Fast patient-specific Monte Carlo brachytherapy dose calculations via the correlated sampling variance reduction technique

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Purpose: To demonstrate potential of correlated sampling Monte Carlo (CMC) simulation to improve the calculation efficiency for permanent seed brachytherapy (PSB) implants without loss of accuracy.

Methods: CMC was implemented within an in-house MC code family (PTRAN) and used to compute 3D dose distributions for two patient cases: a clinical PSB postimplant prostate CT imaging study and a simulated post lumpectomy breast PSB implant planned on a screening dedicated breast cone-beam CT patient exam. CMC tallies the dose difference, ΔD , between highly correlated histories in homogeneous and heterogeneous geometries. The heterogeneous geometry histories were derived from photon collisions sampled in a geometrically identical but purely homogeneous medium geometry, by altering their particle weights to correct for bias. The prostate case consisted of 78 Model-6711 ^{125}I seeds. The breast case consisted of 87 Model-200 ^{103}Pd seeds embedded around a simulated lumpectomy cavity. Systematic and random errors in CMC were unfolded using low-uncertainty uncorrelated MC (UMC) as the benchmark. CMC efficiency gains, relative to UMC, were computed for all voxels, and the mean was classified in regions that received minimum doses greater than 20%, 50%, and 90% of D_{90} , as well as for various anatomical regions.

Results: Systematic errors in CMC relative to UMC were less than 0.6% for 99% of the voxels and 0.04% for 100% of the voxels for the prostate and breast cases, respectively. For a $1 \times 1 \times 1 \text{ mm}^3$ dose grid, efficiency gains were realized in all structures with 38.1- and 59.8-fold average gains within the prostate and breast clinical target volumes (CTVs), respectively. Greater than 99% of the voxels within the prostate and breast CTVs experienced an efficiency gain. Additionally, it was shown that efficiency losses were confined to low dose regions while the largest gains were located where little difference exists between the homogeneous and heterogeneous doses. On an AMD 1090T processor, computing times of 38 and 21 sec were required to achieve an average statistical uncertainty of 2% within the prostate ($1 \times 1 \times 1 \text{ mm}^3$) and breast ($0.67 \times 0.67 \times 0.8 \text{ mm}^3$) CTVs, respectively.

Conclusions: CMC supports an additional average 38–60 fold improvement in average efficiency relative to conventional uncorrelated MC techniques, although some voxels experience no gain or even efficiency losses. However, for the two investigated case studies, the maximum variance within clinically significant structures was always reduced (on average by a factor of 6) in the therapeutic dose range generally. CMC takes only seconds to produce an accurate, high-resolution, low-uncertainty dose distribution for the low-energy PSB implants investigated in this study. © 2012 American Association of Physicists in Medicine. [DOI: 10.1118/1.3679018]

Key words: brachytherapy, correlated sampling, Monte Carlo, TG-43

I. INTRODUCTION

The current standard of practice for brachytherapy dose computation is the lookup table-based AAPM Task Group 43 protocol (TG-43),¹ which assumes that patients are homogeneous water spheres and neglects seed-to-seed attenuation and other applicator-shielding effects. In response to numerous studies^{2–10} documenting significant dosimetric effects caused by tissue heterogeneities and interseed attenuation, the AAPM formed a task group (TG-186) to address this issue.¹¹

For example, in ^{125}I and ^{103}Pd prostate permanent seed brachytherapy (PSB) implants, tissue heterogeneities and

interseed attenuation reduce D_{90} (minimum dose delivered to 90% of the treatment volume, CTV) and V_{200} (volume receiving at least 200% of the prescribed dose) in postimplant dose evaluation by as much as 13% (Refs. 2–6 and 9) and 7% (Ref. 4), respectively. Furthermore Chibani *et al.* showed that the presence of calcifications constituting 1%–5% of the prostate mass decreased D_{100} by as much as 58% (Ref. 2). For a ^{125}I PSB simulated breast implant (50% mammary gland—50% adipose by mass), a decrease in D_{90} of 10.3% was observed.¹⁰ In addition, the authors demonstrated that higher volumes of adipose tissue, relative to mammary glandular tissue, increased this effect. Overall,

these studies show that dose to bony/calcified tissues and adipose tissues differ by as much as a factor of two from absorbed dose to water in the 15–40 keV energy range.

Three classes of model-based dose calculation algorithms have been proposed to address the deficiencies of TG-43: collapsed-cone superposition-convolution (CCSC),^{12,13} discrete-ordinate finite-element methods (DOFE),¹⁴ and Monte Carlo simulation (MC). Carlsson-Tedgren *et al.*¹⁵ has shown the efficacy of using CCSC for accurate subminute brachytherapy dose calculations, but to date their studies have been limited to simple applicator scatter corrections and not applied to patient-specific treatment planning. Recently, Varian Medical Systems released Acuros[®],¹⁶ a radiation-therapy specific rewrite of the DOFE code ATTILA[®] (Ref. 14) within its BrachyVision[™] planning software. Acuros can compute most high dose-rate (HDR) brachytherapy dose distributions in fewer than 10 min. Deterministic solutions offer substantial speed enhancements, but are subject to systematic bias, e.g., ray-effects, due to overly coarse discretization of the radiation transport phase-space. For a single ¹⁹²Ir source in homogeneous medium, Zourari *et al.*¹⁶ found differences between Acuros and MC less than 1% in most voxels, illustrating that DOFE parameters can be tuned to produce accurate results with reasonable computing times within a certain problem domain.¹⁷

CT-based MC methods can also be applied to both applicator-attenuation and tissue-heterogeneity effects for both low and high energy brachytherapy but unlike DOFE and CCSC, give rise to statistically noisy solutions that are generally unbiased, i.e., converge to the exact unbiased solution of the transport equation. However, the central processing unit (CPU) time-intensiveness of MC transport solutions has limited their use in the clinical setting⁵ until recent advent of accelerated MC codes.¹⁸ Although these codes can compute dose distributions in fewer than 5 min, such performance is clinically marginal since treatment planning optimization routines require the dose distribution to be computed multiple times.^{19–21} To overcome this limitation, additional sophisticated variance reduction techniques must be employed to further reduce the CPU time to achieve clinically acceptable uncertainties on cost effective hardware. Due to the limitations imposed by current DOFE and MC solutions, there is still need for an efficient, robust, and accurate general purpose brachytherapy dose calculation engine that overcomes the deficiencies of TG-43.

In this study we describe the implementation of a sophisticated and general variance reduction technique called correlated sampling.^{22,23} We believe this to be first application of correlated sampling Monte Carlo (CMC) to CT-based brachytherapy dose calculation in clinically realistic geometries. Specifically, we investigate its accuracy and efficiency for two patient case studies.

II. METHODS

II.A. Correlated Sampling

To aid the reader, the symbols and acronyms used in this paper are defined in Table I. Correlated sampling was first

proposed for accelerating MC brachytherapy dose calculations by Hedtjrn *et al.*²² who demonstrated the potential of order-of-magnitude efficiency gains in simple two-dimensional geometries. Since their paper described the correlated sampling theory in detail,²² only a brief summary will be given here. Rather than computing absorbed dose directly, CMC estimates the dose difference between heterogeneous and homogeneous geometries on a voxel-by-voxel basis. Conceptually, deviations from unit density water composition (including applicators and tissue composition heterogeneities) are treated as perturbations of the corresponding homogenous (unperturbed) system. This is done by randomly sampling each photon history, consisting of collision sequence, $\mathbf{p}_n^{\text{hom}} = (\mathbf{r}_n, E_n, \Omega_n, W_n^{\text{hom}})$, from the photon-source and transition-kernel probability density functions (PDFs) characteristic of purely homogeneous geometry. In this nomenclature, n denotes order of scattering within the history ($n = 0$ for primary); $\mathbf{r}_n$ denotes the n th interaction location; and E_n , Ω_n , and W_n^{hom} denote the energy, direction, and statistical weight of the photon leaving $\mathbf{r}_n$, respectively. To score the dose difference between heterogeneous and homogeneous geometries, a corresponding heterogeneous geometry history $\mathbf{p}_n^{\text{het}} = (\mathbf{r}_n, E_n, \Omega_n, W_n^{\text{het}})$, is constructed that utilizes the same sequence of collision sites and emergent directions and energies, but a different weight correction factor, W_n^{het} .

The weight correction factor is designed to eliminate the bias due to representing photon transport in the heterogeneous geometry by a sequence of histories derived from the homogeneous transport and scattering kernels and is given by

$$W_n^{\text{het}} = W_n^{\text{hom}} \times \frac{P_{\text{het}}(\mathbf{p}_0^{\text{hom}}, \dots, \mathbf{p}_n^{\text{hom}})}{P_{\text{hom}}(\mathbf{p}_0^{\text{hom}}, \dots, \mathbf{p}_n^{\text{hom}})}, \quad (1)$$

where $P_{\chi}(\mathbf{p}_0^{\text{hom}}, \dots, \mathbf{p}_n^{\text{hom}})$ is the probability of sampling the history $\mathbf{p}_0^{\text{hom}}, \dots, \mathbf{p}_n^{\text{hom}}$ in geometry χ . To simplify calculation of W_n^{het} , a free-electron Compton scattering model that neglects characteristic x-ray emission and coherent scattering is assumed. For the distance between 0 and 10 cm from a model 6711 ¹²⁵I seed, the Klein-Nishina scatter approximation has been shown to support dose estimates that agree within 1% of that delivered in low-Z media by an incoherent and coherent scatter physics model.²⁴ Because $\mathbf{p}_n^{\text{het}}$ and $\mathbf{p}_n^{\text{hom}}$ use the same sequence of collisions to score dose, their respective dose tallies are tightly correlated. In practice, this correlation is exploited by scoring the dose difference

$$\Delta d_{ijk,m,n}^c = f_{ijk}^{\text{het}}(\mathbf{p}_{m,n}^{\text{het}}) - f_{ijk}^{\text{hom}}(\mathbf{p}_{m,n}^{\text{hom}}), \quad (2)$$

where m and n denote history number and order of scatter, respectively; ijk denote the voxel indices along the x, y, and z axes, respectively; f_{ijk}^{χ} is the scoring estimator for geometry χ ; and $\Delta d_{ijk,m,n}^c$ represents the dose difference between the heterogeneous and homogeneous dose tallies. The final sample mean, obtained by summing over interactions within each history and averaging over histories, is given by

$$\bar{\Delta d}_{ijk}^c = \frac{1}{N} \sum_{m=1}^N \sum_{n=1}^{M_m} \Delta d_{ijk,m,n}^c. \quad (3)$$

The heterogeneous dose, $\bar{D}_{ijk}^{\text{het,c}}$ is an estimate of the true mean

TABLE I. Symbols listed in order of appearance.

ΔD	$D^{\text{het}} - D^{\text{hom}}$, the difference between the dose to the heterogeneous and homogeneous media
β_n^{hom}	Photon history phase-space vector at collision n sampled assuming a purely homogeneous surrounding media
N	Order of scatter
$\mathbf{r}_n$	Position of the n th interaction
E_n	Energy leaving $\mathbf{r}_n$
Ω_n	Trajectory leaving $\mathbf{r}_n$
W_n^{hom}	Weight of the photon leaving $\mathbf{r}_n$ in the homogeneous media
$*\beta_n^{\text{het}}$	Photon history phase-space vector at collision n sampling assuming a purely homogenous surrounding media, but having an altered weight correction factor to account for heterogeneities
W_n^{het}	Weight of the photon leaving $\mathbf{r}_n$ in the heterogeneous media
$P_\chi(\beta_0^{\text{hom}}, \dots, \beta_n^{\text{hom}})$	The probability of sampling the history $\beta_0^{\text{hom}}, \dots, \beta_n^{\text{hom}}$ in geometry χ
$\Delta d_{ijk,m,n}^c$	The dose difference between scores to voxel ijk from $*\beta_n^{\text{het}}$ and β_n^{hom} for interaction n in history m
N	The total number of histories
M_m	The number of interactions within history m
f_{ijk}^c	Scoring estimator for geometry χ
$\overline{\Delta D}_{ijk}^c$	The sample mean of ΔD obtained by averaging $\sum_{n=1}^{M_m} \Delta d_{ijk,m,n}^c$, sum over all interactions within a history, over all N histories.
$\bar{D}_{ijk}^{\text{het},c}$	An estimate of the true mean, $\bar{D}_{ijk}^{\text{het},u}$
$\bar{D}_{ijk}^{\text{het},u}$	A sample mean of the true mean, D_{ijk}^{het}
D_{ijk}^{het}	The true, “unbiased” value for the dose to ijk to the heterogeneous media
HCF	The heterogeneous correction factor defined as the ratio between D^{het} and D^{hom}
HCF_{ijk}	$D_{ijk}^{\text{het}}/D_{ijk}^{\text{hom}}$, for voxel ijk
$\overline{HCF}_{ijk}^c$	$\bar{D}_{ijk}^{\text{het},c}/D_{ijk}^{\text{hom}}$
$\bar{D}_{ijk}^{\text{het},u}$	Sample mean of heterogeneous dose to voxel ijk through means of UMC, and is an unbiased estimator of D_{ijk}^{het}
D_{ijk}^{TG43}	AAPM TG-43 solution to homogeneous dose to voxel ijk
$V(v)$	The variance of enclosed value, v

$$\begin{aligned} \bar{D}_{ijk}^{\text{het},c} &= D_{ijk}^{\text{hom}} \cdot \overline{HCF}_{ijk}^c, \text{ where } \overline{HCF}_{ijk}^c = 1 + \overline{\Delta D}_{ijk}^c / D_{ijk}^{\text{hom}} \\ &= 1 + \overline{\Delta D}_{ijk}^c / D_{ijk}^{\text{TG43}}, \end{aligned} \quad (4)$$

where the symbols with macron (over line), e.g., $\bar{D}_{ijk}^{\text{het},c}$ denote sample means derived from a finite set of histories as in Eq. (3), and the corresponding macron-less symbol, D_{ijk}^{het} , denotes the corresponding unbiased “true” value. The heterogeneous correction factor (HCF) is defined as $HCF_{ijk} = D_{ijk}^{\text{het}}/D_{ijk}^{\text{hom}}$, and the corresponding CMC estimate is given by $\overline{HCF}_{ijk}^c = \bar{D}_{ijk}^{\text{het},c}/D_{ijk}^{\text{hom}}$. $\bar{D}_{ijk}^{\text{het},u}$ is the sample mean of heterogeneous dose obtained from traditional, uncorrelated MC (UMC) methodology and, unlike $\bar{D}_{ijk}^{\text{het},c}$, is assumed to be an unbiased estimator of D_{ijk}^{het} . We assume that D_{ijk}^{hom} can be closely approximated by a noiseless and accurate fast deterministic calculation: in our study, the TG-43 formalism was used: $D_{ijk}^{\text{hom}} = D_{ijk}^{\text{TG43}}$ as illustrated in Eq. (4). Since D_{ijk}^{TG43} can be known with negligible statistical uncertainty, it follows that²²

$$V(\bar{D}_{ijk}^{\text{het},c}) = V(\overline{\Delta D}_{ijk}^c) \ll V(\bar{D}_{ijk}^{\text{het}}), \quad (5)$$

where V is the variance, provided that the correlation between $*\beta_n^{\text{het}}$ and β_n^{hom} remains high. However, a positive covariance cannot be guaranteed,²⁵ implying that efficiency decreases are possible given circumstances where the correlation between the homogeneous and heterogeneous histories breaks down. If such circumstances exist throughout the treatment volume, the homogeneous water geometry may be replaced by an average tissue-volume composition that would decrease the spread of HCF values, thus increasing the correlation between $*\beta_n^{\text{het}}$ and β_n^{hom} . Such areas may include those that contain large volumes of adipose tissue,

such as the breast. With this alteration, the needed TG-43 parameters could be recomputed for such nonaqueous homogeneous media with available Monte Carlo tools, enabling use of TG-43.

II.B. Implementation

The correlated sampling technique, described above, was implemented as an option within the more general CT-based MC dose calculation code, PTRAN_CT, which is a member of the PTRAN code family developed by Williamson and colleagues.^{7,8,23,26–28} PTRAN_CT is a MC photon-transport code designed specifically for fast brachytherapy dose calculation, utilizing several novel variance reduction strategies (noted below) previously developed by Chibani and Williamson² within a different code family. Since secondary electrons are not transported, energy deposition is assumed to occur locally when an ionizing event occurs. In contrast to PTRAN_CT CMC option, the uncorrelated MC (UMC) PTRAN_CT option uses a more complete collisional physics model, including characteristic x-ray emission following photoelectric absorption, electron binding corrections to Compton scattering, and coherent scattering. Both the PTRAN_CT UMC and CMC options support history-by-history uncertainty estimation²⁹ and an optional phase-space source model.² A fast ray-tracing algorithm is used to track photons through a voxel-based patient anatomy model and through seeds and applicators based upon a general complex combinatorial geometry (CCG) modeling system.³⁰ Voxel indexing,² which restricts CCG ray-tracing to those modeled structures that intersect voxels along the direct path of the

photon, greatly improves the efficiency of photon tracking in this hybrid geometry. The expected track-length (ETL) scoring method was used by both the CMC and UMC PTRAN_CT runs to further reduce variance.²²

An in-house TG-43 computation engine was used to compute D_{ijk}^{TG43} . To ensure that voxel averaging effects will not confound comparison of $\bar{D}_{ijk}^{het,u}$ to $\bar{D}_{ijk}^{het,c}$, our code integrates the TG-43 dose-at-a-point distribution over each voxel, excluding any voxel subvolumes partially occupied by brachytherapy seeds, the same convention used by the PTRAN_CT ETL implementation. To compare Monte Carlo output with TG-43 calculations, the ΔS_k (the mean air-kerma strength per simulated disintegration²⁴) values used for ^{103}Pd Theragenics model-200 and ^{125}I model 6711 were $0.731\text{cGy} \cdot \text{cm}^2/\text{mCi} \cdot \text{h}$ (Ref. 8) and $0.7559\text{cGy} \cdot \text{cm}^2/\text{mCi} \cdot \text{h}$ (Ref. 7), respectively.

II.C. Patient Cases

Two patient CT image sets are used to evaluate the accuracy and efficiency of CMC relative to UMC. The first case is a simulated ^{103}Pd PSB breast implant designed as recommended by Pignol *et al.*³¹ High-resolution images ($0.335 \times 0.335 \times 0.4 \text{ mm}^3$ voxels) of a patient's right breast in pendant geometry were obtained on a dedicated cone-beam CT imaging system.³² Using a method previously described^{33,34} six tissue types were automatically segmented: skin, chest wall muscle, air, adipose, and two different mammary gland tissues with differences in density. Tissue compositions are taken from Woodard *et al.*³⁵ where the low density glandular tissue was assigned the composition of "mammary gland 1," while elemental compositions of "mammary gland 2" and "mammary gland 3" were averaged and assigned to higher density glandular tissue. The CTV is contoured as a 1 cm isotropic expansion of a simulated spherical lumpectomy cavity (2.4 cm diameter) having the average CTV dimensions reported by Pignol *et al.*'s study with a CTV volume of 44.6 cc. An implant consisting of 87 Model 200 seeds with air-kerma strengths of 1.590 U ($U = 1 \mu\text{Gy} \cdot \text{m}^2/\text{h}$) was designed to deliver a prescribed D_{100} dose of 90 Gy to the CTV using a commercial treatment planning system (Varian VeriSeed 8.0). Because of the high adipose tissue-volume in the breast, rather than using liquid water for computation of D_{ijk}^{hom} via the TG-43 method, we utilized a homogeneous average breast composition³⁶ medium consisting of 85% adipose and 15% fibroglandular tissue to reduce the range of HCF values, and hence, the decorrelation of heterogeneous and homogeneous photon histories.

The second case consisted of a postimplant CT of a PSB patient with an 82 cm^3 prostate implanted with 78 Model-6711 ^{125}I seeds with air-kerma strengths 0.636 U/seed and a prescribed D_{100} of 145 Gy. VariSeed was used to identify seed coordinates in the postimplant CT. A modified version of CTCREATE, taken from the DOSXYZNRC (Ref. 37) code family, was used to convert single-energy CT intensity data to voxel-specific tissue composition and density assignments. Post CTCREATE, streaking artifacts in the postimplant prostate CT were partially mitigated by assigning ICRU adult muscle to voxels within the prostate with attenu-

ation coefficients at 28 keV outside the allowed window of $[0.3716 \text{ cm}^{-1}, 0.4544 \text{ cm}^{-1}]$ corresponding to the range of soft tissue assigned within the prostate. While this method eliminates the seeds and their associated artifacts from the CT images, the seeds themselves were modeled analytically using PTRAN's CCG capability and the VariSeed coordinates. Tissue compositions were taken from ICRU report 44 (Ref. 38), and cross sections derived as previously described by Monroe *et al.*⁸

For both patient studies, the phase-space source model was used. As described previously,^{2,23} in the phase-space source model a single-seed Monte Carlo simulation (based on the full collisional physics model and detailed CCG model of the seed structure), is performed to transport primary and scattered photons to the surface of the seed's titanium capsule. For each of the simulated histories, the resultant state vectors, β_0 , are saved in the phase-space file. During PTRAN_CT execution, primary photons are "sampled" by sequentially reading β_0 vectors from the phase-space file and using them to launch histories from the surfaces of randomly selected seeds. This improves the correlation between β_n^{het} and β_n^{hom} by eliminating attenuation and scattering of primary photons within the seed structure.

Using the postimplant CT coordinates, the prostate case dose was computed in a rectangular region of interest (ROI) of $10.2 \times 15.0 \times 7.2 \text{ cm}^3$ with $1 \times 1 \times 1 \text{ mm}^3$, $2 \times 2 \times 2 \text{ mm}^3$, and $3 \times 3 \times 3 \text{ mm}^3$ voxel dimensions for both CMC and UMC. The simulated breast implant ROI had dimensions of $10.47 \times 10.47 \times 7.44 \text{ cm}^3$ with dose grid voxel sizes of $0.67 \times 0.67 \times 0.8 \text{ mm}^3$ and $1.34 \times 1.34 \times 1.6 \text{ mm}^3$. Hundred million photon histories were simulated by both CMC and UMC simulations. We denote these results as low-uncertainty (LU) CMC (LU-CMC) and LU-UMC, respectively. To minimize confusion, the phrase "finest grid" refers to $1 \times 1 \times 1 \text{ mm}^3$ and $0.67 \times 0.67 \times 0.8 \text{ mm}^3$ voxel sizes for the prostate and breast cases, respectively.

II.D. Evaluating Efficiency and Accuracy

MC simulation efficiency is defined by $\epsilon_{ijk} = 1/(\bar{\sigma}_{D_{ijk}}^2 \cdot T)$ where T is CPU time required to achieve the sample standard deviation about the mean (SDM), $\bar{\sigma}_D$ (generally expressed as percentage of the corresponding local mean, $\bar{D}$). For each individual voxel ijk , the efficiency gain, G_{ijk} , of CMC relative to UMC is given by

$$G_{ijk} = \frac{\bar{\sigma}_{D_{ijk}^{het,u}} \cdot T^{het,u}}{\bar{\sigma}_{D_{ijk}^{het,c}}^2 \cdot T^{het,c}}. \quad (6)$$

Because G_{ijk} varies significantly with $\bar{D}_{ijk}^{het}$ and $\overline{HCF}_{ijk}$, the mean efficiency gain was computed separately for ROIs containing voxels receiving doses greater than 20%, 50% and 90% of D_{90} , denoted as G_{20} , G_{50} , G_{90} , respectively. Additionally, the percentage of voxels in each ROI enjoying a positive gain in efficiency ($G_{ijk} > 1$) was tallied. Finally, mean efficiency gains within the prostate (CTV), the urethra, and rectum ROI subvolumes, for voxels receiving doses greater than 50% of the D_{90} , were calculated. To test the feasibility of

TABLE II. Best fit parameters values of the $f(z)$ distribution, Eq. (8), for the breast and prostate plans.

	Prostate	Breast	Corresponding Error	
			Prostate	Breast
α_1	0.9993	0.05124	3.2×10^{-3} % underestimation in	0.039% underestimation in 5.1% of the voxels
β_1	-0.01822	-0.4502	99.9% of the voxels	
α_2	0.0006508	0.002814	0.54% overestimation in 0.065% of the voxels	0.099% underestimation in 0.28% of the voxels
β_2	3.047	-1.1318		

CMC-based dose planning, the time required for CMC to achieve an average percent SDM of 2% within the CTV, $T_{2\%SDM}^{\text{het,c}}$, was estimated, assuming that variance is inversely proportional to the MC CPU time. The UMC and CMC percent SDMs vs dose and HCF on a voxel-by-voxel basis were compared for the ROI's after using $T_{2\%SDM}^{\text{het,c}}$ for CPU runtime.

To quantitatively evaluate accuracy of $\bar{D}_{ijk}^{\text{het,c}}$ relative to $\bar{D}_{ijk}^{\text{het}}$ benchmarks the distribution of dose differences at each voxel ijk receiving more than 50% of the prescribed dose is evaluated, expressed as multiples of the combined absolute statistical uncertainty

$$z_{ijk} = \left(\bar{D}_{ijk}^{\text{het,c}} - \bar{D}_{ijk}^{\text{het,u}} \right) / \sqrt{\bar{\sigma}_{\bar{D}_{ijk}^{\text{het,c}}}^2 + \bar{\sigma}_{\bar{D}_{ijk}^{\text{het,u}}}^2} - 1. \quad (7)$$

In this expression, $\bar{\sigma}$ represents the absolute SDM. In the absence of any systematic error or bias, the distribution of z_{ijk} should be a Gaussian with a mean of zero and standard deviation of 1. To separate the systematic and random components of CMC error, the z_{ijk} frequency histogram was fit to the model proposed by Kawrakow *et al.*³⁹

$$f(z) = \frac{1}{\sqrt{2\pi}} \left[\alpha_1 e^{-\frac{(z-\beta_1)^2}{2}} + \alpha_2 e^{-\frac{(z-\beta_2)^2}{2}} + (1 - \alpha_1 - \alpha_2) e^{-\frac{z^2}{2}} \right], \quad (8)$$

where $f(z)dz$ is the probability that a voxel has a normalized error in the interval $(z, z + dz)$. This model includes two normally distributed systematic errors with means of β_i , standard deviations of 1.0, and probability of occurrence α_i , where $i = 1, 2$ with the remaining voxels exhibiting only random

errors described by a Gaussian with zero mean and unit standard deviation.. The quantity α_i represents the fraction of voxels that exhibit a mean systematic error β_i . The percentage difference between LU-CMC and LU-UMC corresponding to β_i is estimated by taking the product of β_i and the average percent SDM within investigated region. Fitting was performed using MATLAB's curve-fitting toolbox (MATLAB 7.10.0 (R2010a), Trust-Region algorithm utilizing the least absolute residuals technique for robust fitting).

III. RESULTS

The finest grid with 100 million histories resulted in a mean percent SDM of 0.18% and 0.62% for prostate and 0.087% and 0.77% within the breast for LU-CMC and LU-UMC, respectively, within regions that receive greater than 50% D_{90} . Corresponding run times on an AMD Phenom II X6 1090T processor utilizing only one core were 4.4 and 3.95 h for prostate LU-CMC and LU-UMC, respectively, and 3.84 and 2.33 h for the breast case. This very large number of photon histories was simulated in order to minimize statistical fluctuations.

For the prostate case, Table II shows that nearly all voxels are affected by a very small 0.003% mean systematic error while 0.1% voxels have a larger error of 0.5%. For the breast case, approximately 5% of the voxels have mean systematic errors of 0.04%–0.1%. These data demonstrate that systematic discrepancies between the two codes are very small, i.e., that CMC accurately reproduces UMC results. The distribution of z_{ijk} comparing LU-CMC with LU-UMC for all voxels that receive greater than 50% D_{90} is plotted in Fig. 1 for both

FIG. 1. Plots of z_{ijk} distributions, dots, for prostate (a) and breast (b) with their corresponding fits, line. Fit parameters are in Table II.

the prostate and breast implants along with fits to Eq. (8). Corresponding fit parameters and percentage errors are tabulated in Table II. The R-squared values for prostate and breast implants were 0.99995 and 0.999985, respectively, and clearly demonstrate a good fit. Since the UMC calculations utilized the full collisional physics model, these results demonstrate that the simplified free-electron scattering model used by CMC does not introduce significant systematic errors.

Figure 2 shows that the G_{ijk} distributions with respect to $\bar{D}_{ijk}^{\text{het}}$ and $\bar{HCF}_{ijk}$ have different shapes for the breast and prostate geometries, highlighting the sensitivity of CMC results to underlying implant and tissue geometry differences. For the prostate implant [Fig. 2(a)], the G_{ijk} distribution is sharply peaked around unity HCF; rapidly falls off with larger and smaller values; and displays a large range (a factor of five smaller and larger than unity). Prostate HCF values range from about 0.1 in areas shielded by the pelvic bone to about 10 inside the pelvic bone. Large deviations of HCF from unity are associated with reduced efficiency gain or even efficiency losses. In contrast, breast HCF values have a much smaller range [Fig. 2(b)], ranging from about 0.7 to 1.8, with the majority of voxels falling within 0.10 of

unity. This is due to using a weighted average of glandular and adipose media for the homogeneous medium. Figure 2(b) also reveals a broader maximum near unity HCF with very few voxels experiencing even modest efficiency losses in the limited HCF range of this body site. In contrast, the distributions of G_{ijk} as a function of dose have a much more similar appearance, except that almost no breast PSB voxels experience efficiency losses. In both sites, the largest efficiency gains are generally doses near or exceeding D_{90} while the average efficiency gain systematically decreases with decreasing dose.

Tables III and IV present efficiency summary statistics for the two clinical sites. For the prostate plan, all the voxels within the CTV experience an increase in runtime efficiency with an average G_{ijk} of 38.1 for the finest voxel grid. In contrast, the breast plan shows a larger average G_{ijk} of 59.8 with 99.9% of the voxels within the CTV experiencing an efficiency gain for the finest grid. The average G_{ijk} is larger for the breast case due both to the smaller range of HCF corrections and the fact that an average breast medium was used for the homogeneous geometry, which more closely models the heterogeneous breast than water does the prostate geometry (See discussion below).

FIG. 2. Scatter plot of the efficiency gain vs the HCF for all voxels in the prostate (a) and breast (b) geometries; scatter plot of the efficiency gain vs the delivered dose (Gy) for all voxels in the prostate (c) and breast (d) geometries. The area outlined in red circumscribes the voxels originating from the CTV.

TABLE III. Average efficiency gain for the breast and prostate plans for various ROI's along with the estimated time required to compute Monte Carlo dose to achieve 2% mean standard deviations about the mean. For the prostate plan, data are given for three different voxel dimensions: $(1.0 \text{ mm})^3$, $(2.0 \text{ mm})^3$, and $(3.0 \text{ mm})^3$ relative to uncorrelated Monte Carlo. Percentages within parentheses are the percentage of voxels within the corresponding structure that experience and efficiency gain greater than unity. The times listed are estimated to achieve average 2% standard deviation about the mean within corresponding structure at all dose levels.

Breast	MC Type	Time to achieve mean %SDM of 2%			Average Efficiency Gain $(0.67 \text{ mm})^3$		
Lumpectomy Cavity.	UMC	16.9 min			55.7 (100%)		
	CMC	20.2 s					
CTV	UMC	18.7 min			59.8 (>99.9%)		
	CMC	21.1 s					
Prostate	MC Type	$(1.0 \text{ mm})^3$	$(2.0 \text{ mm})^3$	$(3.0 \text{ mm})^3$	$(1.0 \text{ mm})^3$	$(2.0 \text{ mm})^3$	$(3.0 \text{ mm})^3$
Prostate (CTV)	UMC	15.3min	1.59 min	30.9 s	37.1 (100%)	44.7 (100%)	41.6 (100%)
	CMC	38.6 s	3.3 s	1.1 s			
Bladder	UMC	113 min	12.0 min	4.0 min	12.3 (99.3%)	13.5 (99.0%)	12.7 (97.5%)
	CMC	16.5 min	1.63 min	38.9 s			
Rectum	UMC	45.2 min	4.55 min	1.44 min	14.0 (99.7%)	14.9 (99.1%)	14.3 (98.7%)
	CMC	4.7 min	27.4 s	8.9 s			
Seminal Vesicles.	UMC	29.1 min	3.02 min	56.9 s	12.6 (99.4%)	14.0 (99.8%)	13.3 (99.3%)
	CMC	3.5 min	17.9 s	6.23 s			
Urethra	UMC	18.0 min	1.90 min	36.4 s	43.2 (100%)	54.0 (100%)	54.1 (100%)
	CMC	38.9 s	3.49 s	1.13 s			

The assumption that Monte Carlo variance estimates are inversely proportional to the square-root of runtime, suggests CPU times, $T_{2\%SDM}^{\text{het,c}}$, of only 39 and 21 s are necessary for prostate and breast CTVs, respectively, to achieve 2% statistics. The CMC and UMC dose distributions were recomputed using the smaller number of histories corresponding to these rescaled $T_{2\%SDM}^{\text{het,c}}$ runtimes. Figures 3 and 4 show the resultant distributions of %SDM with respect to $\bar{D}_{ijk}^{\text{het,u}}$ for the clinical ROI regions receiving greater than 50% of D_{90} . The UMC simulations yielded mean %SDM's of 11.3%, 5.1%, and 4.6% for the bladder, rectum and seminal vesicles, respectively. These plots exhibit a dramatic separation between CMC and UMC statistical uncertainties with tightly grouped distributions with moderate dependence on dose. Despite the fact that some voxels experience little efficiency gain or even efficiency losses, for a fixed CPU time, CMC always reduces uncertainty within a given organ, generally by a factor of 6. The UMC SDM distributions are

consistently broader than for CMC for all structures shown, except for the rectum where the SDM spread appears to be equal. Figure 5 shows a central slice through the prostate plan with isodose curves from LU-UMC with and CMC using $T_{2\%SDM}^{\text{het,c}}$ for run time. The differences between them are difficult to distinguish visually.

IV. DISCUSSION

CMC effectively reduces variance under many circumstances. However, regions with low dose or large dose perturbations due to tissue composition heterogeneities can experience diminished gains or even efficiency losses in both breast and prostate plans. Theoretical analyses of CMC indicate that, while the correlated sampling algorithm leads to unbiased results, there is no guarantee of improved efficiency.²⁵ This result is consistent with Hedtjrn's study²² who realized efficiency gains of four orders of magnitude across a wide keV energy spectrum for a simple uniform water geometry with different single cylindrical heterogeneities. Despite efficiency losses in a small number of voxels, both cases investigated by our study demonstrated reduction of the maximum and mean dose-uncertainty in clinically relevant regions of interest. Voxels experiencing CMC efficiency loss generally already have UMC standard deviations well below the mean and maximum UMC standard deviations. Thus, CMC is globally advantageous despite the small number of voxels that exhibit increased statistical uncertainty. The prostate plan demonstrates the greatest loss of CMC efficiency advantage in regions where HCF deviates from unity by more than 20%. Both cases also show that regions with little dose deposition have a higher tendency to experience an efficiency loss. These regions include those

TABLE IV. G_{20} , G_{50} , and G_{90} (average efficiency gain for voxels receiving greater than or equal to 20%, 50%, and 90% of the prescribed dose, respectively) for the breast and prostate plans. The prostate also shows values for larger voxel dimensions (2mm and 3mm). The percentage of the voxel contained in these regions that experience and efficiency gain are contained within the parentheses.

Breast	G_{20}	G_{50}	G_{90}
$0.67 \times 0.67 \times 0.8 \text{ mm}^3$	44.8 (>99.9%)	55.0 (100%)	54.9 (100%)
Prostate			
$1.0 \times 1.0 \times 1.0 \text{ mm}^3$	20.3 (98.2%)	26.8 (99.7%)	33.6 (>99.9%)
$2.0 \times 2.0 \times 2.0 \text{ mm}^3$	23.4 (97.8%)	31.8 (99.7%)	40.5 (100%)
$3.0 \times 3.0 \times 3.0 \text{ mm}^3$	22.2 (97.7%)	30.0 (99.8%)	38.1 (100%)

FIG. 3. Scatter plot of percent standard deviation about the mean vs dose for each individual voxel within the prostate (a), urethra (b), and the rectum (c), for correlated Monte Carlo (lower) and uncorrelated Monte Carlo (upper). The average percent standard deviation about the mean value for correlated Monte Carlo is plotted as green line. The CPU time was 39 s.

shielded by the pelvic bone and those regions outside the CTV in the breast where decorrelation between the homogeneous and heterogeneous histories is greatest, thus leading to the efficiency losses reported.

The larger CMC efficiency advantage realized in the breast cancer plan compared to the prostate implant can be explained by increased correlation between β_n^{hom} and β_n^{het} . This arises from using a uniform mixture of 85% adipose

FIG. 4. Scatter plot of percent standard deviation about the mean vs dose for each individual voxel within the breast CTV (a), and the breast simulated lumpectomy cavity (b) for correlated Monte Carlo (lower) and uncorrelated Monte Carlo (upper). The average percent standard deviation about the mean value for correlated Monte Carlo is plotted as green line. The CPU time is 21 s.

and 15% fibroglandular tissue, which closely matches the mean composition of the breast,³⁶ for the homogeneous medium in the CMC calculations, resulting in heterogeneity corrections no larger than a factor of two. As shown in Fig. 6, if water is used instead, the average HCF of the CTV is approximately 0.5, compared to the prostate CTV, where the distribution of HCFs is centered on unity. This is because the breast CTV and normal parenchyma contains a large fraction of adipose tissue which has a 2–3 fold smaller attenuation coefficient than water at low energies. Every interaction within adipose tissue progressively increases the variability of heterogeneous photon weights, relative to water medium, through repeated application of the weight correction factor, Eq. (1). In future work, we intend to quantify this effect and determine if additional variance reduction techniques, e.g., systematic Russian roulette and splitting, i.e., weight windowing (WW), will further enhance efficiency and robustness of algorithm performance.^{40,41} WW can be used to either constrain photon weights within a desired range, or can be used to implement importance sampling variance reduction that roughly sets photon weights proportional to their detector score “importance.”⁴²

FIG. 5. Isodose curves for low-uncertainty uncorrelated Monte Carlo (dashed lines) and correlated Monte Carlo (solid) for prostate (a) and breast (b) using $T_{het,c}^{2\%SDM}$ CPU times. All calculations use the finest dose grid.

For organs relevant to brachytherapy treatment planning, we have shown that 10- to 41-fold mean efficiency increases can be realized relative to conventional Monte Carlo dose calculations when performed on the finest voxel meshes explored in this study. It should be noted that these proof-of-principle results are based on a sample of only two patients, and, while encouraging, may not be representative of a large patient population. An additional limitation of this study was that the single prostate patient data set used had metal streaking artifacts that were mitigated only incompletely by post reconstruction image processing. Residual artifacts could have diminished potential efficiency gains. Further studies on larger artifact free patient data sets are needed to support claims that our results are representative in general of breast

and prostate patients. Furthermore, testing CMC for higher energy sources, e.g., HDR brachytherapy, and other treatment sites and techniques are also needed to provide the general characteristics of CMC.

A potential application for a fast MC code is in optimized PSB treatment planning optimization (OTP) where dose maps for many candidate seed configurations are computed and tested for quality.^{21,43–46} If the widespread implementation of patient-specific MC-based OTP can be realized, the dose-outcome relationship could be greatly improved, potentially decreasing the incidence of toxicities.⁴⁷ Unfortunately, utilizing CMC, as presented in this study on the finest grid, PSB OTP still requires many hours of computation time. To further increase efficiency, additional studies are underway to assess the clinical practicality of recovering a high spatial resolution dose map from the summation between a low spatial resolution CMC $\overline{AD}_{ijk}^c$ and a high spatial resolution D_{ijk}^{TG43} .

Correlated PTRAN_CT run times compare favorably with other specialized PSB Monte Carlo codes reported in the literature. Taylor *et al.*⁴⁸ and Yegin *et al.*⁴⁹ reported that BrachyDose, an EGSNRC based code, computes full PSB prostate dose distributions within 5 min. More recently, BrachyDose has been shown to compute the prostate dose distribution with an average 2% SDM using $(2\text{ mm})^3$ voxels in 30 s.⁵⁰ Chibani *et al.*² reported calculations in under 1 min for a $2 \times 2 \times 2\text{ mm}^3$ voxel mesh. In contrast, PTRAN_CT CMC computes dose under these conditions in 3.3 s. VMC++ has also recently been commissioned for low-energy brachytherapy, though time benchmarks have not yet been reported.⁵¹ Common variance reduction techniques utilized in these codes include Russian roulette, particle splitting, track-length estimation, and the reuse of photon histories. CMC differs from these techniques as it was directly derived from a transport equation solution to yield unbiased solutions. Though these

FIG. 6. Scatter plot of G_{ijk} vs HCF for all voxels in the simulated breast plan for correlated Monte Carlo based upon generation of photon histories in homogeneous water rather than average breast medium. The area outlined in red circumscribes the voxels originating from the CTV.

techniques were accurate and more efficient than their predecessors, CMC appears to be substantially more efficient, although more rigorous testing (controlling for implant geometry; seed structure complexity; dose specification; and processor speed) are needed to quantitatively measure such performance differences.

Fast dose-computation execution is not the only barrier to clinical implementation of tissue composition heterogeneity corrections in brachytherapy treatment planning. For low-energy brachytherapy, the task of correctly assigning tissue cross sections to organs or individual voxels is an important unsolved problem.^{52–54} Potentially, this issue could be addressed through quantitative imaging techniques such as dual-energy CT.^{55,56}

V. CONCLUSIONS

We have demonstrated that correlated Monte Carlo simulations results in 38–60 fold improvements in average efficiency relative to conventional uncorrelated sampling Monte Carlo in typical low-energy seed implant geometries. Despite the possibility of lowering efficiency in limited subvolumes, CMC appears to reduce maximum variance in the dose grid for all low-energy interstitial implant cases investigated to date. On typical single-processor workstations, CMC has been shown to be a fast and efficient brachytherapy planning tool for more realistically assessing high-resolution dose distributions with run times of the order of 1 min in our hands. Further investigation is needed to mitigate the negative impact of particle weight decorrelation on efficiency.

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