Technical Note: GATE-RTion: a GATE/Geant4 release for clinical applications in scanned ion beam therapy

L. Grevillot, D.J. Boersma, H. Fuchs, A. Aitkenhead, A. Elia, M. Bolsa, C. Winterhalter, M. Vidal, S. Jan, U. Pietrzyk, et al.

Technical Note: GATE-RTion: a GATE/Geant4 release for clinical applications in Scanned Ion Beam Therapy.

Authors:

L Grevillot[1], D J Boersma[1,2], H Fuchs[1,3], A Aitkenhead[4], A Elia[1], M Bolsa[1], C Winterhalter[5], M Vidal[6], S Jan[7], U Pietrzyk[8], L Maigne[9], D Sarrut[10]

Institutes:

[1] MedAustron Ion Therapy Center, Marie Curie-Straße 5, A-2700 Wiener Neustadt
[2] ACMIT Gmbh, Viktor-Kaplan-Straße 2/1, A-2700 Wiener Neustadt, Austria
[3] Medical University of Vienna, Austria. Department of Radiation Therapy, Medical University of Vienna/AKH Vienna, Austria
[4] Division of Cancer Sciences, University of Manchester, Manchester Cancer Research Centre, The Christie NHS Foundation Trust, Manchester, UK
[5] Division of Cancer Sciences, University of Manchester, The Christie NHS Foundation Trust, Manchester, UK
[6] Centre Antoine LACASSAGNE, Université Côte d'Azur – Fédération Claude Lalanne, Nice (France)
[7] UMR BioMaps, CEA, CNRS, Inserm, Université Paris-Saclay, 4 place du Général Leclerc 91401 Orsay France
[8] University of Wuppertal, Germany
[9] Université Clermont Auvergne, CNRS/IN2P3, Laboratoire de Physique de Clermont, UMR6533, 4 avenue Blaise Pascal TSA 60026 CS 60026 63178 Aubière cedex, France
[10] Université de Lyon, CREATIS, CNRS UMR5220, Inserm U1044, INSA-Lyon, Université Lyon 1, France.

Abstract:

Purpose:
GATE-RTion is a validated version of GATE for clinical use in the field of Light Ion Beam Therapy. This paper describes the GATE-RTion project and illustrates its potential through clinical applications developed in three European centers delivering scanned proton and carbon ion treatments.

Methods:
GATE-RTion is a collaborative framework provided by the OpenGATE collaboration. It contains a validated GATE release based on a specific Geant4 version, a set of tools to integrate GATE into a clinical environment and a network for clinical users.

Results:
Three applications are presented: Proton radiography applications at the Centre Antoine Lacassagne (Nice, France); Independent dose calculation for proton therapy at the Christie NHS Foundation Trust (Manchester, UK); Independent dose calculation system for protons and carbon ions at the MedAustron Ion Therapy center (Wiener Neustadt, Austria).

Conclusions:
GATE-RTion builds the bridge between researchers and clinical users from the OpenGATE collaboration in the field of Light Ion Beam Therapy. The applications presented in three European facilities using three completely different machines (three different vendors, cyclotron and synchrotron-based systems, protons and carbon ions) demonstrate the relevance and versatility of this project.

1. Introduction

The OpenGATE collaboration has been created in 2002 with the initial purpose to provide a Geant4-based Monte Carlo (MC) research toolkit for PET and SPECT simulations[1]. In the very first paper[1], the extension of GATE for dosimetry application was discussed, together with the potential of GATE to simulate in-line tomography in hadrontherapy. A few years later, the GATE toolkit was indeed extended to CT and radiotherapy modeling[2,3]. The developments provided new features, such as the modeling of moving sources and motion, thus allowing for IMRT and arc therapy applications. A carbon ion therapy application combining radiation therapy modeling and emission tomography was presented as a proof of concept of the combined imaging and dosimetric, time-resolved, capabilities of the GATE platform[2,4]. In this paper, the terminology Light Ion Beam Therapy (LIBT) is used[5]. Light ions are defined as those nuclei with an atomic number lower or equal to 10, i.e. including all ions from protons to neons[6]. The terminology Scanned Ion Beam Delivery (SIBD, often called pencil beam scanning)[7] is used in contrast with passive beam delivery techniques[6]. More detailed PET-based dose delivery verification for LIBT were presented elsewhere[8,9]. The overall capabilities of GATE for radiation therapy and dosimetry applications were reviewed[10]. In parallel of the GATE developments, the Geant4 MC toolkit was extensively used for passive scattering proton delivery system and TPS evaluation[11,12] and the FLUKA MC code was proven to be a useful tool for in-vivo beam delivery and range verification[13,14]. These pioneer works demonstrated the usefulness of integrating general purpose MC codes into LIBT clinics to support medical physics activities[15]. Several other general purpose Monte Carlo codes are used in the field of medical physics and LIBT, such as MCNP[16], Shield-HIT[17] and PHITS[18]. Due to the complexity of Geant4, several Geant4 applications have been developed over the years to simplify the user interactions with Geant4, such as GATE[10], GAMOS[19], PTSim[20] and TOPAS[21]. To our best knowledge, GATE is historically the first Geant4-based application developed for medical physics purposes and it is currently the reference platform for imaging in nuclear medicine. In addition, following the clinical trend towards SIBD systems , the first modeling of a commercial IBA dedicated nozzle for scanned proton beams was also developed in GATE[22,23] and used as Independent Dose Calculation (IDC) system for validating the XiO TPS from Elekta (Stockholm, Sweden)[24]. These results demonstrated the potential of the GATE platform and generated logically a lot of interest from other LIBT Facilities and TPS vendors. In particular, GATE was used to model complex beam optics variations from the Skandion proton beam lines[25], to support the MedAustron facility start-up and beam line design for proton and carbon ion beams[26–28] and to evaluate the RayStation TPS proton pencil beam algorithm (RaySearch Americas Inc. (NY))[29]. In addition, extensive validation tests were performed at MedAustron for scanned proton beams [30–32] and carbon ion beams (not yet published). Off-line PET-based treatment monitoring was also considered[33]. With the increased interest of GATE for clinical purposes, a GATE satellite workshop was organized in March 2017 by David Sarrut, David Boersma and Loïc Grevillot at the Skandion proton therapy center during the Swedish DOTSKAN meeting. The purpose was to define actions to ease the implementation of GATE in clinical centers. The GATE-RTion project has been developed specifically for this reason. It is a project of the OpenGATE collaboration aiming at building the bridge between researchers and clinical users. The GATE-RTion project has been officially approved by the OpenGATE collaboration in May 2017 and presented at the first ESTRO physics for health workshop in November 2017 (Glasgow, UK). GATE is free, open-source and benefits of a collaborative development model. Indeed, users do not need C++ to run simulations as GATE can be fully configured and controlled via simple macros. However, experienced users can access the code and, therefore, participate in the development of GATE. In the following sections, the GATE-RTion concept is presented together with some validation tests. The result section focuses on clinical applications performed in three different European LIBT facilities.

2. Materials and Methods

a. The GATE-RTion concept

The GATE releases follow every new Geant4 release in order to stay compatible with the latest Geant4 versions and to provide additional features specific to GATE. In contrast, the implementation of a general-purpose MC code in clinical centers requires extensive validation before clinical use, which is not compatible with an annual release cycle. To support the implementation of GATE in clinical centers, three key milestones have been identified: 1) Providing a stable and "long-term" GATE release (See Discussion section 4 for more details), called GATE-RTion, having all necessary features for dosimetric applications in LIBT facilities equipped with SIBD systems. 2) Providing a collection of tools to the clinical users for integrating GATE into the clinics. 3) Developing a clinical user network and establish guidelines. GATE-RTionV1.0[*] based on GATE version 8.1 and Geant4.10.03p03 was released in May 2018. A collection of open source python tools is available in the *GateTools* repository released since December 2019 and contains in particular the functionalities related to beam modeling, DICOM (image, structure, plan, dose, 3D gamma index computation) management and cluster management. Meanwhile, several clinical centers started collaborating on the use of GATE-RTion, thus fostering the development of clinical applications and guidelines for the use of GATE-RTion in LIBT facilities.

b. GATE-RTion key features and validation tests

An overview of the GATE features are presented in references[2,10]. The GATE-RTion clinical users share validation tests under the GATE-RTion folder from the *GateContrib* repository. These validation tests focus on the key features of GATE-RTion necessary for dosimetric applications in LIBT facilities equipped with SIBD systems. Currently two validation tests are available. The first one focuses on the features of the source used for simulating SIBD systems (*TPS Pencil Beam Source*). The second one focuses on the features allowing scoring energy and dose distributions (*Dose Actor*[†]). From a medical physics view point, these validation tests can be considered as acceptance testing. When performing these tests, the user verifies that GATE-RTion delivers scanned beams according to the treatment plan, multiple gantry angles and particle types can be delivered according to the prescription, the nozzle geometry can be explicitly simulated or not, the user can change the beam model and source properties, the dose can be computed in voxelized geometries (such as CT) or non-voxelized phantoms. We rely on Geant4 for the validation of physics processes (Geant4 Medical Physics Benchmarking group[‡] and validation testing [§]). In addition, a list of GATE publications have been presented in Introduction to validate the accuracy of the Geant4 proton physics based on independent data sets and medical physics commissioning data[30–

[*] http://www.opengatecollaboration.org/GateRTion

[†] In GATE terminology, an „Actor" is a kind of scorer that will output simulation results.

[‡] https://twiki.cern.ch/twiki/bin/view/Geant4/G4MSBG

[§] https://geant4.web.cern.ch/publications_validations/testing_and_validation

[32]. Similar work will be performed with carbon ions (and other light ions) in the future. Once accepted at the user facility, the level of accuracy of GATE-RTion must be evaluated as part of the medical commissioning process for each user, as it will depend on user specific input parameters (e.g. the beam model, the CT calibration curves, physics models and settings used, etc.). The definition of tolerances and actions levels used for clinical application must be defined during the medical commissioning process of GATE-RTion for each facility. Of course, establishing GATE-RTion in several clinics will support the users in sharing experience and establishing commissioning guidelines.

c. Applications of GATE-RTion in clinical centers

Usually the first step of the clinical implementation consists in developing and validating a beam model, which is out of scope of this note. Instead, this technical note focuses on the clinical applications performed once the beam model is available. An overview of the three different LIBT centers and SIBD systems available is provided in Table 1.

Table 1: SIBD system properties

LIBT facility	Manufacturer	Machine type	Ion Species	SIBD technique[6]	Gantry angles	Energy range
Centre Antoine Lacassagne (Nice, France)	IBA PT (Louvain-la-Neuve, Belgium)	Synchro-Cyclotron (S2C2) [34,35]	Protons	Discrete scanning	from 320° to 180°	70-230 MeV
Christie NHS Foundation Trust (Manchester, UK)	Varian (Palo Alto, California, US)	ProBeam (Cylcotron)	Protons	Discrete scanning	from 0° to 360°	70-245 MeV
MedAustron (Wiener Neustadt, Austria)	MedAustron	MAPTA [7] (Synchrotron)	Protons Carbon ions	Quasi-discrete scanning	0° and 90° 0° and 90°	60-250 MeV 120-400 MeV/n

The different centers agreed in using similar physics settings. Physics settings were selected using Geant4 recommendations for medical physics applications[**], personal communications with Geant4 developers and independent validation tests using GATE. For protons, the physics-builder QGSP_BIC (containing BInary Cascade for nuclear processes) is used[31], while for carbon ions the SHIELDING physics-builder (containing the Quantum Molecular Dynamics model for nuclear processes) is used [36,37]. For both particle types, the electromagnetic option EMZ (also called electromagnetic option 4, which is the most accurate) is selected[30]. For more details, the reader is referred to the Physics Reference Manual[††] of Geant4. Additional parameters may be set, such as the maximum step size for ions, a range cut and a tracking cut for secondary electrons, positrons and photons, which are usually comprised between 0.1 and 1 mm (compromise between speed and accuracy)[38].

3. Results

i. Proton Radiography at Centre Antoine Lacassagne

The goal of the project consists in evaluating the potential of proton radiography images for patient positioning using GATE-RTion. An anthropomorphic human head phantom (PBU-50, Supertech, USA) was scanned in a CT. Treatment plans used to generate the proton radiography images of the anthropomorphic phantom were prepared with the RayStation 6.0 TPS, using beam ranges larger than the phantom largest dimensions and a Monte Carlo algorithm. Dose distributions were scored downstream the phantom in a plan perpendicular to the beam direction, resulting in 2D proton radiography images. Proton radiography images were then simulated using GATE-RTion at the same positions. In addition, proton radiography images were acquired using the Lynx 2D scintillator (IBA Dosimetry, Schwarzenbrück, Germany) having a spatial resolution of 0.5 mm. The images were all imported into the MyQA software (IBA Dosimetry, Schwarzenbrück, Germany) for comparisons. Isodoses contours were first compared qualitatively, and then γ-index analyses were performed. A good qualitative agreement was found for patient contours between Monte Carlo simulations and measurements (Figure 1). Using a γ-index analysis (2%, 2mm) between GATE-RTion simulations and TPS, more than 95% of the pixels are passing the test. This study demonstrates the feasibility of using GATE-RTion to predict proton radiography images.

[**] https://geant4.web.cern.ch/support/user_documentation

[††] http://geant4-userdoc.web.cern.ch/geant4-userdoc/UsersGuides/PhysicsReferenceManual/fo/PhysicsReferenceManual.pdf

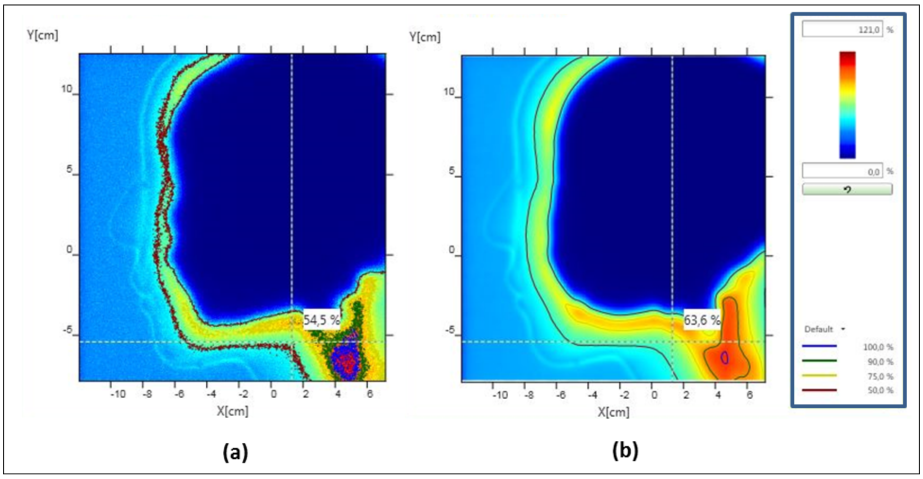

Figure 1: Relative comparison of a GATE dose simulation (a) and a 2D Lynx measurement (b) acquired at the same downstream position for an anthropomorphic phantom.

ii. Independent Dose Calculation of proton beam therapy plans at The Christie

Treatment planning is done using the Varian Eclipse (version 13.7) TPS, with Varian's proton-convolution-superposition (PCS version 13.7.16) analytical dose calculation algorithm. Prior to treatment, measurement-based Patient Specific Quality Assurance (PSQA) is performed on each plan. In addition, Independent Dose Calculation (IDC) using an in-house system called AutoMC and based on GATE-RTion is performed. AutoMC acts as a wrapper around GATE-RTion to fully automate IDCwith the aim to ease the use and minimize the risk of user error when configuring simulations. It is implemented within an Octave [39] environment, and uses modular beam-models and CT calibrations. An example MC re-calculation in patient CT of the first phase of a 2-phase plan treating a craniospinal axis is presented in Figure 2. The prescription for this phase was 23.4 Gy in 13 fractions, delivered using 5 fields: a pair of left/right fields to the brain, and 3 fields to the spine (superior, mid and inferior). A 5 cm WET range-shifter was used for all 5 fields. The percentage of voxels in the patient having $\gamma \leq 1$ was between 92.4% and 95.8% for all fields, and the GATE-RTion simulation was between 1.6% and 2.4% hotter than the TPS in terms of the median dose to the patient. Dose differences occurring outside the patient surface were excluded from the analyses.

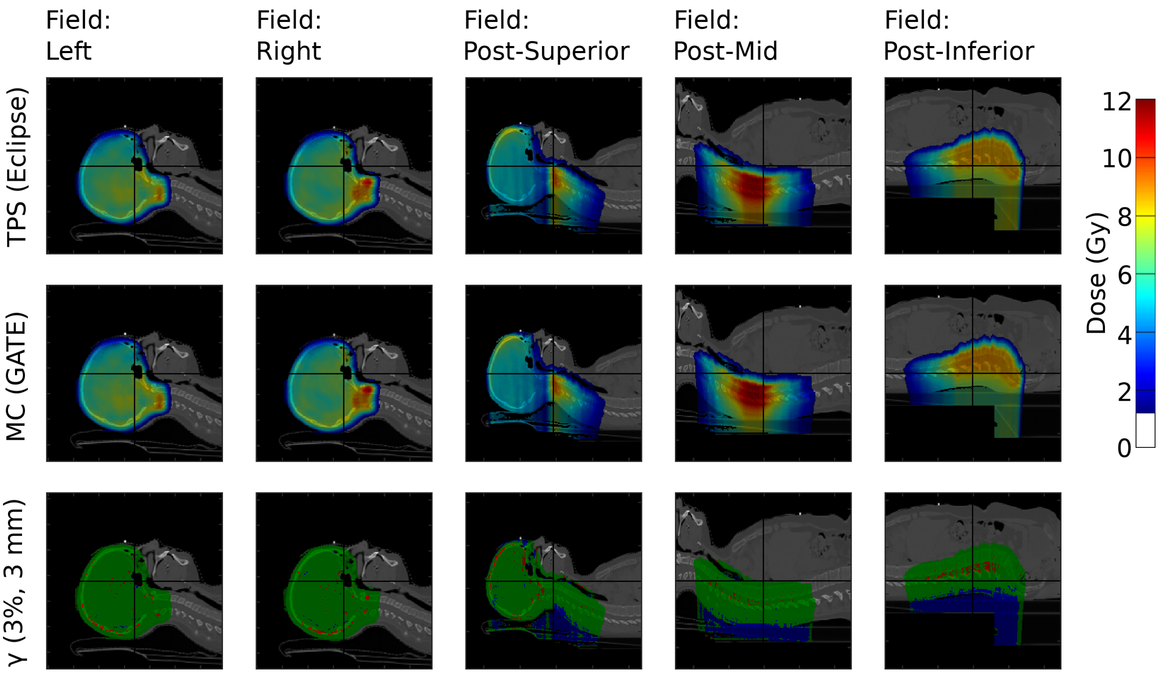

Figure 2: Comparison of TPS (Varian Eclipse) and MC (AutoMC / GATE-RTionV1.0) calculations of a 5-field craniospinal axis pencil beam scanning proton plan, planned at the Christie for delivery on a Varian ProBeam system. Top row: TPS; Middle

row: GATE-RTion; Bottom row: Gamma at 3% (local), 3 mm using a 10% lower dose threshold. Voxels in green have $\gamma \leq 1$, while voxels in (red/blue) have $\gamma > 1$ and are (hotter/colder) than the TPS respectively.

iii. Independent Dose Calculation with Scanned Ion Beams at MedAustron

Treatment planning is performed using the RayStation version 8B from RaySearch Laboratories (Stockholm, Sweden). For protons, the Monte Carlo algorithm version 4.2 is used. For carbon ions, the pencil beam algorithm version 3.0 and the Local Effect Model (LEM) I[40] for Relative Biological Effectiveness (RBE) modeling are used. The measurement-based PSQA process was set-up since the beginning of clinical operation[28]. It is performed in water only and for a limited number of measurements points[28] (using the 3D-block/24 PinPoint ionization chambers type 31015, PTW, Freiburg). In contrary, an IDC has the advantage to evaluate patient treatments in CT geometry and for the entire 3D dose distribution. A key advantage of IDC-based PSQA is to reduce beam time requirements for QA and thus increase the facility treatment capacity. The Independent DosE cAlculation for LIBT (IDEAL) project, including GATE-RTion as dose engine, started in 2017, in a collaboration between the MedAustron ion therapy center, the Medical University of Vienna (MUW) and the Austrian Center for Medical Innovation and Technology (ACMIT). A first prototype has been developed in 2018 in a research network and was transferred into the clinical environment of MedAustron in October 2019. TPS plans are exported to a QA database and IDEAL is run on a cluster of modular capacity (currently featured with 48 cores). A carbon ion treatment recomputed using the IDEAL prototype and including a comparison to the TPS dose distribution is illustrated in Figure 3. This is a curative carbon ion treatment up to 65.6 Gy RBE in 16 fractions of 4.1 Gy RBE (4 fractions per week). The PTV1 is treated with 9 fractions up to 36.9 Gy RBE, using 4 beams with a horizontal beam line and table rotations of 315º, 355º, 320º and 360º.

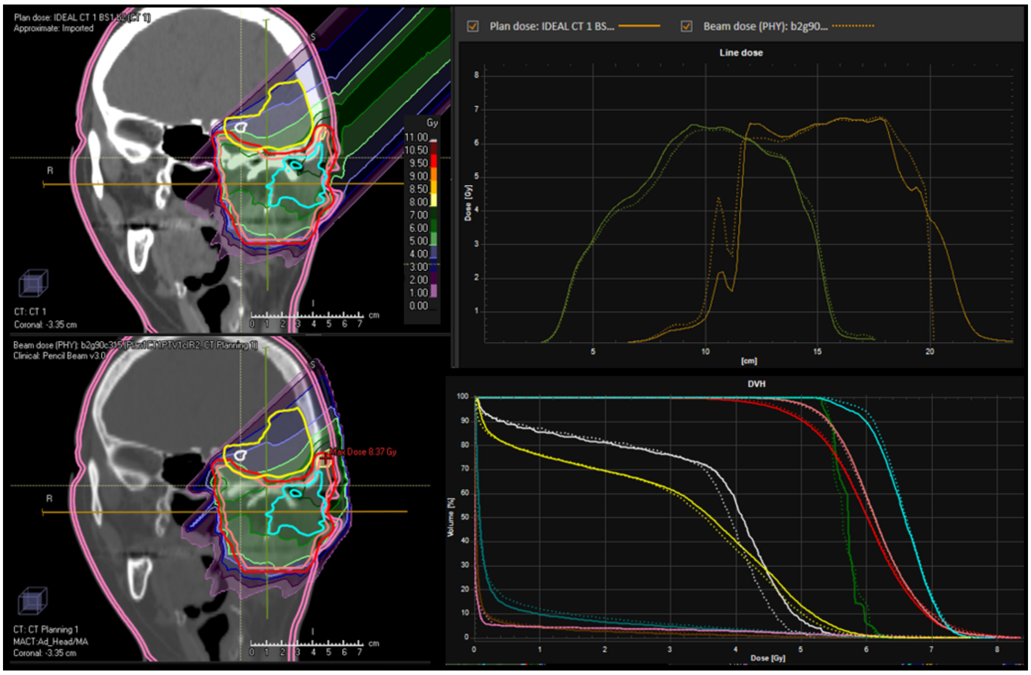

Figure 3: Comparison of the physical dose distribution for a carbon ion beam having an oblique incidence in the head region of a patient. IDEAL/GATE-RTion dose distribution (Top left) is compared to the TPS (bottom left) in terms of DVH (bottom right) and dose profiles (top right). For DVH and dose profiles, solid lines correspond to IDEAL/GATE-RTion and dotted lines to the TPS. The positions of the two orthogonal dose profiles in the patient are visible in the patient images on the left side (orange and green lines).

4. Discussion

The validated GATE-RTion release 1.0 allows clinical users to build confidence in a specific GATE/Geant4 version for clinical applications and share validation results. In parallel, GATE and Geant4 are evolving and may provide new relevant features and improved physics models to the users in the future. For example, with respect to the physics processes, uncertainties of nuclear cross-sections and models are known to be substantial, especially for carbon ions[41]. This is where most improvements could be achieved in future. In addition, every new GATE release provides new features which may be relevant for certain clinical applications, for example code optimization allowing to perform simulations more efficiently or the scoring of new quantities of clinical interest. Also deep learning methods started to be included during Monte Carlo simulations. In its current state, we believe that the proposed GATE features and Geant4 physics models available in GATE-RTion V1.0 are sufficiently accurate for most dosimetric applications in LIBT facilities. Every new GATE-RTion release will need to be thoroughly re-validated and re-commissioned by each user before clinical use, which is a major effort. This can only be justified by substantial improvements in the physics models or by the introduction of new features clinically relevant to the users. The release cycle of GATE-RTion is therefore not planned and will depend on user needs and request. However, bug fixes to GATE-RTion can be ported to the current GATE-RTion version via patch mechanism. This presents the advantage of fixing software bugs (if needed), without modifying the underlying Geant4 physics. GATE-RTion specific validation/acceptance could subsequently be re-run, in order to validate that the patch did not affect the rest of GATE-RTion functionalities except fixing the bug. It is therefore important to develop all necessary validation tests with the users, as described in section 2.b. The results provided in Centre Antoine Lacassagne for proton radiography-based patient-positioning are preliminary but very promising. A dedicated application wrapper would certainly help in future to integrate this innovative GATE-RTion-based application into clinical environments. The IDC applications implemented at The Christie (AutoMC) and MedAustron (IDEAL) are serving both the purpose of IDC, with a key difference that MedAustron extends the application to carbon ions. The Christie is using GATE-RTion clinically since the start of the treatment end of 2018, while MedAustron is still in development and commissioning phase. The commissioning methodology and dosimetric perfromances of GATE-RTion as implemented at The Christie and MedAustron facilities will be published in order to provide reference commissioning reports to support the clinical community.

5. Conclusions

The GATE-RTion project paves the way towards the use of the GATE simulation tool in Light Ion Beam Therapy facilities. GATE-RTion version 1.0 was released in May 2018 and the framework includes a validated GATE release based on a specific Geant4 version, a set of tools to integrate GATE into a clinical environment and a network for clinical users. Three completely different machines were modeled (three different vendors, cyclotron and synchrotron-based systems, protons and carbon ions). Applications such as proton radiography and Independent Dose Calculation (IDC) for scanned proton and carbon ion beam therapy were presented. This project builds the bridge between clinical users and researchers using GATE, fostering the transfer of clinically relevant research applications into the end-user's clinics. While applications at Centre Antoine Lacassagne and MedAustron are still under development, The Christie is running GATE-RTion clinically for IDC since the start of the clinical treatments end of 2018. The results presented within the first two years after the first release of GATE-RTion demonstrate the versatility and relevance of this project.

Acknowledgments

The financial support from ACMIT Gmbh, Medical University of Vienna and MedAustron is gratefully acknowledged. The competence center ACMIT is funded within the scope of the COMET program by Austrian ministries BMVIT and BMWFW, and by the governments of Lower Austria and Tyrol. The competence center program COMET is managed by the Austrian Funding Agency FFG. Part of this work was performed within the framework of the SIRIC LYriCAN Grant INCa-INSERM-DGOS-12563, and the LABEX PRIMES (ANR-11-LABX-0063) of Université de Lyon, within the program "Investissements d'Avenir" (ANR-11-IDEX-0007) operated by the ANR. This work was supported by the Science and Technology Facilities Council Advanced Radiotherapy Network [grant number ST/N002423/1].

The authors would like to thank Priv. Doz. Dipl. Ing. Markus Stock for careful review and advices on the manuscript.

References

1. Jan S, Santin G, Strul D, et al. GATE: a simulation toolkit for PET and SPECT. *Phys Med Biol*. 2004;49(19):4543. http://stacks.iop.org/0031-9155/49/i=19/a=007.
2. Jan S, Benoit D, Becheva E, et al. GATE V6: a major enhancement of the GATE simulation platform enabling modelling of CT and radiotherapy. *Phys Med Biol*. 2011;56(4):881-901. doi:10.1088/0031-9155/56/4/001
3. Grevillot L, Frisson T, Maneval D, Zahra N, Badel J-N, Sarrut D. Simulation of a 6 MV Elekta Precise Linac photon beam using GATE/GEANT4. *Phys Med Biol*. 2011;56(4):903-918.
4. Jan S, Frisson T, Sarrut D. GATE simulation of 12C hadrontherapy treatment combined with a PET imaging system for dose monitoring: A feasibility study. *IEEE Trans Nucl Sci*. 2013;60(1):423-429. doi:10.1109/TNS.2012.2233496
5. Moyers MF, Vatnitsky SM. *Practical Implementation of Light Ion BeamTreatments*. Medical PhysicsPublishing; 2012.
6. ICRU. International Commission on Radiation Units and Measurements report 78: Prescribing and

Recording and And Reporting Proton-Beam Therapy: Contents. *J ICRU*. 2007;7. doi:10.1093/jicru/ndm021

7. Grevillot L, Osorio Moreno J, Letellier V, et al. Clinical implementation and commissioning of the MedAustron Particle Therapy Accelerator for non-isocentric scanned proton beam treatments. *Med Phys*. 2019:1-13. doi:10.1002/mp.13928

8. Robert C, Fourrier N, Sarrut D, et al. PET-based dose delivery verification in proton therapy: a GATE based simulation study of five PET system designs in clinical conditions. *Phys Med Biol*. 2013;58(19):6867-6885. http://stacks.iop.org/0031-9155/58/i=19/a=6867?key=crossref.5c9d5c8b062bf80543bccc0cd3d280e1.

9. Robert C, Dedes G, Battistoni G, et al. Distributions of secondary particles in proton and carbon-ion therapy: a comparison between GATE/Geant4 and FLUKA Monte Carlo codes. *Phys Med Biol*. 2013;58(9):2879-2899. doi:10.1088/0031-9155/58/9/2879

10. Sarrut D, Bardiès M, Boussion N, et al. A review of the use and potential of the GATE Monte Carlo simulation code for radiation therapy and dosimetry applications. *Med Phys*. 2014;41(6):064301. doi:10.1118/1.4871617

11. Paganetti H, Jiang H, Lee SY, Kooy HM. Accurate Monte Carlo simulations for nozzle design and commissioning and quality assurance for a proton radiation therapy facility. *Med Phys*. 2004;31(7):2107-2118.

12. Paganetti H, Jiang H, Parodi K, Slopsema R, Engelsman M. Clinical implementation of full Monte Carlo dose calculation in proton beam therapy. *Phys Med Biol*. 2008;53(17):4825-4853. doi:10.1088/0031-9155/53/17/023

13. Parodi K, Paganetti H, Cascio E, et al. PET/CT imaging for treatment verification after proton therapy: a study with plastic phantoms and metallic implants. *Med Phys*. 2007;34(2):419-435.

14. Parodi K, Ferrari A, Sommerer F, Paganetti H. Clinical CT-based calculations of dose and positron emitter distributions in proton therapy using the FLUKA Monte Carlo code. *Phys Med Biol*. 2007;52(12):3369-3387. doi:10.1088/0031-9155/52/12/004

15. Parodi K, Mairani A, Brons S, et al. Monte Carlo simulations to support start-up and treatment planning of scanned proton and carbon ion therapy at a synchrotron-based facility. *Phys Med Biol*. 2012;57:3759-3784.

16. Ardenfors O, Dasu A, Kopeć M, Gudowska I. Modelling of a proton spot scanning system using MCNP6. *J Phys Conf Ser*. 2017;860(1). doi:10.1088/1742-6596/860/1/012025

17. Bassler N, Hansen DC, Lühr A, Thomsen B, Petersen JB, Sobolevsky N. SHIELD-HIT12A - A Monte Carlo particle transport program for ion therapy research. *J Phys Conf Ser*. 2014;489(1):8-13. doi:10.1088/1742-6596/489/1/012004

18. Sato T, Niita K, Matsuda N, et al. Overview of the PHITS code and its application to medical physics. *Prog Nucl Sci Technol*. 2014;4:879-882. doi:10.15669/pnst.4.879

19. Goma C, Safai S, Voros S. Reference dosimetry of proton pencil beams based on dose-area product: a proof of concept. *Phys Med Biol*. 2017;62(12):4991. doi:https://doi.org/10.1088/1361-6560/aa7008

20. Akagi T, Aso T, Iwai G, et al. Geant4-based particle therapy simulation framework for verification of dose distributions in proton therapy facilities. *Prog Nucl Sci Technol*. 2014;4:896-900.

21. Perl J, Shin J, Schümann J, Faddegon B, Paganetti H. TOPAS: An innovative proton Monte Carlo platform for research and clinical applications. *Med Phys*. 2012;39(11):6818-6837. doi:10.1118/1.4758060

22. Grevillot L, Bertrand D, Dessy F, Freud N, Sarrut D. A Monte Carlo pencil beam scanning model for proton treatment plan simulation using GATE/GEANT4. *Phys Med Biol*. 2011;56:5203-5219.

23. Grevillot L, Frisson T, Zahra N, et al. Optimization of GATE/Geant4 settings for Proton Pencil Beam Scanning simulations towards TPS Quality Assurance. In: *49th Meeting of the Particle Therapy Co-Operative Group (PTCOG)*. ; 2010.

24. Grevillot L, Bertrand D, Dessy F, Freud N, Sarrut D. GATE as a GEANT4-based Monte Carlo platform

for the evaluation of proton pencil beam scanning treatment plans. *Phys Med Biol*. 2012;57:4223-4244.

25. Almhagen E, Boersma DJ, Nyström H, Ahnesjö A. A beam model for focused proton pencil beams. *Phys Medica*. 2018;52:27-32. doi:10.1016/j.ejmp.2018.06.007

26. Fuchs H, Grevillot L, Carlino A, et al. Optimizing the MedAustron proton gantry beam delivery: Providing nozzle design recommendations based on Gate/Geant4 Monte Carlo simulation. In: *PTCOG 55.* ; 2016.

27. Grevillot L, Stock M, Vatnitsky S. Evaluation of beam delivery and ripple filter design for non-isocentric proton and carbon ion therapy. *Phys Med Biol*. 2015;60(20):7985-8005. http://www.ncbi.nlm.nih.gov/pubmed/26418366.

28. Carlino A. Implementation of advanced methodologies in the commissioning of a Light Ion Beam Therapy facility (PhD thesis, Department of Physics and Chemistry, University of Palermo, Italy). 2017.

29. Saini J, Maes D, Egan A, et al. Dosimetric evaluation of a commercial proton spot scanning Monte-Carlo dose algorithm: Comparisons against measurements and simulations. *Phys Med Biol*. 2017;62(19):7659-7681. doi:10.1088/1361-6560/aa82a5

30. Fuchs H, Vatnitsky S, Stock M, Georg D, Grevillot L. Evaluation of GATE/Geant4 multiple Coulomb scattering algorithms for a 160 MeV proton beam. *Nucl Instruments Methods Phys Res Sect B Beam Interact with Mater Atoms*. 2017;410. doi:10.1016/j.nimb.2017.08.006

31. Resch AF, Elia A, Fuchs H, et al. Evaluation of electromagnetic and nuclear scattering models in GATE /Geant4 for proton therapy. *Med Phys*. 2019;46(5):2444-2456. doi:10.1002/mp.13472

32. Elia A. Characterization of the GATE Monte Carlo platform for nonisocentric treatments and patient specific treatment plan verification at MedAustron (PhD thesis, INSA Lyon, 2019LYSE002). 2019.

33. Meißner H, Fuchs H, Hirtl A, Reschl C, Stock M. Towards offline PET monitoring of proton therapy at MedAustron. *Zeitschrift fßr Medizinische Phys*. 2019;29(1):59-65. doi:10.1016/j.zemedi.2018.05.003

34. Kleeven W, Abs M, Forton E, et al. The IBA Superconducting Synchrocyclotron Project S2C2. *Proc Cyclotrons2013*. 2013:115-119. https://accelconf.web.cern.ch/AccelConf/CYCLOTRONS2013/papers/mo4pb02.pdf.

35. Van de Walle J, Abs M, Conjat M, et al. The S2C2: From Source to Extraction. *Proc Cyclotrons 2016*. 2017;THB01:285-289. http://accelconf.web.cern.ch/AccelConf/cyclotrons2016/papers/thb01.pdf.

36. Bolst D, Cirrone GAP, Cuttone G, et al. Validation of Geant4 fragmentation for Heavy Ion Therapy. *Nucl Instruments Methods Phys Res Sect A Accel Spectrometers, Detect Assoc Equip*. 2017;869:68-75. doi:10.1016/j.nima.2017.06.046

37. Böhlen TT, Cerutti F, Dosanjh M, et al. Benchmarking nuclear models of FLUKA and GEANT4 for carbon ion therapy. *Phys Med Biol*. 2010;55(19):5833-5847. doi:10.1088/0031-9155/55/19/014

38. Grevillot L, Frisson T, Zahra N, et al. Optimization of GEANT4 settings for Proton Pencil Beam Scanning simulations using GATE. *Nucl Instruments Methods Phys Res Sect B Beam Interact with Mater Atoms*. 2010;268(20):3295-3305.

39. Eaton JW, Bateman D, Hauberg S WR. GNU Octave version 5.1.0 manual: a high-level interactive language for numerical computations. 2019. https://www.gnu.org/software/octave/doc/v5.1.0/.

40. Scholz M, Kellerer AM, Kraft-Weyrather W, Kraft G. Computation of cell survival in heavy ion beams for therapy: The model and its approximation. *Radiat Environ Biophys*. 1997;36(1):59-66. doi:10.1007/s004110050055

41. Dedes G, Parodi K. Monte Carlo Simulations of Particle Interactions with Tissue in Carbon Ion Therapy. *Int J Part Ther*. 2015;2(3):447-458. doi:10.14338/IJPT-15-00021