

Visual Analysis of Tumor Control Models for Prediction of Radiotherapy Response

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Appendix A:

Quantification of imaging-induced uncertainty and its propagation to TCP modeling

Recently, clinical research started focusing on providing a more targeted treatment, tailored to the patient-specific tumor tissue characteristics. To this end, information from imaging modalities was incorporated in RT planning and, subsequently, to TCP modeling [TOG06]. In this way, properties indicative of tissue characteristics were included to improve the radiobiological accuracy of modeling at a voxel-level [TOG06]. In the present work, we are dealing with a new type of TCP modeling that involves DW-MRI [CMvdHR*16]. This is an in-vivo imaging technique, which quantitatively measures the per-voxel diffusion using the apparent diffusion coefficient (ADC) maps and is employed to identify high density tissue like tumors [BJEK*11].

The ADC-based TCP model described by Casares-Magaz et al. [CMvdHR*16] aims at incorporating cell density (CD) information from imaging acquisitions of the patient. CD is a common measure in tumor tissue characterization, referring to the number of tumor cells within a volume. Among all approaches employed to quantify CD from ADC values, two were chosen for visualization by our clinical partners:

(i) The *sigmoid* approach, where CD is modeled as a sigmoid function of the ADC values [CMvdHR*16].

(ii) The *Gibbs* approach [GPT07], which is based on experimental data. In this approach, Gibbs et al. retrieved for a number of prostate samples the ADC values from imaging and the CD values from histopathology (see Figure 1, blue data points). From these data points, they established a linear relationship between ADC and CD (see Figure 1, red dotted line):

$$CD \approx \frac{2.1 \cdot 10^{-3} - ADC}{3 \cdot 10^{-5}}$$

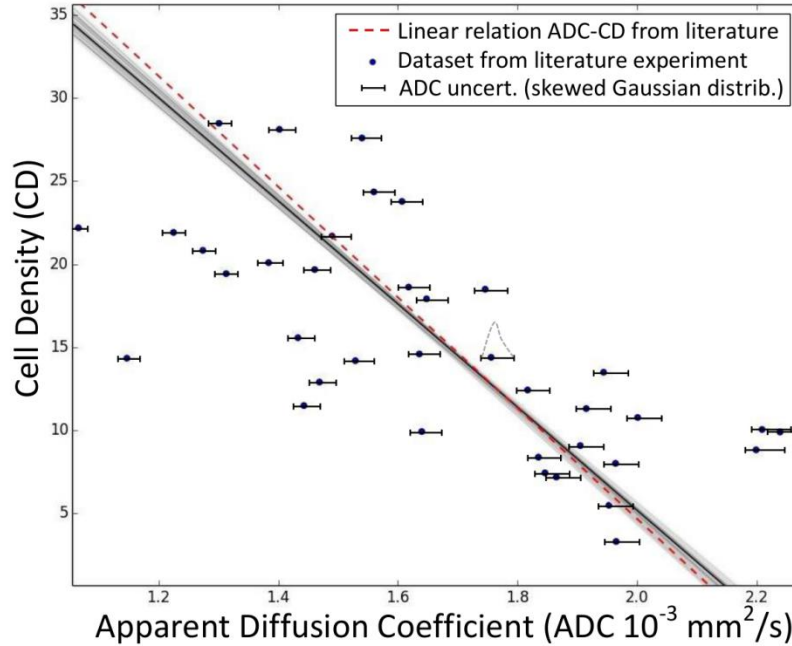


Figure 1. Data set extracted from the experiment of Gibbs et al. (blue points), and linear relation between ADC and CD (red line) [GPT07], without uncertainty. Incorporating ADC uncertainty, results in a set of linear fits (greyscale: dark denotes higher probability).

Both of these approaches are affected by uncertainty. In the first case, only the uncertainty of the ADC, calculated below, is present, while in the second case, there is an additional uncertainty in the experimental set-up that was used to determine the relationship between ADC and CD [GPT07].

Uncertainty in ADC maps is usually measured through experimentation in each clinical institution, specifically for their specific scanning set-up [KTH*10]. Our clinical collaborators (the Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital and Department of Medical Physics - Århus University Hospital) have modeled by experiments the probability density function, $p(m|r)$, representing the probability that an ADC value m is measured in the acquired images, given a quantitative real value, r . This probability density function was modeled as a Gaussian distribution, with a standard deviation σ , being a percentage of r , i.e., $\sigma = \sigma\% r$, as shown in Figure 2.

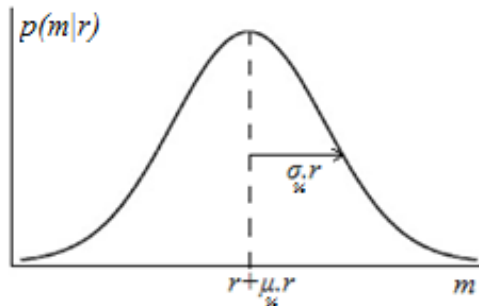


Figure 2. The probability density function, $p(m|r)$, representing the probability that an ADC value m is measured in the acquired ADC images, given a quantitative real value, r . This was calculated by our clinical collaborators (the Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital and Department of Medical Physics - Århus University Hospital), based on their specific clinical set-up.

In practice, we are interested in the probability that the real value r has occurred, given a measurement m in the ADC maps, i.e., $p(r|m)$. Using Bayes' rule, we can calculate this by:

$$p(r|m) = \frac{p(r) \cdot p(m|r)}{p(m)} = \frac{p(r) \cdot p(m|r)}{\int_r p(r) \cdot p(m|r) dr},$$

where $p(r)$ is the prior probability of the value r . This is assumed to be uniform: $p(r) = \frac{1}{R}$, where R is the range of possible values. Since the standard deviation of the $p(m|r)$ probability density function depends on the value r , the calculation of $p(r|m)$ is not trivial and was approximated analytically, using Taylor expansion. The analytical calculation was done in MATLAB and it resulted to be a skewed Gaussian, dependent on the measured value m :

$$p(r|m) = Q(m) \cdot \frac{1}{r} \cdot \exp\left(-\frac{(m - (1 + \mu) \cdot r)^2}{2 \cdot (\sigma \cdot r)^2}\right),$$

where $Q(m)$ is a polynomial of 12th degree of the measured value m , resulting from the approximation. For generalization purposes, $p(r|m)$ could also have been calculated numerically.

The previously calculated uncertainty in ADC maps is propagated in the calculation of the cell density (CD). The two approaches for CD quantification from ADC mentioned above, are influenced by ADC uncertainty in a different way:

(i) In the *sigmoid* approach, where CD is modeled as a sigmoid function of the ADC, the uncertainty of the ADC is directly propagated to the CD calculation. The CD uncertainty $CD(r|m)$ is, hence, a function of $p(r|m)$.

(ii) In the experiment of *Gibbs et al.* [GPT07], no uncertainty was included for the ADC values of the data set. As the CD values were retrieved from histopathological samples, they consist true values, without uncertainty. When we incorporate per data point the ADC uncertainty as calculated before, i.e., $p(r|m)$, we expect that the linear relationship between ADC and CD will also present a variation. To generate the variation on the linear fits, we randomly sample each data point according to its distribution. Then, we pick 2 million different sets of samples and we calculate for all of them, the resulting linear fits. All generated fits can be seen in Figure 1. With the greyscale colormap, we denote the probability of each one of the fitted lines, which is calculated by the product of the probabilities of the sets of samples. White is the least probable and black the most probable. From these calculated fits, we can calculate the resulting CD probability function for each data point in the experiment, or the corresponding CD probability function $CD(r|m)$ for each measured ADC value m at the position of each voxel in the map.

The remaining steps of the ADC-based TCP model are mathematical equations [GPT07, CMvdHR*16], which do not include additional uncertainties and use the CD as input. Therefore, the final TCP uncertainty will depend on the CD uncertainty in the tumor, $CD(r|m)$.

Appendix B:

Parameters of the ADC-based TCP modeling

A number of parameters are involved in the ADC-based TCP model described by Casares-Magaz et al. [CMvdHR*16]. Below, we provide a short description of the most important parameters that are encountered in our paper:

- (i) df : dose per fraction, i.e., division of the total radiation into smaller doses per session over a period of time.
- (ii) nf : number of fractions.
- (iii) α : radiobiological parameter indicating the survival rate of tumor cells.
- (iv) αVar : inter-patient variability in the survival rate of tumor cells.
- (v) β : radiobiological parameter indicating the killing rate of tumor cells.
- (vi) βVar : inter-patient variability in the death rate of tumor cells.
- (vii) α/β : repopulation factor, the ration between the survival and killing rate of tumor cells.

For more details on the ADC-based TCP model and an extensive description of the parameters above, we refer to the paper of Casares-Magaz et al. [CMvdHR*16].

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