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Applications of Simulation Codes Based on Monte Carlo Method for Radiotherapy

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Abstract

Monte Carlo simulations have been applied to determine and study different parameters that are challenged in experimental measurements, due to its capability in simulating the radiation transport with a probability distribution to interact with electrostatic electrons and some cases with the nucleus from an arbitrary material, which such particle track or history can carry out physical quantities providing data from a studied or investigating quantities. For this reason, simulation codes, based on Monte Carlo, have been proposed. The codes currently available are MNCP, EGSnrc, Geant, FLUKA, PENELOPE, as well as GAMOS and TOPAS. These simulation codes have become a tool for dose and dose distributions, essentially, but also for other applications such as design clinical, tool for commissioning of an accelerator linear, shielding, radiation protection, some radiobiologic aspect, treatment planning systems, prediction of data from results of simulation scenarios. In this chapter will be present some applications for radiotherapy procedures with use, specifically, megavoltage x-rays and electrons beams, in scenarios with homogeneous and anatomical phantoms for determining dose, dose distribution, as well dosimetric parameters through the PENELOPE and TOPAS code.

Keywords: Monte Carlo, codes, radiotherapy

1. Introduction

The constant development of medical applications using ionizing radiation requires an understanding of the transport of particles through materials, such as tissues, organs, patients, imaging devices. For this reason, computational simulations, using the Monte Carlo Method, have been extensively used in several areas, specifically, in Radiological Physics, where this tool is applied for modeling a treatment or medical examinations, for example, that for some regions of interest are difficulties and complexities to making experimentally.

Several computational codes, based on Monte Carlo simulation, have been used in radiological protection, radiotherapy source dosimetry, planning systems, and other applications PENELOPE [1–6], MCNP [7–11], EGSnrc [12–15], FLUKA [16–20], TOPAS [21–25], GAMOS [26–29], Geant [30, 31].

In this work, some applications will be presented, in different scenarios to determine dose, relative dose, dose distribution, as well as to determine dosimetric parameters used in radiotherapy, using computational codes through Monte Carlo simulation.

2. Applications of computational codes in radiotherapy

In this section, some applications of computational codes in radiotherapy will be presented.

2.1 Determination of dosimetric parameters of clinical sources of high dose rate brachytherapy using the PENELOPE package

The PENELOPE (PENetration and Energy LOSS of Positrons and Electrons) computational code includes several computational codes written in FORTRAN 77 [32]. The package simulates the transport of electrons, photons, and positrons in arbitrary materials and energy values from 100 eV to 1 GeV, in geometries and materials defined by the user [33]. PENELOPE has a database of cross-sections for materials involving elements with atomic numbers from 1 to 92, and 180 other compounds and mixtures of interest in Radiological Physics.

This computational code has been used in several applications in Radiotherapy, such as determining parameters of brachytherapy sources [4, 34–36].

According to the TG-43 protocol, later revised and entitled TG-43 U1 [37, 38], the calculation of the dosimetric parameter Anisotropy Function is performed through Eq. (1):

$$F(r, \theta) = \left[\dot{D}(r, \theta) / \dot{D}(r, \theta_0) \right] * \left[G_L(r, \theta_0) / G_L(r, \theta) \right] \quad (1)$$

where $\dot{D}$ is the dose rate; r is the distance from the center of the source to the point of interest (in cm), θ is the polar angle that specifies the point of interest, θ_0 is the reference angle (90°); G_L is the geometric factor, determined analytically.

Quevedo et al. [4] determined a dosimetric parameter, using Monte Carlo simulation with the PENELOPE package. The high dose-rate ^{192}Ir brachytherapy source commonly used in gynecological brachytherapy was modeled, and the Anisotropy Function in regions close to the source was determined. **Figure 1** shows (a) the source geometry, modeled in the PENELOPE package, and (b) the Anisotropy Function in regions close to the irradiation source.

To validate the results obtained, using Monte Carlo simulation with the PENELOPE package, dose profiles in the longitudinal direction of the source were compared with data from the BrachyVision planning system. **Figure 2** shows the comparisons of relative doses, as a function of distances, between the PENELOPE package and the BrachyVision treatment planning system for distances (a) 0.4 cm from the center of the source towards the source cable, (b) center of the source and (c) 0.4 cm from the center of the source towards the top of the source encapsulation, adapted from Quevedo et al. [4].

From the comparisons in the three plans, it is possible to verify that the data obtained in the simulations with the PENELOPE package shows agreement greater than 98% of the points, with the data obtained from the treatment planning system, indicating that the PENELOPE package has great potential in the determination of dosimetric parameters of high dose rate brachytherapy sources.

2.2 Applications of the TOPAS code in ocular brachytherapy

The TOPAS (Tool for Particle Simulation) computational code is based on physical Geant4 models and low energy electromagnetic models of the PENELOPE code [39] and has shown great potential for simulations in medical and quality control applications [22, 40–43].

Figure 1.
(a) Source geometry, modeled in the PENELOPE package, adapted from Quevedo et al. [4] and
(b) anisotropy function in regions close to the irradiation source.

TOPAS is based on an innovative parameter control system, which allows the modeling of therapy and imaging devices without the need for programming knowledge, in order to reduce user errors. The code has a vast library of predefined modules for geometry, physical models, and detection. Despite this, it is possible for more experienced users to write their own modules in C++. You can also create patient geometries based on computed tomography (CT) images. Therefore, TOPAS presents itself as a highly extensible and accessible tool for medical physicists for modeling therapy and imaging devices.

Another innovative feature of this code is that it handles time-dependent amounts, that is, it has 4D resources through its Time Feature System. Time-varying amounts are essential for modeling advanced radiotherapy treatment techniques, the Image-Guided Radiotherapy (IGRT) technique is an example of this, where the positioning of the patient or target organ varies. Therefore, TOPAS proposes an approach to 4D simulation to deal with various time-dependent quantities in a single simulation, such as volume change, rotational movement, current variation, magnetic field, etc. [44].

Knoll et al., determined dose deposition from a source of brachytherapy used in ophthalmic treatments [23]. In this work, the applicator used in the treatment, which uses the $^{90}\text{Sr}/^{90}\text{Y}$ source, was modeled in the TOPAS code, including the active part, encapsulation, and simulator object filled with water. A relative dose profile was obtained in a high dose gradient region, normalized at the reference point to 1 mm and, for validation purposes, the data obtained with TOPAS were compared with data from the ICRU (International Commission on Radiation & Measurements) with the same conditions. **Figure 3** shows (a) geometry of the $^{90}\text{Sr}/^{90}\text{Y}$ source with applicator and simulator object and (b) comparison of relative dose, as a function of distance, between TOPAS and ICRU data (Adapted from [23]).

(a)

(b)

(c)

Figure 2. Relative dose comparisons, as a function of distances, between the PENELOPE package and the BrachyVision treatment planning system for distances (a) 0.4 cm from the center of the source towards the source cable, (b) center of the source, and (c) 0.4 cm from the center of the source towards the top of the source encapsulation, adapted from Quevedo et al. [4].

The greatest uncertainty obtained in computer simulations with the TOPAS code was approximately 0.01% at the point where it was normalized. When compared to the ICRU, the greatest difference found was approximately 4% at 1.6 mm depth. Thus, the TOPAS code has been shown to be a promising tool for dosimetry in brachytherapy and radiological applications.

2.3 Applications of the TOPAS-nBio code

Although the TOPAS code provides a wide range of tools for use in radiotherapy at patient scale or clinically applicable geometries, the fundamental unit of biological response to the effects of ionizing radiation is at the cellular or subcellular scale. For this reason, TOPAS has an extension dedicated to the study of the biological effects of radiation in micrometer and nanometer scale, designed based on Geant4-DNA, the extension of Geant4, the basis of TOPAS, so that very low energy are included in the interactions.

When interacting with matter, excitations and ionizations can be caused due to ionizing radiation. In the context of radiotherapy, incident particles cause radiolysis of water and subsequent chemical interactions, inducing molecular damage to the cell, more specifically to DNA, which is the critical target for most biological effects

(a)

(b)

Figure 3.
(a) $^{90}\text{Sr}/^{90}\text{Y}$ source geometry with applicator and simulator object and (b) comparison of relative dose, as a function of distance, between TOPAS and ICRU data (adapted from [23]).

of radiation [45]. For this reason, TOPAS-nBio has several models of cellular and subcellular geometries (such as blood cells and single and double-stranded DNA models, for example) specialized in a pre-defined way [46]. Furthermore, with regard to biological modeling, the code inherits the chemical parameters provided by the Geant4-DNA toolkit and also includes mechanistic DNA repair models to perform water radiolysis simulations. With this, it is possible to develop complete modeling from the initial physical events to the final observed biological result [47].

According to Semenenko et al. [48] the combination of runway structure simulations with core geometry models is considered the gold standard for predicting the spectrum of DNA damage induced by ionizing radiation. Therefore, Hongyu et al. [43] determined the cellular response after proton irradiation using the TOPAS-nBio code for damage induction and repair modeling with MEDRAS, which is a model capable of predicting the main final biological damage in a variety of cell types, including repair kinetics, chromosomal aberrations, and cell survival.

To determine the DNA damage yield, the results were scored in the SSD format and quantified by strand break (SBs), single-strand break (SSBs), and double-strand break (DSBs) yields, compared to published and experimentally measured data.

The initial DNA damage after proton irradiation (0.5–500 MeV, corresponding to the LET region of 60–0.2 keV/μm) was simulated with the code. The core model used was placed in the center of a cubic world with a side length of 14 μm, containing the core, filled with water. Primary protons were randomly initiated on the surface of the nucleus and propagated within the nucleus in a random direction. Induced DNA damage caused by direct and indirect interactions in the physical and chemical stages was quantified as SBs, SSBs, or DSBs and sent in standard DNA damage data format (SDD). To get enough statistics, 100 stories were performed for each energy point. Each simulation had a fixed number of primary particles and deposited a dose of 1 Gy inside the nucleus. Statistical uncertainty associated with DSB dose and yield was less than 2%.

The average LET was recorded as a radiation quality index and calculated by the equation:

$$\text{LET} = \varepsilon/d \quad (2)$$

where d is the average length of the proton path inside the nucleus and ε is the energy deposition of primary and secondary particles inside the nucleus.

The initial DNA damage induced by incident protons was simulated by modeling the physical and chemical interactions within the nucleus with standard process models available in TOPAS-nBio.

As a result, a relationship was obtained between the LET of the proton according to literature references and the simulated particle energy in TOPAS-nBio. In low energy regions, the maximum discrepancy between the results was 32.5%, probably due to the size of the scoring volume, and in this low energy region, the protons do not cross the entire nucleus. However, there was an optimal agreement of 96%, as shown in **Figure 4**.

The results of DNA damage as a function of the LET of the proton simulated with TOPAS-nBio were also obtained, as shown in **Figure 5**.

The figure shows a relationship between the relative contribution of direct and hybrid damage as a fraction of each type of SB, SSB, and DSB break. Thus, it was shown that most SBs and SSBs would be caused by indirect damage and the indirect contribution rate would increase from approximately 60% to approximately 75% at 4.5 keV/μm (10 MeV proton energy) and, then decrease to higher LET values where radiolysis is denser, causing a greater number of chemical interactions. Furthermore, it was shown that most DSB damage was classified as a hybrid type, caused by the combination of direct and indirect damage. Simulations using

Figure 4.
Proton LET as a function of proton energy compared to experimental data [48].

Figure 5.
DNA damage obtained with TOPAS-nBio. Eml A: Total, direct, and indirect SB yield per Gy per Gbp of DNA. In B: Total, direct and indirect SSB yield per Gy per Gbp of DNA. In C: Total, direct, indirect, and hybrid DSB yield per Gy per Gbp of DNA. In D: Contribution of indirect or hybrid damage to SB, SSB, and DSB [43].

TOPAS-nBio showed that Monte Carlo tools can predict DNA damage and can be used to interpret experimental data and design new theories.

3. Conclusion

Monte Carlo simulations have been applied to determine and study different parameters that are challenged in experimental measurements, due to its capability in simulating the radiation transport. In this chapter were presented applications for radiotherapy procedures, in scenarios with homogeneous and anatomical phantoms determining dose values, dose distribution, and dosimetric parameters through the PENELOPE and TOPAS code, showing itself as a useful tool for radiotherapy.

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References

- [1] Mariotti V, Gayol A, Pianoschi T, Mattea F, Vedelago J, Pérez P, et al. Radiotherapy dosimetry parameters intercomparison among eight gel dosimeters by Monte Carlo simulation. *Radiation Physics and Chemistry*. 2022;**190**:109782. DOI: 10.1016/j.radphyschem.2021.109782
- [2] Alva-Sánchez MS, Quevedo A, Bonatto A, Pianoschi T. Preliminary Monte Carlo simulation of non-laser light sources for photodynamic therapy. *Journal of Physics Conference Series*. 2021;**1826**:012052. DOI: 10.1088/1742-6596/1826/1/012052
- [3] Alva-Sánchez MS, Pianoschi T. Study of the distribution of doses in tumors with hypoxia through the PENELOPE code. *Radiation Physics and Chemistry*. 2020;**167**:108428. DOI: 10.1016/j.radphyschem.2019.108428
- [4] Quevedo A, Borges LF, Nicolucci P. Evaluation of dosimetric parameters for brachytherapy source in regions close to the source. *Scientia Plena*. 2018;**14**(4):1-12. DOI: 10.14808/sci.plena.2018.046001
- [5] Verbeek N, Wulff J, Baumer C, Smyczek S, Timmermann B, Brualla L. Single pencil beam benchmark of a module for Monte Carlo simulation of proton transport in the PENELOPE code. *Medical Physics*. 2021;**48**(1):456-476. DOI: 10.1002/mp.14598
- [6] Bosman DF, Balcasa VG, Delgado C, Principi S, Duch MA, Ginjaume M. Validation of the MC-GPU Monte Carlo code against the PENELOPE/penEasy code system and benchmarking against experimental conditions for typical radiation qualities and setups in interventional radiology and cardiology. *Physica Medica*. 2021;**82**:64-71. DOI: 10.1016/j.ejmp.2021.01.075
- [7] Forster RA, Cox LJ, Barrett RF, Booth TE, Briesmeister JF, Brown FB, et al. MCNP version 5. *Nuclear Instruments and Methods B*. 2004;**213**:82-86. DOI: 10.1016/S0168-583X(03)01538-6
- [8] Vahabi SM, Zafarghandi MS. Applications of MCNP simulation in treatment planning: A comparative study. *Radiation and Environmental Biophysics*. 2020;**59**(2):307-319. DOI: 10.1007/s00411-020-00841-2
- [9] Leal-Acevedo B, Gamboa-deBuen I. Dose distribution calculation with MCNP code in a research irradiator. *Radiation Physics and Chemistry*. 2020;**167**:108320. DOI: 10.1016/j.radphyschem.2019.05.010
- [10] Kolacio MS, Brkic H, Faj D, Radojcic DS, Rajlic D, Obajdin N, et al. Validation of two calculation options built in Elekta Monaco Monte Carlo based algorithm using MCNP code. *Radiation Physics and Chemistry*. 2021;**179**:109237. DOI: 10.1016/j.radphyschem.2020.109237
- [11] Kim MJ, Sung SH, Hr K. Spectral resolution evaluation by MCNP simulation for airborne alpha detection system with a collimator. *Nuclear Engineering and Technology*. 2021;**53**(4):1311-1317. DOI: 10.1016/j.net.2020.09.009
- [12] Yani S, Rizkia I, Kamirul RMF, Haekal M, Haryanto F. EGSnrc application for IMRT planning. *Reports of Practical Oncology and Radiotherapy*. 2020;**25**(2):217226. DOI: 10.1016/j.rpor.2020.01.004
- [13] Jayamani J, Osman ND, Tajuddin AA, Noor NM, Aziz MZA. Dosimetric comparison between Monaco TPS and EGSnrc Monte Carlo simulation on titanium rod in 12bit and 16bit image format. *Journal of Radiation Research and Applied Science*. 2020;**13**(1):496-506. DOI: 10.1080/16878507.2020

- [14] Tessier F, Ross CK. Technical Note: Implications of using EGSnrc instead of EGS4 for extracting electron stopping powers from measured energy spectra. *Medical Physics*. 2021;**48**(4):1996-2003. DOI: 10.1002/mp.14567
- [15] Aamri H, Fielding A, Aamry A, Sulieman A, Tamam N, Alkhorayef M, et al. Comparison between PRIMO and EGSnrc Monte Carlo models of the Varian True Beam linear accelerator. *Radiation Physics and Chemistry*. 2021;**178**:109013. DOI: 10.1016/j.radphyschem.2020.109013
- [16] Embriaco A, Attili A, Bellinzona EV, Dong Y, Grzanka L, Mattei I, et al. FLUKA simulation of target fragmentation in proton therapy. *Physica Medica*. 2020;**80**:342346. DOI: 10.1016/j.ejmp.2020.09.018
- [17] Chattaraj A, Selvam TP. Applicability of pure Propane gas for microdosimetry at brachytherapy energies: A Fluka study. *Radiation Protection Dosimetry*. 2020;**189**(3):286-293. DOI: 10.1093/rpd/ncaa041
- [18] Soltani-Nabipour J, Khorshidi A, Shojai F, Khorami K. Evaluation of dose distribution from C-12 ion in radiation therapy by FLUKA code. *Nuclear Engineering and Technology*. 2020;**52**(10):2410-2424. DOI: 10.1016/j.net.2020.03.010
- [19] Sharma A, Singh B, Sandhu BS. A compton scattering technique for wood characteristics using FLUKA Monte Carlo code. *Radiation Physics and Chemistry*. 2021;**185**:109364. DOI: 10.1016/j.radphyschem.2021.109364
- [20] Chattaraj A, Selvam TP. Microdosimetry-based relative biological effectiveness calculations for radiotherapeutic electron beams: A FLUKA-based study. *Radiological Physics and Technology*. 2021;**14**(3):297-308. DOI: 10.1007/s12194-021-00627-1
- [21] Souza LS, Alva-Sánchezb MS, Bonatto A. Computational simulation of low energy x-ray source for photodynamic therapy: A preliminary study. *Brazilian Journal of Radiation Science*. 2021;**9**(1):1-15. DOI: 10.15392/bjrs.v9i1.1639
- [22] Berumen F, Ma YZ, Ramos-Mendez J, Perl J, Beaulieu L. Validation of the TOPAS Monte Carlo toolkit for HDR brachytherapy simulations. *Brachytherapy*. 2021;**20**(4):911-921. DOI: 10.1016/j.brachy.2020.12.007
- [23] Knoll I, de Souza L, Ramon P, Quevedo A, Alva-Sanchez MS. Determination of dose deposition from an Ocular Brachytherapy source: Simulation data with TOPAS. *Radiotherapy and Oncology*. 2021;**158**(1):S182-S183
- [24] Hahn MB, Villate JMZ. Combined cell and nanoparticle models for TOPAS to study radiation dose enhancement in cell organelles. *Scientific Reports*. 2021;**11**(1):6721. DOI: 10.1038/s41598-021-85964-2
- [25] Wu JA, Xie YQ, Ding Z, Li FP, Wang LH. Monte Carlo study of TG-43 dosimetry parameters of GammaMed Plus high dose rate IR-192 brachytherapy source using TOPAS. *Journal of Applied Clinical Medical Physics*. 2021;**22**(6):146-153. DOI: 10.1002/acm2.13252
- [26] Ozbay T, Yourt A, Ozsoykal I. Simulation of water equivalency of polymer gel dosimeters with GAMOS. *Journal of Basic Clinical Health Sciences*. 2020;**4**(1):51-58. DOI: 10.30621/jbachs.2020.899
- [27] Pistone D, Auditore L, Italiano A, Mandaglio G, Minutoli F, Baldari S, et al. Monte Carlo based dose-rate assessment in F-18-Choline Pet Examination: A comparison between

Gate and Gamos Codes. Atti Accademia Peloritana Dei Pericolanti-Classe Di Scienze Fisiche Matematiche e Naturali. 2020;**98**(1):A5. DOI: 10.1478/AAPP.981A5

[28] Dubois PA, Thao NTP, Trung NT, Azcona JD, Aguilar-Redondo PB. A tool for precise calculation of organ doses in voxelised geometris using GAMOS/Geant4 with a graphical user interface. Polish Journal of Medical Physics and Engineering. 2021;**27**(1):31-40. DOI: 10.2478/pjmpe-2021-0005

[29] Al-Tuweity J, Sadiq Y, Mouktafi A, Arce P, Fathi I, Mohammed M, et al. GAMOS/GEANT4 simulation and comparison study of X-ray narrowspectrum series at the national Secondary Standard Dosimetry Laboratory of Morocco. Applied Radiation and Isotopes. 2021;**175**:109789. DOI: 10.1016/j.apradiso.2021.109789

[30] Chrobak A, Konefal A, Wronska A, Magiera A, Rusiecka K, et al. Comparison of various models of Monte Carlo Geant 4 code in simulations of prompt gamma production. Acta Physica Polonica, B. 2017;**48**(3):675-678. DOI: 10.5506/APhysPolB.48.675

[31] Baumann KS, Kaupla S, Bach C, Engenhar-Cabillic R, Zink K. Monte Carlo calculation of perturbation correction factors for air-filled ionization chambers in clinical proton beams using TOPAS/GEANT. Zeitschrift für Medizinische Physik. 2021;**31**(2):175-191. DOI: 10.1016/j.zemedi.2020.08.004

[32] Salvat F, Fernández-Varea J, Sempau J, Llovet X. Monte Carlo simulation of bremsstrahlung emission by electrons. Radiation Physics and Chemistry. 2006;**75**:1201-1219. DOI: 10.1016/j.radphyschem.2005.05.008

[33] Sempau J, Fernández-Varea JM, Acosta E, Salvat F. Experimental

benchmarks of the Monte Carlo Code PENELOPE. Nuclear Instruments and Methods in Physics B. 2003;**207**:107-123. DOI: 10.1016/S0168-583X(03)00453-1

[34] Rodriguez EAV, Alcon EPQ, Rodriguez ML, Gutt F, de Almeida E. Dosimetric parameters estimation using PENELOPE Monte-Carlo simulation code: Model 6711 I-125 brachytherapy seed. Applied Radiation and Isotopes. 2005;**63**(1):41-48. DOI: 10.1016/j.apradiso.2005.02.004

[35] Casado FJ, Garcia-Pareja S, Cenizo E, Mateo B, Bodineau C, Galan P. Dosimetric characterization of an Ir-192 brachytherapy source with the Monte Carlo code PENELOPE. Physica Medica. 2010;**26**(3):132-139. DOI: 10.1016/j.ejmp.2009.11.001

[36] Almansa JF, Guerrero R, Torres J, Lallena AM. Monte Carlo dosimetric characterization of the Flexisource Co-60 high-dose-rate brachytherapy source using PENELOPE. Brachytherapy. 2017;**16**(5):1073-1080. DOI: 10.1016/j.brachy.2017.04.245

[37] Nath R, Anderson LL, Luxton G, Weaver KA, Williamson JF, Meigooni AS. Dosimetry of interstitial brachytherapy sources: Recommendations of the AAPM radiation therapy committee Task Group No. 43. Medical Physics. 1995;**22**(2):209234. DOI: 10.1118/1.597458

[38] Rivard MJ, Ballester F, Butler WM, DeWerd LA, Ibbott GS, Meigooni AS, et al. Supplement 2 for the 2004 Update of the AAPM Task Group No. 43: Report: Joint Recommendations by the AAPM and GEC-ESTRO. Medical Physics. 2017;**44**(9):e297-e338. DOI: 10.1002/mp.12430

[39] Perl J, Shin J, Schümann J, Faddegon B, Paganetti H. TOPAS: An innovative proton Monte Carlo Platform for research and clinical applications.

Medical Physics. 2012;**39**(11):6818-6837.
DOI: 10.1118/1.4758060

[40] Hall D, Perl J, Schuemann J, Faddegon B, Paganetti H. Meeting the challenges of quality control in the TOPAS Monte Carlo Simulation Toolkit for proton therapy. Medical Physics. 2016;**43**(6):3493-3494. DOI: 10.1118/1.4956275

[41] Liu HD, Zhang L, Chen Z, Liu XG, Dai ZY, Li Q, et al. A preliminary Monte Carlo study of the treatment head of a carbon-ion radiotherapy facility using TOPAS. EPJ Web of Conferences. 2017;**153**:04018. DOI: 10.1051/epjconf/201715304018

[42] Baumann KS, Kaupa S, Bach C, Engenhart-Cabillic R, Zink K. Monte Carlo calculation of beam quality correction factors in proton beams using TOPAS/GEANT4. Physics in Medicine and Biology. 2020;**65**(5):055015. DOI: 10.1088/1361-6560/ab6e53

[43] Zhu H, McNamara AL, McMahon SJ, Ramos-Mendez J, Henthorn NT, Faddegon B, et al. Cellular response to proton irradiation: A simulation study with TOPAS-nBio. Radiation Research. 2020;**194**(1):9-21. DOI: 10.1667/RR15531.1

[44] Shin WG, Testa M, Kim HS, Jeong JH, Lee SB, Kim YJ, et al. Independent dose verification system with Monte Carlo simulations using TOPAS for passive scattering proton therapy at the National Cancer Center in Korea. Physics in Medicine and Biology. 2017;**62**(19):7598-7616. DOI: 10.1088/1361-6560/aa8663

[45] Hall EJ, Giaccia AJ. Radiobiology for the Radiologist. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2018

[46] Schuemann J, McNamara AL, Ramos-Méndez J, Perl J, Held KD, Paganetti H, et al. TOPAS-nBio: An

extension to the TOPAS simulation toolkit for cellular and sub-cellular radiobiology. Radiation Research. 2019;**191**(2):125-138. DOI: 10.1667/RR15226.1

[47] McNamara A, Geng C, Turner R, Mendez JR, Perl J, Held K, et al. Validation of the radiobiology toolkit TOPAS-nBio in simple DNA geometries. Physica Medica. 2017;**33**:207-215. DOI: 10.1016/j.ejmp.2016.12.010

[48] Semenenko V, Stewart R. A fast Monte Carlo algorithm to simulate the spectrum of DNA damages formed by ionizing radiation. Radiation Research. 2004