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Estimating statistical uncertainty of Monte Carlo efficiency-gain in the context of a correlated sampling Monte Carlo code for brachytherapy treatment planning with non-normal dose distribution

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Abstract

Correlated sampling Monte Carlo methods can shorten computing times in brachytherapy treatment planning. Monte Carlo efficiency is typically estimated via efficiency gain, defined as the reduction in computing time by correlated sampling relative to conventional Monte Carlo methods when equal statistical uncertainties have been achieved. The determination of the efficiency gain uncertainty arising from random effects, however, is not a straightforward task specially when the error distribution is non-normal. The purpose of this study is to evaluate the applicability of the F distribution and standardized uncertainty propagation methods (widely used in metrology to estimate uncertainty of physical measurements) for predicting confidence intervals about efficiency gain estimates derived from single Monte Carlo runs using fixed-collision correlated sampling in a simplified brachytherapy geometry. A bootstrap based algorithm was used to simulate the probability distribution of the efficiency gain estimates and the shortest 95% confidence interval was estimated from this distribution. It was found that the corresponding relative uncertainty was as large as 37% for this particular problem. The uncertainty propagation framework predicted confidence intervals reasonably well; however its main disadvantage was that uncertainties of input quantities had to be calculated in a separate run via a Monte Carlo method. The F distribution noticeably underestimated the confidence interval. These discrepancies were influenced by several photons with large statistical weights which made extremely large contributions to the scored absorbed dose difference. The mechanism of acquiring high statistical weights in the fixed-collision correlated sampling method was explained and a mitigation strategy was proposed.

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Keywords

Monte Carlo; correlated sampling; efficiency; uncertainty; bootstrap

1. Introduction

Monte Carlo transport simulations offer a powerful tool to accurately calculate absorbed dose distributions in complex geometries. Such simulations have successfully been used in the past to study the perturbing effects of heterogeneities in typical brachytherapy configurations (Williamson et al., 1993; Kirov et al., 1996). Due to the statistical nature of the Monte Carlo method, the results are associated with an uncertainty that is inversely proportional to the number of photon histories simulated and thus to the computing time. For the purpose of clinical patient dose-planning, where the geometry of the problem varies from patient to patient, the central processing unit (CPU) time of no more than a few minutes is desirable. To achieve this goal, variance reduction techniques therefore need to be exploited. Hedtjrn et al. (2002) tested a fixed-collision correlated sampling method (Rief, 1984; Lux and Koblinger, 1991; Sampson et al., 2009) suitable for use in photon transport codes. In contrast to previous applications of correlated sampling to radiation dosimetry transport (Ma and Nahum, 1993; Holmes et al., 1993) where only the initial trajectory and random number seed of particle histories are fixed, the locations and outcomes of photon collisions, in terms of scattered photon energy and angle, are all fixed and only the particle weights are allowed to vary with the perturbing geometry. Use of the fixed-collision method benefits from the applicability of the kerma approximation in calculating absorbed dose implying that only photon collisions need to be fixed.

The efficiency of a Monte Carlo method is inversely proportional to a product of the total CPU time and the variance of the scored quantity. The efficiency gain of a correlated sampling scheme compared to a conventional one is then often defined as the ratio of their efficiencies. Its estimate is a stochastic variable whose realization may differ from the non-stochastic true value; it is affected by uncertainty. Methods for evaluating measurement uncertainty (JCGM, 2009) include: (i) uncertainty frameworks based on the law of propagation of uncertainty, e.g., the GUM report of the Joint Committee for Guides in Metrology (JCGM, 2008b) or Report 1297 from NIST (Taylor, 1994) hereafter referred to as GUM framework; (ii) standard parametric statistics, in which the probability distribution of the output quantity (efficiency gain estimate in our case) is derived via mathematical analysis, and (iii) Monte Carlo or bootstrapping methods, in which the distribution of the output quantity is established by making random draws from the probability distributions of input quantities (JCGM, 2008b). The parametric statistics approach provides the most accurate predictions if its assumptions about distributions of input quantities are correct. The GUM framework is often used in engineering and applied physics if distributions of output quantities can be approximated by normal or t distributions. In other cases, Monte Carlo sampling may be the only viable alternative. Since the ratio of two random variables (the efficiency gain estimate) may deviate from both the normal and t distributions assumed in the GUM framework, and the asymptotic normality of the means of scored absorbed dose and dose difference often assumed in the parametric statistics approach cannot be guaranteed, it is of interest whether these methods can be used to accurately predict the uncertainty of efficiency gain.

The aim of this work is to evaluate the applicability of the GUM framework and a commonly used parametric statistical model for analysis of variance (the F distribution) for the calculation of uncertainty in fixed-collision correlated Monte Carlo efficiency relative to that of a conventional Monte Carlo code for a typical idealized brachytherapy dose

calculation geometry. As the efficiency gain and its uncertainty are closely related to the implementation of the correlated sampling method, the aim is also to analyze the inner working of the method and propose improvements of the current implementation.

2. Theory

In this section we introduce the concepts of efficiency gain, correlated sampling, bootstrap method and highest density intervals; they will be needed for an in-depth discussion of the efficiency gain estimate behavior and construction of confidence intervals for that quantity.

2.1. Efficiency and efficiency gain

Let the term “history” denote a sequence of interactions, initiated by emission of a primary particle by the radioactive source, that the particle experiences as it loses energy. We assume that the Monte Carlo simulation is time independent (does not depend on history number) and interactions in one history are not affected by interactions in previous histories. In mathematical terms, assume that a history i contributes a certain amount Z_i to the scored quantity (e.g., absorbed dose). Z_i is a random variable with a distribution D_Z , mean value $E(Z_i)$ and variance $V(Z_i)$. This distribution and hence the mean value and variance are the same for all histories. Moreover, the Z_i are independent random variables. Under these assumptions, a simulated physical quantity can be estimated by the average

$\bar{Z} = (1/n) \sum_{i=1}^n Z_i$. Efficiency $\varepsilon_{\bar{Z}}$ of the Monte Carlo method is then conventionally defined

as the inverse of the product of the variance $V(\bar{Z})$ of the average $\bar{Z}$ times the computing (CPU) time $t_{\bar{Z}}$:

$$\varepsilon_{\bar{Z}} \equiv \left[V(\bar{Z}) t_{\bar{Z}} \right]^{-1}. \quad (1)$$

For simplicity we assume that the time $t_{\bar{Z}}$ is a non-stochastic quantity. The efficiency $\varepsilon_{\bar{Z}}$ is a non-stochastic quantity too. Since $V(\bar{Z}) = V(Z)/n$, the efficiency of a run consisting of n histories is independent of the number of histories:

$$\varepsilon_{\bar{Z}} \equiv \left[V(\bar{Z}) t_{\bar{Z}} \right]^{-1} = \left[V(Z_1) t_{\bar{Z}}/n \right]^{-1} = [V(Z_1) t_Z]^{-1}. \quad (2)$$

Here, $t_Z = t_{\bar{Z}}/n$ is the average CPU time per one history.

The efficiency of a sampling scheme is usually quantified in terms of the efficiency gain, γ , defined as a ratio of the efficiency of the tested sampling method, $\varepsilon_{\bar{T}}$, to that of the reference sampling method, $\varepsilon_{\bar{R}}$

$$\gamma \equiv \frac{\varepsilon_{\bar{T}}}{\varepsilon_{\bar{R}}} = \frac{V(\bar{R}) t_{\bar{R}}}{V(\bar{T}) t_{\bar{T}}} = \frac{V(R) t_R}{V(T) t_T} = \frac{n_R^{-1} V\left(R \sqrt{t_{\bar{R}}}\right)}{n_T^{-1} V\left(T \sqrt{t_{\bar{T}}}\right)}, \quad (3)$$

where n_R and n_T are the numbers of histories of the reference and tested methods, respectively. This expresses the reduction in CPU time t_T , that is achieved in obtaining equal uncertainties $V(\bar{T})=V(\bar{R})$ of the calculated value compared to the corresponding CPU time t_R using the reference sampling scheme. Alternatively, efficiency gain expresses the increase in statistical precision (reduced variance), that is achieved for equal CPU times $t_T=t_R$.

Efficiency gain γ in equation (3) is a non-stochastic quantity whose value is typically estimated using the (stochastic) efficiency gain estimate G

$$G \equiv \frac{n_R^{-1} S_R^2 t_R}{n_T^{-1} S_T^2 t_T} \quad (4)$$

where the estimate of the variance of the reference sampling method, S_R^2 , is defined for n_R samples R_i as

$$S_R^2 \equiv \frac{1}{n_R - 1} \sum_{i=1}^{n_R} (R_i - \bar{R})^2 \quad (5)$$

and similarly for the estimate of the variance of the tested sampling method, S_T^2 . By introducing variables $X=R\sqrt{t_R}$ and $Y=T\sqrt{t_T}$, equation (4) can also be written as

$$G = \frac{n_R^{-1} S_X^2}{n_T^{-1} S_Y^2}, \quad (6)$$

where S_X^2 and S_Y^2 are sample variances defined by formula (5). For brevity, we often call calculated samples of the efficiency gain estimate G simply as efficiency gain. This should not lead to a confusion since γ cannot be directly calculated.

2.2. Correlated sampling

The correlated sampling algorithm has been described extensively by Hedtjrn et al. (2002); Sampson et al. (2009); only aspects pertinent to this study will be described here. In correlated sampling, the heterogeneous geometry is treated as a perturbation of the corresponding homogeneous (unperturbed) system, which consists solely of uniform density water. As such, the absorbed dose delivered to the heterogeneous system, $D_{\text{het}}(\mathbf{x})$, is assumed to be a correction to the absorbed dose delivered, $D_{\text{hom}}(\mathbf{x})$, in the corresponding homogeneous system:

$$D_{\text{het}}(\mathbf{x}) = \text{HCF}(\mathbf{x}) \cdot D_{\text{hom}}(\mathbf{x}), \quad (7)$$

where $\text{HCF}(\mathbf{x})$ is the heterogeneity correction factor and $\mathbf{x}$ denotes the position of a given voxel in a 3D grid constituting the system. An estimate of the HCF calculated by the correlated sampling method can thus be defined as

$$\text{HCF}^c(x) \equiv 1 + \frac{\Delta D^c(x)}{D_{\text{hom}}(x)}, \quad (8)$$

where

$$\Delta D^c(x) = D_{\text{het}}(x) - D_{\text{hom}}(x). \quad (9)$$

Correlated sampling begins by generating a set of N photon histories

$\left\{ \left(r_{ij}, E_{ij}, \Omega_{ij}, W_{ij}^{\text{hom}} \right) \right\}_{j=0}^{M_i}$ in a homogeneous geometry where E_{ij} , Ω_{ij} , and W_{ij}^{hom} denote the energy, direction, and particle weight, respectively, leaving the j -th collision ($j = 0$ denotes the primary photon) at r_{ij} . A corresponding set of highly correlated histories in

heterogeneous geometry, $\left\{ \left(r_{ij}, E_{ij}, \Omega_{ij}, W_{ij}^{\text{het}} \right) \right\}_{j=0}^{M_i}$, is obtained by performing ray tracing in heterogeneous geometry along the flight paths linking each pair of successive interaction

locations, and recalculating the weight correction factors, W_{ij}^{het} . This is required to offset the bias introduced by ignoring density and composition non-uniformities in the original

sampling process (see equations (15) and (16) below). Rather than calculating $\bar{D}_{\text{het}}^c(x)$ directly from a set of histories sampled directly in heterogeneous geometry, correlated

sampling scores the dose difference $\Delta D^c(\alpha_{ij}, W_{ij}^{\text{hom}}, W_{ij}^{\text{het}} | x)$ for each simulated collision, where $\alpha_{ij} = (r_{ij}, E_{ij}, \Omega_{ij})$, as follows

$$\Delta \bar{D}^c(x) = \frac{1}{N} \sum_{i=1}^N \sum_{j=0}^{M_i} \left(W_{ij}^{\text{het}} \cdot f_D^{\text{het}}(\alpha_{ij} | x) - W_{ij}^{\text{hom}} \cdot f_D^{\text{hom}}(\alpha_{ij} | x) \right), \quad (10)$$

where f_D^{het} and f_D^{hom} denote the dose-scoring functions for the homogeneous and heterogeneous geometries, respectively, see equation (17) below. Then an estimate of the heterogeneity correction factor is

$$\overline{\text{HCF}}^c(x) = 1 + \frac{\Delta \bar{D}^c(x)}{\bar{D}_{\text{hom}}(x)} \quad (11)$$

Here, in equation (11), it is assumed that $\bar{D}_{\text{hom}}(x)$ has been pre-calculated with a high degree of precision so that the uncertainty in $\bar{D}_{\text{hom}}(x)$ can be neglected compared to the uncertainty in $\Delta \bar{D}^c(x)$. Finally, estimate $D_{\text{het}}^{*,c}(x)$ of $D_{\text{het}}(x)$ is obtained from

$$D_{\text{het}}^{*,c}(x) = \overline{\text{HCF}}^c(x) \bar{D}_{\text{hom}}(x). \quad (12)$$

The variance of this estimate is (see Hedtjrn et al. (2002) for details)

$$V(D_{\text{het}}^{*,c}) \approx V(\Delta \bar{D}^c) = V(\bar{D}_{\text{het}}^c) + V(\bar{D}_{\text{hom}}^c) - 2\text{Cov}(\bar{D}_{\text{het}}^c, \bar{D}_{\text{hom}}^c), \quad (13)$$

where $\bar{D}_{\text{het}}^c$ and $\bar{D}_{\text{hom}}^c$ are given by the first and second terms of (9). Provided that a positive correlation between these two estimates is preserved, the variance of this estimate $D_{\text{het}}^{*,c}$ may be greatly reduced compared to a conventional uncorrelated Monte Carlo estimate, $D_{\text{het}}^{\text{unc}}(\mathbf{x})$, in the same computing time: $V(D_{\text{het}}^{*,c}) \ll V(D_{\text{het}}^{\text{unc}}(\mathbf{x}))$ a situation where the dose in the heterogeneous geometry is calculated directly using conventional (uncorrelated) simulation and equal CPU time.

The efficiency of the correlated game relative to the conventional uncorrelated simulation, efficiency gain γ (cf. equation (3)), is then given by

$$\gamma(\mathbf{x}) = \frac{\text{efficiency correlated}}{\text{efficiency uncorrelated}} = \frac{V(\bar{D}_{\text{het}}^{\text{unc}}(\mathbf{x})) t_{\text{unc}}}{V(\Delta \bar{D}^c(\mathbf{x})) t_c}, \quad (14)$$

where t_{unc} and t_c represent the CPU times of the uncorrelated and correlated simulations, respectively.

By using a set of histories generated in a homogeneous medium to calculate the absorbed dose in a heterogeneous geometry, biasing is introduced. To account for this, just before a collision is processed, the photon's weight is multiplied by a corresponding weight correction factor, as given by Hedtjrn et al. (2002). To simplify calculation of this factor, characteristic x-ray emission upon photoelectric absorption, coherent scattering, and electron binding affects on incoherent scattering are ignored. The heterogeneous weight correction factor is as follows (dropping the history index for clarity):

$$W_{j+1}^{\text{het}} = W_j^{\text{het}} \left[\frac{\mu(E_j; \mathbf{r}_{j+1}) e^{-\lambda(\mathbf{r}_j; \mathbf{r}_{j+1}; E_j)}}{\mu(E_j) e^{-\mu(E_j) |\mathbf{r}_j - \mathbf{r}_{j+1}|}} \right] \left[1 - e^{-\mu(E_j) t_{\text{max}}} \right] \left[1 - \frac{\sigma_{\text{PE}}(E_j; \mathbf{r}_{j+1})}{\mu(E_j; \mathbf{r}_{j+1})} \right], \quad (15)$$

where W_{j+1}^{het} denotes the weight of the photon just after $(j+1)^{\text{th}}$ collision, $\mu(E_j; \mathbf{r}_{j+1})$ corresponds to the linear attenuation coefficient of the heterogeneous medium at energy E_j and position $\mathbf{r}_{j+1}$, $\mu(E_j)$ corresponds to the linear attenuation coefficient of the homogeneous medium at energy E_j , $\lambda(\mathbf{r}_j; \mathbf{r}_{j+1}; E_j)$ is the radiological pathlength in the heterogeneous geometry as it traverses the distance from $\mathbf{r}_j$ to $\mathbf{r}_{j+1}$ at energy E_j , $|\mathbf{r}_j - \mathbf{r}_{j+1}|$ is the distance between the j^{th} collision and the $(j+1)^{\text{th}}$ collision, t_{max} is the maximum distance from $\mathbf{r}_j$ to the boundary of the phantom in the direction Ω_j , and $\sigma_{\text{PE}}(E_j; \mathbf{r}_{j+1})$ is the macroscopic cross section for photoelectric effect in the heterogeneous medium at energy E_j and position $\mathbf{r}_{j+1}$. The three factors in square brackets on the right hand side of (15) represent the combination of the (i) heterogeneous geometry correction to the homogeneous medium intercollision distance PDF; (ii) homogeneous medium forced collision correction, and (iii) heterogeneous geometry survival biasing correction. In the homogeneous medium sampling process, only the forced collision and survival biasing factors apply:

$$W_{j+1}^{\text{hom}} = W_j^{\text{hom}} \left[1 - e^{-\mu(E_j) t_{\text{max}}} \right] \left[1 - \frac{\sigma_{\text{PE}}}{\mu(E_j)} \right] \quad (16)$$

It is of interest to note that when $|r_j - r_{j+1}|$ is small and the ratio $\mu(E_j; r_{j+1})/\mu(E_j)$ is large in (15), then $W_{j+1}^{\text{het}}/W_j^{\text{het}}$ can be substantially larger than unity. This can lead to the inflation of statistical uncertainty within a voxel or a group of voxels in the heterogeneous case. Since the same ratio for the homogeneous case, $W_{j+1}^{\text{hom}}/W_j^{\text{hom}}$, is always smaller than one, the large difference between statistical weights of the correlated and uncorrelated sampling schemes in (10) can also lead to an efficiency loss for the voxels affected by this phenomenon. This issue is discussed in section 5.

The dose scoring function, f_D , of the expected-value track length (ETL) estimator is (Hedtjärn et al., 2002)

$$f_D(\Delta V, \alpha_j) = E_j e^{-\lambda(r_j, r_p; E_j)} (1 - e^{-\mu \Delta l}) (\mu_{\text{en}}/\mu) / (\rho_V \Delta V) \quad (17)$$

for voxels intersected by the ray $r_j + t\Omega_j$, where $t \geq 0$, and zero otherwise. In equation (17), $\lambda(r_j, r_p; E_j)$ is the radiological between the point r_j and the proximal-most intersection with the voxel ΔV denoted as r_p , μ_{en} and μ are the energy absorption and linear attenuation coefficients, respectively, for the medium of the scoring voxel, ρ_V and ΔV are the density and volume, respectively, of the scoring voxel, and Δl is the path length of the dose scoring functions f_D^{hom} and f_D^{het} , the radiological paths $\lambda(r_j, r_p; E_j)$ are taken for the homogeneous and heterogeneous environments, respectively.

2.3. Bootstrap methods

Our parameter of interest is the efficiency gain which is a ratio of variances. If the numerator and denominator behave like independent chi-square random variables, the ratio follows the F distribution. However, in our case, the dose distribution being rather non-normal for some voxels, it is difficult to propose one parametric model for all the voxels. For estimating such complicated functions of population parameters, the bootstrap method is a robust and versatile tool. Let $(x_1, x_2, \dots, x_N)$ be the observed random set of histories from the unobserved population distribution given by the cumulative distribution function (CDF) D . The empirical CDF $\widehat{D}$ is the discrete distribution that assigns $1/N$ probability to each of the observed histories. Bootstrap uses this empirical distribution of the sample to generate a plug-in estimate of the parameter of interest. Let $\gamma(D)$ be the parameter of interest as a function of the population distribution D . A bootstrap estimate of $\gamma(D)$, $\gamma(\widehat{D})$, is obtained by randomly sampling with replacement from the original set of histories, $(x_1, \dots, x_N)$, a new sample of N values from which $\gamma(\widehat{D})$ is computed. Replacement means that upon randomly selecting a specific sample X_j , it is returned to the pool, allowing it to be selected multiple times for each randomly selected set $(X_1, \dots, X_N)$. Because of replacement, each randomly selected set of N histories is potentially distinct from others and functions as a randomly selected sample. This process can be repeated many times to form a bootstrap distribution of $\gamma(\widehat{D})$ values, each based upon a randomly selected set of N histories. (Efron and Tibshirani, 1993)

An advantage of bootstrap sampling is that the whole distribution of the parameter of interest is available through a large sample from the empirical distribution and, depending on the nature of the distribution, measures of the center and dispersion can be chosen. However, price of this added robustness is paid in CPU time used for bootstrap sampling.

2.4. Confidence intervals, coverage intervals and highest density sets

A popular method for confidence interval estimation of a population parameter is the equal-tailed confidence interval. For the $100(1 - \alpha)\%$ confidence level, we choose the $\alpha/2$ and $1 - \alpha/2$ quantiles of the observed distribution as the boundary of the interval. This is not always the shortest confidence interval. For multimodal or asymmetric distributions the shortest confidence interval can be described via the concept of the highest probability density (HPD) set of a given level. In the sequel, we will use uppercase letters to denote stochastic variables and lower case letters to denote the realizations of the random variable. HPD of confidence level $1 - \alpha$ is defined for a random variable X with probability density $f_X(\cdot)$ as $H = \{x, \text{ such that } f_X(x) > K \text{ where } K \text{ is selected so that } 1 - \alpha = P(X \in H) \text{ for the specified value of } \alpha\}$. It can be shown easily that this procedure results in the most spatially compact subset H of X that meets this constraint. HPD intervals are often difficult to compute and equal tailed interval is computationally easier option.

The GUM framework introduces the concept of uncertainties evaluated by scientific judgment (type B evaluation of standard uncertainty (JCGM, 2008a)) for which the probability is a measure of the degree of belief that an event will occur rather than a measure of long-run relative frequency of occurrence. To avoid confusion, it terms the interval containing the set of true quantity values of a measurand with a stated probability, based on the information available, as the coverage interval (JCGM, 2008c). In this work, all such intervals can be interpreted via the statistical concept, and thus we opted to use the term confidence interval even for the intervals calculated via the GUM framework.

3. Materials and methods

The case of study for this work is the fixed-collision correlated sampling scheme used by Hedtjrn et al. (2002) and applied to the calculation of absorbed dose distributions in water around a point isotropic photon-emitting source in the presence of a heterogeneity. The Monte Carlo (MC) photon transport code PTRAN version 8.0 was used to calculate the absorbed dose using the kerma approximation.

The geometry consisted of a water sphere with a radius of 100 mm, a point source emitting 400 keV photons positioned at the spheres center, and a heterogeneity of a tungsten alloy (cylinder with diameter 15 mm, height 2.5 mm, density 17.0 g/cm^3 , weight fractions of Fe, Ni, and W were 0.0818, 0.1686, and 0.7496, respectively) positioned perpendicular to the radius of the water sphere and 10 mm away from the source. A 3D scoring mesh with uniform size voxels ($2.5 \text{ mm} \times 2.5 \text{ mm} \times 2.5 \text{ mm}$) was used, scoring being limited to a $70 \text{ mm} \times 50 \text{ mm} \times 30 \text{ mm}$ rectangular region around the source, see figure 1. The source used in this simulation imitates the Ir-192 radionuclide, almost universally used in single stepping source high dose rate (HDR) brachytherapy remote afterloaders. The tungsten-alloy shielding heterogeneity approximates the geometry of shielded intracavitary vaginal applicators, widely used in the treatment of endometrial and cervical cancers by means of HDR brachytherapy.

The expected track-length (ETL) estimator (Williamson, 1987) was used for scoring the mean absorbed dose in the voxels. Scoring was performed on per-history basis; the batching of histories used in previous versions of PTRAN was not used. This change followed the current trend in sequential estimation (Sempau et al., 2001; Walters et al., 2002).

The PTRAN code was modified to create an ‘‘event file’’, which included all non-zero contributions of each history to $\Delta D_{-c}(\mathbf{x})$ and $\Delta D_{\text{het}}^{-\text{unc}}(\mathbf{x})$ to specified voxels, $\mathbf{x}$, along with other information (particle, weights, trajectories and collision locations) useful for off-line

analysis. Each run simulated 10^8 histories; run times were 2.20 h and 1.38 h for correlated and uncorrelated estimates, respectively.

As discussed in section 5, our fixed-collision correlated sampling scheme lead to anomalously high single-history dose scores for photon histories with large statistical weights. For brevity, these are called outliers. Several outliers were identified by visual inspection. To estimate their effect, the corresponding histories were removed from the population and the analysis described in the following sections was repeated.

3.1. Parametric statistics method

Let n_X and n_Y be the number of histories in the uncorrelated and correlated runs, respectively, and let corresponding run times be $\sqrt{t}$ and $\sqrt{t_c}$. Suppose that the variables $X = \bar{D}_{\text{het}} \sqrt{t}$ and $Y = \Delta \bar{D}_c \sqrt{t_c}$ are normally distributed. Then the efficiency gain estimate (6) can be written as

$$G = \frac{n_X^{-1} S_X^2}{n_Y^{-1} S_Y^2} = \frac{n_X^{-1} \sigma_X^2 S_X^2 / \sigma_X^2}{n_Y^{-1} \sigma_Y^2 S_Y^2 / \sigma_Y^2} \stackrel{d}{=} \frac{n_X^{-1} \sigma_X^2}{n_Y^{-1} \sigma_Y^2} Q = \gamma Q, \quad (18)$$

where $\sigma_X^2 \equiv V(X)$ and $\sigma_Y^2 \equiv V(Y)$ denote the (true) variances of the distributions of X and Y ,

respectively, the efficiency gain γ is calculated as $\gamma = \frac{n_X^{-1} \sigma_X^2}{n_Y^{-1} \sigma_Y^2}$, and the variable Q defined above has the F distribution with $(n_X - 1, n_Y - 1)$ degrees of freedom. The symbol $\stackrel{d}{=}$ denotes equality in distribution. The probabilistically symmetric level $(1 - \alpha)$ confidence interval (q_1, q_2) of Q fulfills the conditions

$$P(Q \leq q_1) = P(Q \geq q_2) = \alpha/2 \quad (19)$$

which, for the variable G , can be written as

$$P(G/\gamma \leq q_1) = P(G/\gamma \geq q_2) = \alpha/2 \quad (20)$$

The confidence bounds corresponding to equal tail areas were thus calculated as

$$\begin{aligned} g_1 &= G/q_2 = G/K_{n_X-1, n_Y-1}(1 - \alpha/2) \\ g_2 &= G/q_1 = G/K_{n_X-1, n_Y-1}(\alpha/2). \end{aligned}$$

where $K_{n_X-1, n_Y-1}(\alpha)$ is the quantile function of the F distribution, which, for continuous random variables, is the inverse function of the cumulative distribution function $F_{n_X-1, n_Y-1}(\alpha)$.

The expectation of G is (Bickel and Doksum, 2000)

$$E(G) = E(\gamma Q) = \gamma E(Q) = \gamma \frac{n_Y - 1}{n_Y - 3} \quad (21)$$

The corresponding bias

$$B = E(G) - \gamma = \gamma \frac{2}{n_Y - 3}. \quad (22)$$

converges to 0 for $n_Y \rightarrow \infty$. In our case the sample size being 10^8 , this bias is practically 0.

Since the variance estimate S_x^2 lacks robustness of efficiency (Venables and Ripley, 2002) the use of the F distribution for non-normally distributed samples is problematic. Nevertheless it can still be used if distributions of sample means of D_{het} and ΔD are asymptotically normal (Bickel and Doksum (2000), p. 321 and 470). Considering the large number of samples used in our computation, well behaved dose distributions with square integrable tail probability should follow the central limit theorem. Hence the F distribution should give a good approximation to the efficiency gain distribution.

3.2. Direct bootstrap

The event files created by PTRAN were used to generate 1 000 samples of efficiency gain via bootstrap sampling for voxels with indices ranging from 1 to 24. For each of the 1 000

bootstrap samples, the variances $V(\Delta \bar{D}^c(x))$ and $V(\Delta \bar{D}_{\text{het}}^{\text{unc}}(x))$ were estimated using equation (5) and the efficiency gain estimate G was calculated from equation (4). As the size of each bootstrap sample was very large, the bias of the estimate was negligible and was ignored in our computations. The efficiency gain distribution was empirically represented by the histogram of the 1 000 efficiency gain samples. The algorithm of Chen and Shao (1999) as implemented in the Bayesian output analysis (BOA) package of R v2.8.0 (Smith, 2007) was used to estimate the shortest 95% confidence interval which is same as the 95% highest density set.

3.3. The GUM framework

The relative standard uncertainty of the efficiency gain estimate, $u(G)/G$, was calculated from the functional relationship defined by equation (6) for voxels with indices ranging from 1 to 24 as (JCGM, 2008a)

$$\left[\frac{u(G)}{G} \right]^2 = \left[\frac{u(S_x^2)}{S_x^2} \right]^2 + \left[\frac{u(S_Y^2)}{S_Y^2} \right]^2, \quad (23)$$

where the equality $n_R = n_T$ was assumed. The sample variances S_x^2 and S_Y^2 were calculated using equation (5) from per-history contributions in the event files and the expected

efficiency gain was calculated as $G = S_x^2 / S_Y^2$. The uncertainty $u(S_x^2)$ was calculated via the boot package (Davison and Hinkley, 2006) of R v2.8.0: a set of 1000 samples of S_x^2 was generated from 1000 sets of $N_x = 10^8$ PTRAN histories via the bootstrap method as

described in section 3.2. The uncertainties $u(S_x^2)$ and $u(S_Y^2)$ were calculated as the sample standard deviations of this set. The 95% confidence interval was approximated by the GUM confidence interval, $(G - ku(G), G + ku(G))$, using coverage factor of $k = 2$.

4. Results

Figure 2 shows the mean efficiency gain, $\bar{G}$ for all 28 voxels on the central axis along with the shortest 95% confidence interval predicted by the Monte Carlo method, and the probabilistically symmetric 95% confidence intervals predicted by the F distribution and the GUM framework. Values of $\bar{G}$ upstream of the heterogeneity and at large distances from the source were around 500 and rapidly increased up to 1.3×10^4 in the vicinity of the source. The inhomogeneity decreased values of $\bar{G}$ both in front of and behind it. In the latter case, values around 0.3 – 0.5 were typical. Clearly, the F distribution noticeably underestimated the confidence intervals calculated via the bootstrap sampling method and the GUM framework.

To investigate the causes of the above discrepancies, confidence intervals for voxels 6, 14, 20 and 24 were analyzed in detail. Actual location of these voxels is showed in figure 1. Voxel 6 represented voxels on the same side of the heterogeneity as the source and distant from the photon source so the heterogeneity is expected to have very little impact on the absorbed dose. Voxel 14 was located close to the point source on the same side of the heterogeneity as the source, and voxels 20 and 24 were just downstream the cylindrical heterogeneity and experienced very large dose perturbations. Figure 3 shows empirical distribution of efficiency gains for these voxels estimated by the histogram of the 1 000 bootstrap estimates, the shortest 95% confidence interval, and the Gaussian kernel density estimate of the probability density function obtained via smoothing of raw histogram values with weights from a Gaussian kernel. The distributions for voxels 20 and 24 were multimodal. The irregular shape of the histogram for voxel 24 indicates that the multimodality was a result of the particular sample of histories rather than a general property of the distribution. This was confirmed by removing the two most striking outlier histories from the event file; resulting in consistently unimodal bootstrap distributions (see figure 4) with narrower 95% HDP confidence intervals for all considered voxels. Nevertheless, the bootstrap confidence intervals were still noticeably different from those predicted by the F distribution, see table 1. It can be shown algebraically that the F distribution confidence intervals are a function of only $K_{nX-1,nY-1}(\alpha/2)$, hence those are same for all voxels and are insensitive to the removal of outlier histories. Of particular interest was the physical mechanism generating the outliers. It was found that photons with largest contributions to the scored quantities were those that repeatedly interacted within the cylindrical heterogeneity; see section 5 for an in-depth explanation. The probability of such events was very low; of 10^8 histories only 3-5 histories exhibited this behavior. Nevertheless they significantly affected the variance (and hence the confidence interval) of the efficiency gain distribution. The mean values of efficiency gain were affected only slightly by the presence of these outliers. The source of disagreement between the shortest 95% confidence interval and F distribution confidence interval comes from slow convergence of the asymptotic distribution of sample efficiency gain as well as lack of robustness of the F distribution to outliers.

5. Discussion

354 Uncertainty of the efficiency gain estimate was strongly influenced by photons that were emitted from the source and then interacted two or more times in the water-filled "footprint" of the shielding cylinder during the homogeneous geometry simulation used to generate the collision sites. Their statistical weight was so high that they added additional modes to the otherwise unimodal probability distribution function of the efficiency gain estimate. To understand this phenomenon, we analyzed how individual photon trajectories affected the efficiency gain (equation (14)). First, we discuss three

different ways how statistical weights W_{ij}^{het} and W_{ij}^{hom} change as the photon passes through the geometry, and then we discuss the combined effect of statistical weights and dose scoring functions on the variance of $\Delta \bar{D}^c(x)$ in the denominator of equation (14) which affects the efficiency gain of the correlated sampling scheme.

Suppose that three photons are emitted from the point source as shown in figure 5 with identical initial homogeneous and heterogeneous weights $W_{i0}^{\text{hom}} = W_{i0}^{\text{het}} = 10^4$, $1 \leq i \leq 3$. The numerical details of these histories are summarized as histories 1, 2, and 3 in table 2.

Photon number 1 passes through the heterogeneity and the homogeneous medium without any interaction before reaching voxel 24 at $\mathbf{r}_1$. Just after the collision in voxel 24, its homogeneous weight decreases to $W_{11}^{\text{hom}} = 6.5 \times 10^3$ (see table 2) owing to the forced collision and survival biasing factors, cf. equation (16). Its heterogeneous weight is decreased to $W_{11}^{\text{het}} = 3.2 \times 10^3$ by the two last named factors and also by the intercollision distance PDF correction in equation (15) which reflects the difference in radiological paths, $\lambda(\mathbf{r}_0, \mathbf{r}_1, E_0) - \mu(E_0)|\mathbf{r}_0 - \mathbf{r}_1|$, between the source and collision positions $\mathbf{r}_0$ and $\mathbf{r}_1$, respectively.

Photon number 2 first interacts in the homogeneous environment at $\mathbf{r}_1$ in the water replaced with the heterogeneity which changes its statistical weights to $W_{11}^{\text{hom}} = 6.5 \times 10^3$ and $W_{11}^{\text{het}} = 7.8 \times 10^4$. The latter is determined by the $\mu(E_0; \mathbf{r}_1)/\mu(E_0) = 26.9$ ratio in the intercollision distance PDF correction factor of equation (15), the difference in radiological paths in $\exp(\lambda(\mathbf{r}_0, \mathbf{r}_1, E_0) - \mu(E_0)|\mathbf{r}_0 - \mathbf{r}_1|)$, homogeneous geometry forced collision factor, and the survival biasing factor $1 - \sigma_{\text{PE}}(E_j; \mathbf{r}_{j+1})/\mu(E_j; \mathbf{r}_{j+1}) = 0.53$. The heterogeneous weight just after the subsequent collision at $\mathbf{r}_2$ of figure 5 is then affected by the different radiological paths as discussed for photon 1. The resulting $W_{22}^{\text{het}} = 2.4 \times 10^4$ is approximately 6 times larger than $W_{22}^{\text{hom}} = 4.1 \times 10^3$. In general, a collision in the heterogeneity may increase W_{ij}^{het} depending on the path length traversed in the heterogeneity; for long path lengths the exponential factor may dominate and the resulting intercollision distance PDF correction factor may be lower than 1. Repeated collisions in the heterogeneity may inflate W_{ij}^{het} , as illustrated by history number 4 in table 2.

Photon number 3 collides in the homogeneous environment only at $\mathbf{r}_1$ and $\mathbf{r}_2$, and does not pass through the heterogeneity. Its statistical weights decrease to $W_{31}^{\text{hom}} = W_{31}^{\text{het}} = 6.5 \times 10^3$ and $W_{32}^{\text{hom}} = W_{32}^{\text{het}} = 5.0 \times 10^3$ just after the first and second collisions, respectively. The complete history is in table 2.

The dose scoring functions are affected by the radiological paths between the collision and the scoring voxel; for no heterogeneity in between them $f_D^{\text{hom}} = f_D^{\text{het}}$ and thus the contribution to $\Delta \bar{D}^c(x)$ is $\Delta D^c = f_D^{\text{hom}} (W_{ij}^{\text{het}} - W_{ij}^{\text{hom}})$. For type 1 histories, W_{ij}^{het} is always lower than W_{ij}^{hom} and thus ΔD^c is negative. For type 2 histories, W_{ij}^{het} may be larger than W_{ij}^{hom} . These histories may contribute positive ΔD^c and, in case of repeated collisions inside the heterogeneity, the ΔD^c may become an outlier. Type 3 histories contribute $\Delta D^c = 0$. If only type 3 histories had been present, the variance $V(\Delta \bar{D}^c(x)) = 0$ and the efficiency gain would have been infinity.

Type 1 and type 2 histories increase the variance of $\Delta \bar{D}^c(x)$ by contributing non zero values of ΔD^c . If there is a heterogeneity between the collision and the scoring voxel, the lower

value of f_d^{het} compared to f_d^{hom} amplifies the effect of type 1 histories and suppresses the effect of type 2 histories. This qualitative description explains the mechanism of decorrelation between $\bar{D}_{\text{hom}}^c$ and $\bar{D}_{\text{het}}^c$ responsible for the decrease of the efficiency gain and the mechanism that leads to outlier histories. It does not, however, pinpoint a single cause of the decrease of the efficiency gain in a region as the resulting $V(\Delta \bar{D}^c(x))$ reflects contributions from all three history types and their combinations.

We hypothesize that the loss of efficiency, which continuously increases with deviation from $\text{HCF} = 1.0$, is due to progressive decorrelation of homogeneous and heterogeneous history particle weights. Further we believe that this decorrelation is manifested in increased variability of weight correction factors with increasing $|\Delta D^c|$. If so, the efficiency gain losses might be mitigated by use of Russian roulette and splitting to reduce particle weight fluctuations, see Booth and Hendricks (1984).

Similar photon behavior is expected for any brachytherapy geometry containing a shielding made of high atomic number material as one of the main factors responsible for the increased statistical weight of photons is the ratio between linear attenuation coefficients of the heterogeneity and water in equation (15). As this ratio increases with decreasing photon energy, the decorrelation of corresponding photon weights is expected to increase for low energy photons.

6. Conclusion

In practical Monte Carlo code applications where efficiency gain estimation is an outcome metric and only one set of histories is analyzed on the fly, it is impossible to know in advance whether efficiency uncertainty can be estimated via the GUM uncertainty framework or Fisher F statistic method. In our case study of the fixed-collision correlated Monte Carlo sampling scheme, the Fisher F statistic failed to accurately describe the efficiency gain confidence intervals. This can be attributed to the presence of several histories contributing extremely large values (outliers) to the scored quantities—an indication the actual distributions have highly non-normal thick tails. Removal of extreme outlier histories improved the performance of the F statistic, nevertheless its high sensitivity to deviations from data normality made its predictions inaccurate even in this case. The GUM framework predicted confidence intervals reasonably well, but required the same effort as using direct bootstrap sampling of efficiency gain. Direct bootstrap sampling is clearly the method of choice for the analysis of variance in settings where the underlying distributions significantly deviate from normality. However, it requires modification of the code to generate and store history-by-history event files; this approach significantly reduces run-time efficiency and requires many gigabytes of storage as well as time consuming bootstrap sampling and specialized data analysis. While bootstrap sampling is not practical for routine Monte Carlo runs, it is a useful tool for assessing the statistical quality of Monte Carlo outputs and the applicability of simple parametric statistics models.

Clearly the presence of high impact but highly unlikely outlier histories is a drawback of the current implementation of our fixed-collision correlated sampling scheme, in which photons repeatedly interacting in a region containing a highly attenuating material can achieve very high statistical weights. Techniques such as particle splitting combined with Russian roulette can limit the statistical weight of photons and can be used to address this limitation in this sampling scheme.

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Figure 1.

The location of 28 voxels on the central axis; voxels of interest are depicted in grey. The quantity i_v denotes the voxel index which ranges from 1 to 28. Heterogeneity is a right circular cylinder of tungsten alloy, diameter 15 mm, height 2.5 mm.

Figure 2.

The mean value of the efficiency gain estimate as a function of the voxel index, and the shortest 95% confidence interval predicted by the Monte Carlo method (HPD limits) and probabilistically symmetric 95% confidence intervals predicted by the F distribution and GUM framework.

Figure 3.

Empirical distribution of efficiency gain for voxels 6, 14, 20 and 24 estimated by the histogram of the 1 000 bootstrap estimate along with the Gaussian kernel density estimate of the density. The thick grey line along the bottom of each histogram represent the 95% highest density region.

Figure 4.

Empirical distribution of efficiency gain for voxels 6, 14, 20 and 24 estimated by the histogram of the 1 000 bootstrap estimate after removal of the outlier histories along with the Gaussian kernel density estimate of the density. The thick grey line along the bottom of each histogram represent the 95% highest density region.

Figure 5. Schematic view of trajectories of three photons that were emitted from the source and passed through the voxel 24. Photons 1 and 2 passed through the shielding cylinder. Photons 2 and 3 interacted in the heterogeneity and the homogeneous medium, respectively.

Efficiency gain, G , and its uncertainty u_M calculated via the Monte Carlo method for selected voxels. Also listed are relative uncertainties u_F/G , u_G/G , and u_M/G predicted by the F distribution, the GUM framework, and the bootstrap method. Uncertainties u_F and u_M were calculated as one half of the width of the confidence interval. The uncertainty u_M^* was calculated as u_M after removing outlier histories. All uncertainties correspond to the 95% confidence probability.

Table 1

voxel	$G \pm u_M$	u_F/G	u_G/G	u_M/G	u_M^*/G
6	$(5.8 \pm 1.2) \times 10^2$	12%	23%	22%	22%
14	$(1.3 \pm 0.3) \times 10^4$	12%	22%	21%	21%
20	$(3.1 \pm 0.4) \times 10^{-1}$	12%	17%	14%	5.6%
24	$(2.8 \pm 1.0) \times 10^{-1}$	12%	53%	37%	7.2%

Table 2

Selected photon histories: the history number i , collision number j , medium m_{ij} (1=water, 2=tungsten alloy), and position of collision (x_{ij} , y_{ij} , z_{ij}). Symbols E_{ij} , W_{ij}^{hom} , and W_{ij}^{het} denote the photon's energy and homogeneous and heterogeneous weights, respectively, just after collision j , where $j = 0$ denotes the primary photon.

i	j	m_{ij}	x_{ij}/mm	y_{ij}/mm	z_{ij}/mm	W_{ij}^{hom}	W_{ij}^{het}	E_{ij}/keV
1	0	1	0.0e+00	0.0e+00	0.0e+00	1.0e+04	1.0e+04	4.0e+02
1	1	1	2.3e+01	-1.7e+00	-1.2e+00	6.5e+03	3.2e+03	3.2e+02
1	2	1	5.0e+01	2.4e+01	-7.2e+00	4.0e+03	2.0e+03	1.9e+02
...								
2	0	1	0.0e+00	0.0e+00	0.0e+00	1.0e+04	1.0e+04	4.0e+02
2	1	2	8.9e+00	-2.0e-01	1.2e+00	6.5e+03	7.8e+04	3.9e+02
2	2	1	2.4e+01	-1.6e+00	-7.8e-01	4.1e+03	2.4e+04	1.7e+02
...								
3	0	1	0.0e+00	0.0e+00	0.0e+00	1.0e+04	1.0e+04	4.0e+02
3	1	1	1.0e+01	-1.8e+01	-4.5e+00	6.5e+03	6.5e+03	1.9e+02
3	2	1	2.4e+01	-1.2e+00	-3.6e-01	5.0e+03	5.0e+03	1.2e+02
...								
4	0	1	0.0e+00	0.0e+00	0.0e+00	1.0e+04	1.0e+04	4.0e+02
4	1	2	9.2e+00	3.2e+00	-5.3e+00	6.5e+03	6.9e+04	3.9e+02
4	2	2	1.0e+01	3.4e+00	-6.1e+00	4.0e+03	3.8e+05	3.6e+02
4	3	2	1.0e+01	3.6e+00	-6.3e+00	2.5e+03	2.6e+06	1.5e+02
4	4	2	9.8e+00	3.2e+00	-5.9e+00	2.0e+03	4.4e+06	1.3e+02
4	5	1	-3.9e+01	2.6e+01	2.9e+01	1.6e+03	4.8e+04	9.3e+01
4	6	1	-1.6e+01	4.3e+01	-2.3e+01	1.4e+03	4.1e+04	7.3e+01
4	7	1	-3.3e+01	-3.7e+01	-3.5e+00	1.2e+03	3.6e+04	7.2e+01
4	8	1	-4.2e+01	-5.7e+01	3.0e+00	7.4e+02	2.2e+04	7.1e+01
4	9	1	-4.3e+01	-6.2e+01	9.1e+00	3.6e+02	1.1e+04	6.3e+01
4	10	1	-6.7e+00	-8.9e+01	-3.1e+00	2.4e+02	7.1e+03	5.1e+01
4	11	1	-3.4e+01	-1.3e+01	9.0e+00	2.1e+02	6.1e+03	5.1e+01