

Analytical probabilistic proton dose calculation and range uncertainties

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Abstract. We introduce the concept of analytical probabilistic modeling (APM) to calculate the mean and the standard deviation of intensity-modulated proton dose distributions under the influence of range uncertainties in closed form. For APM, range uncertainties are modeled with a multivariate Normal distribution $p(\mathbf{z})$ over the radiological depths \mathbf{z} . A pencil beam algorithm that parameterizes the proton depth dose $d(\mathbf{z})$ with a weighted superposition of ten Gaussians is used. Hence, the integrals $\int d\mathbf{z} p(\mathbf{z}) d(\mathbf{z})$ and $\int d\mathbf{z} p(\mathbf{z}) d(\mathbf{z})^2$ required for the calculation of the expected value and standard deviation of the dose remain analytically tractable and can be efficiently evaluated. The means μ_k , widths δ_k , and weights ω_k of the Gaussian components parameterizing the depth dose curves are found with least squares fits for all available proton ranges. We observe less than 0.3% average deviation of the Gaussian parameterizations from the original proton depth dose curves. Consequently, APM yields high accuracy estimates for the expected value and standard deviation of intensity-modulated proton dose distributions for two dimensional test cases. APM can accommodate arbitrary correlation models and account for the different nature of random and systematic errors in fractionated radiation therapy. Beneficial applications of APM in robust planning are feasible.

1. Introduction

The quality of radiation therapy treatment simulations may be compromised by uncertainties originating from inter- and intra-fraction motion, setup errors, or inaccuracies during target volume definition, among others. Approaches to quantify the influence of these uncertainties on the resulting dose distribution and derivative treatment plan quality indicators include worst case simulations and variance calculations based on dose blurring or sampling [1, 2, 3, 4]. However, these approaches remain computationally challenging or suffer from inherent limitations [5].

In order to quantify the influence of range uncertainties on intensity-modulated proton dose distributions, we apply the concept of analytical probabilistic modeling (APM). Therefore, we describe the uncertainty in the radiological depths \mathbf{z} with a multivariate Normal distribution $\mathcal{N}(\mathbf{z}; \bar{\mathbf{z}}, \Sigma)$ with mean vector $\bar{\mathbf{z}}$ and covariance matrix Σ and approximate the proton dose $d(\mathbf{z})$ with a functional form that can be integrated analytically against Gaussian probability distributions. Hence, it is possible to calculate the m th moment of the dose distribution d at depth \mathbf{z} in closed form and thereby the mean $E[d(\mathbf{z})]$ and the variance $E[d(\mathbf{z})^2] - E[d(\mathbf{z})]^2$ of the dose distribution.



$$E[d(z)^m] = \int dz \mathcal{N}(z; \bar{z}, \Sigma) d(z)^m \quad (1)$$

2. Material and methods

The proton depth dose $Z_j(z_{ij})$ of a pencil beam j at voxel i with the radiological depth z_{ij} is approximated with a weighted superposition of Gaussians. We found that ten components are sufficient to describe proton depth dose curves with ranges $R \leq 35$ cm.

$$Z_j(z_{ij}) = \sum_{k=1}^{10} \frac{\omega_{jk}}{\sqrt{2\pi}\delta_{jk}} e^{-\frac{(z_{ij}-\mu_{jk})^2}{2\delta_{jk}^2}} \quad (2)$$

For this study, the weights ω_{jk} , widths δ_{jk} , and means μ_{jk} are determined with a least squares fit of analytically calculated proton depth dose curves [6] but it is also possible to use measured depth dose data. The least squares fit is performed with an open source MATLAB optimizer¹. The gradient components used for optimization are

$$\frac{\partial Z_j}{\partial \omega_{jk}} = \frac{1}{\sqrt{2\pi}\delta_{jk}} e^{-\frac{(z-\mu_{jk})^2}{2\delta_{jk}^2}}; \quad \frac{\partial Z_j}{\partial \mu_{jk}} = \frac{\omega_{jk}}{\sqrt{2\pi}\delta_{jk}} e^{-\frac{(z-\mu_{jk})^2}{2\delta_{jk}^2}} \frac{(z-\mu_{jk})}{\delta_{jk}^2}; \quad \frac{\partial Z_j}{\partial \delta_{jk}} = \frac{\omega_{jk}}{\sqrt{2\pi}\delta_{jk}} e^{-\frac{(z-\mu_{jk})^2}{2\delta_{jk}^2}} \left\{ \frac{(z-\mu_{jk})^2}{\delta_{jk}^2} - \frac{1}{\delta_{jk}} \right\}$$

Figures 1 (a) and (b) show the approximation of proton depth dose curves for four different ranges. We observe less than 0.3% average deviation of the Gaussian parameterization from the analytically calculated proton depth dose curve for proton ranges $R \leq 35$ cm.

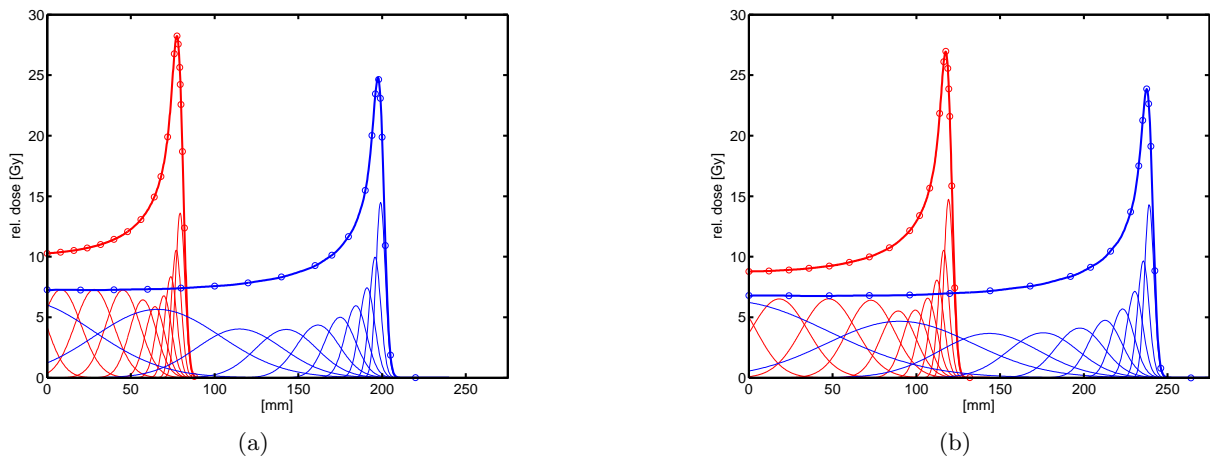


Figure 1. Analytically calculated proton depth dose curves (circles) [6] and functional approximation (bold solid lines) with a weighted superposition of ten Gaussian components (thin solid lines) for (a) ranges $R = 8$ cm (red), $R = 20$ cm (blue) and (b) ranges $R = 12$ cm (red), $R = 24$ cm (blue).

We apply the Gaussian approximation for the proton depth dose in combination with a conventional pencil beam algorithm where the proton dose factorizes in lateral direction and in

¹ We found that *minimize* (available online at <http://learning.eng.cam.ac.uk/car1/code/minimize/>) is considerably more efficient than built-in solvers.

depth [7]. Hence, the three dimensional dose in an intensity modulated field can be described by

$$d(x_i, y_i, z_i) = \sum_j w_j L_{ij}(x_{ij}, y_{ij}, z_{ij}) \cdot \sum_k \frac{\omega_{jk}}{\sqrt{2\pi}\delta_{jk}} e^{-\frac{(z_{ij}-\mu_{jk})^2}{2\delta_{jk}^2}} \quad (3)$$

where w_j corresponds to the weight of pencil beam j and L_{ij} specifies the lateral proton dose profile of pencil beam j at voxel i with the lateral coordinates x_{ij} and y_{ij} .

The influence of range uncertainties can be modeled with an offset Δ_j^z of the radiological depth z_{ij} according to

$$d(z_i) = \sum_{jk} w_j L_{ij} \cdot \frac{\omega_{jk}}{\sqrt{2\pi}\delta_{jk}} e^{-\frac{(z_{ij}-\mu_{jk}+\Delta_j^z)^2}{2\delta_{jk}^2}}. \quad (4)$$

If we assume that the offsets Δ_j^z are distributed according to a multivariate Normal distribution

$$p(\Delta) = p\left(\begin{matrix} \Delta_1^z \\ \Delta_2^z \\ \vdots \end{matrix}\right) = \mathcal{N}(\Delta^z; \bar{\Delta}^z, \Sigma^z) \quad (5)$$

the expected value of the dose is given by

$$\begin{aligned} E[d(z_i)] &= \int d\Delta \mathcal{N}(\Delta^z; \bar{\Delta}^z, \Sigma^z) \sum_{jk} w_j L_{ij} \frac{\omega_{jk}}{\sqrt{2\pi}\delta_{jk}} e^{-\frac{(z_{ij}-\mu_{jk}+\Delta_j^z)^2}{2\delta_{jk}^2}} \\ &= \sum_{jk} w_j L_{ij} \int d\Delta_j^z \mathcal{N}(\Delta_j^z; \bar{\Delta}_j^z, \Sigma_{jj}^z) \frac{\omega_{jk}}{\sqrt{2\pi}\delta_{jk}} e^{-\frac{(z_{ij}-\mu_{jk}+\Delta_j^z)^2}{2\delta_{jk}^2}} \\ &= \sum_{jk} w_j L_{ij} \frac{\omega_{jk}}{\sqrt{2\pi(\delta_{jk}^2 + \Sigma_{jj}^z)}} e^{-\frac{(z_{ij}-\mu_{jk})^2}{2(\delta_{jk}^2 + \Sigma_{jj}^z)}} \end{aligned} \quad (6)$$

where Σ_{jj}^z corresponds to the variance of Δ_j^z . The quadratic term $E[d(z_i)^2]$ required for the calculation of the dose variance $E[d(z_i)^2] - E[d(z_i)]^2$ is given by

$$\begin{aligned} E[d(z_i)d(z_l)] &= \int d\Delta \mathcal{N}(\Delta^z; \bar{\Delta}^z, \Sigma^z) d(z_i)d(z_l) \\ &= \int d\Delta \mathcal{N}(\Delta^z; \bar{\Delta}^z, \Sigma^z) \cdot \left\{ \sum_{jk} w_j L_{ij} \cdot \frac{\omega_{jk}}{\sqrt{2\pi}\delta_{jk}} e^{-\frac{(z_{ij}-\mu_{jk}+\Delta_j^z)^2}{2\delta_{jk}^2}} \right\} \\ &\quad \cdot \left\{ \sum_{mn} w_m L_{lm} \cdot \frac{\omega_{mn}}{\sqrt{2\pi}\delta_{mn}} e^{-\frac{(z_{lm}-\mu_{mn}+\Delta_m^z)^2}{2\delta_{mn}^2}} \right\}. \end{aligned} \quad (7)$$

To rewrite this equation as a quadratic form over two dimensional Gaussians we define

$$\mathbf{z}_{ijlm} = \begin{pmatrix} z_{ij} \\ z_{lm} \end{pmatrix}, \quad \mu_{jkmn}^z = \begin{pmatrix} \mu_{jk} \\ \mu_{mn} \end{pmatrix}, \quad \Delta_{jm}^z = \begin{pmatrix} \Delta_j^z \\ \Delta_m^z \end{pmatrix}, \quad \Theta^{jkmn} = \begin{pmatrix} \delta_{jk}^2 & 0 \\ 0 & \delta_{mn}^2 \end{pmatrix}, \quad \Sigma^{jm} = \begin{pmatrix} \Sigma_{jj}^z & \Sigma_{jm}^z \\ \Sigma_{mj}^z & \Sigma_{mm}^z \end{pmatrix} \quad (8)$$

to obtain

$$\begin{aligned}
 E[d(z_i)d(d_l)] &= \sum_{jknm} w_j w_m L_{ij} L_{lm} \int d\Delta_{jm}^z \mathcal{N}(\Delta_{jm}^z; \bar{\Delta}_{jm}^z, \Sigma^{jm}) \\
 &\quad \cdot \frac{\omega_{jk}\omega_{mn}}{2\pi\sqrt{|\Theta^{jkmn}|}} e^{-\frac{1}{2}(\mathbf{z}_{ijlm} - \boldsymbol{\mu}_{jkmn}^z + \Delta_{jm}^z)^\top (\Theta^{jkmn})^{-1} (\mathbf{z}_{ijlm} - \boldsymbol{\mu}_{jkmn}^z + \Delta_{jm}^z)} \\
 &= \sum_{jknm} w_j w_m L_{ij} L_{lm} \frac{\omega_{jk}\omega_{mn}}{2\pi\sqrt{|\Theta^{jkmn} + \Sigma^{jm}|}} e^{-\frac{1}{2}(\mathbf{z}_{ijlm} - \boldsymbol{\mu}_{jkmn}^z)^\top (\Theta^{jkmn} + \Sigma^{jm})^{-1} (\mathbf{z}_{ijlm} - \boldsymbol{\mu}_{jkmn}^z)}
 \end{aligned} \tag{9}$$

If we are to account for the different nature of random and systematic errors [2] within APM we have to include an additional summation over multiple fractions F as exercised in [5]. For the construction of Σ^{jm} we have to consider that systematic errors are also correlated over different fractions, while random errors of different fractions are uncorrelated.

3. Results

Figure 2 (a) compares the analytically calculated and sampled mean dose and standard deviation for a spread-out Bragg peak with range $R = 20$ cm and modulation $M = 5$ cm assuming a perfectly correlated range error of all underlying proton pencil beams of 3%. The analytical calculation is exact; analytically calculated and samples values are identical up to sampling error.

Figure 2 (b) visualizes the different influence of random and systematic errors in the context of fractionated radiation therapy. While the influence of random errors averages out when increasing the number of fractions from $F = 1$ to $F = 35$, the influence of systematic errors remains.

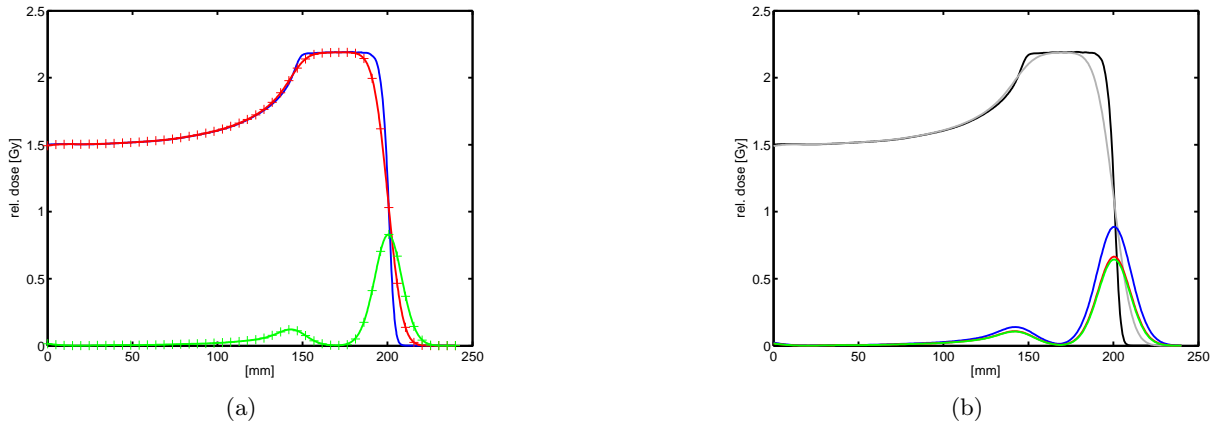


Figure 2. (a) Nominal proton dose of a spread-out Bragg peak (blue), expected value (red), and standard deviation (green) assuming a 3% range error. Analytical calculations are shown as solid lines, sampled values as crosses. (b) Nominal proton dose (black), expected value (gray), and standard deviation assuming a systematic range error of 3% and a random range error of 5 mm for 1 (blue), 5 (red), and 35 fractions (green).

The influence of different correlation assumptions is visualized in figure 3. We simulate a single field applying a uniform dose to a C-shaped target volume surrounding an organ at risk within a homogeneous water phantom². For the calculation of the standard deviation in figure

² Note that APM is generally applicable to full-fledged multi-field IMPT treatments with appropriate weights of the constituting pencil beams $w_{j/m}$.

3 (a), we assumed that the range errors of all constituting pencil beams are perfectly correlated. In this case we observe dose standard deviations of up to 9 Gy. For figure 3 (b), we assumed that only the range errors of pencil beams impinging at the same lateral position and thereby penetrating the same tissue are perfectly correlated. This relaxed correlation assumption yields a reduction of the dose standard deviation.

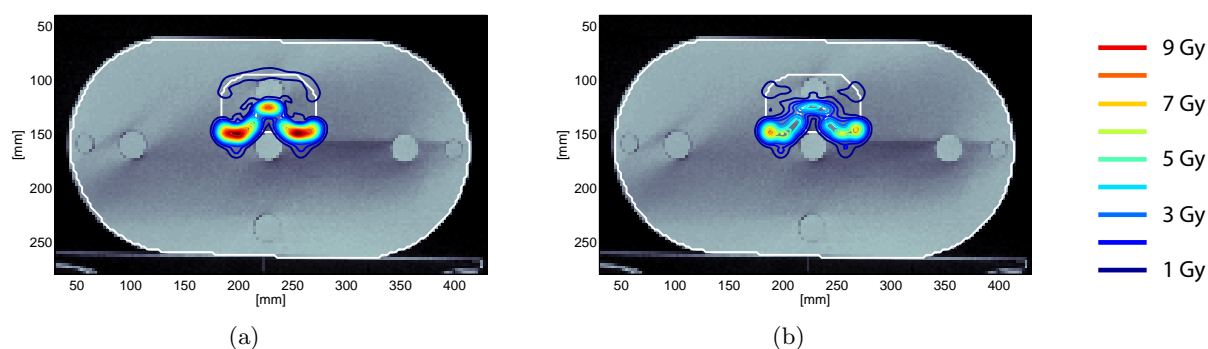


Figure 3. Dose standard deviation [Gy] for a single field uniform dose assuming that (a) the range errors of all pencil beams are perfectly correlated and (b) only range errors of pencil beams impinging at the same lateral position are correlated.

4. Discussion and conclusion

We introduced the concept of analytical probabilistic modeling (APM) for the quantification of range uncertainties in intensity-modulated proton therapy.

Based on a pencil beam algorithm that factorizes in lateral direction and in depth [7] we present closed form expressions for the calculation of the expected value and the standard deviation of the dose. For our derivations to remain analytically tractable, we parameterize the proton depth dose curve with a weighted superposition of ten Gaussians. This gives an approximation of very high numerical quality and allows analytical Gaussian error propagation through the nonlinearities in the proton dose calculations. Potential inaccuracies of APM in heterogeneous geometries due to the applied pencil beam model are part of ongoing research and might be resolved through sub pencil beam decomposition [8].

APM allows for the explicit quantification of the non-trivial interplay of random and systematic errors in the context of fractionated radiation therapy and for the incorporation of structured correlation assumptions about the range errors of the individual pencil beams. While these aspects are often neglected by existing approaches to quantify the influence uncertainties, our preliminary study shows that the correlation assumptions and the different nature of random and systematic errors have a critical impact on the resulting dose uncertainty, as depicted in figures 2 (b) and 3.

APM also applies, with minor variations, to lateral proton dose profiles, other ion species, and photons [5]. In combination with a quadratic objective function [9], such an analytical probabilistic model may lower the computational complexity of robust planning [5].

References

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