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<https://escholarship.org/uc/item/9qz0t5q0>

Journal

Physics in medicine and biology, 62(22)

ISSN

0031-9155

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Publication Date

2017-10-01

DOI

10.1088/1361-6560/aa8d9e

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Determination of Mean Ionization Potential using Magnetic Resonance Imaging: Theory and Application Towards the Reduction of Proton Beam Range Uncertainties

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Abstract

Accurate determination of mean ionization potential (I_m) has the potential to reduce range uncertainty based margins and therefore allow for more focal treatments in proton radiotherapy. Many methods have been proposed to reduce uncertainty in I_m and stopping power ratios (SPR) each with varying degrees of accuracy and issues. In this work, we present on a simple parameterized model to determine I_m in human biological tissue, which allows for computation of patient-specific I_m at the voxel level using magnetic resonance imaging (MRI). The model requires the measurement of three parameters by MRI with only two parameters, mass percent water content and mass percent hydrogen content in organic molecules, required for the special case of soft tissues. The accuracy of this I_m determination method was evaluated in available “standard” (ICRU Report #44) human tissues. The sensitivity of this I_m determination method to *in-vivo* perturbations was also tested by calculating the effect of 10% variations of the experimentally measurable parameters on I_m and SPR. For the human tissues modeled in this work, a high level of accuracy with low susceptibility to perturbations in measurement error was achieved in the prediction of I_m . Root-mean-square errors (RMSE) in I_m were within 0.77% and 1.8% for both soft and bony tissues and were 0.09% and 0.2% for soft and bony tissues SPR, respectively, assuming knowledge of electron density. Proof of principle MR measurements and model-based computations of I_m and SPR were taken in phantom for a series of hydrogenous solutions and compared against expected I_m and SPR calculations from known elemental composition. MR determined I_m and SPR values in a known composition solution were determined to within 5% and 0.52%, respectively. We present on a novel model to accurately calculate mean ionization potential from measurements acquirable by MRI and show feasibility in phantom.

1. Introduction

Heavy charged particle (HCP) therapy is a growing modality for cancer treatment with the number of centers steadily increasing (Durante and Loeffler, 2010). HCP therapy has a distinct advantage of being able to deliver a high dose at deep depths while potentially sparing healthy tissue proximal and distal to the target position (Smith, 2009). This advantage is physically manifested by the Bragg peak in which the HCPs (most commonly protons) deposit a significant portion of their dose immediately before reaching the end of their range. In radiation therapy, the position of the Bragg peak is calculated using the stopping power ratio (SPR) relative to water. These SPR values are typically determined using kV planning computed tomography (CT) scans. Errors in the determined SPR translate to positional inaccuracies of the

Bragg peak within the patient relative to the planned dose delivery position. These errors are typically handled by increasing the proximal and distal margins along the beam path with common margins of 3.5% + 3 mm (Paganetti, 2012) at MD Anderson Proton Therapy Center, Loma Linda University Medical Center (Moyers *et al.*, 2001; Moyers *et al.*, 2010), and Roberts Proton Therapy Center at the University of Pennsylvania. The University of Florida Proton Therapy Institute and Massachusetts General Hospital employ margins of 2.5% + 1.5 mm (Paganetti, 2012) and 3.5% + 1 mm (Paganetti, 2012), respectively. These margins result in a substantial increase of the irradiation length on the distal beam end of 8 mm for a 20 cm target distance in soft tissue for a 3.5% + 1 mm margin (Paganetti, 2012).

Unlike megavoltage photon radiation therapy, individual elemental compositions significantly impact proton and other HCP therapies with the potential for a geographical miss in the latter when inadequate margins along the beam path are used despite aiming a beam directly at the target. kV single-energy CT (SECT) imaging with the stoichiometric calibration method is the currently most common clinically used method to calculate the SPR within a patient. This method comes with significant uncertainties as there is a degeneracy in CT Hounsfield Unit (HU) with elemental composition. Previously, Yang *et al* (Yang *et al.*, 2010; Yang *et al.*, 2012) have comprehensively investigated the uncertainties associated with the calculation of proton SPR for biological tissues. In their analysis of the sources of the uncertainty (Yang *et al.*, 2012), they found that uncertainties due to deviation of actual human body elemental compositions from ICRU standard tissue were the largest single component of uncertainty (1σ) for both soft and bony tissues at 1.2% and 1.6%, respectively out of a total (root-sum-square) uncertainty of 1.6% and 2.4%, respectively. This uncertainty component in SPR is primarily due to density changes and elemental composition changes in the mean ionization potential (I_m). Their results are in line with those of Andreo (Andreo, 2009) who concluded that a 5% - 15% uncertainty of the I_m value exists for different tissues. This I_m uncertainty results in a SPR or range uncertainty of ~1.5% (Paganetti, 2012).

A number of techniques have recently been proposed to better account for the compositional uncertainties associated with kV SECT including dual-energy CT (DECT) and proton CT. As of this work, DECT has the distinct advantage of being available on clinical CT equipment. Theoretical uncertainty estimates of SPR by DECT have been low (sub-0.5%) but practical uncertainties with DECT remain high at up to 2.4% + 1.2 mm (Bar *et al.*, 2017). Proton CT offers the potential to directly determine the proton SPR (Schulte and Penfold, 2012) but currently lacks a clinical implementation as a number of challenges await its development (including numerous small-angle scatterings due to Coulomb interactions and high energy requirements to penetrate the body for imaging) (Li *et al.*, 2006). Recently, magnetic resonance imaging (MRI) images converted to pseudoCT or syntheticCT (sCT) scans have been proposed as a reasonable alternative to SECT (Edmund *et al.*, 2014; Koivula *et al.*, 2016; Rank *et al.*, 2013a; Rank *et al.*, 2013b) for SPR determination. In the case of the prior work of sCT to SPR conversion, the efforts have been to simulate kV SECT images and not necessarily to increase the information content beyond SECT and/or improve the accuracy of SPR determination relative to kV SECT. Their results suggest that it is feasible to create accurate sCT images that are reasonable for HCP therapy although the limitations of standard SECT may still apply with the added potential error of MRI to sCT conversion.

In this manuscript, we describe a simple and accurate parameterization of the chemical composition of biological tissues for mean ionization potential determination by three quantities measurable by MRI. Clinical MRI is an excellent modality that can be used to quantitatively measure ^1H proton signals *in vivo* (Meyers *et al.*, 2016; Neeb *et al.*, 2008; Neeb *et al.*, 2006) with recent developments allowing for measurement of nearly all hydrogenous compounds including short T_2/T_2^* relaxation time constituents (such as solids, plastics, and collagen) through zero and ultra-short echo time (ZTE and UTE, respectively) sequences (Siu *et al.*, 2015; Seifert and Wehrli, 2016b; Springer *et al.*, 2008). We propose a model that requires knowledge of hydrogen (^1H) density and phosphorus (^{31}P) density with two components for hydrogen density, an organic (lipid, carbohydrate and protein) and a water component. We present data on model theoretical accuracy in the tissue compositions of ICRU Report #44 (ICRU, 1989) and White *et al* (White *et al.*, 1991) along with proof of principle data in phantom. Initial results show the potential of this model with specific MRI sequences to accurately determine I_m *in vivo* and reduce uncertainties in proton beam ranges.

2. Materials and methods

2.1. Unified Compositions (UC) model

In our unified compositions (UC) model, we assume that human biological tissues can be segmented into three general components: water (hydrogenous), organic (hydrogenous) and mineralized tissues (calcium/phosphorous rich). In this model, we determined the mean ionization potential, I_m , of molecules by the Bragg additivity rule (BAR) of elemental constituents:

$$\ln I_m = \left(\sum_i \frac{w_i Z_i}{A_i} \ln I_i \right) \left(\sum_i \frac{w_i Z_i}{A_i} \right)^{-1} \quad (1)$$

where w_i is the fraction by mass of an element (i), Z_i is the atomic number for an element (i), and A_i is the atomic mass for an element (i). The majority of tissues in humans are composed of five major types of molecules: water, lipids, carbohydrates, proteins, and minerals/hydroxyapatite with the exact proportions dependent on the particular tissue/organ (Heymsfield, 2005; Wang *et al.*, 1992). Five-component models of molecules in the human body have been used previously in the study of the human body (Heymsfield, 2005; Wang *et al.*, 1992) and are assumed, in this study, to be sufficient to accurately calculate the mean ionization potential for naturally occurring biological tissues. From the work of Yang *et al* (Yang *et al.*, 2010; Yang *et al.*, 2012), they found that the primary contributor to uncertainties in an individual's tissues was hydrogen content in soft tissues and calcium content in mineralized/bony tissues. We investigated the hydrogen dependence of I_m for water, lipids, carbohydrates and proteins by determining I_m in water, lipids such as triglycerides, glucose and glycogen, and the 20 common (+2 highly uncommon) amino acids that compose proteins. These highly hydrogenous molecules constitute the vast majority of molecules within human tissues. Those molecules are summarized in Table 1 along with elemental compositions and I_m as determined by the Bragg additivity rule. In the majority of molecules that comprise human tissues, I_m has an exponential relationship with hydrogen content. That relationship is shown in Figure 1. Notable exceptions to this relationship are: water, three uncommon amino acids (cysteine, methionine and selenocysteine), and hydroxyapatite. The three uncommon amino acids are low in occurrence in human proteins (cysteine 2.3%, methionine 2.13% and selenocysteine <1%) (Kozlowski, 2017) and were not considered towards the exponential fit of organic molecules. To accurately accommodate water and bone mineral compositions

(hydroxyapatite [HA]), we propose a three-component model (water [H₂O], organic molecules [org], and minerals/hydroxyapatite [HA]) for I_m determination in a finite sized subset (such as a voxel) of biological human tissues:

$$\ln(I_{voxel}) = \left(\sum_{molecule} \frac{w_{molecule} Z_{molecule}}{A_{molecule}} \ln(I_{molecule}) \right) \left(\sum_{molecule} \frac{w_{molecule} Z_{molecule}}{A_{molecule}} \right)^{-1} \\ = \left[\left(\frac{w_{H_2O} Z_{H_2O}}{A_{H_2O}} \ln(I_{H_2O}) \right) + \left(\sum_{org} \frac{w_{org} Z_{org}}{A_{org}} \ln(I_{org}) \right) + \left(\frac{w_{HA} Z_{HA}}{A_{HA}} \ln(I_{HA}) \right) \right] \left(\sum_{molecule} \frac{w_{molecule} Z_{molecule}}{A_{molecule}} \right)^{-1} \quad (2)$$

where I_{voxel} is the mean ionization potential for a particular voxel, w_i is the fraction by mass of a molecule (i) to all molecules in the voxel such that $\sum_{molecule} w_{molecule} = 1$, Z_i is the total atomic number for a molecule (i), A_i is the total atomic mass for a molecule (i), and I_i is the mean ionization potential for a molecule (i). For molecules within the body considered in this study, molecular Z/A values range between 0.47 (selenocysteine) and 0.56 with averages for water (0.56), lipids (0.56), carbohydrates (0.53), amino acids (0.53), and hydroxyapatite (0.50). For the remainder of this work, we will assume that the Z/A ratios for all biological molecules are identical allowing us to simplify Equation 2 to:

$$\ln(I_{voxel}) \approx (w_{H_2O} \ln(I_{H_2O})) + (\sum_{org} w_{org} \ln(I_{org})) + (w_{HA} \ln(I_{HA})). \quad (3)$$

Maximal errors may occur in the mixing of water/lipids with bony tissue. For soft tissue, this approximation may be within the errors of practical mass fraction determination methods. We tested the accuracy of this assumption on the tissue compositions of ICRU Report #44 and White *et al* which are shown in our results. Additional factors to account for the Z/A difference between molecules can be empirically derived to increase the accuracy of this approximation. In Figure 1, we show that there exists an exponential relationship between I_{org} and hydrogen density by mass from organic molecules, h_{org} , such that $I_{org} = A \cdot \exp(Bh_{org})$ where A and B are constants ($A = 93.23$ eV, $B = -3.47$ with $R^2 = 0.93$). Then we can further simplify Equation 3 to:

$$\ln(I_{voxel}) \approx (w_{H_2O} \ln(I_{H_2O})) + (w_{org,total} [\ln A + Bh_{voxel}^{org}]) + (w_{HA} \ln(I_{HA})) \quad s. t. \sum_i w_i = 1 \quad (4)$$

where $w_{org,total}$ is the sum total fractional mass of all organic molecules, A and B are constants that relate hydrogen content in organic molecules to I_{org} , and h_{voxel}^{org} is the total organic molecule hydrogen density by fractional mass in the voxel. For soft tissue, we can consider that the mineral/HA content is negligible. And thus, I_m for each voxel in soft tissue can be determined as a function of two quantities measurable by MRI: 1) percentage of water/organic materials by mass (w_{H_2O}) and 2) the hydrogen (1H) content of the organic molecules (h_{org}). For soft tissue, $w_{org,total} = (1 - w_{H_2O})$ and does not need to be independently determined. For the case of voxels containing mineralized tissues (such as HA), w_{HA} must be determined. ^{44}Ca , the 96.941% abundant isotope of calcium, has no magnetic moment and is not amenable to an MRI signal. An alternative to the ^{44}Ca signal for mineralized tissues is to image ^{31}P . HA has a particular chemical form, $Ca_5(PO_4)_3(OH)$, with a fixed ratio of Ca to P with which P can be used as a proxy for the mineralized tissue (HA) content. The theoretical ratio of the mass content of Ca to P in HA should be 2.1566 which is in line with the mean Ca to P ratio found from the elemental analysis data of White *et al* (White *et al.*, 1991) in cortical bone. In Table 2, we show the relationship of P density to total mineral content by percent mass in the dataset of White *et al* (White *et al.*, 1991) to support that a relationship exists between P to mineral content, w_{HA} , in the human body. The theoretical value for mineral content by mass to phosphorus content by mass (Minerals/P) is 5.41 for HA. The average ratio of minerals to P from

Table 2 was 5.57 and in line with the theoretical value from HA. As MRI for ^{31}P in solid materials is still an active area of research (Frey *et al.*, 2012; Seifert *et al.*, 2014; Seifert and Wehrli, 2016a, b) with potential for ^{31}P density measurements, we note the theoretical potential for signal acquisition but will not show imaging data support in this study.

Figure 1. Plot of hydrogen density by mass (h) versus I_m (log scale axis) for each molecule studied in Table 1. An exponential fit ($I_m = (93.23 \text{ eV}) \exp(-3.47h)$) of the organic molecules (black plus) is shown as a black line ($R^2 = 0.93$). Notable exclusions to this fit are: water (blue circle), low occurrence amino acids (purple asterisk), and hydroxyapatite (red triangle). Water and hydroxyapatite are modeled separately from the remaining organic materials.

2.2. UC Model Evaluation

Elemental composition of human tissues and their mean percentage of water, lipid, protein and minerals have been reported in ICRU Report 44 Tables 4.2 and 4.4 (ICRU, 1989) and White *et al* (White *et al.*, 1991) and are regularly cited as “standard” tissue compositions for the purposes of DECT and stoichiometric calibrations and proton stopping power ratio calculations. We evaluated the accuracy of the UC model in these tissues by calculating I_m and SPR values by two methods: 1) complete elemental composition (using Bragg’s additivity rule [BAR] for each element as in Equation 1 and 2) UC model parameterization using Equation 4 assuming a known electron density for both. Results are tabulated and shown in Table 2 for cortical bone and Table 3 for soft tissue. We also determined the stability of our model in soft tissue to uncertainties in the two parameters by calculating changes in I_m due to $\pm 10\%$ changes in $w_{\text{H}_2\text{O}}$ and h_{org} . Errors of about $\pm 10\%$ were found in these two parameters in our MR measurements in this study and were considered reasonable

variations away from actual values for the purposes of the stability analysis. The proton SPR can be approximated by the Bethe-Bloch equation:

$$SPR = \rho_{e,water} \frac{\ln[2m_e c^2 \beta^2 / I_m (1 - \beta^2)] - \beta^2}{\ln[2m_e c^2 \beta^2 / I_{water} (1 - \beta^2)] - \beta^2} \quad (5)$$

where $\rho_{e,water}$ is the electron density normalized to water electron density, m_e is the electron mass, c is the speed of light, β is the velocity of the proton normalized to c , I_m is the mean ionization potential of the medium, and I_{water} is the mean ionization potential of water. A proton of energy equal to 250 MeV was assumed for all SPR calculations in this work.

2.3. Determination of UC model parameters using MRI

Spin-echo MR is one of the simplest MR imaging techniques and signals are determined by the following equation:

$$S \propto \rho_H (1 - \exp(-TR/T_1)) \exp(-TE/T_2) \quad (6)$$

where ρ_H is the voxel total ^1H content, TR is the repetition time of the pulse sequence, T_1 is the longitudinal relaxation time of the ^1H , TE is the echo time of the pulse sequence, and T_2 is the spin-spin relaxation time of the ^1H . For the UC model, we must obtain the ^1H content of the organic (non-water) molecules. Technically, a pure ρ_H signal requires knowledge and correction of T_1 , and T_2 , both determinable by MR imaging. To a large extent, a proton (^1H) density-weighted MRI using a spin-echo sequence with $TR \gg T_1$ and $TE \ll T_2$ will produce a reasonable approximation for ρ_H that is not weighted by T_1 or T_2 contrast mechanisms. The ρ_H value can be used in conjunction with specific MRI pulse sequences (such as water excitation, water/fat suppression, two-point Dixon, FLAIR, STIR, and SPAIR) to determine the water ^1H versus organic ^1H content. With a proton-density weighted scan and a water/organic ^1H separation scan, we can obtain all the values for the two parameters of interest for the UC model ($w_{H_2O}/w_{org,total}$ and h_{org}) in soft tissue.

MRI measurements were carried out on a standard clinical 3T Verio scanner (Siemens Medical Systems GmbH, Erlangen, Germany) using the body coil to minimize signal non-uniformities. The proton density-weighted protocol was implemented using the Siemens spin-echo (referred to below as the spin-echo proton-density [SE PD]) sequence. The following parameters were used: 2D multi-slice acquisition, $TR = 10,000$ ms, $TE = 4.9$ ms, flip angle $\theta = 180^\circ$, field of view: $(256 \text{ mm})^2$, isotropic voxel size: $(2 \text{ mm})^3$, slices = 64 (interleaved), phase partial Fourier = 4/8, and bandwidth = 797 Hz. Parameters were chosen to maximize proton-density weighting at reasonable acquisition time of about 11 minutes. T_1 for oleic acid was estimated by acquiring SE PD scans with varying TE (4.9, 10, 20, 40, 80 and 160 ms) and fitting the values to a mono-exponential. A value of 72 ms was determined to be the T_1 relaxation time for oleic acid at room temperature. An additional scan was acquired to separate water from non-water chemicals (referred to below as the turbo spin-echo two-point Dixon [TSE Dixon] sequence). The following parameters were used: 2D multi-slice acquisition, $TR = 15,000$ ms, $TE = 7.2$ ms, flip angle $\theta = 180^\circ$, field of view: $(256 \text{ mm})^2$, isotropic voxel size: $(2 \text{ mm})^3$, slices = 64 (interleaved), bandwidth = 1563 Hz, and turbo factor = 3.

SE PD scans were acquired in a set of chemicals with known compositions to create a calibration curve of total ^1H proton density versus MRI signal (SE PD scan). For calibration curve creation, we used the following liquid compounds: water,

acetone, 92% (by volume) isopropyl alcohol, and propargyl alcohol. Chemicals were chosen to span the ^1H content range of organic molecules examined in this study from 7.0% (propargyl alcohol) to 11.2% (water). Results for this calibration curve are shown in Figure 2D. As a proof of concept, we selected a fifth compound of known composition, analytical standard grade (>99.0% pure) oleic acid (Sigma-Aldrich St. Louis, MO USA), to be tested but not included in the generation of the calibration curve. A fatty acid was specifically selected for proof of concept testing as adipose tissue (composed of lipids) showed the most potential for instability due to uncertainties in the two parameters of the UC model due to high hydrogen content and low mean ionization potential (relative to water). The mean ionization potential (I_m) was calculated using the UC model with its parameters measured by MRI. This I_m value was compared to a calculation using only the known chemical composition and Bragg's additivity rule.

3. Results

3.1. Model Evaluation

ICRU Report 44 (ICRU, 1989) has a number of soft tissue organs in which the mean $w_{\text{H}_2\text{O}}$ and mean total hydrogen content h are known and are often used as “reference” tissue compositions. These tissues were used in this study to determine the error in modeling all the elements in the calculation of $I_m(\text{BAR})$ versus the UC two-parameter model for I_m (UC). Results are tabulated in Tables 2 and 3. For cortical bone, the mean percentage difference in $I_m(\text{BAR})$ versus $I_m(\text{UC})$ is 1.8% with a maximum difference of 2.1%. For the soft tissues studied, the mean percentage difference in $I_m(\text{BAR})$ versus $I_m(\text{UC})$ is 0.2% with a maximum difference of 1.3% for the eye lens. The high percentage difference for the eye lens organ and cortical bone may in part be due to the high protein content of these organs as amino acids have differing Z/A from water or lipids and individual amino acid compositions in proteins have a larger degree of variation from our molecular fit to I_m . Differences in I_m result in minimal differences in calculated stopping power ratios (SPR). All calculated SPR from the UC model were within 0.3% of the values calculated by $I_m(\text{BAR})$.

The sensitivity of our model was tested in soft tissue by determining the effect of +10% and -10% perturbations on $w_{\text{H}_2\text{O}}$ and h_{org} on I_m (UC) and SPR. Table 4 shows the resulting errors due to a miss determination of $w_{\text{H}_2\text{O}}$ and h_{org} , respectively, by +/- 10%. All values of the perturbed $I_m(\text{UC})$ were within 4% of the unperturbed $I_m(\text{UC})$ regardless of the type of error. The largest errors were in adipose tissue, which have high fatty acid content. The $I_m(\text{UC})$ value perturbations result in minimal errors overall to the SPR. SPR values for adipose tissue were, again, most affected by uncertainties in $w_{\text{H}_2\text{O}}$ or h_{org} with maximal errors under 0.4% for a 250MeV proton.

3.2. MRI Measurements

MR images of the five chemicals listed in the methods are shown in Figure 2, panels A-C. In Figure 2A, we see the SE PD image with increasing signal for chemicals with higher hydrogen density. In Figures 2B and 2C are MR images of the TSE Dixon sequence for non-water (panel B) and water (panel C) components. The chemicals with significant MR signal on Figure 2C are water and the 92% isopropyl alcohol solution (with 8% water by volume). There is no significant signal from water in Figure 2B. A calibration curve (Figure 2D) of normalized MRI signal versus hydrogen density, h , was

created for the four hydrogenous chemicals listed in the methods. For the range of molecules (and their respective hydrogen density) considered in this work, there is a linear relationship between MRI signal and total hydrogen density, h . This calibration curve, which did not include oleic acid, was used to estimate the total hydrogen density, h , in oleic acid. The total hydrogen density content was determined to be 11%, 12%, and 12.1% by MRI, T_2 decay corrected MRI, and calculated by elemental analysis of the composition, respectively, resulting in a 9.7% and 4.2% difference in calculated hydrogen density by MRI and T_2 decay corrected MRI, respectively. TSE Dixon estimated the oleic acid to be 12% water and 88% non-water. These values were used to calculate $I_m(\text{UC})$ by MR measurement for oleic acid. Values for $I_m(\text{BAR})$ by elemental composition and $I_m(\text{UC})$ by MR measurement (using SE PD and TSE Dixon) were 61.1 eV and 65.3 eV, respectively, with a 6.9% difference between the two resulting in an 0.76% difference in calculated SPR for a 250 MeV proton. $I_m(\text{UC})$ estimates for oleic acid improve to 63.9 eV when accounting for T_2 decay with a 4.7% difference between $I_m(\text{UC})$ and $I_m(\text{BAR})$ with a resulting 0.52% difference in calculated SPR for a 250 MeV proton. Recently developed sequences (such as UTE/ZTE) can be employed to reduce influences on T_1 and T_2 relaxation which may further improve these results.

Figure 2. MR images of A) SE PD, B) TSE Dixon (non-water), and C) TSE Dixon (water). The chemicals in the MR images are (counter-clockwise): water (large circle on the lower left), oleic acid (small circle), isopropyl alcohol, propargyl alcohol, and

acetone. Panel D is a plot of MR signal versus total hydrogen content for the four chemicals used to create a calibration curve (black plus) and oleic acid uncorrected signal (red triangle) and oleic acid corrected for T2 decay (green asterisk). A linear fit of the calibration chemicals is shown as a black line ($R^2 = 0.99$).

4. Discussion

In this study, we introduced the UC model, a novel way to parameterize the biological molecules in the human body for calculation of the mean ionization potential by quantities measurable using MRI. Tests of this parameterization on tissue compositions (from ICRU Report #44 and White *et al*) suggest a high degree of accuracy is technically achievable. Of the tissues theoretically tested, this model parameterization leads to a mean error in SPR (for a 250 MeV proton) of 0.03% (<0.2% max error) and 0.2% (<0.3% max error) relative to a calculation by all elemental constituents using Bragg's additivity rule for soft tissue and cortical bone, respectively. UC model root-mean-square errors (RMSE) in soft tissue were 0.77% and 0.09% for I_m and SPR, respectively. Of particular note is the low UC model error in thyroid which is 0.8% and 0.1% for I_m and SPR, respectively. The thyroid tends to have a poorly correlated relationship with effective atomic number (as measured with DECT) relative to other tissues (Han *et al.*, 2016; Yang *et al.*, 2010) which can lead to a greater uncertainty in the determination of I_m and SPR. UC model RMSE in cortical bone were 1.8% and 0.2% for I_m and SPR, respectively. SECT stoichiometric method calculation RMSE are typically much larger for SPR calculations. Taasti *et al* determined that the SECT stoichiometric method can result in RMSE of 1.49% with maximum errors at 5.2% (Taasti *et al.*, 2016) for SPR calculations when tested in "reference" tissues. The accuracy of DECT parameterizations for SPR determination have varied RMSE from 0.12% - 0.28% with maximum errors ranging between 0.39% to 0.98% (Taasti *et al.*, 2016) depending on the type of parameterization used when tested in "reference" tissues. Nearly all of these SECT (stoichiometric) and DECT parameterization methods require parameterization to "reference" human tissues (as those of ICRU Report #44) and suffer from increased errors as elemental compositions for particular tissue types deviate away from them (Taasti *et al.*, 2016; Yang *et al.*, 2010; Yang *et al.*, 2012). In practice, errors from SECT and DECT calculation of I_m and SPR can be much larger. In a study from Bar *et al* (Bar *et al.*, 2017), they determined that the benefit of DECT drops dramatically in the presence of modest amounts of noise (8 to 12 HU). They estimate that DECT based parameterizations may practically only result in proton beam range uncertainty reductions of 0.4% in soft tissue and that the overall uncertainty with DECT may still remain high with margins recommended at 2.4% + 1.2mm.

Distinct to this work, the UC model parameterization is at the molecular level with the potential to tease out individual molecular constituents by MRI (such as water) rather than composite electron density or effective atomic number. The UC model is therefore able to account for variations in an individual's tissue composition at a unique level rather than rely on parameterization to "reference" standard human tissue elemental compositions that may not be representative of patient-specific compositions. Compositions of water, fat and protein vary significantly from individual to individual with estimates of 1.2% (1σ) error in SPR for soft tissue being due to deviations in human body tissue composition differences from "reference" standard human tissue compositions (Yang *et al.*, 2012). Voxel to voxel differences in composition may

also exist even within a single organ. In the normal brain, water content varies from ~68% to ~83% (Abbas *et al.*, 2015; Neeb *et al.*, 2008; Sabati and Maudsley, 2013) and lipid content varies from ~36% to ~81% of dry weight (O'Brien and Sampson, 1965). In addition, tumors may have significant variations in composition relative to normal anatomy with sparse data on molecular or elemental compositions in the literature to fully estimate these variations. In the case of neural tumors, concentrations of water may be higher with lower lipid content (~20% of dry weight for astrocytoma and glioblastoma multiforme) (Yates *et al.*, 1979) than normal brain. In the work of Maughan *et al* (Maughan *et al.*, 1997), they found significant differences in the hydrogen content of tumor samples (9.7% by mass) than the average for soft tissue (10.55%). Hydrogen, water, and lipid content variations can have a large impact on I_m and SPR. These compositional variations have significant implications on proton range uncertainties if they're not correctly accounted for. The results presented in this work demonstrate the possibility of accurate mean ionization potential calculations for soft tissue using MR imaging that could account for such elemental/molecular variations. Our results show that hydrogen content can be calibrated on an MRI and additional pulse sequences can be used to separate out water from other organic molecules (Bernard *et al.*, 2008; Bley *et al.*, 2010), the two components necessary for UC model computation in soft tissue. The UC model with MR imaging provides an alternative methodology that can be used to accurately determine *in vivo* tissue specific compositions relevant for I_m and SPR calculations.

A potential workflow to calculate SPR with MR and CT imaging techniques is as follows:

- (i) Develop an MR protocol to maximize ^1H (proton) and ^{31}P density weighting and to minimize the effects of B_1 , T_1 , and T_2 . For ^1H MRI, determine the content of water with sequences such as Dixon and water/fat suppression.
- (ii) Scan an object with these MR sequences along with known hydrogen and phosphorous content standards to convert the signal intensity to quantitative ^1H and ^{31}P density to use in equation 4 (UC model).
- (iii) Scan an object with CT and convert the intensity to electron density. Register this CT image with the MR scans.
- (iv) Calculate the water mass fraction based off the water component MR sequence.
- (v) Subtract out the ^1H signal that's due to the water component from the ^1H proton-density weighted scan to calculate the remaining organic ^1H density, h_{org} .
- (vi) Compute the UC model I_m value (with equation 4) using the water mass fraction, organic ^1H density (h_{org}), and ^{31}P density for the HA mass fraction. The organic material mass fraction is calculated as the remaining mass.
- (vii) Calculate the SPR with equation 5 with the UC model I_m value and the electron density from the CT.

Our proposed methodology (MR imaging with UC model) has limitations that are unique from SECT, DECT and proton CT methods. MR, unlike kV, MV, and proton CT, obtains images from specific nuclei (^1H and ^{31}P are considered in this study) that have magnetic moments. All other atomic constituents are not measured and may not directly contribute to the signal. In this work, only biologically based molecules were considered so non-biologically based molecules may have chemical compositions that are unanticipated for in the model. Unanticipated for deviations in chemical composition from the molecules modeled may have a significant impact on the accuracy of I_m calculation. In addition, metals and other non-hydrogenous materials, such as fiducials and other implanted devices, may show up as signal voids. These limitations are

inherent to MR imaging based radiation therapy planning methods but can be supplemented with additional imaging modalities such as kV or MV CT. Unlike pseudo or synthetic CT generation from MRI, our proposed approach only provides the methodology to accurately calculate mean ionization potential and still requires additional information about electron density to calculate SPR. Other groups have completed significant prior work on conversion of MR images to electron density for the purposes of radiation therapy planning with accuracy reasonable for photon radiation therapy. It may therefore be feasible to accurately calculate SPR from MR imaging alone but this possibility was not studied in this work. Alternatively, the electron density component can be accurately obtained from kV SECT, kV DECT and MV CT.

5. Conclusions

We have proposed a novel method to model human tissue compositions for the purpose of accurate mean ionization potential and stopping power ratio calculation (with additional knowledge of electron density). For soft tissue, this model requires quantification of two parameters, percent water content by mass and percent content of hydrogen in organic molecules by mass, both of which are measurable using clinically available MR imaging techniques. In this work, we have demonstrated that these parameters, and therefore mean ionization potential, are accurately quantifiable by MRI.

Acknowledgements

We would like to thank Adam Cunha from the University of California, San Francisco Department of Radiation Oncology for lending me his eyes, ears, and brain in the development and review of this work.(ICRU, 1993)

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