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Monte Carlo treatment planning for molecular targeted radiotherapy within the MINERVA system

Joerg Lehmann[1,2], Christine Hartmann Siantar[1,2], Daniel E Wessol[3], Charles A Wemple[3], David Nigg[3], Josh Cogliati[4], Tom Daly[1], Marie-Anne Descalle[1], Terry Flickinger[1], David Pletcher[1] and Gerald DeNardo[2]

[1] University of California, Lawrence Livermore National Laboratory, 7000 East Ave, Livermore, CA 94550, USA
[2] University of California Davis, School of Medicine, Sacramento, CA 95817, USA
[3] Idaho National Engineering and Environmental Laboratory, PO Box 1625, Idaho Falls, ID 83415-3885, USA
[4] Department of Computer Science, Montana State University, Bozeman, MT 59717, USA

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Abstract

The aim of this project is to extend accurate and patient-specific treatment planning to new treatment modalities, such as molecular targeted radiation therapy, incorporating previously crafted and proven Monte Carlo and deterministic computation methods. A flexible software environment is being created that allows planning radiation treatment for these new modalities and combining different forms of radiation treatment with consideration of biological effects. The system uses common input interfaces, medical image sets for definition of patient geometry and dose reporting protocols. Previously, the Idaho National Engineering and Environmental Laboratory (INEEL), Montana State University (MSU) and Lawrence Livermore National Laboratory (LLNL) had accrued experience in the development and application of Monte Carlo based, three-dimensional, computational dosimetry and treatment planning tools for radiotherapy in several specialized areas. In particular, INEEL and MSU have developed computational dosimetry systems for neutron radiotherapy and neutron capture therapy, while LLNL has developed the PEREGRINE computational system for external beam photon–electron therapy. Building on that experience, the INEEL and MSU are developing the MINERVA (modality inclusive environment for radiotherapeutic variable analysis) software system as a general framework for computational dosimetry and treatment planning for a variety of emerging forms of radiotherapy. In collaboration with this development, LLNL has extended its PEREGRINE code to accommodate internal sources for molecular targeted radiotherapy (MTR), and has interfaced it with the plugin architecture of MINERVA. Results from the extended PEREGRINE code have been compared to published data from other codes, and found to be in general

agreement (EGS4—2%, MCNP—10%) (Descalle *et al* 2003 *Cancer Biother. Radiopharm.* **18** 71–9). The code is currently being benchmarked against experimental data. The interpatient variability of the drug pharmacokinetics in MTR can only be properly accounted for by image-based, patient-specific treatment planning, as has been common in external beam radiation therapy for many years. MINERVA offers 3D Monte Carlo-based MTR treatment planning as its first integrated operational capability. The new MINERVA system will ultimately incorporate capabilities for a comprehensive list of radiation therapies. In progress are modules for external beam photon–electron therapy and boron neutron capture therapy (BNCT). Brachytherapy and proton therapy are planned. Through the open application programming interface (API), other groups can add their own modules and share them with the community.

1. Introduction

The MINERVA (modality inclusive environment for radiotherapeutic variable analysis) project intends to extend accurate and patient-specific treatment planning to new modalities, such as molecular targeted radiation therapy (MTR). Many patients who receive MTR have previously been treated with other modalities of radiation therapy, which makes the availability of biologically weighted combined plans highly desirable (Bodey *et al* 2003). MINERVA offers the clinician the potential to evaluate treatment strategies consisting of composite plans of different forms of radiation treatment incorporating specific biological factors. The project is a joint effort of the Idaho National Engineering and Environmental Laboratory (INEEL), Montana State University (MSU), Lawrence Livermore National Laboratory (LLNL) and the University of California Davis School of Medicine. MINERVA builds on accrued experience in the design of three-dimensional Monte Carlo treatment planning tools. INEEL and MSU have developed the BNCT_rtpe and SERA computational dosimetry systems for neutron radiotherapy and neutron capture therapy (Nigg *et al* 1997, Nigg 2003), while LLNL has developed the PEREGRINE Monte Carlo system for external photon beam therapy (Hartmann Siantar *et al* 2001). MINERVA employs an integrated, lightweight plugin architecture to accommodate multi-modal treatment planning using standard interface components.

The work presented here focuses on the treatment planning for MTR within MINERVA, as accurate treatment planning is important to the success of MTR treatment (DeNardo *et al* 1985, 2003, Thomas 2002). For external beam radiation therapy, calculation of patient-specific doses delivered to tumour and normal tissues before treatment is generally accepted as necessary. Studies conducted over several decades have shown that individualized treatment planning improves the response to the radiation treatment and decreases morbidity. The necessity to expand patient-specific radiation treatment planning to radionuclide therapy has been acknowledged (Flux *et al* 2002, Stabin 1999). The available knowledge of the response of specific tumour types to radiation and the relation between radiation dose and early and late tissue toxicity (Rubin 1989, Benua *et al* 1962) will facilitate this effort.

In MTR, radionuclides provide biologically distributed vehicles for radiotherapy of multi-focal cancer. Only an individualized method for prescribing radionuclide dose takes variations in drug pharmacokinetics into consideration, and studies have shown that optimally safe and effective therapy can be best achieved when the prescription is influenced by estimated

radiation dose (Flux *et al* 2003, DeNardo *et al* 2003). The imaging possibilities of MTR are powerful and unique, since they allow the clinician to visualize the distribution of the treatment agent before the treatment. The visualization is achieved by a tracer amount of the radiolabelled drug to be used in the individual patient to determine the pharmacokinetics and subsequently the radiation dose distribution (Siegel *et al* 1999, Bolch *et al* 1999, Williams 1995). Using the images acquired with the tracer dose, treatment planning in MTR can provide information to the physician to (1) qualify the patient for the treatment by estimating the potential benefit and (2) optimize the prescription of targeted radionuclide (Hartmann Siantar *et al* 2002). MINERVA provides three-dimensional, patient-specific Monte Carlo-based dosimetry for MTR. The advantages of the additional dosimetric accuracy achieved with three-dimensional Monte Carlo methods have been described (Johnson and Vessella 1989, Furhang *et al* 1996, 1997, Buffa *et al* 2003).

2. Methods

2.1. MINERVA system overview

The overall MINERVA system is described in detail elsewhere (Lehmann *et al* 2004, Wemple *et al* 2004) and will be introduced here only briefly. MINERVA is a flexible software environment for planning of radiation treatment for multiple modalities with an emphasis on newer forms of radiation therapy and the possibility to create combined plans of different radiation modalities considering biological factors. The system is written in the Java programming language (Gosling *et al* 1996). It consists of a program framework with several universal modules, and supports a standardized interface for implementing certain computational components and for extending the capabilities of the application (application programming interface—API). The main modules are the image module, for import of patient image data in various formats, the model module, for building a model of the patient based on the images to be used for the calculations and the analyze module, for design and analysis of treatment strategies. The actual dose calculating engines are implemented as plugins to allow maximal flexibility. The entire MINERVA system is controlled through the patient module and makes use of a modern database structure. Figure 1 gives an overview of the system.

2.2. Activity map—MTR source module

MTR treatment planning is accomplished within MINERVA through the use of the MTR source module and the MTR transport plugin. The MTR source module offers methods to define the activity map for a targeted radionuclide treatment plan based on patient image information, as described in this section. An explanation of the MTR transportation plugin follows in the next section.

The MTR source module currently supports activity map generation in two modes: manual assignment of a constant value to a region and back projected calculation of the average region activity from gamma camera images.

Manual assignment of a constant activity to an organ or any other type of region (specified previously in the model module) is a simple method that can be used if the more sophisticated methods fail, i.e., due to insufficient image quality or complete lack of radiographic images. The method is also useful as an investigational tool in testing transport codes and comparing the new methods to previously used strategies. Through a menu, an activity can be assigned

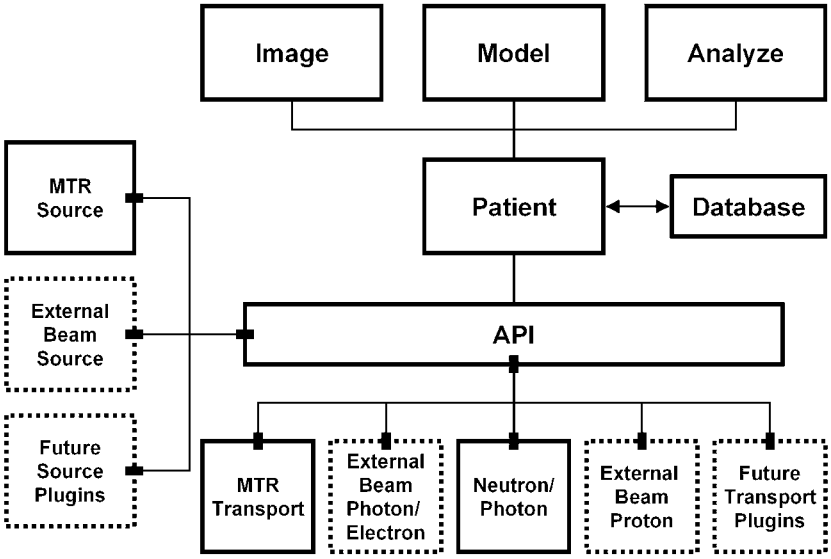

Figure 1. Overview of the MINERVA system. Reprint from Wemple *et al* (2004).

to any number of regions. The assigned activity can be visualized in an activity view, where grey scale levels correspond to the activity (figure 2).

Radiographic emission images taken with a tracer amount of radioactivity attached to the drug are used in the back projection method. Back projection also requires the patient geometry information derived from images in the model module. To employ the method, organs and other regions outlined in the modelling process are selected for display in a projected view, which is then used to align the patient geometry with the emission image. At this point, the activity calculation utilizes a single anterior or posterior image of the patient acquired with a gamma camera. This image can either be obtained with a tracer dose of the treatment isotope, as in the case of gamma emitting isotopes (Zelenetz 2003, Wahl 2003), or with a specific imaging surrogate isotope for exclusively beta emitting treatment isotopes (DeNardo *et al* 1997).

The graphical user interface provides several tools to translate, scale and rotate the patient model in order to align it with the radiographic image (figure 3). To facilitate this process, the user has the option to enable or disable the display of specific regions (e.g., organs).

When aligned, each pixel in the image is correlated with a stack of voxels of the patient geometry, defined as the voxels intersected by a ray projected normal to the image plane at that point. In MINERVA, all voxels are rectangular parallelepipeds of the same dimensions, called univels. Patient images are re-sliced accordingly in the model module to achieve this geometry (Frandsen *et al* 1998).

The calculation of the activity distribution begins with determining the background activity. The user selects a location in the image that is representative of the tissue composition of the background region. The system performs an attenuated backprojection to determine the average activity for the selected location in the image and the 24 nearest neighbouring univels. This value is considered the background activity. The user is prompted to select from a checklist which regions in the patient geometry should be considered to contain only background activity. The activity is calculated for all other regions by first subtracting the attenuated background activity and the activity calculated for other relevant regions from the

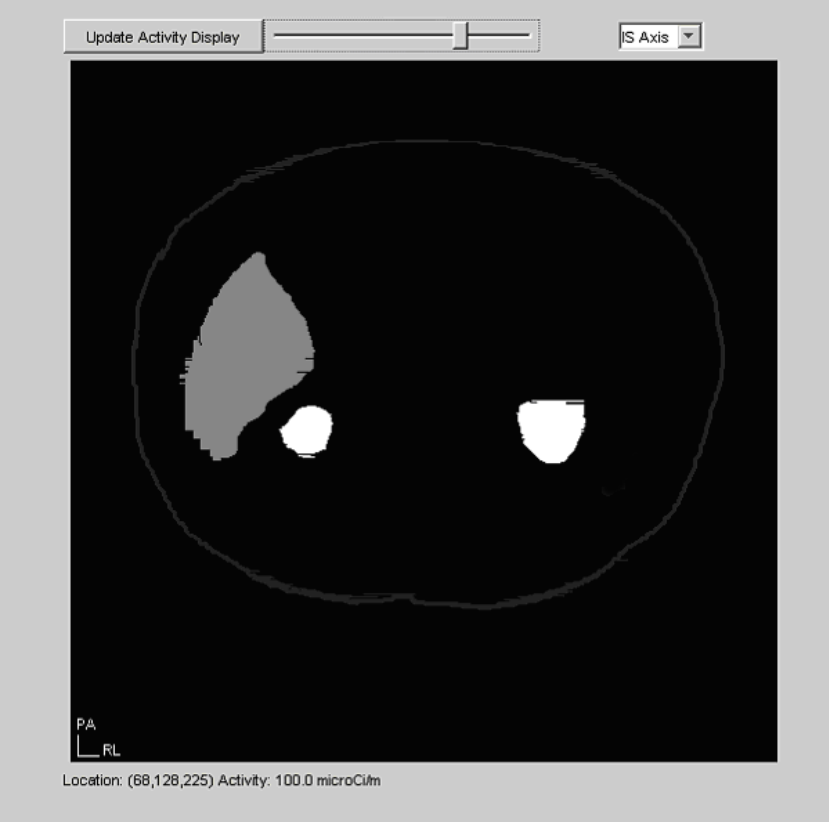

Figure 2. Activity view in the MTR source module. A homogeneous activity has been assigned to liver and both kidneys. Grey level corresponds to activity. The pointer is over the liver and activity (100.0 μCi m^{-1}) is displayed in lower left corner.

image activity at each pixel. The region activity is determined by averaging over all pixels of the region. If the stack of univels contains one or more regions that have no assigned activity, then that stack is not included in the average. Performing this procedure for each region of the patient yields a full three-dimensional activity map of the patient. The user determines the order in which the regions are calculated, and it is advisable to first calculate those regions that have the least overlap with uncalculated regions. The calculated activity map can be visualized in an activity view.

2.3. Dose calculation in the MTR transport plugin

The dose calculation for MTR is performed by the PEREGRINE Monte Carlo dose calculation system (Hartmann Siantar *et al* 2001). PEREGRINE is configured, invoked and controlled from the MINERVA program framework using a plugin module, as described in section 2.1. The PEREGRINE system is a coupled photon–electron Monte Carlo transport simulator that has been designed to compute dose distributions for external beam radiotherapy. For the application in MINERVA, the PEREGRINE code has been extended to include internal photon and electron sources. The code has been successfully tested against published data from other systems. Agreement was found to be generally within 2% in comparison with EGS4 and within 10% in comparison with MCNP (Descalle *et al* 2003). The transport code

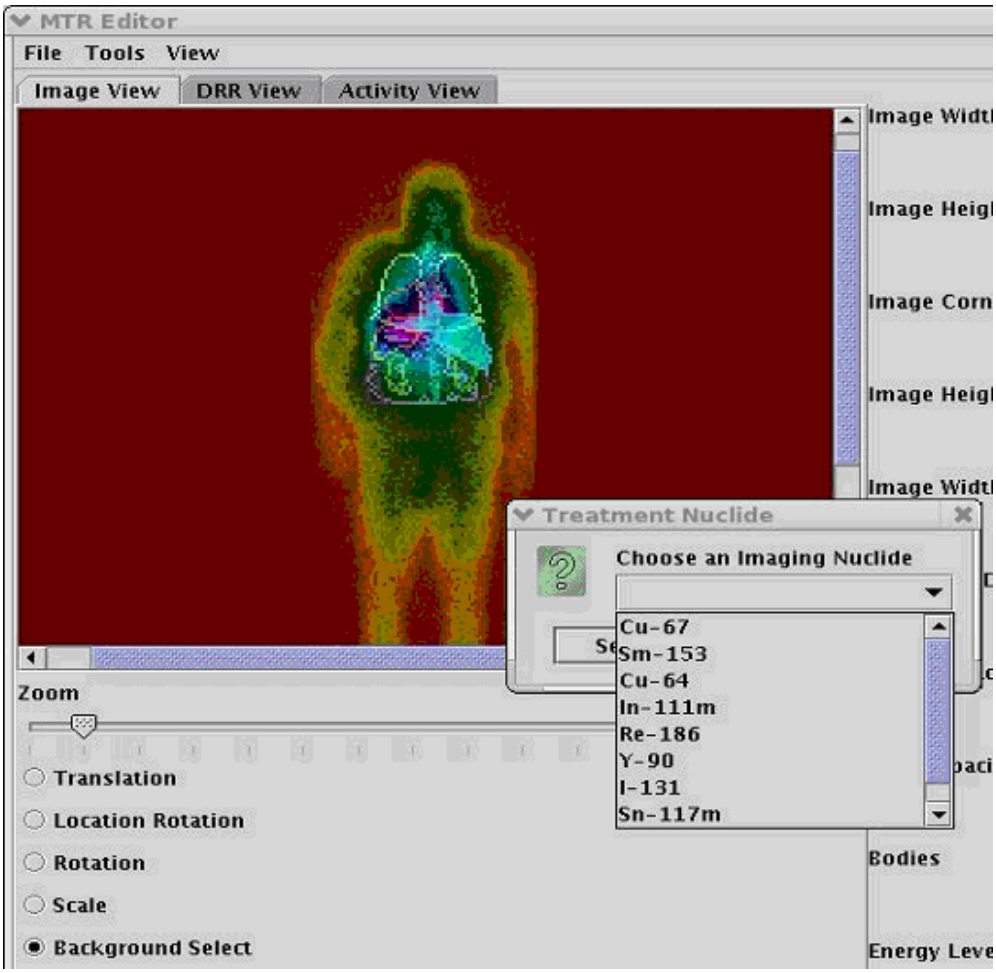

Figure 3. Image view in the MTR source module. The outlined patient organs are aligned with the emission image and the imaging isotope is specified.

is currently being benchmarked against experimental data using an extended liquid source in a solid phantom and incorporating inhomogeneities encountered in the human body such as bones and lungs.

A Java plugin module provides MINERVA users with the seamless capability to invoke the PEREGRINE system for dose calculation from the analyze module for a specific treatment field. The patient data, including the CT image set and the 3D activity distribution, are read in from the database and formatted as input data for the simulation.

Calculation of the dose distribution is made based on a single three-dimensional activity map. The fact that the activity in the patient changes with time can be accounted for with multiple calculations based on activity maps acquired at different time points and appropriate summation of the dose distributions in the analyze module. The way the different time points are combined is intentionally not hard-coded into the system but left to the user since the kinetics are not yet completely understood and are subject to ongoing investigations. MINERVA can therefore be used as a tool in such investigations; dose distributions can be

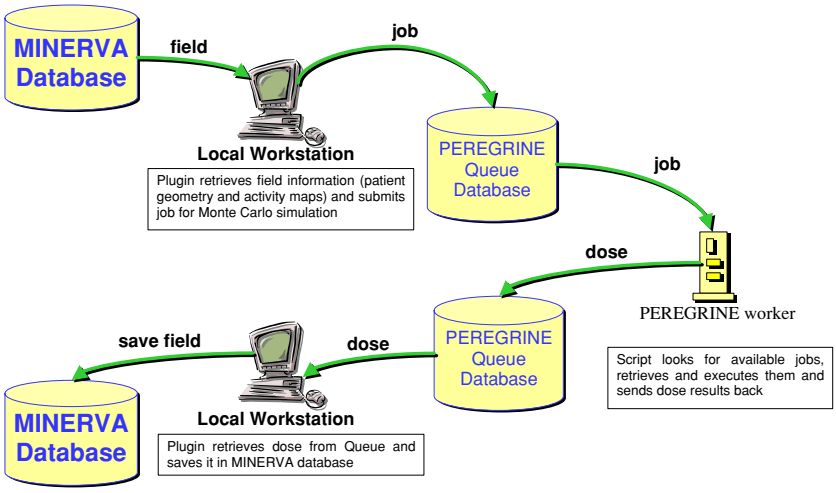

Figure 4. Workflow of the MTR transport plugin. The plugin retrieves all necessary information from the MINERVA database, combines it with the user input simulation parameters and sends a job to the PEREGRINE queue database. A script on a PEREGRINE workers checks the database for waiting jobs in regular intervals, retrieves the information for the job from the database, executes the simulation according to the given parameters and sends the calculated dose distribution back to the database. The user on the local workstation can connect to the database through the MTR transport plugin to check on the status of any simulation and retrieve the dose distribution information once it is available. From the local workstation, the dose information is then saved in the MINERVA database.

combined in various ways and do not have to be recalculated for different combinations of activity distributions.

The user interface of the plugin allows the user to control simulation parameters such as requested statistical uncertainty or number of histories. The MTR transport plugin manages the run of the Monte Carlo simulation automatically. A typical workflow is illustrated in figure 4. The plugin, running on the local workstation, retrieves all necessary information from the MINERVA database (patient geometry, activity distribution), combines it with the user input simulation parameters, formats the input data and sends a job to the PEREGRINE queue database. This database can be local or at a central machine. The connection between the workstation and the database is only necessary for the time of data transmission. One or several machines (PEREGRINE workers) run a script that checks the PEREGRINE queue database for waiting jobs in regular intervals (30 s in the current implementation). If a job is waiting in the database, the script on the PEREGRINE worker retrieves the information for the job from the database, executes the simulation according to the given parameters. It provides updates on the status of a simulation to the PEREGRINE queue database while it is working on a job. After the simulation is finished, the script sends the calculated dose distribution back to the database. The user on the local workstation can connect to the database, using the MTR transport plugin, to check on the status of any simulation and retrieve the dose distribution information once it is available. From the local workstation the dose information is then saved in the MINERVA database.

Tools in the analyze module are available to display the dose distribution overlaid on the CT images or integrated in dose volume histograms (DVH), two common display features in current treatment planning systems.

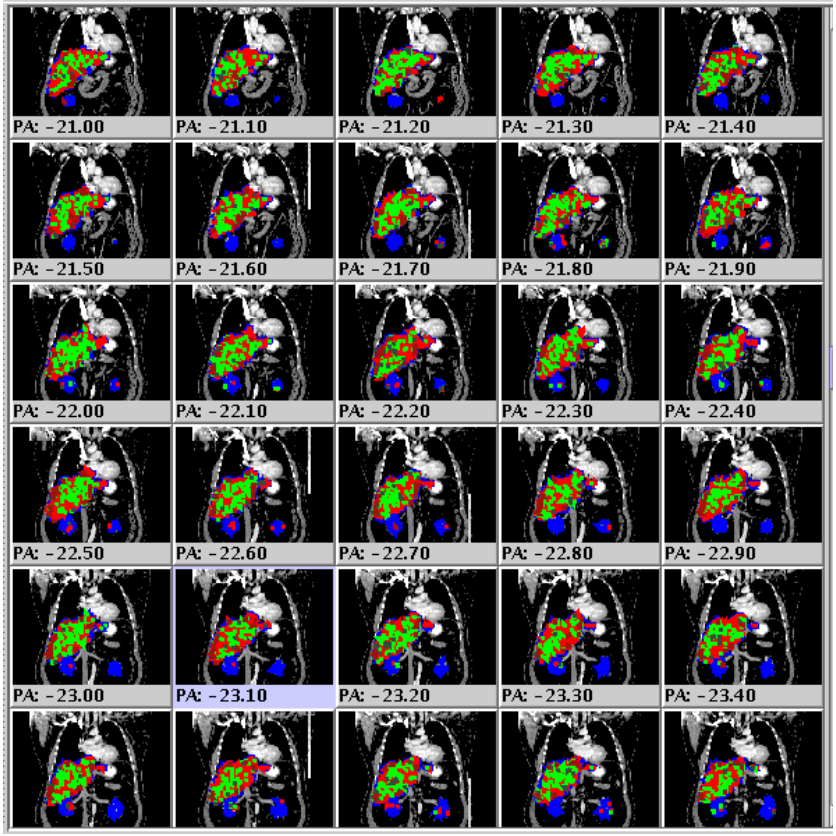

Figure 5. Dose display for an MTR plan. Monte Carlo-based dose distribution for an MTR with the isotope I-131. Light box view with coronal cuts.

3. Results and discussion

Molecular targeted radiation therapy (MTR) is the first implemented operational capability of the new MINERVA system. Using the plugin principle, an MTR source module and an MTR transport module have been designed, implemented and successfully tested. The Monte Carlo simulations for the dose calculation are run as independent processes with the option of running several of them in parallel on multiple CPUs or machines. Current simulation time for MTR is in the order of several hours to days (depending on desired statistical uncertainty) on of-the-shelf personal computers running the Linux operating system.

The accuracy of the PEREGRINE Monte Carlo simulations for MINERVA has been previously reported (Descalle *et al* 2003). This report includes comparisons of specific absorbed fractions calculated with MINERVA to specific absorbed fractions published in the revised MIRD pamphlet 5 (Snyder *et al* 1978) following the validation approach of Johnson (Johnson *et al* 1999). Table 1 shows the results of this comparison for the source organs such as liver, kidneys and adrenals (100 keV photon sources uniformly distributed) paired with each of the target organs such as lungs, adrenals, kidneys, liver, pancreas and the spleen in a heterogeneous phantom. The agreement is within 3.7% for all specific absorbed fractions within the source organs themselves and within 5% for most others.

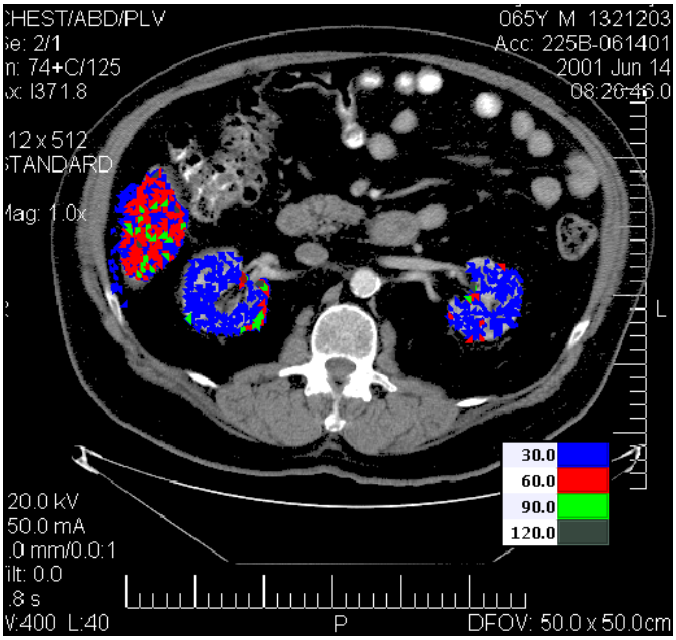

Figure 6. Dose display for an MTR plan. Monte Carlo-based dose distribution for an MTR with the isotope I-131. The axial view with legend of the dose level overlaid. For demonstration purposes only four dose levels are shown.

Table 1. Comparison of specific absorbed fractions calculated with the MINERVA code and the specific absorbed fractions given in revised MIRD pamphlet 5 (Snyder *et al* 1978) for 100 keV photons emitted by source organs of a heterogeneous phantom. Source organs are adrenals, kidneys and liver, and target organs are lungs, adrenals, kidneys, liver, pancreas and spleen. (Table partially adapted with permission from Descalle *et al* (2003).)

	Source organs (relative difference in absorbed fraction MIRD 5/ MINERVA (%))		
Target organs	Adrenals	Kidneys	Liver
Lungs	−11.9	0.8	3.5
Adrenals	−3.7	7.1	−23.4
Kidneys	5.7	1.0	4.0
Liver	3.4	−0.9	−1.6
Pancreas	5.0	−1.5	−0.5
Spleen	−2.3	−3.6	−3.9

The MINERVA MTR implementation has been tested with patient image data. Figures 5 and 6 show the dose displays from the analyze module for a Monte Carlo-based dose distribution for the treatment isotope I-131. In the MTR source, module homogeneous activities have been assigned each to the liver and the kidneys. For experimental purposes, the specific activity in the liver was chosen double the specific activity in the kidneys. Figure 5 shows the light box view with coronal cuts. Figure 6 shows an axial slice that contains part of liver and kidneys. It has a legend of the dose level overlaid. For demonstration purposes, only four dose levels are shown. As expected for the given activity distribution, the dose delivered to the voxels within the liver is approximately double the dose to the voxels

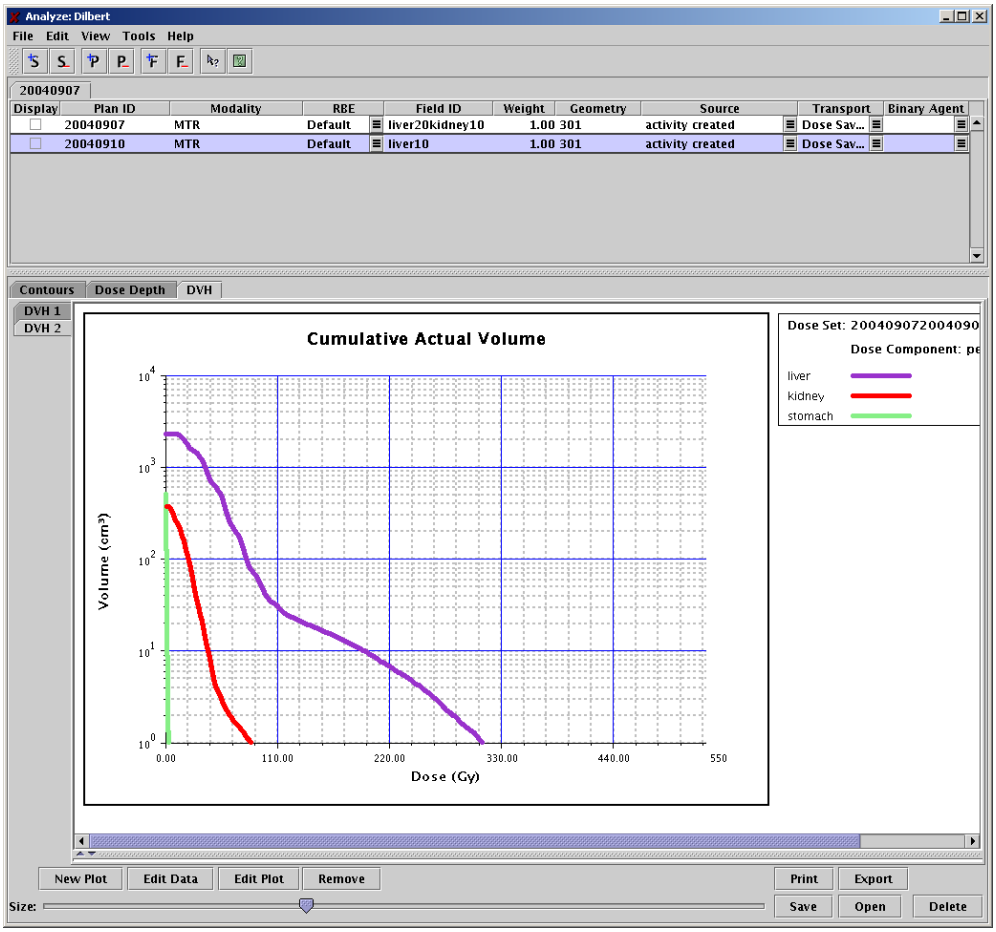

Figure 7. Dose display for an MTR plan. Monte Carlo-based dose distribution for an MTR with the isotope I-131. Sample dose volume histograms for liver, kidneys and stomach are shown within the user interface of the analyze module.

within the kidney. The dose is mainly confined to those organs. There are inhomogeneities in the dose distribution within the organs, which are due to statistical uncertainty of the particular simulation, a concern that needs to be addressed for all Monte Carlo simulations. Figure 7 shows the entire user interface of the analyze module for this I-131 case with a DVH tab selected.

While several components of MINERVA are still under development, the successful implementation of MTR calculations is an important step on the way to a system that will incorporate several radiotherapy modalities. MINERVA will enable the physician to make clinical decisions based on composite plans with biological weighting factors for the various radiotherapy modalities. It will assist researchers with tools to identify these factors.

MINERVA is open for extension by users through the API. Several groups have already indicated strong interest in working with the code. The next step underway at INEEL and MSU is the implementation of the neutron transport plugin. External beam photon and electron capabilities using widely available codes are to follow.

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