Published in final edited form as:

Phys Med Biol. 2013 July 21; 58(14): 4717–4731. doi:10.1088/0031-9155/58/14/4717.

Investigation of effect of variations in bone fraction and red marrow cellularity on bone marrow dosimetry in radio-immunotherapy

S J Wilderman¹, P L Roberson², W E Bolch³, and Y K Dewaraja⁴

S J Wilderman: sjwnc@umich.edu

¹Department of Nuclear Engineering and Radiologic Sciences, University of Michigan, Ann Arbor, MI

²Department of Radiation Oncology, University of Michigan, Ann Arbor, MI

³Department of Biomedical Engineering, University of Florida, Gainesville, FL

⁴Department of Radiology, University of Michigan, Ann Arbor, MI

Abstract

A method is described for computing patient-specific absorbed dose-rates to active marrow which accounts for spatial variation in bone volume fraction and marrow cellularity. A module has been added to the 3D Monte Carlo dosimetry program DPM to treat energy deposition in the components of bone spongiosa distinctly. Homogeneous voxels in regions containing bone spongiosa (as defined on CT images) are assumed to be comprised only of bone, active (red) marrow and inactive (yellow) marrow. Cellularities are determined from biopsy, and bone volume fractions are computed from cellularities and CT-derived voxel densities. Electrons are assumed to deposit energy locally in the three constituent components in proportions determined by electron energy absorption fractions which depend on energy, cellularity, and bone volume fraction, and which are either taken from the literature or are derived from Monte Carlo simulations using EGS5. Separate algorithms are used to model primary β particles and secondary electrons generated after photon interactions. Results: Treating energy deposition distinctly in bone spongiosa constituents leads to marrow dosimetry results which differ from homogeneous spongiosa dosimetry by up to 20%. Dose rates in active marrow regions with cellularities of 20, 50, and 80% can vary by up to 20%, and can differ by up to 10% as a function of bone volume fraction. Conclusions: Dose to bone marrow exhibits a strong dependence on marrow cellularity and a potentially significant dependence on bone volume fraction.

1. Introduction

Mitigation of active marrow toxicity is the dose-limiting factor in radio-immunotherapy treatment of non-Hodgkin's lymphoma patients using I-131 labeled tositumomab. A current treatment protocol at the University of Michigan limits therapeutic activity administration at the level estimated to produce no more than 65–75 cGy whole-body dose, based on a planar gamma-camera assessment from a tracer study. Radiation-induced myelotoxicity varies greatly between patients for a fixed whole-body dose (Kaminski, Zelenetz, Press, Saleh, Leonard, Fehrenbacher, Lister, Stagg, Tidmarsh, Kroll, Wahl, Knox & Vose 2001), however, leading to the possibility that patients who exhibit low degrees of active marrow suppression may have been unnecessarily under-dosed. Therefore, an accurate method for

the *a priori* prediction of hemotoxicity would permit patient-specific treatment planning and could lead to better therapeutic outcomes.

One of the first steps required for predicting patient-specific myelotoxicity is the development of an accurate model for determining absorbed dose to active bone marrow. We present such a model in the current work, in which we extend and expand a previously developed imaged-based Monte Carlo dosimetry methodology for tumor (Wilderman & Dewaraja 2007, Amro, Wilderman, Dewaraja & Roberson 2010, Dewaraja, Schipper, Roberson, Wilderman, Amro, Regan, Koral, Kaminski & Avram 2010) to active marrow, accounting for patient-specific spatial variations in bone volume fraction and active marrow cellularity (the fraction of all marrow which is active marrow) in the spongiosa of marrow-bearing bone regions.

As in prior work with tumors, the imaged-based active marrow dosimetry model begins with registered SPECT/CT images acquired at various times during each study. Because most tumors being treated in the current work are in the abdominal region, images of lumbar and sacrum regions containing significant bone marrow are usually available. Active marrow volumes of interest are outlined on CT, as seen in figure 1.

The difficulty in estimating active marrow dose arises because while Monte Carlo dosimetry programs necessarily model voxels of macroscopic dimension (roughly $1 \times 1 \times 5$ mm in this work) as homogeneous mixtures, dose deposition in active marrow is a microscopic (sub-voxel) process. The thicknesses of bone trabeculae are typically on the order of several hundred microns, and so photon and electron transport processes leading to marrow dose deposition occur inside each voxel. The DPM (Wilderman & Dewaraja 2007) program used in our prior tumor dosimetry work for computing time-dependent 3D dose rate maps models all voxels as water of varying density, and so the computed dose delivered to bone spongiosa combines the dose to marrow, bone, and non-marrow components into an average dose to each voxel. The dose to active marrow must then be extracted from the average voxel doses using some manner of approximate dose-apportionment scheme which accounts for the amount of bone, active marrow and inactive marrow in the voxel.

Unfortunately, the approximations involved in any such scheme can be rather severe. First, the exact composition of the voxels in marrow-bearing regions is usually not known. Additionally, because antibodies in RIT preferentially attach to active marrow sites (Hindorf, Glattin, Chiesa, Linden & Flux 2010), the activity in such voxels is not uniformly distributed among the various components of the marrow voxels, as is the assumption inherent in macro-level Monte Carlo models such as DPM. Because of this non-uniform binding, the exact geometry of the bone trabeculae in the spongiosa can have a large effect on active marrow dosimetry, even when the relative composition of the constituent materials within the voxel are known. Because of these factors, as well as the difference between the density of bone and marrow, neither the voxel-average dose nor any sort of relative-weight scaling of the macroscopic dose produces a reliable estimate of the marrow dose.

To address the inadequacies of macroscopic active marrow dosimetry models, Bolch and co-workers developed the “Paired-Image Radiation Transport Model” (PIRT), in which marrow-bearing voxels in a macro-level Monte Carlo dosimetry program were coupled to a micro-level Monte Carlo program which references approximate, analog models of the structure of trabecular bone (derived from micro-CT or MRI) on the microscopic level (Shah, Bolch, Rajon, Patton & Jokisch 2005). In PIRT, the simulation of particle transport is handed back and forth between the macro-code and the micro-code whenever particles enter or leave marrow-bearing regions. Such a treatment is, however, quite time consuming, since the geometric regions modeled in the micro-code are on the order of 10s of microns.

Recently, this same group published tables of electron energy absorption fractions as a function of cellularity for all marrow-bearing bones in adults and infants (Hough, Johnson, Rajon, Jokisch, Lee & Bolch 2011, Pafundi, Lee, Watchman, Bourke, Aris, Shagina, Harrison, Fell & Bolch 2009). In generating the tables, the PIRT methodology was followed. Microscopic-level bone spongiosa anatomy was derived by voxelizing micro-CT images of marrow-intact spongiosa harvested from the cadaver bone samples.

The availability of electron energy absorption fractions as a function of cellularity for different marrow-bearing bones opens up the possibility for a new method for active marrow dosimetry which does not rely on the PIRT methodology, which is computationally very expensive and yet still approximate, as microscopic spongiosa geometry is derived or assumed rather than explicitly measured. We thus propose in this work an alternative to PIRT in which macro-level dosimetry computations using DPM are coupled with a novel tallying scheme using electron energy absorption fractions to generate active marrow doses at the voxel level, taking into account patient-specific variations in bone volume fractions and cellularities.

2. Methods

Throughout this work, we follow the terminology used to describe bone anatomy found in the various publications of Bolch and co-workers. Abbreviations for the various components are given in table 1. Hough's energy absorption fraction tables (Hough et al. 2011) include active marrow specific energy absorption fraction data as a function of energy for all of the source regions in table 1, and for active marrow as a function of cellularity. For the current work, we ignore cortical bone, and we ignore TBS as a source, and instead assume that all decays occur within the active marrow, as tositumomab binds only in active marrow (Hindorf et al. 2010). In addition to electron energy absorption in active marrow, Hough also considers dose to total shallow marrow, which is defined as marrow lying within 50 microns of bone surfaces. Shallow marrow dose plays a significant role in the development of bone cancer, but is not important for the current study and so is not treated explicitly. All constituents of bone spongiosa apart from active marrow and trabecular bone volume are treated as part of the inactive marrow, a common approximation (used by Hough, for example).

The general framework of our current tumor dosimetry method involves Monte Carlo computation of 3D dose rate maps at six times, followed by numerical integration over time of maps of dose rate times activity. Activity and anatomical data are taken from registered SPECT and CT images (512 by 512 by 78 CT voxels roughly 1 mm by 1 mm by 5 mm) acquired with an integrated Siemens Symbia scanner three times (from 0 to 7 days) after administration of tracer activity and three times (from 2 to 7 days) after administration of therapy activity. Patient-specific marrow cellularities are taken from bone marrow biopsies already obtained for clinical purposes, and typically corresponding to iliac regions.[‡]

As noted earlier, the Hough electron energy absorption fractions were derived from a single cadaver specimen. Thus, even though absorption fraction data is available for a nearly complete set of marrow-bearing regions, the anatomy (including the bone volume fractions), are fixed at each region. Unfortunately, measurements of patient bone volume fractions in our current study display wide variation from those of the Hough cadaver, as seen in table 2, which presents the region average, voxel minimum and voxel maximum bone volume fractions for 14 patients.

[‡]Preliminary efforts at measuring regionally varying cellularities in lumbar and sacrum using quantitative dual-energy CT imaging (Howard, Goodsitt, Wilderman & Dewaraja 2011) have shown some promise but have been deemed not yet fully reliable.

Further, as seen in figure 2, which presents Hough's electron energy absorption fractions for various bone regions with different bone volume fractions, there is some variation in the absorption fractions at energies relevant to RIT dosimetry.

To more faithfully account for the patient-specific and voxel-level variation in bone fraction, we have computed generic electron energy absorption fractions as a function of energy for varying bone volume fraction and cellularity, using the general purpose Monte Carlo program EGS5 (Hirayama, Namito, Bielajew, Wilderman & Nelson 2005) and a method described in the appendix.

For the current work, DPM has been modified to use electron energy absorption fractions to compute marrow dose. By overlaying new tallying subroutines on top of the existing dose algorithm (which was not altered), marrow dosimetry calculations can now be done in parallel with standard DPM dosimetry simulations (usually for tumor), but with independent tallies computed and reported. The main assumption invoked in the energy absorption fraction methodology is that whenever an electron is found in a spongiosa voxel, all of its energy is immediately deposited in red (active) marrow, yellow (inactive) marrow and bone. Note that this does not imply that the energy is deposited within the source voxel, just that it is absorbed somewhere in the active marrow matrix.

Electrons enter marrow voxels in three distinct ways. They can be born there, as primary betas (or other atomic relaxation products); they can be generated as secondary particles subsequent to photon collisions; and they can cross into a marrow voxel from a non-marrow voxel. In practice, this latter manner rarely occurs, as electron ranges are usually small relative the voxel sizes, and most electrons born as primary betas are deposited locally (or within several voxels) at birth. Only those electrons crossing from the cortical bone regions surrounding the marrow into the marrow enter marrow-bearing regions from non-marrow regions through boundary crossing.

As noted above, for the current work, when a decay is sampled as occurring in a marrow voxel, it is assumed to have taken place in the active marrow. DPM models decays in a direct analog manner, treating distinctly the production of any gammas, betas, conversion electrons, characteristic x-rays, and so on, at each individual decay site. For the method developed here, energetic gammas emitted from marrow voxels are tracked in the usual way. Energy from all electrons and low energy gammas is fully deposited, in red marrow, bone and inactive marrow. Red marrow energy deposition is computed from the energy absorption fraction interpolated in energy and cellularity from tabulated data. Electron absorption fractions are used for deposition of low energy photon energy as well, given that all photon energy will eventually be converted to electron energy (most likely in the form of photo-electrons carrying close to the x-ray energy) and that the absorption fractions are roughly constant at low energies anyway. The remaining energy is apportioned to yellow marrow and bone based on their relative weight fractions, which can be computed from either the region cellularity and the reference bone fraction for the region (as reported by Hough) or from the cellularity and the voxel density. The combined active plus inactive marrow density can be computed from the cellularity, and from this value plus the overall voxel density (taken from CT), the bone volume fraction is uniquely determined. Note that using this latter method in conjunction with the Hough absorption fractions is somewhat inconsistent, in that the Hough data is reported as the average absorption fraction for an entire bone region with a known average bone fraction. This is not the case when EGS5 data tables are used, as those energy fractions are tabulated in energy, cellularity, and arbitrary bone fraction rather than for a given bone fraction.

Electrons arising from secondary particles are treated differently. First, DPM is interrupted at the point of the secondary particle generation (for photon processes only, as all electrons in marrow-bearing voxels will already have been fully treated). The constituent material (bone, red or yellow marrow) in which the interaction is assumed to have taken place is then sampled from the relative macroscopic cross sections in each of the three constituent materials for the given interaction type. If the interaction is determined to have taken place in active marrow, the tallying proceeds as described above for primary particles. If the interaction is determined to have taken place in bone or inactive marrow, energy is first deposited in marrow using the absorption fraction appropriate for the source, and the remaining energy is then apportioned to fat and bone as above.

One loophole in the methodology is that energy can be double-counted should a fully deposited electron (primary or secondary) give rise to an energetic bremsstrahlung photon which later interacts in a marrow region. This a rare occurrence, however, as energetic bremsstrahlung production is a low probability event at typical energies (0.6% for a 200 keV beta), and even when photons are produced, their range is great enough that they are likely to escape the spongiosa. Simulations showed the net average overestimation in marrow energy deposition to be approximately 30 eV for a 200 keV beta.

Validation of energy apportionment methodology

The method described above for modeling primary electrons, in which we assume that all primary electron energy is deposited locally, should be accurate enough that it does not require explicit validation. The average beta particle in the current study has an energy of approximately 200 keV and a range of roughly .5 mm in liquid water, which is shorter than the dimensions of the image voxels (1 by 1 by 5 mm). Equally importantly, the electron energy absorption fractions already take into account energy deposition in the constituent materials when electrons migrate across the boundaries between marrow-bearing voxels. Only those betas which travel from marrow bearing voxels to non-marrow regions will be modeled incorrectly. Since the number of such electrons will be a small fraction of the total, and since they will most likely exit the marrow at low energies, the overall error in the method given here for depositing primary beta energy will be quite small. Test simulations showed the over-estimation in red marrow dose due to scoring electron energy which was actually transported out of spongiosa to be on the order of 600 eV for a 200 keV beta.

To further test the reliability of the method described above for appropriately apportioning energy deposition in bone, active marrow, and inactive marrow from secondary electrons resulting from photon interactions, simulations were performed using the EGS5 bone and marrow lattice geometry described in the appendix. First, for various combinations of bone fraction and cellularity, energy deposition in bone and in red and yellow marrow was computed for mono-energetic photons of various energies normally impinging at random positions on the inner half (128 by 128) pixels on one surface of the lattice. Next, the energy apportionment methodology described above for DPM was implemented in EGS5, and simulations performed on the same lattice geometries, but with the media of all regions set to the homogeneous mixture of bone and marrow, corresponding to the lattice being evaluated. Results from the two sets of runs were then compared. Representative data is shown in tables 3 and 4.

Discrepancies between the results of direct analog simulations and the apportionment method of the current work are generally on the order of 1–3%. The exception is for very low and very high cellularities at very low photon energies, where differences of up to 8% were observed.

3. Results and Discussion

Using the method described above, dose to active marrow was computed for several patients who had been imaged with SPECT/CT following I-131 tositumomab administration. Electron energy absorption fractions were taken from Hough for specific bone regions and also from tabulations for arbitrary bone fractions and cellularities, generated in this work using EGS5 (as described in the appendix). Representative results for three marrow regions in two patients are shown in tables 5 through 7. Each table includes the homogeneous region average dose rate and the dose rates computed with the electron energy absorption fraction method using data from the appropriate Hough bone data set, from EGS5 at several BVFs near the Hough cadaver BVF (for comparison), from EGS5 at BVFs corresponding to the actual patient BVF, and from the full, generic EGS5 data set using BVFs applied on a voxel-by-voxel basis. The DPM homogeneous region dose rates were included for comparison, since spongiosa dose rates have been suggested as a crude surrogate for active marrow dose rates (Dewaraja, Roberson, Schipper, Regan, Avram, Kaminski & Wilderman 2012).

Patient A sacrum active marrow dose rates computed using the Hough reference sacrum absorption fractions differ by roughly 12% from those computed with EGS5 generated fractions appropriate to each voxel, as seen in table 5. The average sacrum BVF for this patient was 8%, while the reference cadaver sacrum upon which the Hough tabulations are based had a BVF of 11.8%. Results using EGS5 data at constant BVFs of 7% and 9% (the EGS5 data is tabulated only at odd values of BVFs) differ from the voxel-level EGS5 results by approximately 1%, indicating that explicit modeling of variations in BVF between voxels may not significantly impact active marrow dosimetry.

Table 6 gives the dose rates in the lumbar region for this same patient (BVF was 10%). Results computed with Hough (reference lumbar BVF 10%) and voxel-level EGS5 electron energy absorption fractions differ by approximately 6% in this case. Once again, the voxel-level results differ from those using the most representative constant BVF EGS5 data by just 1–2%.

Although the energy absorption fractions for both the Hough and the EGS5 tabulations were derived for reference phantoms with roughly the same BVF, the absorption fractions differ somewhat, especially at higher electron energies and low cellularities. The disagreements in the calculated dose rates found in the table most likely arise from these differences.

The most probable cause of the discrepancies between the Hough and EGS5 data sets is differences in the spongiosa geometry model. The Hough data was generated using the PIRT methodology and simulated spongiosa geometry based on cadaver samples specific to the region in question. The EGS5 electron energy absorption fractions were generated using an approximate geometry model based on lumbar marrow cavity chord length distributions, and uses a slightly different physics model than that underlying PIRT. Additionally, Hough's analysis showed a wide variation in the anatomical structure of vertebrae, particularly in L1–L3 vs. L4–L5. Hough's data tables, however, present absorption fractions averaged over the lumbar region. The EGS5 energy absorption fractions in contrast were derived using an approximate spongiosa geometry based on a fixed distribution of L2 and L4 lumbar marrow chord sizes.

Note that in both regions for patient A, the spongiosa region average dose rate is within 2–5% of the active marrow dose rate computed with the current model. This is not the case for the lumbar dose rates computed for patient B, as shown in table 7, where the discrepancies are on the order of 20%. Curiously, the Hough and EGS5 results agree to within 2%, even though the Hough lumbar tables were compiled for a 10% BVF region, while the EGS5 data

matched the patient BVF of 20%. This anomaly is again most likely due to differences in the underlying geometry model used in the Hough and EGS5 calculations.

The effects of cellularity on active marrow dosimetry using the current model are demonstrated in tables 8 and 9. For the current study, cellularities determined from biopsy, though typically around 50%, ranged from 5% to 80%.

Dose rates are seen to change by roughly 20% as cellularities vary from 20% to 80%, and to differ from the dose rate at the patient average (mode) of 50% cellularity by +15% and -5% respectively. The fact that the effect is more significant at lower cellularities could have bearing on the current study, as the population is generally older and includes a high fraction of refractory patients, for which lower cellularities are more common. Of the 50 patients in the current study for which cellularity data is available, 18 were assessed as having cellularity values of 30% or less, while just 8 had values above 50%.

4. Conclusions and Future Work

A method has been devised for Monte Carlo computation of dose rates to active bone marrow in RIT treatment using an apportionment scheme based on electron energy absorption fractions. The method is capable of treating patient-specific variations in bone volume fractions and active marrow cellularity on a voxel-by-voxel basis. Results from a simulated problem designed to test the basic model of the algorithm showed excellent agreement with analog results.

Despite some theoretical inconsistencies, dose rates computed with a single set of electron absorption fractions (taken from a reference phantom with a constant, region-average BVF) did not differ significantly from dose rates computed with absorption fractions consistent with the voxel-level distributions of BVFs in the region, provided that the reference BVF was similar to the patient region-average BVF.

The effect of using electron energy absorption fractions from a reference phantom with a spongiosa BVF not equivalent to the actual patient BVF was not perfectly quantifiable. Qualitatively, based on simulations using only the EGS5 data, the effect appeared to be on the order of 1–2% in dose rate for each 1% discrepancy in BVF. For some patients in the current study, this could lead to as much as a 10–15% difference in dose rate because of variation in BVF from reference data.

The magnitude of this potential error is what motivated the construction and implementation of the EGS5-based electron energy absorption fraction data sets throughout the range of patient BVFs, and clearly warrants additional study. The current results suggest that patient-specific absorbed dose to active marrow clearly should, at a minimum, be calculated using energy absorption fractions for BVFs corresponding to patient anatomy.

Additionally, the ambiguity in the quantitative evaluation of variations in BVFs indicate that the details of spongiosa geometry can have a potentially large effect on marrow dose. A patient spongiosa region with thick bone trabeculae and large marrow cavities can have the same BVF as a region with thinner bone and smaller cavities, and yet will have significantly different marrow dosimetry properties. Future studies should investigate the magnitude of this effect and lead to the development of methods for computing absorption fraction data sets encompassing both BVF and anatomical spongiosa details, taken either from extended cadaver studies or more realistic simulated geometries.

Computed active marrow dose rates were seen to vary by 20% as cellularity ranged from 20–80%. Since this effect is quite large and as the uncertainty in the biopsy measurements is

also quite large (indeed, the biopsies are not taken from the same region that is imaged and analyzed), alternative methods for quantifying cellularity, such as using dual energy quantitative CT(Howard et al. 2011) or MRI(Pichardo, Milner & Bolch 2011), are being investigated.

Lastly, the current work involves only the computation of dose rates in one or two marrow regions of each patient. Methods for extrapolating average marrow dose from these dose rates should be investigated.

Acknowledgments

This work has been partially supported through grant 2R01 EB001994 awarded by the National Institutes of Health, United States Department of Health and Human Services.

References

- Amro H, Wilderman SJ, Dewaraja YK, Roberson PL. Methodology to incorporate biologically effective dose and equivalent uniform dose in patient-specific 3-dimensional dosimetry for non-Hodgkin's lymphoma patients targeted with I 131 tositumomab therapy. *Journal of Nuclear Medicine*. 2010; 51:654–659. [PubMed: 20237032]
- Dewaraja YK, Roberson PL, Schipper MJ, Regan DD, Avram AM, Kaminski MS, Wilderman SJ. Dose-hematotoxicity correlation for I-131 radioimmunotherapy (RIT) using a SPECT/CT imaging based estimate of the radiation absorbed dose to the lumbar vertebrae. *European Journal of Nuclear Medicine and Molecular Imaging*. 2012; 39 (Suppl 2):S304–S353. DOI 10.1007/s00259-012-222 -2 9.
- Dewaraja YK, Schipper MJ, Roberson PL, Wilderman SJ, Amro H, Regan DD, Koral KF, Kaminski MS, Avram AM. I-131 tositumomab radioimmunotherapy: initial tumor dose-response results using 3-D dosimetry including radiobiological modeling. *Journal of Nuclear Medicine*. 2010; 51:1155–1162. [PubMed: 20554734]
- Hindorf C, Glattin G, Chiesa C, Linden O, Flux G. EANM Dosimetry Committee guidelines for bone marrow and whole-body dosimetry. *European Journal of Nuclear Medicine and Molecular Imaging*. 2010; 37:1238–1250. [PubMed: 20411259]
- Hirayama, H.; Namito, Y.; Bielajew, AF.; Wilderman, SJ.; Nelson, WR. Report SLAC-R-730. Stanford Linear Accelerator Center; Stanford, CA: 2005. The EGS5 Code System.
- Hough M, Johnson P, Rajon DA, Jokisch DW, Lee C, Bolch WE. An imaged-based skeletal dosimetry model for the ICRP reference adult male – internal electron sources. *Physics in Medicine and Biology*. 2011; 56:2309–2346. [PubMed: 21427487]
- Howard, DM.; Goodsitt, M.; Wilderman, SJ.; Dewaraja, YK. Evaluation of Dual-Energy Quantitative CT to determine the spatial distribution of red marrow for dosimetry in internal emitter therapy. 2011. URL: <http://m.rsna.org/rsna2011/program/eventdisplay.cfm?emid=11007879>
- Kaminski MS, Zelenetz AD, Press OW, Saleh M, Leonard J, Fehrenbacher L, Lister TA, Stagg RJ, Tidmarsh GF, Kroll S, Wahl RL, Knox SJ, Vose JM. Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. *Journal of Clinical Oncology*. 2001; 19(19):3918–3928. [PubMed: 11579112]
- Pafundi D, Lee C, Watchman C, Bourke V, Aris J, Shagina N, Harrison J, Fell T, Bolch WE. An imaged-based skeletal dosimetry model for the ICRP reference newborn. *Physics in Medicine and Biology*. 2009; 54:4497–4531. [PubMed: 19556686]
- Pichardo JC, Milner RJ, Bolch WE. MRI Measurement of Bone Marrow Cellularity for Radiation Dosimetry. *Journal of Nuclear Medicine*. 2011; 52:1482–1489. [PubMed: 21799087]
- Rajon DA, Jokisch DW, Patton PW, Shah AP, Bolch WE. Voxel size effects in three-dimensional nuclear magnetic resonance microscopy performed for trabecular bone dosimetry. *Medical Physics*. 2000; 27:2624–2635. [PubMed: 11128316]
- Rajon DA, Shah AP, Watchman CJ, Brindle JM, Bolch WE. A hyperboloid representation of the bone-marrow interface within 3D NMR images of trabecular bone: applications to skeletal dosimetry. *Physics in Medicine and Biology*. 2003; 48:1721–1740. [PubMed: 12870579]

- Shah AP, Bolch WE, Rajon DA, Patton PW, Jokisch DW. A paired-image radiation transport model for skeletal dosimetry. *Journal of Nuclear Medicine*. 2005; 46:344–353. [PubMed: 15695796]
- Shah AP, Rajon DA, Jokisch DW, Patton PW, Bolch WE. A comparison of skeletal chord-length distributions in the adult male. *Health Physics*. 2005; 89:199–215. [PubMed: 16096496]
- Whitwell, JR. PhD thesis. University of Leeds; 1973. Theoretical investigations of energy loss by ionizing particles in bone.
- Wilderman SJ, Dewaraja YK. Fast CT/SPECT derived 3D Monte Carlo dose computations for I-131 internal emitter therapy. *IEEE Transactions on Nuclear Science*. 2007; 54:146–151. [PubMed: 20305792]

Appendix A. Model of bone spongiosa and computation of generic electron energy absorption fractions

As mentioned above, to permit modeling of the voxel-by-voxel variation in bone fraction within marrow-bearing regions, the EGS5 Monte Carlo program was used to compute electron energy absorption fractions for arbitrary BVF and cellularity. The main approximation involved in these computations lies in the modeling of the non-regular geometry of the bone spongiosa and surface edge effects which arise when modeling relatively smooth surfaces as voxels.

In the current work, the method of Rajon *et al* (Rajon, Jokisch, Patton, Shah & Bolch 2000) was adopted (with modification) for constructing a voxelized, simulated geometry for modeling bone spongiosa. In that method, the marrow cavities of the spongiosa are approximated by a set of non-overlapping spheres of varying radii, selected so that the distribution of chord lengths in the model is approximately equivalent to the distributions measured by Spiers and colleagues at the University of Leeds (Whitwell 1973). Thus, a mathematical model of spongiosa is generated by placing the appropriate spheres into a target volume, and assuming that that portion of the target not occupied by any sphere will approximate the bone trabeculae.

The choice of spheres as the shape for the cavities is judicious in that the distribution of chord lengths l for a sphere of radius R is known analytically, and is given by

$$f(l) = \frac{l}{2R^2}.$$

This makes it possible to compute the average chord distribution for the simulated geometry, provided that the distribution of sphere radii is known. Rajon used an exponential distribution for the sphere radii, with the constant in the exponential chosen so that the chord length distribution for the simulated geometry was a close fit to the Leeds data. The model constructed by Rajon consisted of a cube with sides of 1.6 cm. Voxel sizes of 200, 80, 40 and 16 microns were examined.

The current approach differs slightly. First, since the majority of the patient bone marrow image data available in the current work focuses on the lumbar region, the measured chord distribution to be simulated was chosen to be the lumbar distribution measured at the University of Florida (Shah, Rajon, Jokisch, Patton & Bolch 2005). Next, the spongiosa lattice was fixed to be a cube of 256 voxels of dimension 50 μm , based on data presented by Rajon *et al* in a further examination of voxel size effects in mathematical representations of spongiosa (Rajon, Shah, Watchman, Brindle & Bolch 2003). The spheres to be situated in the lattice were limited to those with radii of an integer number of voxels, and the measured

marrow chord distribution to be simulated was similarly discretized in bins defined by the voxel dimension.

Noting that if one fixes the maximum sphere radius to be included in the simulated geometry, under the constraints that one is working with spheres of discrete radii only and given the total area allocated for marrow cavities (determined by the bone volume fraction being simulated), it is seen that if one truncates (at the top) the discretized measured distribution, it is possible to calculate the number of chords at each voxel dimension that should be present in the simulated geometry. Noting that the number of chords of the maximum length defines the number of spheres of maximum radius which must be contained in the simulated geometry, we start by placing this number of largest spheres in the volume. We now note that if we then place in the volume spheres of progressively smaller radii, we can determine the number of spheres required at each smaller bin width, based on the difference between the number of chords in the measured distribution being simulated and the number of chords of that size which were contributed by spheres of greater radii. This is seen in the expression below:

$$S_j = C_j - \sum_{k=j+1}^N S_k l_j / 2R_k^2.$$

In the above the subscripts j and k refer to the discrete bin numbers, S_j is the number of spheres of radius R_j , and C_j is the measured number of chords of length l_j (with $l_j = 2R_j$, of course).

To account for the large marrow cavity chords lost when the top of the distribution was truncated by setting a maximum sphere radius, some overlap of the spheres was permitted during the cavity construction process, though it was limited to 5% by volume for any given sphere. Voxel dimensions of 50 and 25 microns were both used initially, and several values of the maximum chord length were examined. It was found that a maximum chord of 2350 microns best reproduced the measured chord distribution. A representative table of the discretized measured chord distribution and the corresponding number of spheres as a function of bin number is given in table A1.

The mathematical spongiosa geometry map was generated with perl scripts which randomly placed sphere centers (beginning with the largest spheres) in available space, subject to the 5% overlap constraint. In practice, it was sometimes found that open areas could not be found for situating the desired number of spheres. When this happened, the appropriate number of smaller spheres required to preserve the input BVF were used. At the last pass, enough spheres of radii given by 2 bins were randomly placed throughout the volume so as to preserve the desired bone fraction. A slice from a representative mathematical spongiosa volume is shown in figure A1.

The general purpose Monte Carlo program EGS5 was then adapted to compute electron energy absorption fractions in trabecular bone, active marrow, and inactive marrow for mono-energetic electrons originating in the bone and marrow volumes and on bone surfaces for a range of electron energies, bone volume fractions and active marrow cellularities. The tables of electron energy absorption fractions which were constructed from the data thus mimic those published by Hough, except that instead of being collated by bone region they are grouped by bone volume fraction.

Representative results are shown in the plots in figure A2. The top figure shows the EGS5 result for BVF of 11% plotted along with the Hough data for the sacrum, which had a BVF

of 11.8%, for three cellularities. The middle figure shows EGS5 electron absorption fractions at 11% for various cellularities along with Hough data for lumbar (BVF of 10%), and the bottom figure shows EGS5 and Hough lumbar active marrow electron energy absorption fractions for electron sources in inactive marrow. Since the EGS5 and Hough bone volume fractions do not correspond exactly, perfect agreement is not expected. The figures do show that the EGS5 generated data and the data presented by Hough express similar trends.

Table A1

Number of spheres as a function of radius for mathematical geometries representing 5% and 25% bone volume fraction

Radius	5% BVF Spheres	25% BVF Spheres
25	4.9	3.9
75	7.1	5.6
125	15.4	12.2
175	22.2	17.6
225	30.5	24.1
275	49.9	39.4
325	67.7	53.4
375	81.9	64.7
425	75.6	59.7
475	93.3	73.7
525	75.3	59.5
575	65.5	51.7
625	65.9	52.1
675	66.3	52.3
725	66.6	52.6
775	52.6	41.5
825	52.8	41.7
875	53.0	41.8
925	44.5	35.1
975	42.8	33.8
1025	41.0	32.4
1075	39.0	30.8
1125	37.0	29.2
1175	34.9	27.5

Figure A1.
Slice of overlapping sphere spongiosa model, 11% BVF, 50 μm pixels

Figure A2.
Comparison of EGS5 and Hough electron energy absorption fractions

Figure 1.
Patient combined SPECT/CT coronal lumbar image with spongiosa outlined. Image was acquired 2-days post-therapy administration of I-131 tositumomab.

Figure 2.
Variation in electron energy absorption fractions for various bone regions.

Table 1

Regions of bone

AM	active (red) marrow
IM	inactive (yellow) marrow
TBS	trabecular bone surfaces
TBV	trabecular bone volume
CBV	cortical bone volume
BVF	bone volume fraction

Table 2

Variation in patient lumbar bone volume fractions (in percent). Reference lumbar BVF for Hough data set was 10% (Hough et al. 2011).

Patient	Bone Volume Fraction (%)			
	Average	Median	Minimum	Maximum
1	9.7	9.3	5.2	36.6
2	19.8	17.8	10.2	57.7
3	15.3	14.5	6.6	40.7
4	17.3	16.7	10.9	38.0
5	11.5	10.8	5.0	31.8
6	13.6	12.5	7.7	43.3
7	14.0	12.8	6.3	46.7
8	9.2	8.9	6.1	18.4
9	20.5	19.1	9.3	54.1
10	10.1	9.2	5.6	24.5
11	9.3	9.1	3.2	32.4
12	14.5	14.3	0.1	25.7
13	19.3	17.4	7.7	54.8
14	10.1	9.8	6.4	18.2

Active marrow fractional energy absorption for photons incident on heterogeneous simulated spongiosa (top) and homogeneous spongiosa with energy apportioning (bottom), 7% bone fraction

Table 3

Energy (MeV)	Cellularity (%)			
	90	70	50	30
0.0500	2.27×10^{-3}	1.74×10^{-3}	1.20×10^{-3}	7.12×10^{-4}
0.1000	2.85×10^{-3}	2.19×10^{-3}	1.56×10^{-3}	9.32×10^{-4}
0.2000	6.34×10^{-3}	4.90×10^{-3}	3.51×10^{-3}	2.12×10^{-3}
0.3000	1.02×10^{-2}	7.89×10^{-3}	5.60×10^{-3}	3.35×10^{-3}
0.4000	1.40×10^{-2}	1.08×10^{-2}	7.69×10^{-3}	4.60×10^{-3}
0.5000	1.74×10^{-2}	1.34×10^{-2}	9.63×10^{-3}	5.71×10^{-3}
Energy (MeV)	Cellularity (%)			
	90	70	50	30
0.0500	2.44×10^{-3}	1.72×10^{-3}	1.14×10^{-3}	6.61×10^{-4}
0.1000	2.81×10^{-3}	2.15×10^{-3}	1.51×10^{-3}	9.00×10^{-4}
0.2000	6.35×10^{-3}	4.93×10^{-3}	3.52×10^{-3}	2.11×10^{-3}
0.3000	1.02×10^{-2}	7.94×10^{-3}	5.65×10^{-3}	3.41×10^{-3}
0.4000	1.40×10^{-2}	1.09×10^{-2}	7.70×10^{-3}	4.66×10^{-3}
0.5000	1.78×10^{-2}	1.37×10^{-2}	9.81×10^{-3}	5.92×10^{-3}

Active marrow fractional energy absorption for photons incident on heterogeneous simulated spongiosa (top) and homogeneous spongiosa with energy apportioning (bottom), 15% bone fraction

Table 4

Energy (MeV)	Cellularity (%)			
	90	70	50	30
0.0500	1.99×10^{-3}	1.53×10^{-3}	1.06×10^{-3}	6.34×10^{-4}
0.1000	2.59×10^{-3}	2.01×10^{-3}	1.41×10^{-3}	8.43×10^{-4}
0.2000	5.85×10^{-3}	4.53×10^{-3}	3.20×10^{-3}	1.93×10^{-3}
0.3000	9.23×10^{-3}	7.24×10^{-3}	5.10×10^{-3}	3.09×10^{-3}
0.4000	1.26×10^{-2}	9.85×10^{-3}	7.05×10^{-3}	4.19×10^{-3}
0.5000	1.58×10^{-2}	1.24×10^{-2}	8.77×10^{-3}	5.25×10^{-3}
Energy (MeV)	Cellularity (%)			
	90	70	50	30
0.0500	2.16×10^{-3}	1.52×10^{-3}	1.01×10^{-3}	5.88×10^{-4}
0.1000	2.58×10^{-3}	1.98×10^{-3}	1.36×10^{-3}	8.20×10^{-4}
0.2000	5.85×10^{-3}	4.50×10^{-3}	3.22×10^{-3}	1.93×10^{-3}
0.3000	9.39×10^{-3}	7.27×10^{-3}	5.18×10^{-3}	3.10×10^{-3}
0.4000	1.29×10^{-2}	9.99×10^{-3}	7.10×10^{-3}	4.28×10^{-3}
0.5000	1.62×10^{-2}	1.25×10^{-2}	8.91×10^{-3}	5.34×10^{-3}

Table 5

Active marrow dose rate for patient A, sacrum, 8% BVF, 50% cellularity. The Hough reference sacrum BVF is 11.8%

Active Marrow Dose Methodology	Dose Rate (mGy/MBq-sec)
DPM Region Average Dose	2.15×10^{-6}
Hough Sacrum E_{abs} fractions	2.01×10^{-6}
EGS5 e_{abs} fractions at 7% BVF	2.27×10^{-6}
EGS5 e_{abs} fractions at 9% BVF	2.23×10^{-6}
EGS5 voxel-level E_{abs} fractions	2.26×10^{-6}

Table 6

Active marrow dose rate for patient A, lumbar, 10% BVF, 50% cellularity. The Hough reference lumbar BVF is 10.0%

Active Marrow Dose Methodology	Dose Rate (mGy/MBq-sec)
DPM Region Average Dose	2.64×10^{-6}
Hough Lumbar E_{abs} fractions	2.67×10^{-6}
EGS5 e_{abs} fractions at 9% BVF	2.85×10^{-6}
EGS5 e_{abs} fractions at 11% BVF	2.77×10^{-6}
EGS5 voxel-level E_{abs} fractions	2.82×10^{-6}

Table 7

Active marrow dose rate for patient B, lumbar, 20% BVF, 50% cellularity. The Hough reference lumbar BVF is 10.0%

Active Marrow Dose Methodology	Dose Rate (mGy/MBq-sec)
DPM Region Average Dose	4.71×10^{-6}
Hough Lumbar E_{abs} fractions	5.67×10^{-6}
EGS5 e_{abs} fractions at 20% BVF	5.57×10^{-6}
EGS5 voxel-level E_{abs} fractions	5.58×10^{-6}

Table 8

Active marrow dose rate for patient A, lumbar, 10% BVF at various cellularities. The Hough reference lumbar BVF is 10.0%

Methodology	Dose Rate (mGy/MBq-sec)		
	20% cellularity	50% cellularity	80% cellularity
DPM Region Average Dose	2.64×10^{-6}	2.64×10^{-6}	2.64×10^{-6}
Hough Lumbar E_{abs} fractions	3.03×10^{-6}	2.67×10^{-6}	2.56×10^{-6}
EGS5 e_{abs} fractions at 9% BVF	3.19×10^{-6}	2.85×10^{-6}	2.73×10^{-6}
EGS5 e_{abs} fractions at 11% BVF	3.10×10^{-6}	2.77×10^{-6}	2.67×10^{-6}
EGS5 voxel-level E_{abs} fractions	3.10×10^{-6}	2.82×10^{-6}	2.74×10^{-6}

Table 9

Active marrow dose rate for patient B, lumbar, 20% BVF, at various cellularities. The Hough reference lumbar BVF is 10.0%

Methodology	Dose Rate (mGy/MBq-sec)		
	20% cellularity	50% cellularity	80% cellularity
DPM Region Average Dose	4.71×10^{-6}	4.71×10^{-6}	4.71×10^{-6}
Hough Lumbar E_{abs} fractions	6.59×10^{-6}	5.67×10^{-6}	5.38×10^{-6}
EGS5 e_{abs} fractions at 20% BVF	6.40×10^{-6}	5.57×10^{-6}	5.31×10^{-6}
EGS5 voxel-level E_{abs} fractions	6.36×10^{-6}	5.58×10^{-6}	5.35×10^{-6}