_a}$ for wavelet (d), respectively. The negative peak, in the case of wavelet (c),
204 arrived at 104.5 μs (denoted by $\tau_n^{(c)}$), and was superior to the positive one for the same reason
205 specified above. Similarly, in the case of wavelet (d), the positive peak is higher than the
206 negative peak and it arrives at 111.6 μs , symbolized by $\tau_p^{(d)}$.

207 Finally, wavelet (b) is the resonance wave generated in the acrylic wall. Because both water
208 and air have a lower acoustic impedance than acryl, nodes occur at both ends. We did not use

209 this wavelet for relative TOF, because the acoustic source of the resonance wave has a finite size
210 and we did not have a clear idea which point in the wall can be regarded as the wave origin.
211 Meanwhile, the resonance frequency was used to derive the sound speed of acryl in the
212 experiment.

213 Figure 5A shows the frequency spectrum of the waveform in Figure 4. The sampled data over
214 a time interval between 0 μs and 120 μs were Fourier transformed. The peaks at 0.12, 0.43, and
215 0.72 MHz originated from the resonance wave (b). The periodic dips on the spectrum are
216 because of the repeated arrival of the γ -waves ((a), (c), and (d)).³⁴ To extract the spectrum of
217 wavelet (a) (the time interval of $5 \mu\text{s} \leq t < 50 \mu\text{s}$) and wavelets (c) and (d) ($100 \mu\text{s} \leq t < 120 \mu\text{s}$),
218 data out of these intervals were set to zero and zero-padding was applied until $t < 1,311 \mu\text{s}$
219 before Fourier transformation (Figure 5B). The figure suggests that both frequencies of the
220 direct and reflected γ -waves were concentrated below 0.6 MHz, with the maximum reached at
221 ~ 60 kHz or ~ 340 kHz, respectively.

222 The upper row of Table 2 summarizes the relative TOF between (a) and (c) and between (a)
223 and (d) and the estimated beam ranges. Negative peak maxima were selected for (a) and (c),
224 whereas positive peak maximum was selected for (d), since, if the BP shape was symmetric
225 along the beam line, such as Gaussian assumed in ref.³⁰, it should give the correct beam range.
226 In addition, the smaller peaks of the reflected wavelets (positive peak in (c) and negative peak
227 (d)) are challenging to address. Comparing these values with the range estimated by the BPC,
228 the estimation error of two metrics $\tau_n^{(c)} - \tau_n^{(a)}$ and $\tau_p^{(d)} - \tau_n^{(a)}$ were both 0.6 mm. As a comparison,
229 TOF and beam range calculated from the positive peak maximum of wavelet (a) were shown
230 together, showing that the range error amounts to 1.8 mm with this metric.

231 Table 3 shows the water equivalent thickness (WEL) of the acrylic plates (actual thickness \times
232 1.16) and the shift of the BP positions estimated from the change in the two metrics $\tau_n^{(c)} - \tau_n^{(a)}$
233 and $\tau_p^{(d)} - \tau_n^{(a)}$ from those without additional acrylic plates, respectively. The data show that the

234 metrics can predict the BP position shift with a <0.2 mm accuracy.

235

236 3.2 Acoustic simulation

237 Finally, the red curves in Figure 4 represent the simulated acoustic waveform. The four
238 wavelets observed in the experiment were observed in the simulation and the maximum
239 pressure of about 7.5 Pa was reached. The lower row of Table 2 summarizes the TOF and range
240 values calculated from the three metrics. Comparing these values with the range of the 100 MeV
241 protons used as the input of the simulation ($R_{sim} = 76.3$ mm), the estimation errors of all metrics
242 were within 1 mm.

243 The red curves in Figure 5 show the frequency spectrum of the wavelet (a) and wavelets (c)
244 and (d) together. The spectrum shows that both the frequencies of the direct and reflected
245 γ -waves were concentrated below 0.5 MHz, with the maximum reached at ~ 80 kHz or ~ 50 kHz,
246 respectively.

247

248 4. Discussion

249 FFA is emerging as one of the accelerator candidates for upcoming proton therapy. This can
250 achieve high beam intensities and stop acceleration when the required energy has been reached,
251 permitting extraction at arbitrary energies. We have established that, with its short pulse
252 duration, the ionoacoustic pressure amplitude reaches approximately 7.5 Pa at 2 cm distal to the
253 BP, per 0.35 Gy dose at BP. In the meantime, the preceding research that exploited the proton
254 energies greater than or equal to 50 MeV stated their pulse width as 2–17 μ s, with the highest
255 amplitude achieved per 2 Gy dose being 11 Pa, at 6.5 mm distal to the BP (Table 4).^{19,22,23,35} This
256 indicates that, at the same distance from the BP, the short pulse of FFA (20 ns) has the potential
257 to yield a pressure of about 2–100 times that with the μ s pulse, which gives an advantage to the
258 FFA compared with other clinical machines (See the second right column in Table 4). Note that
259 the large pressure generated by the cyclotron in ref¹⁹ is partly due to the large Gy/pulse. If the

260 BP dose is normalized to 1 Gy, the pressure yielded by the FFA may be comparable to the
261 synchrocyclotron, as shown in the rightmost column in Table 4.²³

262 With the hydrophone used in this experiment, we could not validate the absolute pressure
263 amplitude of the k-WAVE simulation since it does not have the pressure–voltage conversion
264 constant. The k-WAVE simulation will have to be validated by a detector cross-calibrated with a
265 reference transfer standard hydrophone in the future measurement. In a meantime, in a different
266 experimental setting,³⁶ we showed that the k-WAVE simulation and the measured waveforms
267 generated from FFA are similar but an absolute difference in the pressure amplitude was
268 observed. The reduction of the difference between these waveforms may be possible by
269 including detailed information about the structure and composition material of the hydrophone
270 in the simulation, and thus further improvements in the accuracy of the simulation will be
271 required.

272 In the current work, we applied the absolute and relative TOF metrics for range assessment,
273 among which the former exploits the direct wave, and the signal amplitude is relatively larger
274 than the reflection wave. Table 5 comprehends the maximum detected range variation amid 100
275 measurements and was given by several averages (each measurement consists of 1, 5, 10, and
276 50 events).²³ Regarding absolute TOF, the range variation was suppressed to 1 mm, even with a
277 five-fold averaging. Nevertheless, it is subject to a detector-positioning error, as well as
278 systematic errors prompted by the frequency-dependent delay of the hydrophone, which resulted
279 in the range estimation error of 1.8 mm. Relative TOF is not impacted by these errors, and
280 submillimeter range accuracy was achieved with this metric. However, since it uses the
281 reflection wave, 50-fold averaging was required (Table 5). As Patch et al has denoted in their
282 recent research, acoustic hardware fine-adjusted to the thermoacoustic emissions (around 100
283 kHz in case of the γ waves of this study) may be indispensable to achieve the range detection
284 without averaging, and it is a subject we will address in further investigation.²⁴

285 As in a preliminary study, we used a single element hydrophone, while Patch et al. explored a

286 clinical transducer array to acquire a standard ultrasound image of the underlying anatomy, just
287 before proton beam delivery. Their approach solves the above-stated issue of hydrophone
288 positioning-derived error, by co-registering the BP and the underlying anatomy images. In
289 addition, array transducers may be used to estimate the *in vivo* sound speed for the liver³⁷ and
290 breast,³⁸ increasing the accuracy of *in vivo* range verification. Methods that utilize multiple
291 hydrophones simultaneously to reconstruct the dose distribution were also explored in
292 simulation study, using 3D filtered backprojection,³⁹ time-reversal algorithms,⁴⁰ and dictionary
293 method.⁴¹ Such lines of approach may be more suitable for heterogeneous tissues in clinical
294 settings.

295 The simulation results with an ideal point detector shown in Table 2 indicate that the
296 submillimeter range estimation error persists with the relative TOF metrics. The deviation of the
297 range determined by $\tau_n^{(c)} - \tau_n^{(a)}$ or $\tau_p^{(d)} - \tau_n^{(a)}$ from the range used as the simulation input was 0.8
298 mm, reflecting the asymmetry of the Bragg curve along the beam path and is inherent to the
299 beam shape. If the dissimilarity in the dose gradient of proximal and distal portions of the BP is
300 minimized, which could be achieved by using the ripple filter to broaden the distal fall-off,⁴² the
301 accuracy of range estimation could be improved. On the other hand, the range error of 0.3 mm
302 with the absolute TOF method could be due to definition of time zero and the acoustic wave
303 arrival time. Even though this study made use of the compression peak of the γ -wave to
304 characterize the arrival time of the direct γ -wave, as was done beforehand,^{21,22,23} it does not
305 necessarily lead to the correct TOF, as underlined by Jones et al.²² and the analytical method.⁴³
306 Consequently, fine adjustment might be crucial to eliminate this systematic error.

307

308 **5. Conclusion**

309 The short-pulsed proton beams from FFA could generate large ionoacoustic waves at
310 clinically relevant beam energy. Only five-fold averaging was required to suppress the range
311 deviation to less than 1 mm for absolute TOF, yet the precision was restricted by systematic

312 error arising from the detector positioning and signal delay. In contrast, the range determined
313 using the relative TOF metrics was in agreement with the value calculated from the depth-dose
314 measurement to better than 1 mm, but 50-fold averaging was essential, with the detection
315 system employed in our work. This drawback may be untangled by resorting to fine-tuned
316 detectors and amplifiers, which will be investigated in the future.

317

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322

323 **Competing Interests**

324 We disclose conflict of interest as following; Authors Taisuke Takayanagi is paid from Hitachi, Ltd.,
325 Tokyo, Japan. Other authors have no conflict of interest.

326

327 **Appendix A.**

328 As described in the main text, the reflected γ -wave (wavelets (c) and (d) in Figures 4) is
329 approximately obtained by applying time-reversal and sign inversion operations to the direct
330 γ -wave (wavelet (a) in Figures 4) up to a scale factor. In this appendix, this relation is derived
331 using a simplified model in which the BP is assumed as a one-dimensional finite length heat
332 source lying on the z -axis (spreading over a range of $R_2 < z < R_1$, where $0 < R_2 < R_1$, as
333 shown in Figure 6(a)).

334 As denoted in Sec. 2.5, the acoustic source term was expressed as $(\Gamma/v^2)E(\vec{r})I'(t)$. If the
335 Gaussian pulse structure of the proton beam is assumed, $I'(t)$ is anti-symmetric under the
336 time-reversal operation: $I'(t) = -I'(-t)$. In the following, the energy distribution of BP $E(\vec{r})$
337 is approximated as $E(z)\delta(x)\delta(y)$, where $\delta(x)$ is the Dirac delta function and $E(z)$ has finite

338 support over $R_2 < z < R_1$. First, if we consider an infinite homogeneous water medium and
 339 solve the wave equation using the Green's function approach,²⁴ the pressure wave is expressed
 340 as

$$341 \quad p(t, z) = \int_{-\infty}^t dt' \int_{R_2}^{R_1} dz' G(z, t; z', t') E(z') (\Gamma/v^2) I'(t') \quad (1)$$

342 where $G(z, t; z', t')$ is the Green's function satisfying the wave equation in three-dimensional
 343 free space

$$344 \quad G(z, t; z', t') = \frac{\delta(t - t' - \frac{|z-z'|}{c_w})}{4\pi|z - z'|}$$

345 and c_w is the sound speed in water. In the following, the detectors are assumed to be positioned
 346 at z_1 and z_2 , satisfying $z_1 \gg \bar{R} + \Delta R$ and $z_2 \ll \bar{R} - \Delta R$, respectively, where $\bar{R} \equiv$
 347 $(R_1 + R_2)/2$ and $\Delta R \equiv R_1 - R_2$. Here, the denominator of the Green's function in the
 348 integrand could be approximated as $z_1 - \bar{R}$ and $|z_2 - \bar{R}|$, respectively, and Eq (1) reduces to

$$349 \quad p_+(t, z_1) \sim \frac{1}{4\pi(z_1 - \bar{R})} \int_{R_2}^{R_1} dz' E(z') (\Gamma/v^2) I\left(t - \frac{z_1 - z'}{c_w}\right)$$

350 and

$$351 \quad p_-(t, z_2) \sim \frac{1}{4\pi|z_2 - \bar{R}|} \int_{R_2}^{R_1} dz' E(z') (\Gamma/v^2) I\left(t - \frac{z' - z_2}{c_w}\right),$$

352 at z_1 and z_2 , respectively. The subscript \pm indicates the wave propagating toward the positive
 353 and negative z direction, respectively. By using $I'(t) = -I'(-t)$, we obtain the relation
 354 between $p_+(t, z_1)$ and $p_-(t, z_2)$ as

$$355 \quad p_-(t, z_2) = -\xi \eta p_+(-t + \Delta t, z_1) \quad (2)$$

356 where ξ expresses the products of transmission (T) and reflection (R) coefficients at the
 357 interface of the heterogeneous media and is 1 in this case. $\eta = \frac{z_1 - \bar{R}}{|z_2 - \bar{R}|}$ is the geometrical factor

358 and $\Delta t = \frac{z_1 - z_2}{c_w}$ is the acoustic wave propagation time between two detectors, indicating that

359 with some simplifications, waves propagating in the positive and negative directions are related

360 to the time-reversal and sign conversion up to a scale factor.

361 Next, we consider the geometry where the layers of air, acrylic wall, and water are stacked next
362 to each other (Figure 6(b)). Here, Eq. (2) holds as follows. Because no phase change occurs at
363 the acrylic wall-water boundary for wavelet (c), ξ is positive in Eq. (2), and ξ and Δt
364 are $\xi = R_{\text{acryl-water}}$ and $\Delta t = \frac{2(L_1+L_2)}{c_w}$, respectively. However, for wavelet (d), the phase is
365 shifted by 180° on reflection; hence, ξ becomes negative. In this case, ξ and Δt are $\xi =$
366 $-(T_{\text{acryl-water}})^2 R_{\text{acryl-air}}$ and $\Delta t = \frac{2(L_1+L_2)}{c_w} + \frac{2L_{\text{wall}}}{c_a}$, respectively.

367

368 **Data availability**

369 Data that support the findings of this study are available from the corresponding author upon
370 reasonable request.

371

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472

473

474 **Figure captions**

475

476 **Figure 1.** (A) Experimental setup. Proton beam accelerated by the FFA is incident on the water
477 phantom, crossing the acrylic wall. A scintillator is set at the exit of the beam duct and it
478 indirectly measures the beam pulse shape. A hydrophone is positioned 20 mm downstream of
479 the beam range, facing this beam. (B) The signal measured by the scintillator and the Gaussian
480 fitting curve.

481

482 **Figure 2.** (a) Bragg curve and (b, c) lateral beam profiles obtained by the Bragg peak ionization
483 chamber and radiographic films, respectively. In (a), the solid curve shows the results obtained
484 using Monte Carlo simulations.

485

486 **Figure 3.** Schematic representation of the wave propagation implied in TOF metrics to estimate
487 the beam range. (a) Direct γ -wave from the BP, (c) the γ -wave reflected at the acrylic wall-water
488 boundary, and (d) the γ -wave reflected at the boundary between the acrylic wall and the air.
489 Because of the higher acoustic impedance of acryl compared to water and air, the resonance is
490 formed in the acrylic wall. The resonance frequency of the wavelet (b), emitted from the wall,
491 allowed to derive the sound speed in the acryl.

492

493 **Figure 4.** The time domain waveforms observed in the experiment (upper left) and the
494 simulation (upper right), with the enlarged figures around wavelet (a) (lower left) and wavelets
495 (c) and (d) (lower right). The red curves represent the simulation. In the lower figures, the
496 simulation plot is shifted to match measured results for easing comparison. The thick arrows
497 show the peaks selected for TOF or relative TOF metrics. The thin arrows refer to the peaks that
498 were not used for TOF metrics.

499

500 **Figure 5.** Frequency spectrum of the waveforms shown in Figure 4, representing the experiment
501 (black) and simulation (red). Frequency spectra of wavelet (a) (solid curves) and wavelets (c)
502 and (d) (dashed curves) are shown in the right panel.

503

504 **Figure 6.** Schematic figure of the geometries considered in a simplified model in which the
505 Bragg peak is assumed as a one-dimensional finite length heat source lying on the z -axis.

506 (a) Homogeneous medium (b) Layer structure consisting of air, acrylic wall, and water

507

508 **Tables**

509

510 **Table 1.** Acoustic properties of water, acryl, and air.

	$\rho(\text{kg/m}^3)$	$\beta(\text{K}^{-1})$	$v(\text{m/s})$	$C_p(\text{J/K/kg})$	Γ	$Z(\text{Ns/m}^3)$
Water (22°C)	1000	2.06×10^{-4}	1488	4180	0.11	1.56×10^6
Acryl	1180	2.10×10^{-4}	2930	1400	1.29	3.46×10^6
Air	1.293	3.66×10^{-3}	340	1006	0.42	4.40×10^2

511 ρ : mass density, β : coefficient of volumetric thermal expansion, v : speed of sound, C_p : heat

512 capacity at constant pressure, Γ : Gruneisen coefficient, and Z : acoustic impedance.

513

514

515 **Table 2.** Relative and absolute TOF of the wavelets (c) and (d) and of the wavelet (a),
 516 respectively, and the beam range estimated with these distinct metrics, both from the experiment
 517 (upper row) and simulation (lower row). The values are the mean and SE of 100 independent
 518 measurements (each consisting of 50 events).

		$\tau_n^{(c)} - \tau_n^{(a)}$	$\tau_p^{(d)} - \tau_n^{(a)}$	$\tau_p^{(a)}$
Experiment	Time (μ s)	89.47 ± 0.02	96.27 ± 0.01	13.98 ± 0.01
$R_{BPC} = 77.6$ mm	Range (mm)	78.16 ± 0.01	78.15 ± 0.01	75.80 ± 0.01
Simulation	Time (μ s)	85.98	92.74	13.42
$R_{sim} = 76.3$ mm	Range (mm)	75.57	75.52	76.63

519

520

521

522 **Table 3.** The water equivalent thickness of the additional acrylic plates (actual thickness \times
523 1.16) and the shift in the BP positions (mean \pm SE), estimated from the variation in the two
524 metrics $\tau_n^{(c)} - \tau_n^{(a)}$ and $\tau_p^{(d)} - \tau_n^{(a)}$ from those obtained without the acrylic plates.

Thickness of additional acrylic plates (mmWEL)	$\Delta(\tau_n^{(c)} - \tau_n^{(a)})$ (mmWEL)	$\Delta(\tau_p^{(d)} - \tau_n^{(a)})$ (mmWEL)
4.6	4.8 ± 0.03	4.6 ± 0.03
9.3	9.2 ± 0.03	9.5 ± 0.03
13.9	14.1 ± 0.04	14.1 ± 0.03
18.6	18.6 ± 0.04	18.5 ± 0.02
23.2	23.3 ± 0.04	23.3 ± 0.03

525

526

527

528 **Table 4.** List of the absolute pressure values in ionoacoustics that can be retrieved from
529 previous research.

	Energy [MeV]	Pulse duration (FWHM) [μ s]	Gy/pulse	Pressure, detector position (distance from the BP)	Expected pressure at 5 cm from the BP	Expected pressure per 1 Gy at 5 cm from the BP
cyclotron ²²	190	15-19	0.034	5.2 mPa ^{*a} , 5 cm	29 mPa	0.85 Pa
synchrocyclotron ²³	145–227	2.5-3.7	0.01	58 mPa ^{*b} , 5–10 cm	58–116 mPa ^{*c}	5.8–11.6 Pa ^{*c}
cyclotron ¹⁹	50	1.76	2	11 Pa, 6.5 mm	1.4 Pa ^{*c}	0.72 Pa ^{*c}
FFA	100	0.047	0.35	7.5 Pa, 2 cm	3 Pa ^{*c}	8.6 Pa ^{*c}

530 ^{*a} This value is per 6.1 mGy according to the ref.²¹ ^{*b} The maximum pressure amplitude of about 23

531 mV (Fig. 1 in ref.²³) was converted to the pressure using the detector sensitivity (-168 (dB, re 1 V

532 μ Pa⁻¹) and the amplifiers (40 dB). ^{*c}These values were roughly estimated assuming that the

533 pressure size is inversely proportional to the distance from the BP.²²

534

535

536

537 **Table 5.** The maximum variation of the detected range (in mm) among 100 measurements,

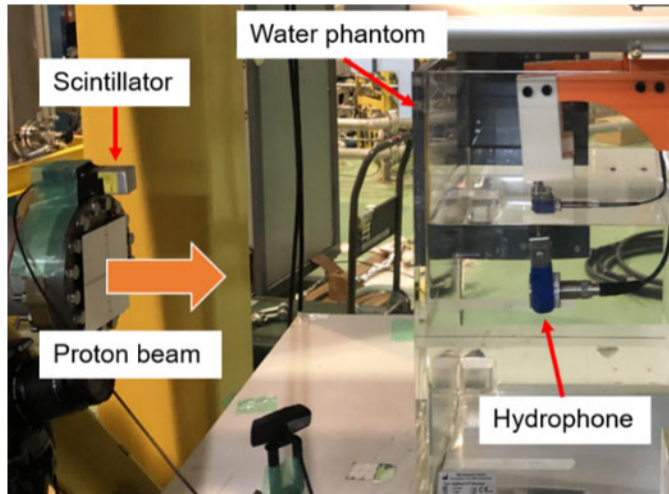
538 with numerous measurement averages.

Number of averages	Total dose [Gy]	Time used for range detection		
		$\tau_n^{(c)} - \tau_n^{(a)}$	$\tau_p^{(d)} - \tau_n^{(a)}$	$\tau_p^{(a)}$
1	0.35	10.8	13.3	2.1
5	1.75	4.8	1.1	0.7
10	3.5	3.1	0.7	0.6
50	17.5	0.7	0.5	0.4

539

540

(A)



(B)

