TECHNICAL REVIEW

Torch®: Voxel-Based Dosimetry for Radiopharmaceutical Therapy

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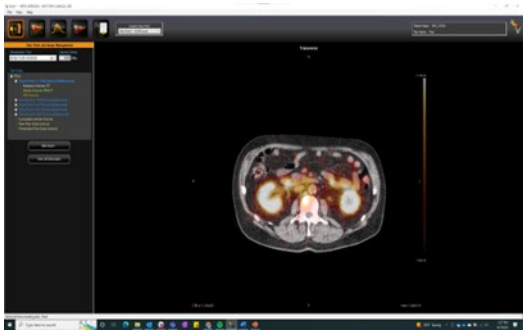
Voximetry, Inc. offers a software product called Torch that brings accuracy and simplicity to the otherwise complex task of performing dosimetry for radiopharmaceutical therapy (RPT) procedures. Torch introduces semi-automated workflows that reduce time, staffing, and required expertise to perform dosimetry without compromising the accuracy and precision needed to ensure safe and effective RPT procedures. This unique solution is made possible by carefully architecting dosimetry tasks such as image registration, contour propagation, kinetic modeling, and radiation transport to exploit the enormous parallel processing capabilities of GPUs. At the core of Torch is our proprietary GPU-accelerated Monte Carlo (MC) radiation transport algorithm that will provide superior dosimetric accuracy compared to existing dosimetry products, so that dosimetry can be used as a predictive biomarker for toxicity and tumor response for each individual patient.

Torch consists of a dosimetry workflow which enables busy and resource limited clinics to complete personalized and accurate RPT dosimetry in five general steps. It can be operated either in an automated “Click and Go” fashion where the complete workflow is executed automatically or in an “Advanced” mode where the user interacts at each step manually.

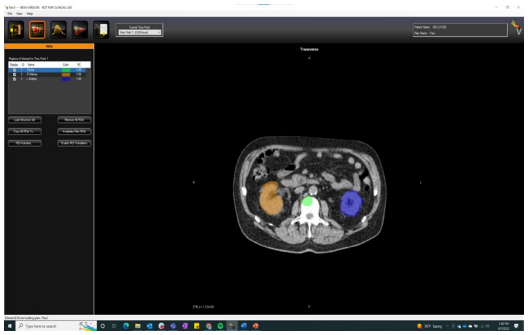
Overview of Software Worksteps

The following section outlines the Torch dosimetry workflow:

Image Import The first step is DICOM import where the user imports a CT and PET or SPECT dataset for each timepoint that the patient was imaged. Currently, Torch does not perform SPECT calibration, so the user must input a calibration factor (i.e., cps/MBq) when importing SPECT data that is calculated using another software. It is recommended that the calibration factor is measured onsite by imaging a uniform phantom with the same imaging parameters as the patient data. To maintain data integrity, Torch only accepts DICOM images and automatically reads information from the header including patient information and radionuclide type. This information is cross-checked with user-required manual entries in the Patient Catalog to ensure data accuracy. Also, in this work step, the user enters the administration time and date. Based on this user-entered information, Torch automatically determines the time post administration for each time point to prevent user error. The user will be notified If any mismatch occurs between DICOM tags and patient catalog information.

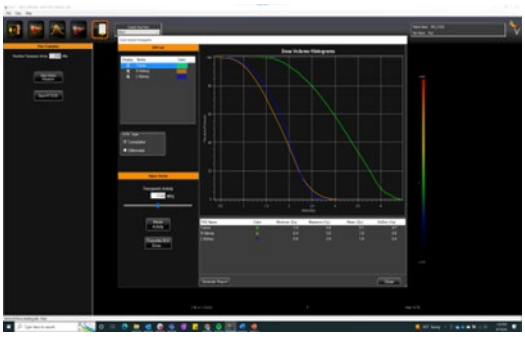


ROIs User imports regions of interest (ROIs) in the form of DICOM structure sets for at least one imaging time point. For multiple timepoint dosimetry, the user can also choose to import their own ROIs for these additional timepoints. For subsequent timepoints, Torch will propagate the contours across timepoints using proprietary GPU-accelerated deformable registration algorithms which ensure accurate alignment of voxels across time. The user is provided with an image fusion tool that allows visual confirmation of the alignment between images across different timepoints to confirm correct alignment between images from different timepoints. If the user finds minor misalignments between them after the import, Torch provides a tool to manually adjust the relative position of image volumes through rigid translations at voxel resolution. The user can also define an ROI-specific recovery coefficient.



Pharmacokinetics User defines ROI pharmacokinetics. Torch provides kinetic modeling tools within a graphical user interface to describe how the radiopharmaceutical distributes into and out of each ROI and outside of the measured time points (i.e., interpolation and/or extrapolation). To simplify the modelling process for the user, Torch utilizes Akaike Information Criterion (AIC) (I.e., goodness of fit) to find the function which best fits the data points. The user can either accept the AIC results or choose from other fitting functions within Torch, manually adjusting the parameters of the selected function if needed. During the fitting process, Torch supports various kinetic models that exhibit different forms of uptake and multi-phasic clearance. Users that prefer numerical methods can choose to apply trapezoidal integration followed by physical decay after the final time point.

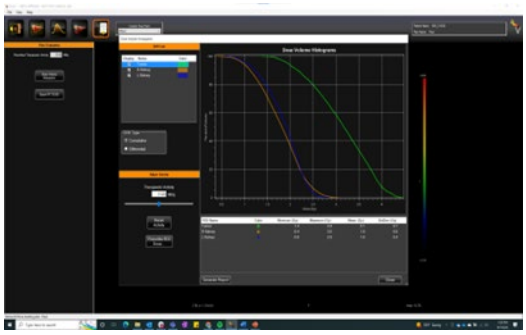
Dose Calculation The time activity volume is used as input into the dosimetry engine. Each voxel of the patient CT volume is converted to electron density following Schneider et al(*1*). Radioactive decays in each activity rich voxel are sampled, and all radiation particles: alphas, betas, gammas, Augers, are transported throughout the entire patient CT volume using Torch MC radiation transport algorithm, which is a modified version of the MC dose calculation code Dose Planning Method (DPM)(*2*) that has been optimized to operate on GPUs.



The MC algorithm uses an accurate and efficient coupled electron-photon transport scheme that retains many of the performance gain enhancements of the original DPM code. Electron transport is done using the condensed history method where large energy transfers are accounted for in the analogue sense and small energy transfers are accounted for by the continuous slowing down approximation. By analogue, it is meant that particles are transported on an event-by-event basis with no dependencies on variance reduction techniques or physics input other than physical cross sections. After each step, the angular distribution of electrons is determined using a step size independent multiple scattering theory. Photons are transported using a standard analogue approach accounting for photoelectric absorption, Compton scattering, and when applicable, pair production. Improvements in photon transport

performance are achieved by implementing the δ-scattering method. Radioactive decay is handled using a per-decay sampling approach with source biasing. Absorbed dose is quantified on the voxel level, resulting in the creation of a dose cloud and isodose lines. Torch v1.0 will support only FDA approved radiopharmaceuticals which are radiolabeled with either ^{177}Lu, ^{90}Y, ^{223}Ra, or ^{131}I. Next,

Dose Assessment User evaluates the radiation transport distribution using dose volume histograms (DVHs), ROI dose statistics, and dose cloud visualizations with optional isodose lines overlaid. Dose volumes can be exported as DICOM-RT to be visualized in other software packages or summed with other DICOM-RT volumes for possible combination with external beam radiotherapy. In addition, a dosimetry report can be generated in PDF format, including digital signatures from the assigned Physicist and Physician. The dosimetry report always includes background information about the treatment including patient identifiers, radiopharmaceutical, imaging time points, and ROI dose statistics. It can also be customizable to include DVHs, dose clouds, and time activity curves with fitting parameters for each ROI. The dosimetry report can be generated which is structured to meet the requirements for "Complex Dosimetry" billing codes in the U.S.



Overview of Software Benchmarking and Validation

Torch has been thoroughly benchmarked and validated using both computational and physical phantoms. Its dose calculations have been benchmarked against the general-purpose Monte Carlo code Geant4(*3*), which is a versatile object-oriented simulation toolkit that allows for the modeling of complex geometries, radiation sources, and detectors, has been used for a variety of different medical physics applications including RPT dosimetry(*4*–*9*). Voxel S-kernels for multiple RPT isotopes in water have been calculated in Torch and compared to Geant4 (data not shown). In addition, Torch has also been benchmarked using data provided by the OpenDose collaboration, which averages the results of six Monte Carlo codes: EGSnrc/EGS++, FLUKA, GATE, Geant4, MCNP/MCNPX, and PENELOPE (*10*). Reference S-values (as defined by the MIRD formulism) have been calculated in the ICRP 110 adult male and female standard phantoms (*11*) for both monoenegetic sources and RPT isotopes. **Figure 1** shows how S-values were calculated using the ICRP 110 male phantom in Torch so that they could be compared with OpenDose. **Figure 2** shows the results of the S-value comparison between Torch and OpenDose using the liver, right kidney, left kidney, spleen, left lung, and lumbar spongiosa as both target and source organs.

A head-to-head comparison of the dose distributions calculated in Torch and Geant4 was also performed using the ICRP phantom (**Figure 4**). For the Torch simulations, decays from 46945 activity voxels were simulated to 2% uncertainty in 1609 seconds for ^{131}I (requiring 22,990 iterations), 8 seconds for ^{90}Y (100 iterations), and 150 seconds for ^{177}Lu (2250 iterations) on an NVIDIA GeForce RTX 3070 GPU card.

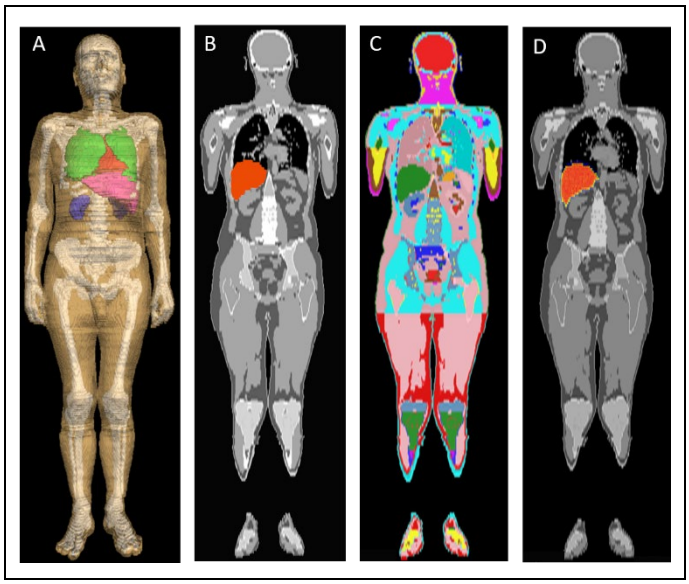


Figure 1. (A) Isosurface of Adult male ICRP 110 phantom with organs of interest, (B) A synthetic nuclear medicine volume was created within the liver for each radioisotope (i.e., target), (C) Regions of interest were created based on the identification numbers (ID) from the ICRP Publication 110, (D) A dose map was generated in Torch

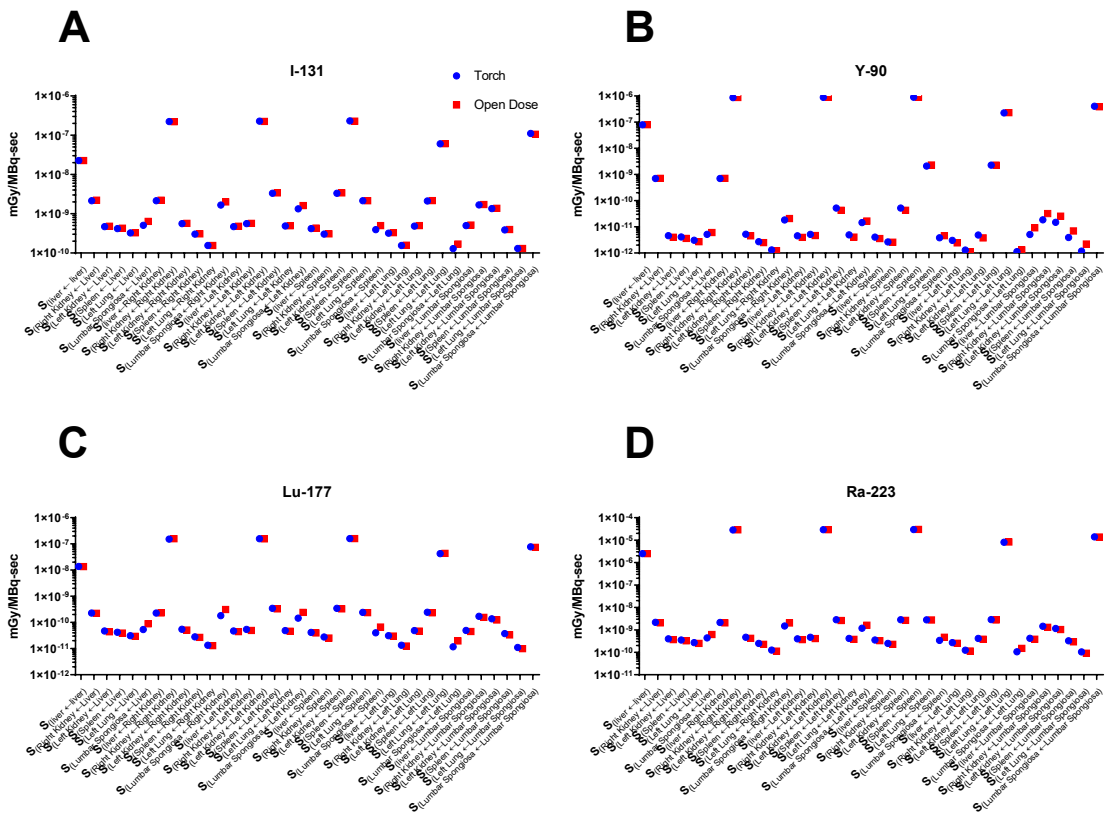


Figure 2. S-value comparison between Torch and Open Dose with respect to target and source organs. (A) I-131, (B) Y-90, (C) Lu-177, and (D) Ra-223 are shown for the liver, right kidney, left kidney, spleen, left lung, and lumbar spongiosa as both target and source organs.

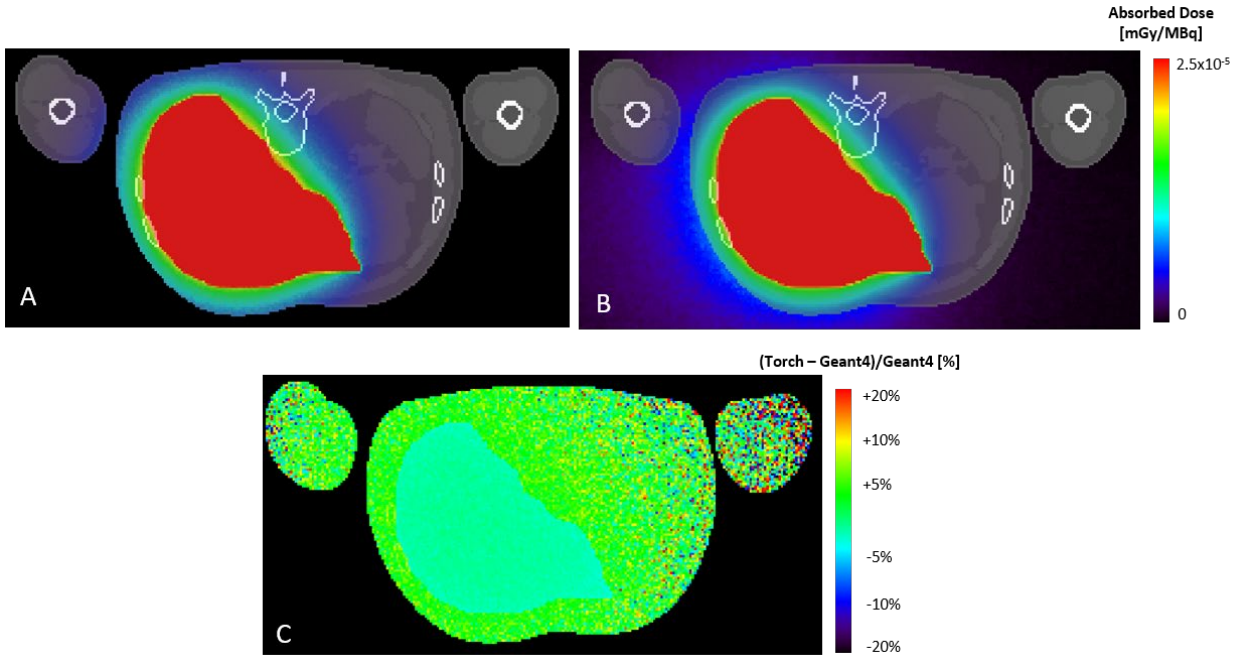


Figure 3. Axial slice of the absorbed dose distribution in the ICRP 110 adult male phantom from a uniform activity of ^{131}I in the liver calculated using (A) Torch and (B) Geant4. Absorbed dose distribution are provided. As expected, most of the deposited dose is within the liver; however, in contrast to dose kernels, there is significant dose in the lungs and chest cavity as well. (C.) Percent difference color wash between Torch and Geant4. Note, the regions or larger percent differences are significantly impacted by statistical uncertainties associated with both simulations.

Voximetry has partnered with the University of Wisconsin Accredited Dosimetry Calibration Laboratory (ADCL) to design and acquire physical measurements that demonstrate the accuracy of Torch. A custom-made film phantom was developed in collaboration UW ADCL to benchmark the electron transport in Torch MC. The film phantom (see **Figure 4**) consisted of a film stack (alternating active layer (top) and protective layer (bottom)), separated with thin slabs of solid water in the case of ^{90}Y exposures. Above the film stack was a cylindrical shell of PMMA that houses the radioactive solution. This solution was separated from the film stack by a very thin Kapton layer (7.62 µm). The film was calibrated using a 250 kVp NIST traceable x-ray beam. Liquid solutions of ^{90}Y and ^{131}I were injected into the phantoms for continuous exposures. Activities and exposure times were adjusted to deliver approximately 350 cGy to the first film layer. Excellent agreement is achieved for between Torch and measured depth-dose distributions (e.g., ^{90}Y comparison shown in **Figure 4D-E**).

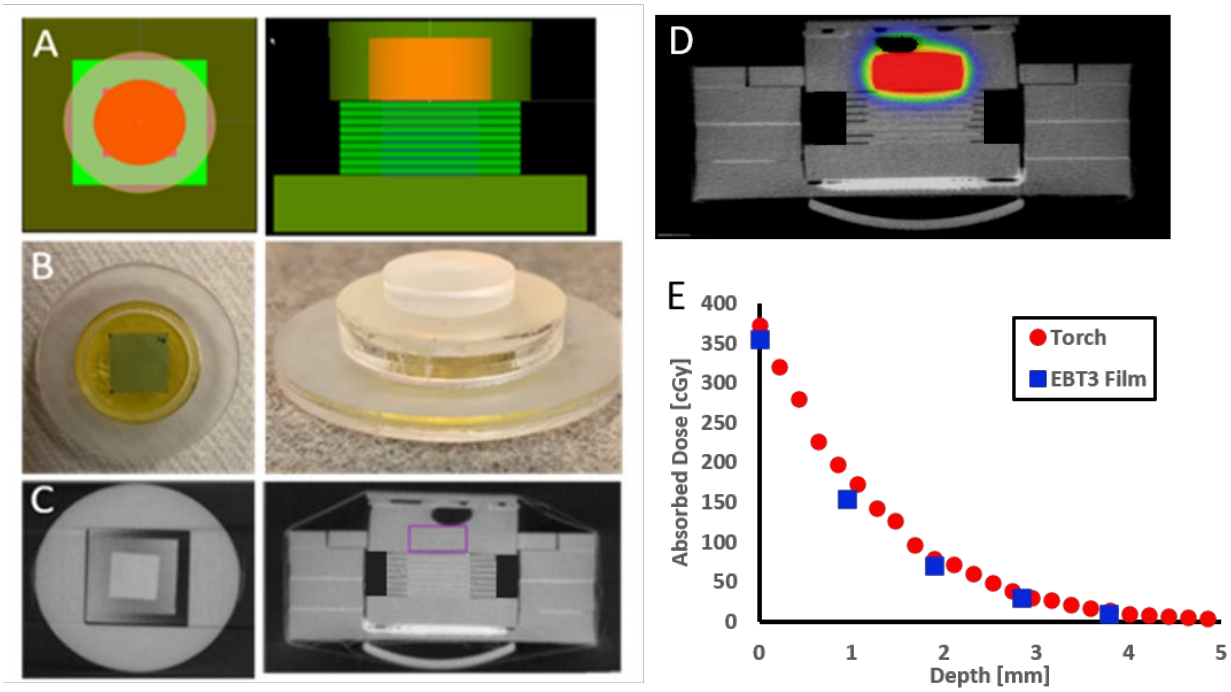


Figure 4: Phantom (A) Film phantom in EGS, (B) Physical phantom design, (C) CT scan of film phantom, (D) Dose distribution of the phantom in Torch, and (E) depth dose results comparing film, EGS, and Torch for ^{90}Y.

Conclusions

Torch will be the first commercial coupled electron-photon Monte Carlo algorithm for RPT dosimetry. It leverages the enormous computing power of graphics processing units (GPUs) to calculate absorbed dose distributions at the voxel level. Torch automated workflows will make RPT treatment planning faster and more accurate, so that it can be used clinically to complete complicated patient-specific dosimetry tasks within minutes thereby decreasing the time and staffing needs typically required to compete these procedures.