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# Hybrid High-precision In-vivo Imaging in Particle Therapy (H2I2)

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***ABSTRACT***

H2I2 designed and evaluated the expected performance of a highly innovative hybrid high-precision in-vivo verification system, integrated with a new gantry concept that dramatically reduces the footprint and complexity of particle therapy treatment rooms. The expected performance of the PET-based range monitor in a clinical situation is better than the state-of-the-art, while the prompt gamma signal yields a precision on the single spot delivery of the order of a few mm. The feasibility of the proposed design is discussed through an assessment of the technological improvements required to start the construction and commissioning of a system prototype.

*Keywords: Particle therapy; Toroidal gantry; beam monitor; treatment verification; PET; PGT.*

## 1. Introduction

The cost, complexity, and large footprint of Particle Therapy (PT) installations have somehow limited its diffusion; moreover, the lack of well-established real-time verification tools to precisely validate the compliance between the planned and delivered treatment further limits the full exploitation of its clinical potential.
The Hybrid High-precision In-vivo Imaging in Particle Therapy (H2I2) project is based on the use of a clever combination of innovative concepts and novel technologies, well beyond the state-of-the-art, to design, for the first time, a fully integrated delivery and monitoring system.
The proposed layout, by combining a static toroidal gantry (*GaToroid*) [1,2], compact and fast beam monitors, and a hybrid high-precision in-vivo treatment verification system, would dramatically reduce the complexity of treatment rooms, while increasing the treatment quality. H2I2 would allow: highly flexible and fast beam delivery, with a static gantry much lighter and smaller than the existing ones; beam monitoring with high space and time resolution, providing single particle counting for high-precision treatments; online range verification by means of a 3D measurement of the beam-induced activity distribution and of the prompt gamma emission profile.
The gantry magnetic design was optimized to maximize the energy acceptance in the complete range of treatment energies. A single coil scaled-down demonstrator in High Temperature Superconductors (HTS) is presently under construction [3]. The beam monitoring, based on fast silicon detectors, will provide high resolution spatial and timing information for single particles. The in-vivo range verification will be based on a in-beam PET system, innovatively used to detect also prompt photons, whose time correlation with the beam monitor signals will allow the implementation of the Prompt Gamma Timing (PGT) technique. The performance of the range verification system was evaluated by simulating an open ring detector configuration completely integrated inside the gantry [4]. The PET 3D reconstruction of the activity induced by a proton treatment plan yields a precision in the range measurement below 2 mm. The PGT, thanks to a completely original data analysis, provides a spot-by-spot prompt range evaluation, with a few mm precision.

## 2. STATE OF THE ART

Operating PT facilities implement beam delivery through either a fixed beam line or a mobile gantry, whose mechanical structure is remarkably large and bulky, especially for heavy ions: existing carbon ion gantries can exceed 14 m in diameter and 600 tons in weight. Several new concepts of superconducting rotating gantries have been proposed recently to reduce the size, but the rotation of cryogenic parts and the ramping of the magnetic field create challenging operating conditions for superconducting systems, particularly sensitive to transients.

The beam monitoring functionality is presently based on gas detectors, whose slow collection time and poor sensitivity prevent their use in fast delivery modalities, required, for example, to improve the treatment of moving targets. Segmented Low-Gain Avalanche Detectors (LGAD) [5], could concurrently provide position and time information for each beam particle with extremely high resolution for fast and precise measurements of beam fluence, position and profile [6] and to determine the start time for PGT applications. As of now, few results were obtained in clinics. A collimated system based on prompt gamma detection was used to monitor proton irradiations on head-and-neck [7,8] tumors. Real time dual-head PET monitoring provides a range agreement between consecutively clinical delivery sessions within 1 mm [9, 10], but its potential is not fully exploited yet. The development of a fully integrated hybrid system would reduce the safety margins typically implemented in the treatment plans, presently up to 3.5% + 3 mm.

## 3. BREAKTHROUGH CHARACTER OF THE PROJECT

H2I2 challenges the limitations that prevent a full exploitation of PT, thanks to its highly innovative and disruptive design integrating, for the first time, beam delivery and imaging devices in one structure. Strongly improved performances and highly reduced footprint, cost, and operation complexity could foster the deployment of PT, in particular with ions heavier than protons, well beyond present expectations (Tab. 1).

The beam delivery is completely redesigned, by means of a recently patented [1] lightweight, static toroidal gantry (Fig. 1) that will allow a high precision treatment delivery, exploiting very fast gantry direction switching and delivery time. Still, the delivery will retain the flexibility of firing the beam from many directions, with no rotation of major mechanical components and no variations of the magnetic field. These features properly suit the use of superconductive technology, remarkably increasing the intensity of the generated magnetic field, as well as simplifying cryogenics stability.

Solid state detectors are the natural choice for a beam monitoring device due to their enhanced timing and spatial resolution with respect to traditional gas detectors and their insensitivity to the residual magnetic field in the vicinity of the *GaToroid* magnetic coils.

**Tab. 1:** Comparison of the H2I2 target parameters to the state of the art.

| | State of the art | | | H2I2 |
|---|---|---|---|---|
| **Beam delivery** | **Fixed Line** | | **Rotating Gantry** | **Toroidal Gantry** |
| Gantry Radius (m) | - | | 5-7 | 1.5-3 |
| Gantry weight (t) | - | | 300-700 | 10-20 |
| Beam directions | 1 | | many | 16-20 |
| **Beam monitoring** | **Ionization chamber** | | **Ionization chamber** | **Fast Silicon Detectors** |
| Max. Rate (Hz) | $>>10^{10}$ | | $>>10^{10}$ | $10^{10}$ |
| Sensitivity (min. Nr. of particles | $10^4$ | | $10^4$ | 1 |
| Charge collection time (ns) | $10^5$ | | $10^5$ | 1 |
| Single particle counting | No | | No | Yes |
| **Online range verification** | **Custom prototypes** | | **No** | **Yes** |
| Modality | PET | Prompt gamma | - | PET & Prompt gamma |
| Precision (mm after 1 minute) | 3-4 | 3-4 | - | 1 |
| Reconstruction | 2D | 1D | - | 3D |

An innovative hybrid verification system, based on the detection of both positron emitters and prompt gamma signals, will provide the online assessment of the delivered dose: indeed, the symmetric configuration seamlessly allows a ring-like layout similar to clinical scanners, enhancing the statistics and minimizing the effect of geometry-related artefacts. The measurement of the 3D image of the beam-induced activity distribution with a millimetric precision, in online mode, will validate the treatment delivery compliance within about one minute of the treatment start. Time-of-flight information provided by the beam and range monitors will enable the prompt-gamma-timing analysis technique to validate the particle range spot by spot and complement the 3D activity map.

The proposed project, if successful, would pave the way for a radical redesign of PT treatment rooms. The integrated system would represent a breakthrough from the point of view of both performance and cost-effectiveness and achieve a treatment control level at the millimetre scale, good enough to implement ambitious, adaptive treatment plans and fully exploit the intrinsic advantages of PT. These characteristics would be extremely attractive for clinicians, as well as for vendors of particle therapy facilities. The paradigm shift in plan delivery and monitoring would likely rekindle the industry's interest in PT with ions heavier than protons.

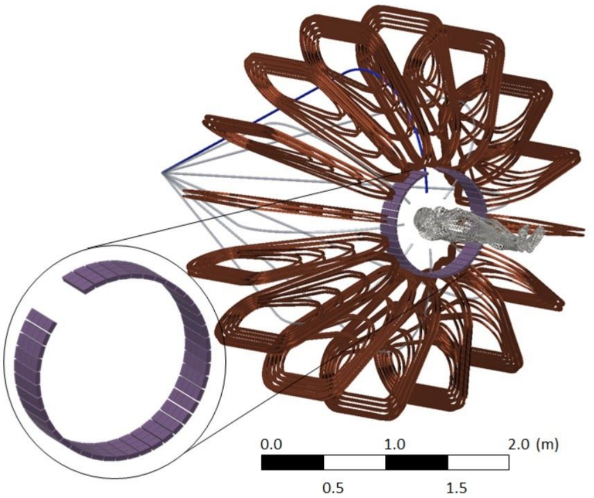


**Fig. 1**. Representation of the *GaToroid* coil configuration for the beam delivery together with the open PET ring used for the range monitoring simulations. The beam lines start diverging after the vector magnet, that directs them towards the *GaToroid* with the appropriate angles.

## 4. PROJECT RESULTS

For the proof of concept, we focused on a *GaToroid* design for proton beams constituted by 16 coils, with an inner free bore diameter of 0.8 m, an outer diameter of 3.3 m (Fig. 1), and a total mass of about 12 tons, including the main mechanical supports. The magnet was designed to allow the use of both Low (LTS) and High (HTS) Temperature Superconductors, limiting the peak field to about 8 T. The selected configuration is the most suitable to address the magnetic design challenges. The first scale-down demonstrator of a *GaToroid* single coil based on HTS technology is currently under construction. Using intermediate prototyping steps and optimizing winding, insulation and impregnation procedures, our goal is to wind and test the final HTS prototype by the end of 2020.

The selected configuration allows the incorporation of solid state beam monitoring devices and PET detectors. A beam monitoring device prototype based on 50 μm LGAD silicon sensors segmented in strips and a dedicated readout ASIC is being finalized within the INFN MoVeIT project. Preliminary results show that the number of particles of a therapeutic beam can be measured with a maximum error of 1% up to a flux of several $10^8$ p/(cm$^2$s), limited by pile-up effects at higher fluxes, and that a fast online measurement of the beam energy for each spot can be obtained with the required clinical accuracy with time-of-flight techniques exploiting the high time resolution of the LGAD technology [11]. However, a measurement of the number of beam particles up to therapeutic fluxes of $10^{10}$ p/(cm$^2$s) or more requires silicon sensors segmented in pixels and the development of a dedicated custom readout electronics.

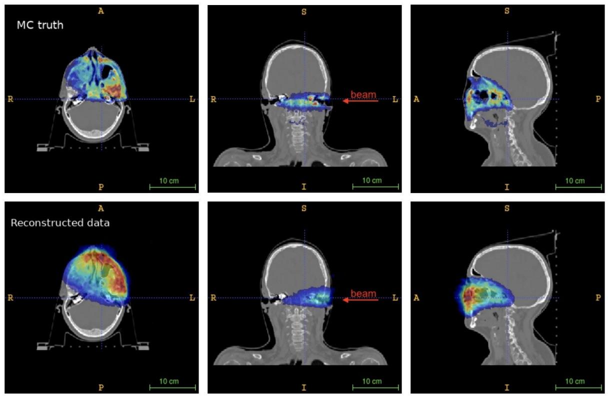


**Fig. 2**. Axial (left), coronal (center) and sagittal (right) sections of the patient CT with the superposition of the MC truth (top row) and reconstructed simulated activity distributions (bottom row) of an ACC treated with protons.

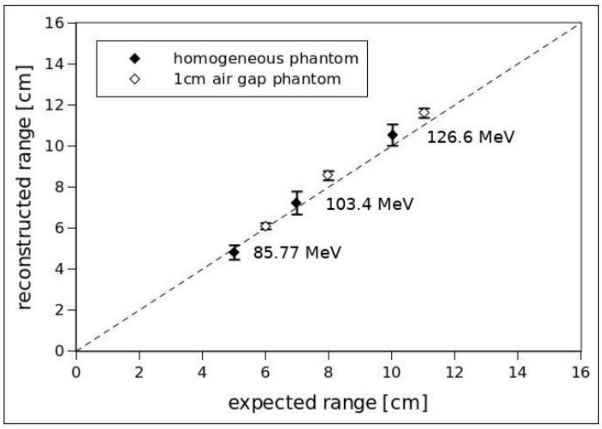


**Fig. 3.** Average reconstructed range versus expected proton range. Experimental values refer to a set of PGT MC simulations, the error bars represent their maximum variability.

For the hybrid in-vivo verification device, several geometrical configurations have been studied assessing their foreseen performance with a FLUKA-based Monte Carlo (MC) tool [12] previously validated both in controlled conditions (phantom tests) and in a clinical environment [10]. A single-ring design, to be installed on a rotating structure inside the gantry, comprising a gap for the integration of the beam monitor, was found to be the most likely choice for a prototype. Lutetium-based state-of-the-art scintillating modules are considered as PET detectors elements (16x16 pixels of 3.1x3.1x20 mm$^3$ size, with 3.2 mm pitch), coupled one-to-one to Silicon PhotoMultiplier tiles. A total of 164 (41 x 4 arrays) PET detector modules are considered for the single-ring design. The size of the opening for the beam passage is 16 cm, compatible with the *GaToroid* beam window dimension. MC simulations of activity distributions inside PMMA phantoms were performed to assess the range detection capability of the selected geometry. Moreover, a real clinical case of an Adenoid Cystic Carcinoma (ACC) treated with protons ($1.8 \times 10^9$ protons in the [62, 141] MeV energy range) was simulated and the reconstructed distribution compared to its MC truth (Fig. 2). The activity images (140x70x165 pixels, 1.6 mm pixel size) were reconstructed using a previously validated [13] MLEM algorithm computed with a single-ray-tracing system matrix. A good agreement is found between the reconstructed activity distribution and the MC truth, without image artefacts typical of dual-head geometry. The activity profiles of the reconstructed and MC distributions were evaluated, considering an area of 7x7 voxels at the image center, along the beam direction, showing an agreement between the expected and measured range within 1 (2) mm in the phantom and clinical case, respectively [4].

PET detectors can be also configured to detect single events, such as prompt photons (1-10 MeV energy range), emitted because of the beam-induced excitation of nuclei. A simulation of three monoenergetic spots at 85.77, 103.4, and 126.6 MeV, delivered at the isocenter in a 10x10x20 $cm^3$ PMMA phantom either homogeneous or containing a 1 cm air gap, was performed. Each simulation was run 10 times, considering $10^7$ primaries. The time and depth of the prompt gamma distribution,correlated to the primary particle range inside the target, was simultaneously reconstructed using a novel 4D extension of the MLEM algorithm [14]. As shown in fig. 3, an agreement of about 0.5 cm is found between the range reconstructed from prompt photons emission and the one of the primary protons.

## 5. FUTURE PROJECT VISION

The activity carried on in the framework of H2I2 provides a thorough study supporting the proposed innovative technology concepts. The system feasibility and performance were assessed by considering different layouts. Many simulation-based decision tools were developed, which will be very helpful in the next steps to improve the Technology Readiness Level (TRL). The possibility of designing a proton radiography rotating insert, exploiting the high timing LGADs integrated in the system, is also being evaluated, as it would allow a fast and completely integrated imaging system that could be used for patient positioning, treatment planning and validation. The first scale-down demonstrator of a *GaToroid* single coil based on HTS technology is currently under construction. Meanwhile, experimental tests of a proof-of-concept hybrid detector for PET and PGT are foreseen in the next months within the framework of the INFN I3PET project [15].

Within 3 years, we aim at constructing a prototype of the hybrid imaging system, scaled down in size in order to meet the budget requirements, with a modular structure that will allow its expansion.

The *GaToroid* development will proceed in parallel, with other funding sources. The use of HTS, above liquid helium temperature is an intriguing, yet challenging proposal, and the possibility to use Rare-earth Barium Copper Oxide (ReBCO) conductors is being investigated. HTS would allow either operating in simpler cryogenics conditions, i.e. helium gas at 20 K, reducing cooling cost and power consumption, or, if used in liquid helium (i.e. 4.2 K), open the possibility for a magnetic field increase beyond 10 T, with a drastic reduction of the gantry footprint and weight, but an increased complexity in terms of mechanics and quench protection. During the construction of the demonstrator, we will tackle crucial challenges of HTS technology, such as insulation, impregnation and quench protection and we will gather fundamental insight for the realization of the full-scale *GaToroid* magnets.

### 5.1. Technology Scaling

In order to successfully reach the technology validation (TRL5) and demonstration (TRL6) in relevant environments and pave the way for a system prototype demonstration in operational environment (TRL7), during ATTRACT Phase 2 H2I2 will address challenges related to technological limits due to the frontier innovation on which the project is based. The use of the same block detectors in dual-modality data acquisition mode (PET, prompt gamma) requires the development of custom front-end electronics, while the on-the-fly data analysis will be based on dedicated reconstruction algorithms under study. The integration of the dose delivery and in-vivo verification devices into *GaToroid* will be part of a common effort for the design of the full system.

### 5.2. Project Synergies and Outreach

During ATTRACT phase 1, a collaboration with two clinical facilities (CNAO, MedAustron) has already started, in order to design a system that meets clinical requirements (e.g., allow non-coplanarity). Two companies have been identified as potential partners: their role will be crucial in addressing engineering issues and market strategies. Further R&D activities required for building and commissioning the prototype will require the involvement of larger groups from INFN (front-end electronics) and University of Torino (beam monitor). A collaboration with the nuclear imaging group from the University of Lubeck, involved in the ATTRACT MERMAID project, will address the development of custom reconstruction and analysis algorithms.

### 5.3. Technology application and demonstration cases

H2I2 is clearly focusing on Health-related Societal Challenges. Improved performance, better control and lower costs are crucial features to expand the access to PT and increase the likeliness of recovery for cancer patients who cannot undergo surgery and/or radiotherapy. If successful, our approach will be available to the whole PT community and partnerships with other European Research institutions to foster its further development and diffusion will be envisaged.

### 5.4. Technology commercialization

H2I2 will design a new, fully integrated system for PT, but both the beam monitoring system and the hybrid in-vivo verification device could be tailored to existing facilities. Thanks to its modular structure, the imaging part just requires a custom mechanical layout. The commercialization strategy will mostly be defined in agreement with the industrial partner(s).

### 5.5. Envisioned risks

The use of HTS conductors for large scale magnets yields a high potential return (mastering it is of utmost importance not only for PT, but also for the development of new fusion reactors and accelerator magnets) but also a high risk. Therefore, a more traditional LTS (Nb-Ti) version is also being considered. The development of a large area pixelated LGAD silicon detectors with beam monitoring capabilities and concurrently providing timing information for PGT applications is a technological challenge with some potential risks (radiation resistance, cost, cooling and material thickness). As a mitigation alternative, a more conventional design for a beam monitoring device, based on gas detectors (ionization chambers or micro channel plates) could be considered, with the inclusion of a smaller area LGAD device for inter-calibration purposes and to provide timing measurements of a fraction of the incoming particles. The development of custom electronics to process data in real time and correlate the signals from the dose delivery and the in-vivo verification systems is a potential risk as well.

### 5.6. Liaison with Student Teams and Socio-Economic Study

Collaborations with MSc. Level students have already taken place, and will continue: all the project partners are available as host institutions for MSc. and PhD students and the group coordinators will enable this activity in the future. The project members are also available for providing input to socio-economic studies.

## 6. Acknowledgement

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