OPTIMIZATION OF PERMANENT BREAST
SEED IMPLANT DOSIMETRY
INCORPORATING TISSUE HETEROGENEITY

by

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Abstract

“Optimization of Permanent Breast Seed Implant Dosimetry Incorporating Tissue Heterogeneity”

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Seed brachytherapy is currently used for adjuvant radiotherapy of early stage prostate and breast cancer patients. The current standard for calculation of dose around brachytherapy sources is based on the AAPM TG43 formalism, which generates the dose in homogeneous water medium. Recently, AAPM task group no. 186 (TG186) emphasized the importance of accounting for heterogeneities. In this work we introduce an analytical dose calculation algorithm in heterogeneous media using CT images. The advantages over other methods are computational efficiency and the ease of integration into clinical use.

An Inhomogeneity Correction Factor (ICF) is introduced as the ratio of absorbed dose in tissue to that in water medium. ICF is a function of tissue properties and independent of the source structure. The ICF is extracted using CT images and the absorbed dose in tissue can then be calculated by multiplying the dose as calculated by the TG43 formalism times ICF. To evaluate the methodology, we compared our results with Monte Carlo simulations as well as experiments in phantoms with known density and atomic compositions.

The dose distributions obtained through applying ICF to TG43 protocol agreed very well with those of Monte Carlo simulations and experiments in all phantoms. In all cases, the mean relative error was reduced by at least a factor of two when ICF correction factor was applied to the TG43 protocol.

In conclusion we have developed a new analytical dose calculation method, which enables personalized dose calculations in heterogeneous media using CT images. The methodology offers several advantages including the use of standard TG43 formalism, fast calculation time and extraction of the ICF parameters directly from Hounsfield Units. The methodology was implemented into our clinical treatment planning system where a cohort of 140 patients were processed to study the clinical benefits of a heterogeneity corrected dose.
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List of Scientific Contributions

During my thesis research (Mar 2010 - Oct 2014), several scientific contributions were published in peer-reviewed journals and presented at different conferences. They are listed here for reference.

**Journal Publications:**


**Article in preparation:**

Conference Abstracts and Proceedings:


**Mashouf S. and Pignol J.** - Optimization of breast permanent seed implant dosimetry incorporating tissue heterogeneity. *CCSRI Annual Meeting, July 16-17, 2012, Quebec City, Quebec.*


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Chapter 1

Introduction
1.1 Breast cancer

Breast carcinogenesis is a multistep process where progressive accumulation of genetic alterations gives rise to the cancer [2]. These alterations lead to an imbalance between cancer promoters and suppressors, as well as cellular immortality, invasion, and metastasis. These alterations could be due to hereditary or acquired causes [3].

Breast cancer remains the most frequent cancer diagnosed in Canadian women. The combination of screening leading to the diagnosis of the disease at an earlier stage and more effective therapies has resulted in reduction in mortality by 40% since 1986 [1]. Surgery, radiation, anti-mitotic chemotherapy and anti-hormones have traditionally been associated and constituted the main modalities of therapy. The recent advances in molecular biology techniques have resulted in the development of targeted therapies which are only effective if the tumor cells express specific target molecules [4].

1.1.1 Types of breast cancer

The breast glandular tissue is composed of lobules (milk-producing glands) and ducts (tubes which carry the milk). Other tissues include blood and lymphatic vessels as well as fatty and connective tissue (Fig. 1.1). The breast gland is limited by the skin and the fascia pectoralis, which is an aponeurosis on the top of the pectoralis muscle. Breast cancer mainly originates from the cells lining the ducts [3].
Figure 1.1 - Internal structure of breast. Breast cancer arises mostly from epithelial cell linings of ducts. Source: [3]

One way for breast cancer to spread is through the lymphatic system, which consists of a network of lymph vessels and nodes. If cancer has already migrated to lymph nodes (node positive) there is a higher chance that it might have also spread to other organs. The first lymph node where the tumor basin drains into is referred to as Sentinel Lymph Node (SLN).
Most breast lumps are benign. Only 20% of the newly found breast lumps need to be sampled and carefully followed up for cancer screening or diagnosis [3]. Most benign breast lumps are formed as a result of fibrosis (scar tissue) or cyst formations.

Breast cancer can be divided into four major categories based on origin of the cancer and the extent of cell growth as below [3]:

**i. Ductal carcinoma in situ (DCIS)**

This type of tumor originates from the cell linings of the ducts but the cancer cell proliferation remains confined within the walls of the ducts because the cancer cells have not yet acquired the capacity to infiltrate the surrounding tissues or spread to other organs (in situ or non-invasive cancer).

**ii. Lobular carcinoma in situ (LCIS)**

Like DCIS, this is a non invasive form of cancer starting from the cell lining the lobule which is the milk-producing glands.

**iii. Invasive (or infiltrating) ductal carcinoma (IDC)**

It starts in epithelial cell linings of the breast ducts but the cancer cell breaks through the walls and invades the surrounding fatty tissue. At this point, the cancer cells are fed by neo-vessels and could spread to other parts of the body through the blood stream or lymphatic system.

**iv. Invasive (or infiltrating) lobular carcinoma (ILC)**
This type of cancer originates in lobules and spreads to surrounding tissue. About 1 in 10 of invasive cancers of breast is lobular. Since they do not obstruct the ducts, they more rarely produce micro-calcification and they are more deeply situated than the IDC. As a result they are more difficult to diagnose through mammography screening. They also tend to be multifocal and metastasize to odd locations.

### 1.1.2 Causes

Risk factor for breast cancer include gender, age (the older the higher the risk), family history, personal history, race and ethnicity, breast density, preexisting benign breast lumps, previous chest radiation, having children, birth control, alcohol, physical activity and being overweight or obese. [2].

On cellular level, the underlying mechanisms leading to cancer are more or less known. In a typical cell, there are genes controlling the cell growth, division and death. The genes speeding up the cell division are referred to as *Oncogenes* and those responsible for slowing down the cell division or inducing cell death are called *Tumor Suppressor Genes (TSGs)*. An imbalance in cell proliferation caused by activation of oncogenes and deactivation of tumor suppressor genes due to changes (mutations) in DNA may cause a normal cell to become cancerous [3].

#### 1.1.2.1 Genetics

DNA changes which give rise to cancer can be due to hereditary or acquired gene mutations. Mutations in BRCA tumor suppressor genes, for example, can be inherited from the parents. When these genes are silenced, they can no longer prevent abnormal growth which might lead to cancer [3]. Most DNA mutations related to breast cancer, however, are acquired rather than inherited. They may be caused due to radiation or chemical carcinogens. But for the
most part, the underlying mechanisms which lead to acquired mutations are not exactly known [3]. Fig. 1.2 displays the distribution of genetic mutation sources in breast cancer population.

Figure 1.2 - Genetics of breast cancer. Source: [2]

Mutations in BRCA1 and BRCA2 genes cause genomic instability which in turn results in alterations in other important oncogenes and TSGs as well [5]. Lack of BRCA1 or BRCA2 in cells results in deficiency in error free DNA Homologous Recombination Repair (HRR) pathways. Instead of HRR, cells utilize non-homologous end joining and single-strand annealing repair mechanisms which are prone to errors and potentially mutagenic. Genomic instability manifests itself in chromosomal aberrations, large gains and losses in chromosomes as well as other changes in DNA [6].

Some breast cancers could be also due to inactivation of important DNA repair genes such as BRCA1, ATM, CHK2 and P53 due to epigenetic causes which is related to alterations in the expression of genes rather than changes in the actual DNA sequences of the genes [2].
P53 is a tumor suppressor gene which is termed “guardian of the genome”. It induces cell cycle arrest and apoptotic cell death when genome endures and accumulates damage. P53 is mutated and implicated in about 30% to 50% of all breast cancer cases.

1.1.2.2 Growth Factor Receptors

Growth factor receptors play an important role in initiating signals leading to proliferation in epithelial cells of breast. These receptors are proteins located on the surface of the cell and constitute part of the cell plasma membrane. They can attach to certain substances circulating in the blood such as some hormones [3]. The structure of these receptors consists of three parts: an extracellular ligand binding region, a transmembrane region and a tyrosine kinase domain inside cytoplasm, which can initiate a cascade of downstream signals and functions [2].

i. Estrogen and progesterone receptors

Normal breast cells and some breast cancer cells have receptors for estrogen and progesterone hormones stimulating the cell growth. *ER-positive* (ER+) and *PR-positive* (PR+) are the terminology used for breast cancer cells with estrogen and progesterone receptors respectively. If any of these receptors are present, the cancer is referred to as hormone receptor-positive. About two third of breast cancers are hormone receptor-positive and this ratio is higher in older women. Hormone receptor positive tumors tend to grow more slowly [3].

ii. HER2 receptors

HER2 or human epidermal growth factor receptor type 2 is a transmembrane tyrosine kinase receptor (HER2 receptor) which is encoded by the ERBB2 gene. It belongs to the same family
of endothelial growth factor receptors as EGFR, HER3 and HER4. Since HER2 receptor does not bind directly with any ligand, it functions through forming heterodimerization with other members of the receptor family mainly HER3. The over expression of HER2 receptor is present in about 20% of newly diagnosed breast cancers and indicates a more aggressive disease progression. HER2 over-expression is associated with growth autonomy and genomic instability [4].

iii. VEGFR receptors

New blood vessel formation or angiogenesis is closely associated with the development of breast cancer. There is evidence that angiogenesis precedes the transformation of breast hyperplasia to malignancy [7]. Vascular endothelial growth factor receptors (VEGFRs) are tyrosine kinase receptors which are involved in tumor angiogenesis.

1.1.3 Treatment

The treatment modalities of breast cancer include surgery, radiation therapy, chemotherapy, hormone therapy, and targeted therapy. Surgery and radiation therapy are termed as local therapies as they only target the tumor site and its regional extension, but chemotherapy, hormone therapy and targeted therapy are referred to as systemic therapies as they reach the entire body. Chemotherapy works by targeting cells which are dividing fast which is the case of cancer cells. Hormone therapy is administered for hormone receptor-positive breast cancer. It lessens the proliferation potency of estrogen either by blocking the estrogen receptors (e.g. Tamoxifen) or by lowering the body estrogen level (e.g. Aromatase inhibitors) [3]. Targeted therapies are the term used for drugs targeting a specific molecular aberration of the disease such as the over expression of epidermal growth factor receptors
(EGFRs), DNA repair pathways and angiogenesis [8]. Trastuzumab (also known as Herceptin®), a humanized monoclonal antibody targeting HER2 over-expressing cells, and Lapatinib, a small molecule tyrosine kinase inhibitor, are examples of targeted therapy drugs [2].

1.1.3.1 Management of noninvasive disease

i. Ductal carcinoma in situ (DCIS)

DCIS currently accounts for 15% to 20% of the cancers detected by mammography. The current consensus for the treatment of localized DCIS (with clear surgical margins) includes breast conserving surgery followed by whole breast radiation. Mastectomy is reserved for multicentric DCIS with diffused calcifications when negative margins cannot be obtained [9]. Considering 80% of DCIS lesions are ER+, Tamoxifen could also be considered following lumpectomy and radiation to reduce the risk of recurrence [4,9,10].

ii. Lobular carcinoma in situ (LCIS)

Since LCIS rarely turns invasive, it does not require a treatment. Women with LCIS, however, have 7 to 11 fold higher risk of developing invasive cancer later on. Therefore close follow-up of both breasts and administration of Tamoxifen is recommended [3].

1.1.3.2 Management of invasive disease

i. Early stage

The standard treatment for early stage breast cancer (tumor size < 2 cm) includes breast conserving surgery (lumpectomy), followed by whole breast radiation which is delivered daily over a period of 5 to 6 weeks. Several studies have shown that mastectomy does not provide
any advantage in terms of survival for early stage breast cancer patients [11-13]. In 2005, a meta-analysis performed by Early Breasts Cancer Trialists Collaborative Group (EBCTCG) demonstrated the addition of radiation therapy results in improvements not only in the local control but also the 15 year overall survival [14]. Systemic therapies for early stage breast cancer has survival benefits [15] and should be considered based on the receptor status (ER+, PR+, HER2+). If the cancer is triple negative (no receptors), chemotherapy is the modality of choice [4].

**ii. Locally advanced**

A locally advanced breast cancer is defined as a disease with a primary tumor larger than 5 cm attached to the chest wall or skin, or involving bulky palpable disease in axilla without evidence of distant metastases [4]. This type of cancer is initially treated with chemotherapy so as to shrink the size of tumor prior to surgery. Pre-surgery chemo increases the likelihood of obtaining negative surgical margins and hence increasing the possibility of conserving the breast. Another advantage of using chemo before surgery is that the tumor response to the drug can be evaluated and another drug can be used if the tumor is not responsive [3]. If the patient does not respond to pre-operative chemotherapy, mastectomy plus radiation is used [4].

**iii. Recurrent**

Recurrence after breast conserving surgery does not necessarily indicate a systemic disease. It could be a recurrence near the site of original primary tumor or it may be a new primary lesion. In the case of a failure in conserved breast, the treatment involves salvage mastectomy [4].

**iv. Metastatic**
At this stage of the disease, the tumor has spread beyond the breast, chest and regional lymph nodes. The common sites of metastasis include bone, lung and brain. The metastatic disease remains incurable and the therapy is largely palliative [2,4]. The systemic therapy involves hormone therapy for hormone positive lesions, HER2 targeted therapy for HER2+ and chemotherapy if triple negative and angiogenesis targeting drugs such as Sunitinib which is an inhibitor for VEGF receptors.

1.1.4 Breast irradiation

The standard treatment for early stage breast cancer, i.e. the cancer that has not spread beyond the primary tumor or the regional lymph nodes, includes breast conserving surgery plus whole breast radiation and is referred to as Breast-Conserving Therapy (BCT). Level I evidence exists that BCT is equivalent to mastectomy for early stage breast cancer patients [14]. In other words breast irradiation replaces the need to remove the entire breast and affords preservation of the breast. Several studies have tried to identify subset of early stage breast cancer patients for whom radiation can be safely eliminated but in all cases lack of radiation led to significant increase in the local recurrence rate [16-18].

Several studies, however, show that majority of failures in patients receiving breast conservation treatment happens at the site of the resected tumor [19,20]. This suggests the radiation can be limited to breast tissue adjacent to the lumpectomy cavity for carefully selected patients with low risk of microscopic disease migration. As a result Accelerated Partial Breast Irradiation (APBI) has been investigated as a potential alternative to whole breast radiation for early stage breast cancer [19,20]. Though the equivalence of APBI to standard whole breast radiotherapy is still currently being evaluated through 7 large randomized clinical
trials, the loco-regional outcomes reported to date along with shorter treatment time have made many healthcare facilities to adopt this treatment [21,22]. APBI is delivered using different modalities including interstitial brachytherapy, 3D conformal external-beam and intra-operative irradiation.

1.1.4.1 Permanent Breast Seed Implant (PBSI)

In 2004, our group at Sunnybrook Odette Cancer Centre started a new APBI delivery method similar to prostate brachytherapy, using interstitial brachytherapy in which $^{103}\text{Pd}$ seeds are implanted within the tumor bed [23]. The procedure is referred to as Permanent Breast Seed Implant (PBSI) and is realized in a single 1 hour session under local freezing and light sedation. PBSI offers the patient the benefit of avoiding logistical problems of time and travel associated with whole breast external beam, which is delivered daily over a period of 6-7 weeks. It is also associated with a lower risk of acute and delayed skin toxicities. Finally, the results of a cohort of over 130 patients who have been treated at our centre show a loco-regional control similar to external beam radiotherapy. The patient selection criteria includes: patients with infiltrating ductal carcinoma measuring less than 3 cm, age ≥ 40 years and negative lymph nodes. The procedure is delivered as follows:

i. Planning

When a patient is eligible based on pathology criteria, a CT scan is done with patient in supine position and arm lifted above the head. The Radiation Oncologist contours the clinical target volume (CTV) on the CT scan. The planning target volume (PTV) is then defined as CTV plus a margin of 1 cm and an additional 0.5 cm of security modified to leave a 5mm margin with skin and to remain above the fascia pectoralis [24]. The direction of the
implantation needles is defined to avoid skin or chest wall perforation. At that stage if the patient is deemed technically doable her consent is obtained. If the patient agrees, the images are resampled perpendicular to the implantation direction and exported to the brachytherapy treatment planning system.

**ii. Dosimetry**

In PBSI, the prescribed minimal peripheral dose around the PTV is 90 Gy. In an optimized plan, the fraction of the PTV receiving 100% of the prescribed dose or higher ($V_{100\%}$) should be above 95% and the volume receiving 200% or higher of the prescribed dose ($V_{200\%}$) should be kept below 30% [25]. It has been shown that there is a significant risk of delayed complication like telangiectasia (permanent red marking of the skin by new vessel growing under a thin skin surface) if the 85% isodose cross the skin surface over an area of 1 cm$^2$. So to protect the skin, the 85% isodose line should not bulge through the skin [26].

The dose calculation method is based on AAPM TG-43 protocol, which calculates the dose surrounding a seed assuming water as the medium [27].

**1.1.4.2 Skin toxicity**

Skin is considered an organ at risk (OAR) for radiation treatment of breast cancer due to cosmetic reasons and patient discomfort resulting from damages to the skin. Other OARs include heart and lung due to proximity to the site of radiation [28,29]. Unlike deeply seated cancers, dose to the skin is a limiting factor for radiation delivery to cancers located close to the surface of skin such as breast [30].

The structure of skin has been illustrated in Fig. 1.3. The outer shell is epidermis and measures 30 to 300 μm in thickness ('A' in Fig. 1.3(a)). It consists of several layers of cells including an
Figure 1.3 - (a) Schematic drawing showing different layers of skin. 'A' represents epidermis, 'B' dermis papillary, 'C' rete dermis, 'D' subcutaneous junction to dermal plexus and 'E' subcutaneous layer. (b) Skin functional unit (FU). Source: [30]

inner proliferative basal cell monolayer and an outer layer of dead cells (corneum). The life cycle of a basal cell from generation to being shed through the corneum lasts 26 days [31]. Dermis is the inner layer of skin. The upper 350 μm portion ('B' in Fig. 1.3(a)) contains microvessel tufts which supply the epidermis. A microvessel tuft with associated epidermis and dermis is referred to as a skin functional unit (FU) (Fig. 1.3(b)). The dose response of a skin functional unit is similar to that of the whole skin. Therefore, for dosimetry purposes, the top 1 mm layer for skin represents the sensitive volume of the skin. The function of skin is compromised by the loss of FUs due to irradiation. The defect in an FU is compensated by the growth of epidermal cells nourished by the adjacent tufts. A minimum density of FUs is required in order to preserve the integrity of the skin. Even though basal cells of epidermis are able to regenerate after radiation damage, this is not the case for microvessel endothelial cells [32,33]. A cell lost in a basal cell monolayer is eventually replaced by another cell in a 2D
plane, while a cell lost in a vessel can only be replaced by two adjacent cells in a 1D arrangement. The mechanism of damage to an FU is through loss of microvessel endothelial cells due to lack of proliferation. The progression of microvessel changes in a skin functional unit leading to telangiectasia (permanent red marking of skin displaying multiple thin-walled dilated vessels) has been illustrated in Fig. 1.4.

![Figure 1.4 - Progression of microvessel changes in the skin functional unit due to radiation representing the late effect of radiation damage leading to telangiectasia. Source: [30]](image)

The early changes of radiation sorted in the order of increasing dose of onset include epilation, erythema, pigmentation and desquamation. Moist desquamation, which is associated with higher values of dose, either heals by 50 days or progresses to necrosis [31]. The late effect of radiation occurs after 10 weeks following radiation and includes scaling, atrophy, telangiectasia, subcutaneous fibrosis and necrosis.

Similar to other APBI techniques, PBSI compares favorably to standard whole breast irradiation in regards to skin toxicities [26]. The reported rate of moist desquamation is 10.4%
for PBSI versus 37-49% in whole breast radiation [34]. The rate of telangiectasia at 2 years is 14% in PBSI compared to 31% for standard whole-breast radiation [35].

1.2 Physics of ionizing radiation

A radiation capable of ionizing atoms in matter is referred to as ionizing radiation [36]. This includes particulate radiation such as electrons, protons, neutrons and heavy charged particles (e.g. He$^{2+}$, C$^{6+}$) or non-particulate such as electromagnetic radiation. Since the minimum energy required to release a valence band electron from atom is in the order of 4-25 eV, ionizing radiations should carry kinetic or quantum energies in excess of this magnitude. For electromagnetic radiation this would translate to wavelengths up to 320 nm, which includes the ultraviolet (UV) band. UV rays have very limited penetration into matter and do not penetrate the body any deeper than the skin, however they can cause skin cancer [37]. The importance of ionization radiation stems from their profound effect on biological systems. If exposed to ionizing radiation, a mere energy deposition of 4 J/kg throughout the human body leads to death in 50% of cases [38]. This amount of energy raises the body temperature by only 0.001 °C. The biologic effect of ionizing radiation is largely through damage to the cell DNA.

1.2.1 Sources of ionizing radiation in radiation therapy

The radiation therapy today is delivered using two general methods: external beam and brachytherapy. Photons with energies ranging from 20 keV to 18 MeV are the most common type of radiation used in both modalities [39]. High energy electrons are also used but less frequently. More exotic particles such as protons, heavy ions, neutrons and negative π mesons, which are all produced by special accelerators, can also be used for radiotherapy.
Most external beam radiotherapy treatments are delivered by linacs, which is an abbreviation for the term linear accelerator [40]. In a linac, electrons are accelerated to high energies and directed towards a special metallic target to produce bremsstrahlung and characteristic x-rays.

In brachytherapy, the radiation is delivered using small sources or seeds placed within a short range of the site to be irradiated. Today, the most common brachytherapy sources are, $^{192}$Ir, $^{125}$I and $^{103}$Pd. The brachytherapy sources are encapsulated to contain the radioactivity, provide source rigidity, and absorb any α and β radiation produced during the source decay.

Fig. 1.5 shows the structure and dimensions of a typical Low-Dose Rate (LDR) brachytherapy seed used in permanent breast seed implants with $^{103}$Pd as a source for photons. $^{103}$Pd decays via electron capture to the excited states of $^{103}$Rh which is de-excited almost entirely through the process of internal conversion, leading to production of characteristic x-rays with average photon energy of about 21 keV[41].

![Figure 1.5 - Schematic of IsoAid Advantage $^{103}$Pd LDR brachytherapy seed. Source: [42]](image-url)
1.2.2 Interaction of ionizing radiation with matter

Ionizing radiation leads to ionization of matter either directly or indirectly. Directly ionizing radiation refers to charged particles interacting directly with orbital electrons through Coulomb-force interactions. Photon beams and neutrons are example of indirectly ionizing radiation setting in motion ionizing charged particles. Photons and electrons constitute the most common type of ionizing radiation used in radiation therapy today and their interactions with matter will be discussed next.

1.2.2.1 Photon interactions

Electromagnetic radiation is composed of packets of energy referred to as photons. The quantum energy of a photon \( E \) is related to the frequency of the electromagnetic wave \( \nu \) by the following relation [36]:

\[
E = \hbar \nu \quad (1.1)
\]

where \( \hbar \) is the Planck's constant \( = 6.63 \times 10^{-34} \text{ J s} \)

Photons undergo different interactions with atoms as they propagate through the matter. During the interaction they can be completely absorbed or scattered by the atoms. The scattering can be coherent (Raleigh scattering) in which the photon does not lose any energy or incoherent with partial loss of the energy. The probability of each interaction is represented by the interaction cross section (in units of \( \text{cm}^2/\text{atom} \)) which is a function of photon energy and the atomic number \( Z \) of the attenuator [39]. The mass attenuation coefficient of an interaction \( \frac{\mu}{\rho} \) is defined as total cross section per unit mass of a material (in \( \text{cm}^2/\text{g} \)) [36] and can be expressed as [43]:

\[ \frac{\mu}{\rho} = \frac{\sigma N_A}{A} \]  

(1.2)

where \( \sigma \) is the interaction cross section, \( \rho \) is the density, \( \mu \) is the linear attenuation coefficient, \( A \) is the atomic weight and \( N_A \) is Avogadro's number. It can be shown that for a parallel monoenergetic photon beam passing through a material with thickness of \( l \), number of primary interactions is [43]:

\[ \Delta N = N_0 (1 - e^{-\mu l}) \]  

(1.3)

where \( N_0 \) is the number of incident photons.

There are five types of photon interactions which include Compton effect, photoelectric effect, Rayleigh (coherent) scattering, pair production and photonuclear interactions. Since pair production and photonuclear interactions happen at photon energies greater than 1 MeV, they are not important for low energy photon sources of interest in this thesis and are not discussed further.

i. **Compton effect**

In the Compton effect, the photon is scattered by an orbital electron and transfers part of its energy to the electron. As the photon energy decreases, Compton effect resembles coherent scattering as a higher fraction of the incident photon energy is retained (see Fig. 1.6). This elastic form of the Compton effect is also referred to as Thomson scattering. For Pd-103, which is used as a radioisotope in permanent seed implants, 96% of the photon's energy (\( \bar{h}\nu = 20.7 \) keV) is retained in a Compton interaction. Later we will use this property to conclude the seed encapsulation does not significantly change the photon spectrum since the photons are either scattered at the same energy or completely absorbed due to photoelectric effect.
The Compton mass attenuation coefficient \( \frac{\sigma}{\rho} \) is given by:

\[
\frac{\sigma}{\rho} = \frac{N\Delta Z}{A} e\sigma
\]

(1.3)

which is obtained by replacing \( \sigma = e\sigma \cdot Z \) in Eq. (1.2) where \( Z \) is the atomic number of the attenuator and \( e\sigma \) is the electron cross section of an electron.

i. Photoelectric effect

Photoelectric effect is an important type of photon interaction with matter for low energy photons \( (h\nu \leq 100 \text{ keV}) \). Photoelectric interaction cross-section increases rapidly while Compton effect's interaction cross approaches a constant value as the energy decreases. Unlike Compton scattering, in photoelectric effect the incident photon is completely absorbed by an atomic-shell electron. The kinetic energy of the recoiled electron in a photoelectric interaction is given by:
\[ T = h\nu - E_b - T_a \]  

(1.4)

where \( h\nu \) is the energy of incident photon, \( E_b \) is the binding energy of the electron and \( T_a \) is the kinetic energy transferred to the atom. Since \( \frac{T_a}{T} = \frac{m_e}{M_o} \cong 0 \) (ratio of the rest mass of electron to that of the recoiling atom), Eq. (1.3) can be simplified as:

\[ T = h\nu - E_b \]  

(1.5)

The resulting vacancy left by photo-electron is filled by another electron from a less tightly bound shell. The potential difference between the donor and the recipient level is compensated by either emission of a fluorescence x-ray or release of Auger electrons. This process creates new vacancies at higher shells filled through a similar process leading to a cascade of events. There is a sudden increase in photoelectric cross section above \( K \) and \( L \) binding energies as \( K \) and \( L \)-shell electrons contribute significantly to the photoelectric effect. Filling of \( K \)- and \( L \)-shell vacancies may lead to an emission of fluorescence x-ray. Probability of x-ray emission from filling of an \( M \) (or higher) shell vacancy is negligibly small [36]. Auger effect is an alternative mechanism by which the atom can dispose of a potential energy difference. Fig. 1.7 displays the probability of a fluorescent event (i.e. fluorescence yield) when a \( K \)- and \( L \)-shell vacancy is filled \((Y_K, Y_L)\).
It is important to note that $Y_K$ and $Y_L$ become zero for low atomic number materials ($Z \leq 10$) such as water and tissue, meaning that fluorescent emission is negligible in water and tissue. We will use this property to assume propagation of monochromatic low energy photons remains monoenergetic throughout the tissue, since they are either completely absorbed by photoelectric effect or scattered at the same energy due to Thomson or Rayleigh scattering.

The photoelectric mass attenuation coefficient can be approximated by [36]:

\[ \frac{\tau}{\rho} \approx k \left( \frac{Z}{\hbar \nu} \right)^3 \]  \hspace{1cm} (1.6)
where $k$ is a constant and $Z$ is the atomic number of the attenuator.

### iii. Rayleigh (coherent) scattering

In Rayleigh scattering a photon is scattered off an atom without losing any energy. The event is essentially elastic which is why it is referred to as coherent scattering. The mass attenuation coefficient of Rayleigh scattering is given by:

$$\frac{\sigma_R}{\rho} = k' \frac{Z}{(\hbar \nu)^2} \quad (1.7)$$

The relative importance of Rayleigh scattering in comparison to other photon interactions has been illustrated in Fig. 1.8. For low energy sources ($\hbar \nu < 50$ keV), the Rayleigh scattering cross section becomes significant for low $Z$ materials and below $K$ and $L$ photoelectric absorption edges for high $Z$ materials.

![Figure 1.8 - Rayleigh scattering contribution in the total interaction cross section as a function of $Z$ and photon energy. Source: [43]](image-url)
1.2.2.2 Electron interactions

Electrons interact with medium in a distinctly different manner than photons. The mechanism of interaction is through Coulomb-force interactions with other electrons as well as the atomic nuclei. Coulomb interactions of an incident electron with orbital electrons in an absorber lead to ionization or excitation of an absorber atom. During each interaction the incident electron transfer parts of its kinetic energy to the absorber. Another mode of interaction involves Coulomb-force interactions with the nucleus and takes place when the incident electron passes close to the nucleus of an absorber atom. In 97-98% of such encounters the electron scatters elastically and does not lose any energy. In the other 2-3% of the cases, an inelastic radiative interaction occurs in which an x-ray photon is emitted [36]. This is referred to as bremsstrahlung (braking) radiation producing a continuous spectrum of photon energies. Bremsstrahlung interaction cross section is proportional to \( Z^2 \) and is insignificant in low-\( Z \) (tissue-like) materials for electrons below 10 MeV which includes LDR brachytherapy sources.

1.2.3 Absorbed dose and kerma

The absorbed dose is best described in terms of the energy absorbed (\( \epsilon \)) in volume \( V \) defined as below [36]:

\[
\epsilon = (R_{\text{in}}_u - (R_{\text{out}}_u) + (R_{\text{in}}_c - (R_{\text{out}}_c) + \sum Q \quad (1.8)
\]

where \( R_{\text{in}}, R_{\text{out}} \) represent radiant energy entering and leaving \( V \), subscripts \( u, c \) represent respective values for uncharged and charged radiation and \( \sum Q \) is the net energy derived from the rest mass in \( V \).
The absorbed dose in the medium at point P in space is defined as the ratio of energy departed in an infinitesimal volume $dv$ at P to the mass of $dv$ as below:

$$D = \frac{\text{de}}{\text{dm}} \quad (1.9)$$

The kerma ($K$) is another important quantity which is the amount of energy transferred from uncharged radiation to the charged particles per unit mass. The kerma for a monoenergetic photon beam is given by:

$$K = \frac{\mu_{tr}}{\rho} \Psi \quad (1.10)$$

where $\Psi$ is the energy fluence of photons and $\frac{\mu_{tr}}{\rho}$ is the mass energy-transfer coefficient of the medium. Not all of the energy transferred to charged particles is deposited in the medium as some charged particles radiate their energy away through bremsstrahlung. Therefore kerma is broken into two parts based on whether the transferred energy to charged particles creates excitation and ionization ($K_c$) or is carried away by photons ($K_r$):

$$K = K_c + K_r \quad (1.11)$$

where subscripts $c$, $r$ refer to collision and radiative interactions, respectively. The collision Kerma is given by [36]:

$$K_c = \frac{\mu_{ab}}{\rho} \Psi \quad (1.12)$$

where $\frac{\mu_{ab}}{\rho}$ is the mass energy-absorption of the medium. Collision kerma of a multi-energetic photon beam can be obtained by integrating Eq. (1.12) over the entire range of photon energies.

Under conditions of charged particle equilibrium, $(R_{in})_c = (R_{out})_c$ in Eq. (1.8) and the dose is equal to collision kerma:
\[ D = K_c = \frac{\mu_{ab} \psi}{\rho} \quad (1.13) \]

The collision kerma closely approximates dose due to the short range of the secondary electrons produced by low energy photons in LDR brachytherapy seeds.

1.2.4 Radiation Dosimetry

Radiation dosimetry deals with determining the amount of absorbed dose resulting from the interaction of ionizing radiation with matter. There are three methods to accomplish this, including direct measurements by dosimeters, Monte Carlo simulations and analytical methods or a combination of these methods.

1.2.4.1 TG-43 Protocol

The current standard for calculation of dose surrounding low-energy brachytherapy sources is based on American Association of Physicist in Medicine (AAPM) TG-43 protocol which calculates the dose in homogenous water medium [27]. TG-43 protocol combines an analytical method using pre-calculated tabulated data for each source model with measurements of air-kerma strength \( S_k \) of the source to calculate dose distributions around a brachytherapy seed. \( S_k \) is defined in terms of the air-kerma rate of the source in vacuum at distance of \( d (\sim 1m) \) on transverse plane of the source as below:

\[ S_k = \bar{K}_\delta(d)d^2 \quad (1.14) \]

where subscript \( \delta \) is an energy cutoff intended to exclude low energy contaminant photons. These contaminant photons (if not removed) increase the value of \( \bar{K}(d) \) but do not contribute to
dose in tissue. $S_k$ is measured in units of $\mu$Gy·m$^2$·h$^{-1}$ or equivalently cGy·cm$^2$·h$^{-1}$ [44] which is denoted by the symbol U, that is:

$$1 \text{ U} = 1 \mu\text{Gy} \cdot \text{m}^2 \cdot \text{h}^{-1} = 1 \text{ cGy} \cdot \text{cm}^2 \cdot \text{h}^{-1}$$ (1.15)

It is the responsibility of the user to verify the source strength provided by the vendor. The user typically uses a well-type ionization chamber with traceable calibration to the standardization laboratories. In-air calibration is only performed at standardization laboratories (National Institute of Standards and Technology, NIST, and accredited dosimetry calibration laboratories, ADCLs in the USA and the National Research Council of Canada).

Due to the symmetry of seeds along the longitudinal axis $z$, a cylindrical coordinate system is used to describe the geometry as shown in Fig. 1.9.
Based on TG-43 formalism, dose rate $\hat{D}(r, \theta)$ at point $P(r, \theta)$ in homogenous water medium (see Fig. 1.9) can be obtained as shown in Eq. (1.14) below:

$$\hat{D}(r, \theta) = S_K \cdot \Lambda \cdot \frac{g_L(r, \theta)}{g_L(r_0, \theta_0)} \cdot g_L(r) \cdot F(r, \theta) \quad (1.14)$$

Where:

- $S_K$ is the air-kerma strength of the seed;

- $g_L(r, \theta)$ is the geometry function and defined as:

$$g_L(r, \theta) = \left\{ \begin{array}{ll}
\frac{b}{L_r \sin \theta} & \text{if } \theta \neq 0 \\
\left(\frac{r^2 - L^2/4}{r^2 - L^2/4}\right)^{-1} & \text{if } \theta = 0
\end{array} \right. \quad (1.15)$$

where $b$ is the angle subtended by the active length of the source ($L$) at point $P$. This function accounts for dose drop off around the seed due to geometry of the seed (line source). In case of a point source ($L \rightarrow 0$ or $r \rightarrow \infty$) it is equivalent to $\frac{1}{r^2}$.

- $\Lambda$ is the dose rate constant which is a conversion factor between air-kerma strength ($S_K$) of the seed and dose rate at point $P(r_0, \theta_0)$;

- $g_L(r)$ is the radial dose function which reflects the dose fall-off as a function of radial distance due to photon absorption in the medium;

- $F(r, \theta)$ is the anisotropy function which accounts for dose anisotropy surrounding the seed caused by finite length of the seed and non-spherical distribution of radioactive sources.
The total dose rate due to several seeds at each point of space is then calculated through superposition by adding up contributions of all individual seeds. Since in PBSI seeds are permanently placed in the tissue, the total dose absorbed is obtained by integrating the dose rate over infinite time.

1.2.4.2 Model-based dose calculation algorithms

TG-43 protocol as described above generates the dose in homogeneous water medium and hence ignores the effects of tissue and applicator heterogeneities, interseed attenuation and finite patient dimensions. Model-based dose calculation algorithms (MBDCAs) offer the possibility to depart from simple water model by accounting for material composition of the surrounding medium. They are capable of generating more realistic dose distributions which are actually delivered to patient. MBDCAs have long been implemented in external beam therapy and are now considered standard of practice in many modalities such as IMRT and hypofractionated early stage lung cancer [49]. In contrast little use of MBDCAs have been made in brachytherapy in spite of higher sensitivity to material composition due to lower photon energy used in this modality [45]. It has been suggested that adopting MBDCAs would lead to at least 5% correction in accepted clinical dose parameters of brachytherapy [9].

Methods for heterogeneity correction in brachytherapy have been largely adopted from those of external beam and include semiempirical analytical approaches, Monte Carlo simulations and solving the Boltzmann radiation transport equation. Semiempirical analytical approaches have the advantage of being computationally efficient while methods based Monte Carlo simulations and solving the radiation transport equation are more accurate [45].
1.3 Thesis overview

The TG-43 formalism as described above suffers from two shortcomings. Firstly, it intrinsically generates the dose in the water medium, meaning that all heterogeneities in the surrounding medium are ignored. Secondly, the photon inter-seed attenuation (ISA) is not taken into account. In this work we propose a new methodology where effects of tissue heterogeneity can be accounted for in an actual clinical setting in accordance with the mandate of AAPM Radiation Therapy Committee Task Group 186 [45] to suggest dose calculation algorithms which can address TG43 shortcomings as explained.

1.3.1 Motivation

Breast is composed of glandular and adipose tissues and it is therefore highly heterogeneous [46]. Moreover the breast is surrounded by air, ribs and lung, with different physical properties than water. Previous research shows a significant difference in dosimetric parameters is produced when breast composition and ISA is taken into consideration [47]. The difference between TG43 formalism and the dose delivered increases proportionally to the relative amount of adipose tissue in breast. The dependence of some dosimetric parameters is shown in Fig. 1.10. Recent publications show that breast on average contains a higher percentage of adipose tissue than previously thought (80% vs. 50%) [48]. This adds to the necessity of having a tool to be able to account for tissue heterogeneity as fat content in particular plays an important role in dose delivered to breast.
Figure 1.10 - Deviation of dosimetry parameters from TG43 as a function of Glandular/Adipose proportion (Gx%/A100-x%) in (a) breast tissue (b) skin. Source: [47]

Although this issue is a priori less critical for external beam radiotherapy using megavoltage X-rays, methods accounting for tissue heterogeneity have been implemented in this modality for more than 15 years [49]. In brachytherapy, however, TG43 formalism based on dose calculation in homogenous water has been the main stay, even though the interaction physics of low energy photons is much more dependent on tissue composition compared to external beam radiation. This is largely due to the domination of photoelectric effect at low energy levels compared to Compton effect [50]. The photoelectric mass attenuation coefficient is related to atomic number (Z) and the photon energy (E) by a factor of $\frac{Z^{3-4}}{E^{3-4}}$ while for Compton interactions it's almost independent of Z [36]. Therefore, the dosimetric consequences of tissue heterogeneity is more pronounced at lower photon energy levels.

In the clinic we have noticed unexpected skin toxicities in 25% of PBSI patients presenting moist desquamation. The toxicity could not be explained by the current methodology of calculating dose to skin based on TG-43 formalism. Using this method the dose to skin calculated on post-implant CT images was much lower than threshold for 5% incidence rate of grade 2 toxicity [25,51]. Since actual values of skin dose could vary
significantly based on fat content of breast (see Fig. 1.10), dose outcome criteria established based on TG-43 protocol are not accurate and have to be revisited by introducing tissue heterogeneity corrections into calculations of dose. In this work, we propose a new heterogeneity correction methodology algorithm designed to facilitate integration into clinical use.

### 1.3.2 Hypothesis

The working hypothesis of this thesis is that heterogeneity corrected estimates of skin dose is a better predictor of skin toxicities in patients receiving permanent breast seed implant.

### 1.3.3 Objectives

In order to test the hypothesis as set forth above, several objectives were defined and completed as part of this thesis. These objectives included:

1) Development and validation of a novel dose calculation algorithm in heterogeneous media by applying an Inhomogeneity Correction Factor (ICF) at each point of space to TG-43 dose distributions.

2) Development and validation of a methodology to extract spatial values of ICF using dual-energy CT images.

3) Implementation of the ICF method into our treatment planning system.

4) Processing and extracting DVH parameters of skin for all PBSI patients using both TG-43 and ICF method.
5) Comparing TG-43 and the ICF method in terms of their capacity to predict skin toxicities.

Chapters 2, 3, and 4 describe the methodology, results, and discussions as relates to these objectives. Chapters 2 and 3 explore the second and third objectives and chapter 4 discusses the remaining objectives. Chapter 5 provides a summary and highlights the advantages of the ICF method over other methods.

As part of this work, we also designed, implemented and verified a dedicated treatment planning system for patients receiving permanent breast seed implant (PBSI) using TG-43 dose calculation formalism. The system has since received FDA and Health Canada approval (MIM Symphony™).
References


Chapter 2

A Simplified Analytical Dose Calculation Algorithm Accounting for Tissue Heterogeneity for Low Energy Brachytherapy Sources
This chapter represents a reprint of "Mashouf S, Lechtman E, Beaulieu L, Verhaegen F, Keller B M, Ravi A and Pignol J 2013 A simplified analytical dose calculation algorithm accounting for tissue heterogeneity for low-energy brachytherapy sources Phys. Med. Biol. 58 6299–315" Copyright 2013 IOP Publishing Ltd. Minor formatting modifications have been made to maintain consistency throughout this thesis. The published article can be found online at: http://iopscience.iop.org/0031-9155/58/18/6299.

2.1 Abstract

The AAPM TG-43 formalism is the standard for seeds brachytherapy dose calculation. But for breast seed implants, Monte Carlo simulations reveal large errors due to tissue heterogeneity. Since TG-43 includes several factors to account for source geometry, anisotropy and strength, we propose an additional correction factor, called Inhomogeneity Correction Factor (ICF), accounting for tissue heterogeneity for Pd-103 brachytherapy. This correction factor is calculated as a function of the media linear attenuation coefficient and mass energy absorption coefficient, and it is independent of the source internal structure. Ultimately the dose in heterogeneous media can be calculated as a product of dose in water as calculated by TG-43 protocol times the ICF. To validate the ICF methodology, dose absorbed in spherical phantoms with large tissue heterogeneities was compared using the TG-43 formalism corrected for heterogeneity versus Monte Carlo simulations. The agreement between Monte Carlo simulations and the ICF method remained within 5% in soft tissues up to several centimeters from a Pd-103 source.
Compared to Monte Carlo, the ICF methods can easily be integrated into a clinical treatment planning system and it does not require the detailed internal structure of the source or the photon phase-space.

2.2 Background

Brachytherapy using permanent seed implantation has been widely used for low risk prostate cancers with excellent results in terms of local control and treatment tolerance [1,3]. This method also has the advantage of being delivered as a single day outpatient procedure. In 2004, our group initiated a partial breast irradiation technique using permanent breast seed implant (PBSI) [4,5]. PBSI involves the implantation of stranded Pd-103 seeds around the seroma using ultra-sound guidance and a template to guide needles loaded with the stranded seeds similarly to permanent prostate seed implants. The whole procedure is performed under light sedation in about one hour such that the patient is discharged home the same day. The treatment is offered to early stage breast cancer patients after conventional CT simulation to ensure that the treatment volume is less than 120 cm³. In the planning process, CT images are re-sliced perpendicularly to the needle directions and the seed positions are optimized to deliver a minimal peripheral dose of 90 Gy [6].

For permanent seed implant procedures the currently used dose calculation algorithm is based on American Association of Physicists in Medicine Task Group No. 43 (AAPM TG-43) formalism [7]. The TG-43 formalism assumes two simplifications. First it intrinsically generates the dose in a homogenous water medium, which means that dose variations due to heterogeneities in the media are ignored. And second, the inter-seed attenuation is not taken into account in calculations of dose when multiple seeds are present [8,9]. There are many
publications reporting on these simplifications and higher dose variations due to tissue heterogeneity have been reported in breast LDR brachytherapy than in prostate [10-12]. PBSI uses Pd-103 low energy sources (mean photon energy of ~21 keV [7]) and at that energy level the absorbed dose is strongly affected by the atomic number of the medium. This is largely due to the dominance of photoelectric effect, which has an interaction cross section proportional to the atomic number to the power of 3 to 5.

Using Monte Carlo simulations, Afsharpour demonstrated that the absorbed dose varies depending on the fat content in breast [12]. Assuming an average weight ratio of 20/80 for glandular tissue to adipose in breast patients [13], errors up to 40% can be generated in skin dose. This is a clinically significant finding for breast brachytherapy as there has been a documented correlation between skin dose and toxicity [6]. Increased dose to the skin may lead to increased risk of moist desquamation, which could increase the risk of long-term cosmetic impacts such as telangiectasia. Since one of the main purposes of breast conserving therapy is to provide a better cosmetic outcome than mastectomy, it is essential to avoid those side effects and thus carefully evaluate the dose to skin during treatment planning and avoid hot spots at this level.

There have been several methods published to account for tissue heterogeneity, including analytical methods, Monte Carlo simulations, and solving the Boltzmann radiation transport equation [9]. Monte Carlo simulations and radiation transport equation require accurate knowledge of tissue atomic composition. The current methods to extract or assign atomic composition from a planning CT are generally based on automatic segmentation of the CT voxels followed by assigning population based approximations of the tissue composition, which could introduce uncertainties and decrease accuracy [14]. Finally, these dose calculation
algorithms are computationally intensive which could limit their applications to real-time intra-operative planning and/or inverse planning optimization [15]. Analytical models, on the other hand, have the advantage to be computationally efficient [16]. Those based on heterogeneity correction factors are specially of interest due to the availability of pre-calculated dose distributions in water in treatment planning systems. The concept of heterogeneity correction factor is not new and has been used previously in external beam [17] as well as brachytherapy dose calculations [16]. Williamson et al [18] defined a heterogeneity correction factor (HCF) as a ratio of dose in heterogeneous media to dose in water to quantify the effect of different thicknesses of high Z materials irradiated by I-125, Cs-137 and Ir-192. Research groups have taken different approaches to calculate the heterogeneity correction factors for brachytherapy sources [16,19]. Since the final goal is to improve the patient dose calculations in a clinical setting, we propose a new dose calculation algorithm for Pd-103 sources which uses the standard TG-43 parameters of the seed, accounts for tissue heterogeneity and source anisotropy.

2.3 Material and methods

2.3.1 Analytical solution

2.3.1.1 General formalism for a point source in heterogeneous media.

The total dose deposited at a given point in space away from a point source can be divided into the dose due to primary photons emitted by the source, and the dose due to scattered primary photons (secondary photons). Following Carlsson and Ahnesjo [20], the primary dose surrounding an isotropic point source emitting mono-energetic photons is given by:
\[ D_p(\vec{r}) = \frac{E}{4 \cdot \pi \cdot r^2} \frac{\mu_{ab}(\vec{r})}{\rho(\vec{r})} \exp\left(-\int_0^r \mu(l) dl\right) \] \tag{2.1}

where \( \vec{r} \) is the position vector with the origin being at the point source, \( r \) is the radial distance, \( E \) is the radiant energy in MeV, \( \mu \) is the linear attenuation coefficient and \( \frac{\mu_{ab}(\vec{r})}{\rho(\vec{r})} \) is the mass energy absorption coefficient of the medium at the point of interest. In Eq. (2.1) the integration is performed on the line connecting the source (origin) to the point of interest (\( \vec{r} \)) with \( l \) being the distance to source.

From Kornelsen and Young [21] the total dose in homogeneous water medium can be estimated by multiplying the primary dose by a build-up factor as below:

\[ D_{Total,w}(\vec{r}) = D_p(\vec{r}) \cdot B_w(\vec{r}) \] \tag{2.2}

with

\[ B_w(\vec{r}) = 1 + k_a (\mu_{w,r})^k_b \] \tag{2.3}

where \( \mu_w \) is the attenuation coefficient in water and \( k_a \) and \( k_b \) are constants.

Substituting Eq. (2.1) into Eq. (2.2), the total dose in homogenous water medium is:

\[ D_{Total,w}(r) = \frac{E}{4 \cdot \pi \cdot r^2} \left( \frac{\mu_{ab}}{\rho} \right)_w e^{-\mu_w r} \left[ 1 + k_a (\mu_{w,r})^k_b \right] \] \tag{2.4}

The coefficients \( k_a \) and \( k_b \) are determined by the best fit of Eq. (2.4) to the total dose in water.

Similar to Eq. (2.4), the dose in heterogeneous media can be expressed as:
\(D_{\text{Total, Het}}(\vec{r}) = D_p(\vec{r}) \cdot B_{\text{Het}}(\vec{r}) = \frac{E}{4 \cdot \pi \cdot r^2} \frac{\mu_{ab}(\vec{r})}{\rho(\vec{r})} \exp(-\int_0^r \mu(l) \cdot dl) \cdot B_{\text{Het}}(\vec{r}) \tag{2.5}\)

where \(B_{\text{Het}}(\vec{r})\) is the build-up factor in heterogeneous media and is defined as below:

\[B_{\text{Het}}(\vec{r}) = 1 + k_a(\vec{r})(\int_0^r \mu(l) dl)^{k_b} \tag{2.6}\]

In Eq. (2.6), \(k_a(\vec{r})\) is a function of position and \(k_b\) is the same constant as obtained in homogeneous water medium for the same source. Assuming a water-like medium in which volumetric average of linear attenuation coefficient is \(\mu_w\) and in which the scattered photon fluence is equal to that of homogeneous water along any given direction, \(k_a(\vec{r})\) can be approximated by \(k_a\) (see Appendix 2.A) and Eq. (2.5) is simplified as below:

\[D_{\text{Total, Het}}(\vec{r}) = \frac{E}{4 \cdot \pi \cdot r^2} \frac{\mu_{ab}(\vec{r})}{\rho(\vec{r})} \exp\left(-\int_0^r \mu(l) dl\right) \times \left[1 + k_a(\int_0^r \mu(l) dl)^{k_b}\right] \tag{2.7}\]

where \(k_a\) and \(k_b\) are the same parameters as obtained through Eq. (2.4) in a water medium.

### 2.3.1.2 Formalism for a line source in heterogeneous media.

The dose around an ideal line source can be obtained by dividing the source into infinitesimal point sources and integrating the contributions of each at a point of interest (see Appendix 2.B) which results in:

\[D_{\text{Line}}(\vec{r}) = \frac{E}{4 \cdot \pi} G(r, \theta) \frac{\mu_{ab}(\vec{r})}{\rho(\vec{r})} \exp\left(-\int_0^r \mu(l) dl\right) \times \left[1 + k_a(\int_0^r \mu(l) dl)^{k_b}\right] \tag{2.8}\]
where $\vec{r}$ is the position vector with origin being in the middle of the line source, $\theta$ is the angle between $\vec{r}$ and symmetry axis of the source, $G(r, \theta) = \frac{\beta}{L_r \sin \theta}$ is the geometry function of a line source as defined in TG-43, and $L$ is the source length.

For low energy sources ($< 50$ keV), the photons which interact with encapsulation are either completely absorbed or scattered at a relatively same energy due to Thomson/Rayleigh scattering. Therefore the net effect of encapsulation is to reduce the radiant energy $E$ in Eq. (2.8). The seed can then be modeled as an ideal line source encapsulated into a void cylinder. Eq. (2.8) becomes:

$$D(r) = \frac{E'}{4\pi} G(r, \theta) \frac{\mu_{ab}(\vec{r})}{\rho(\vec{r})} \exp \left( - \frac{r}{r_s} \int_{r_s}^{r} \mu(l)dl \right) \times \left[ 1 + k_a \left( \int_{r_s}^{r} \mu(l)dl \right)^{k_b} \right]$$

(2.9)

where $E'$ is the radiant energy escaping the seed into the medium and $r_s$ is the portion of the radial distance $r$ falling within the void cylinder. Eq. (2.9) can be used to calculate the dose in homogenous water medium, $D_{\omega}(\vec{r})$, as well as in a heterogeneous medium, $D_{\text{Het}}(\vec{r})$.

### 2.3.1.3 Inhomogeneity Correction Factor (ICF)

Since the seeds are a complex assembly of various materials, there are major limitations to the ideal line source model. For example, the radionuclide is generally adsorbed on the surface of low-Z carriers such that the spatial distribution of radioactivity within a brachytherapy seed is not continuous [22]. Also the presence of a high-Z radio opaque marker creates large variation in the fluence of photons around a brachytherapy source. Those variations are effectively incorporated in the TG-43 formalism [7]. Since TG-43 is calculated
in water, a simple strategy to calculate the dose in heterogeneous media is to multiply the TG-43 values with an Inhomogeneity Correction Factor (ICF) derived from Eq. (2.9) as below:

$$ICF(\vec{r}) = \frac{D_{Het}(\vec{r})}{D_w(\vec{r})} = \frac{\left(\frac{\mu_{ab}(\vec{r})}{\rho(\vec{r})}\right)_{Het}}{\left(\frac{\mu_{ab}(\vec{r})}{\rho(\vec{r})}\right)_w} \exp\left(-\int_{r_s}^{r} \left(\frac{\mu_{Het}(l) - \mu_{w}(l)}{\rho(l)}\right) dl\right) \times \left[1 + \frac{\int_{r_s}^{r} \mu_{Het}(l) dl}{k_b} \right]$$

Eq. (2.10) assumes that the radioisotope emits monochromatically and the photon energy spectrum remains unchanged through the seed encapsulation. This condition is met in Pd-103 sources as they emit almost monochromatically in 20-30 keV range and the contribution of higher energy photons ( > 30 keV) to dose remains insignificant up to 10 cm away from the source [23].

If we replace $D_w(\vec{r})$ in Eq. (2.10) with the values obtained through TG-43 protocol, the dose in heterogeneous media can be ultimately obtained as:

$$D_{Het}(\vec{r}) = D_{TG43}(\vec{r}) \times ICF(\vec{r})$$ (2.11)

where $ICF$ is defined by the right side of Eq. (2.10). In Eq. (2.11), source details such as strength and anisotropy are taken into account by the $D_{TG43}$ term and the medium properties are accounted for by the $ICF$. In this work the deposited dose is always reported as dose in medium as a preferred method to report dose according to TG-186 recommendations on model-based dose calculation algorithms [24].

To determine ICF for a Pd-103 source, values of mass attenuation coefficient ($\mu/\rho$) and mass energy absorption coefficient ($\mu_{ab}/\rho$) at 20.7keV (weighted mean photon energy of Pd-103 [7])
were obtained from National Institute of Standards and Technology online database [25] for each phantom material (see Sec. 2.3). The values of linear attenuation coefficients (\( \mu \)) were subsequently obtained by multiplying (\( \mu/\rho \)) to the corresponding density of each material as summarized in Table 2.1. In routine clinical practice, where the atomic composition and density of tissue structures are not known, the ICF parameters could be extracted using dual-energy CT images [26].

Matlab\textsuperscript{®} ver. 7.9.0 was used to calculate the ICF in spatial domain as well as processing data and generate all the figures.

Table 2.1. Values of attenuation (\( \mu \)) and mass energy absorption (\( \mu_{ab}/\rho \)) coefficients at mean photon energy of Pd-103.

<table>
<thead>
<tr>
<th>Material</th>
<th>Density [g/cm\textsuperscript{3}]</th>
<th>( \mu ) [cm\textsuperscript{-1}]</th>
<th>( \mu_{ab}/\rho ) [cm\textsuperscript{2}/g]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>1.00</td>
<td>7.56E-01</td>
<td>4.91E-01</td>
</tr>
<tr>
<td>Fat \textsuperscript{a}</td>
<td>0.95</td>
<td>5.10E-01</td>
<td>2.91E-01</td>
</tr>
<tr>
<td>Mammary Gland \textsuperscript{a}</td>
<td>1.02</td>
<td>6.60E-01</td>
<td>3.93E-01</td>
</tr>
<tr>
<td>Muscle \textsuperscript{a}</td>
<td>1.05</td>
<td>8.04E-01</td>
<td>5.04E-01</td>
</tr>
<tr>
<td>Lung \textsuperscript{a}</td>
<td>0.60</td>
<td>4.65E-01</td>
<td>5.13E-01</td>
</tr>
<tr>
<td>Air</td>
<td>1.20E-03</td>
<td>8.71E-04</td>
<td>4.83E-01</td>
</tr>
<tr>
<td>Skin \textsuperscript{a}</td>
<td>1.09</td>
<td>7.83E-01</td>
<td>4.60E-01</td>
</tr>
<tr>
<td>Bone \textsuperscript{a}</td>
<td>1.92</td>
<td>6.96E+00</td>
<td>3.23E+00</td>
</tr>
<tr>
<td>Lead</td>
<td>11.34</td>
<td>8.92E+02</td>
<td>6.31E+01</td>
</tr>
<tr>
<td>Palladium</td>
<td>12.02</td>
<td>2.18E+02</td>
<td>1.58E+01</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Elemental compositions are based on ICRU report No. 44 (ICRU 1989)
2.3.2 Monte Carlo simulations

2.3.2.1 Build-up factors in water

Monte Carlo simulations were performed using MCNP code version 5 in photon transport mode. The code makes use of ENDF/B-VI.8 photon cross section library with lower energy cut off threshold value of 1 keV. The radial dose was determined from 1-10 cm away from a Pd-103 point source in a 15cm spherical water phantom using the *f8 tally which scores deposited energy. A maximum uncertainty of 0.6% incurred in radial dose for a total of $10^8$ photons simulated (nps). Build-up factors $k_a$ and $k_b$ were then determined by obtaining the best fit of Eq. (2.4) to values of the radial dose in water. In Eq. (2.4) the values of $\mu_w$ and $(\frac{\mu_{ab}}{\rho})$ were evaluated at the weighted mean photon energy of Pd-103 (i.e. 20.7 keV). $k_a$ and $k_b$ were determined to be 0.4465 and 1.0734 respectively with a corresponding uncertainty of less than 0.8% in fitted data.

2.3.2.2 Radioactive seed design and evaluation

The Theragenics – Model 200 Pd-103 seed, which is used at our centre for PBSI procedure, was selected as the brachytherapy source for the simulations. The seed geometry and photon spectrum has been fully described by Monroe and Williamson in their MC simulation [27]. To validate our Monte Carlo simulations, basic TG-43 parameters including the radial dose and 2D anisotropy functions were simulated using MCNP5 *f8 tally. The seed was placed in the centre of a spherical water phantom of 15 cm radius and the dose was evaluated along the radial and longitudinal axes inside cones of $10^\circ$ open angle. The ratio of the dose at a given distance along the radial and longitudinal axis was calculated to derive the values of 2D anisotropy function along the seed longitudinal axis.
2.3.2.3  **Phantom designs**

Three different geometries were used to compare dose in heterogeneous media as obtained by Monte Carlo simulations and the dose calculated using the ICF methodology. In all phantoms the tissue atomic composition and densities are based on ICRU Report 44 [28] with the exception of lung tissue where the average density of 0.6 g/cm$^3$ was used as ICRU only provides the density of fully inflated and deflated lungs. The first phantom (Fig. 2.1(a)) presents a simple breast geometry, which is a 2 cm radius sphere of adipose tissue. This sphere is half immersed into a hemisphere of water ($\rho = 1$ g/cm$^3$ and containing 11.1% H and 88.9% O in elemental weights) and is covered by a 0.3 cm layer of skin and is surrounded by a 7.7 cm layer of air ($\rho = 1.2 \times 10^{-3}$ g/cm$^3$ and containing 23.2% O, 75.5% N and 1.3% Ar in elemental weights).

The second phantom was designed to test the robustness of the ICF algorithm in calculating the dose absorbed in concentric layers of highly variable tissue densities. It consisted of several spherical layers of common tissues introduced in a cone surrounded by a buffer of water as shown in Fig 2.1(b). The spherical layers surrounding the radioactive seed included 0.25 cm of water, 0.25 cm of fat, 0.5 cm of muscle, 0.2 cm of bone, 0.8 cm of air, another 0.5 cm of fat, 0.2 cm of bone, 1 cm of lung and 6.3 cm of water.

The third phantom mimics a clinically relevant geometry where three layers including three strands each containing three seeds (total of 27 seeds) have been implanted in a 2 x 2 x 2 cm$^3$ cubic structure. Seeds were spaced in a 1cm array format and placed in a 5 cm radius spherical cap representing a breast. The sphere was filled with fat and with an ellipsoid fibro-glandular heterogeneity as shown in Fig 2.1(c). In addition, the sphere outer layer includes a 0.2 cm layer composed of skin tissue and is surrounded by air. To evaluate the effect of interseed
attenuation in the worst case scenario, the dose distribution from only one source was simulated.

![Schematic representation of the phantoms used for the Monte Carlo simulations](image)

**Figure 2.1** - Schematic representation of the phantoms used for the Monte Carlo simulations: (a) the simple breast model (phantom 1), (b) the complex heterogeneous phantom (phantom 2) and (c) the 3D breast model with multiple seeds and fibro-glandular heterogeneity (phantom 3)

In all phantoms, the source was placed at the origin. The ICF factor was calculated at all dose scoring points using Eq. (2.10) and the values in Table 2.1. In phantoms 1 & 2, the dose was scored along the $y$ direction using MCNP5 *f8 tally in heterogeneous media as well as homogeneous water medium. *f8 tally calculates energy absorbed in each cell which needs to be divided by the mass of the corresponding cell to yield absorbed dose. To observe the effect
of anisotropy, the seed longitudinal axis was oriented along two different directions (x and y). In phantom 3, *fmesh4 tally multiplied by energy dependant dose functions was used to calculate dose across the x-y plane. *fmesh4 tally calculates energy fluence of photons at different energy bins which is then multiplied by corresponding mass energy absorption coefficient and summed to yield collision kerma.

2.4 Results

Fig. 2.2 compares the radial dose function and 2D anisotropy function at $\theta = 0^\circ$ values obtained through our MC simulations in a water phantom with published TG-43 parameters of the seed. Number of starting photons (nps) simulated were $10^8$ and $10^9$ for scoring dose along transversal and axial directions respectively which resulted in statistical uncertainty of 0.8% and 1.4% in dose at $r = 10$ cm. The values calculated compare well with those provided by TG-43 for the TheraSeed® [7] with mean relative errors of 3.5% and 2.7% respectively.

Fig. 2.3 compares the dose distribution as calculated by Monte Carlo simulations, in heterogeneous and homogeneous water medium, to the ones calculated using the ICF algorithm in phantom 1. In each case, $2 \times 10^9$ photons were simulated which lead to uncertainties less than 1% up to 10 cm away from the source. In the homogeneous water model the dose is overestimated in the fat portion of the phantom and largely underestimated in the layers of skin and air. Specifically in the skin layer the dose is between 39.8 to 48.8% higher than dose in water only (TG-43 like) model. Fig. 2.5(a) displays the relative errors in dose in homogeneous water vs. ICF model for the dose scoring points along the y-direction in phantom 1. On average the relative error in dose is reduced from 55.0% in homogeneous water model to 5.81% when ICF correction factor is applied in layers of fat, skin and air up to 10cm away from the source.
Fig. 2.4 evaluates the ICF model using a phantom with large variation of tissue composition and densities (phantom 2). Fig. 2.4(a) shows the dose calculated along the seed axial direction and Fig. 2.4(b) along the seed radial direction. In each case, $2 \times 10^9$ photons were simulated which led to statistical uncertainties less than 1% up to 10 cm away from the source. The degree of agreement between the ICF algorithm and Monte Carlo simulation is similar in both cases, suggesting that the ICF algorithm appropriately accounts for anisotropy. Fig. 2.5(b) displays the relative errors in dose in homogeneous water vs. ICF model for the dose scoring points along the $y$-direction in phantom 2. Over all, the mean relative error in dose is reduced from 81.6% using TG-43-like water model to 21.1% using ICF formulation for dose measurement points up to 10 cm away from the source.

Fig. 2.6 evaluates the ICF model in phantom 3 where multiple seeds and a fibroglandular nodule are present in breast. Fig. 2.6(a) displays relative isodose across $x$-$y$ plane as obtained using the ICF model and Fig. 2.6(b) using Monte Carlo simulations ($nps = 2 \times 10^9$). The agreement between the two graphs is striking except behind the seeds. Because of the imperfect account of photon scatter, the ICF formulation underestimates the dose in the shadow area of the seeds where the primary photons are attenuated by lead and palladium. Across the whole calculation domain on $x$-$y$ plane ($-5 \text{ cm} < x < 5 \text{ cm}, 0 < y < 3.5 \text{ cm}$), the voxel mean relative error is reduced from 40.83% to 12.66% when ICF correction factor is applied to the TG-43 protocol.
Figure 2.2 - Comparison between Monte Carlo simulations and (a) TG-43 radial dose function and (b) 2D anisotropy function at $\theta = 0^\circ$ for the TheraSeed® Pd-103 seed. The error bands represent the standard deviation in the tallied dose.
Figure 2.3 - Dose distributions in phantom 1 comparing Monte Carlo (MC) simulated doses in heterogeneous media (solid line) and homogenous water medium (dotted line) to the ICF algorithm (dashed line) along the seed (a) axial and (b) transversal directions. The error bands represent the statistical uncertainty in MC simulations.
Figure 2.4 - Dose distributions in phantom 2 using either Monte Carlo (MC) simulations in heterogeneous media (solid line), homogenous water medium (dotted line) or the ICF correction for water (dashed line) along (a) the axial and (b) transversal directions of the seeds.
Figure 2.5 - Relative error in dose for homogeneous water model vs. ICF model as a function of distance from the source in (a) phantom 1 and (b) phantom 2. Solid and dotted lines represent different orientation of the seed (axial and trasversal) with relation to y-axis respectfully.
Figure 2.6 - Normalized dose distributions in \(x-y\) plane of phantom 3 calculated by: (a) ICF formulation (b) Monte Carlo simulations in heterogeneous geometry. All results have been normalized to dose at point \((x = 0, y = 0.75\, \text{cm})\) and include maximum uncertainty of 1%. (c) Error incurred using the ICF formulation in comparison to Monte Carlo.
2.5 Discussion

The current standard for calculating the dose surrounding brachytherapy sources is based on AAPM TG-43 formalism, which generates the dose in homogenous water medium [7]. This method of calculation has been broadly adopted in most treatment planning systems. However, in the case of PBSI, since the breast is composed of glandular and adipose tissues, the photons interact with highly heterogeneous tissues in density and atomic composition. As the breast adipose content increases, it also becomes more ‘transparent’ to photons. Eventually the dose absorbed in the skin, could be up to 40% higher than what is calculated by TG-43 formalism for a patient having a mostly adipose breast and hence a tissue composition and density different than the average population [12]. Since the air interface tends to work in the opposite direction and decrease the skin dose due to lack of back scatter photons, this overall increase in skin dose underscores the fact that the effect of tissue heterogeneity on the final dose distribution is even more important.

Our team previously reported on the association between an excess of 90% of the prescribed dose to a significant portion of the skin and the occurrence of acute and delayed permanent skin toxicities like telangiectasia after PBSI [5]. Patients receiving more than 90% of the prescribed dose to the skin developed telangiectasia in 47% of the cases compared to 9% for skin dose below 90%. In the low skin dose group, telangiectasia toxicities were found in 4 patients with skin dose ranging from 57% to 82%. None of those patients had other factors that could explain this toxicity but all had very fatty breasts and, since the skin dose was calculated using TG-43, it is possible that it was largely underestimated. Implementing a dose calculation algorithm accounting for tissue heterogeneity during treatment planning may help prevent or at least better understand the correlation between dose and skin toxicities for PBSI. It is therefore
reasonable to use a treatment planning system with heterogeneity correction capability for PBSI patients. If such capability doesn't exist in the clinic, patients with fatty breast should be advised of a higher risk of permanent toxicities and may choose external beam radiation instead of seed implants.

In essence, the proposed analytical method uses a combination of the TG-43 formalism multiplied by an inhomogeneity correction factor or ICF to calculate the dose absorbed at each point. The ICF is a function of media properties and is independent of the seed internal structure such as the radioactivity distribution along the seed, the capsule thickness and the presence of a lead/silver rod that are accounted for by the TG-43 formalism. This means that the ICF formulation can be applied to any type of seed without a need to know its detailed internal structure as long as its TG-43 parameters are known. On the other hand, there are limitations inherent to semi-empirical or analytical methods that do not take into account accurately subtle physical events. For example the ICF algorithm assumes that photon spectrum hardening through the tissues heterogeneities or the spectral shift from scattered photons is minimal and this is obviously not true. However this approximation may be acceptable as long as the ICF correction is applied to low-energy sources (Pd-103, I-125, and Cs-131). Also, while the ICF reduces the dose distribution error accounting for tissue heterogeneity, it does not account perfectly well for the inter-seed attenuation shadowing effect. In the present work we calculated the inter-seed attenuation effect in the worst case scenario which corresponds to the dose distribution around a single radioactive source. When multiple sources are present, however, this effect is balanced by the cross coverage from other seeds and by the seed motion during patient’s normal daily activities. The overall effect of inter-seed attenuation is typically limited to 3-4% for patients receiving permanent seed
implants [8,12]. This is minimal compared to the effect of tissue heterogeneity which accounts for up to 30% variations in the same parameters of breast [12].

Calculating the ICF requires the estimation of attenuation coefficient and mass energy absorption attenuation coefficient for each dose calculation voxel. Using dual-energy CT imaging, these parameters can be extracted directly from CT images [26] rather than being derived from atomic compositions obtained through tissue segmentation, or through a correlation with the Hounsfield units from the CT simulation images [29] or a combination of both [30]. This step can be done in advance at the time of importing CT images, where the CT image is transformed into a matrix that contains the attenuation coefficient and mass energy absorption coefficient for each voxel, which ensures computation efficiency of the dose calculation [31]. As CT scanners with simultaneous dual-energy scanning capability become commercially available [32,33], the enhanced automation and faster planning afforded by this technology, would make it an attractive modality for heterogeneity corrections around low energy photon sources. It is, however, unclear at this point whether the whole sequence of extracting attenuation and mass energy absorption attenuation coefficients from a dual-energy CT images set followed by ICF correction would lead to accuracy significantly better than TG-43. Errors are introduced in estimating the values of attenuation and mass energy absorption attenuation coefficients due to noise, non uniformity and streaking artifacts present in commercial CT scanners. Future validation work includes comparisons of dose distributions obtained by MC, TG-43 and ICF algorithm into phantoms of known materials using dual-energy CT images.
2.6 Conclusions

A new analytical dose calculation method which enables patient-specific dose calculations in heterogeneous media around Pd-103 sources is presented. This methodology includes the use of standard TG-43 formalism and ICF parameters that could be extracted from dual energy CT images.

The technique was developed to facilitate implementation into a clinical setting by making use of pre-calculated TG-43 dose distributions to ensure efficiency. Using dual energy CT images, the ICF can be also calculated efficiently without the need for tissue segmentation.

Acknowledgements

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2.7 Appendix 2.A

Build-up factor in tissue for low energy photon sources

The dose around an isotropic point source emitting mono-energetic photons in heterogeneous media can be expressed as below:

\[
D_{\text{Het}}(\vec{r}) = D_p(\vec{r}) \times B_{\text{Het}}(\vec{r}) \quad (2.A.1)
\]

where \(D_p(\vec{r})\) is the primary dose as defined in Eq. (2.1) and \(B_{\text{Het}}(\vec{r})\) is the build-up factor in heterogeneous media and is defined as below (see Eq. 2.6):

\[
B_{\text{Het}}(\vec{r}) = 1 + k_a(\vec{r})(\int_0^r \mu(l) \, dl)^{k_b} \quad (2.A.2)
\]

The scattered dose in heterogeneous media can be obtained as the difference between total dose and the primary dose as below:

\[
D_{\text{Het,s}}(\vec{r}) = D_{\text{Het}}(\vec{r}) - D_p(\vec{r}) = D_p(\vec{r})k_a(\vec{r})(\int_0^r \mu(l) \, dl)^{k_b} \quad (2.A.3)
\]

Substituting \(D_p(\vec{r})\) from Eq. (2.1) in Eq. (2.A.3), yields:

\[
D_{\text{Het,s}}(\vec{r}) = \frac{E}{4\pi r^2} \frac{\mu_{ab}(\vec{r})}{\rho(\vec{r})} \exp\left(-\int_0^r \mu(l) \, dl\right)k_a(\vec{r})(\int_0^r \mu(l) \, dl)^{k_b} \quad (2.A.4)
\]

The scattered dose in homogeneous water medium can be similarly obtained using Eq. (2.4) as:

\[
D_{\text{w,s}}(\vec{r}) = \frac{E}{4\pi r^2} \frac{\mu_{ab}(\vec{r})}{\rho(\vec{r})} \exp(\mu_w r) \cdot k_a(\mu_w r)^{k_b} \quad (2.A.5)
\]

For low energy sources (\(hv < 50\) keV), the propagation remains almost monochromatic due to Thomson and Rayleigh scattering. Therefore the scattered dose can be expressed as the product
of energy fluence of scattered photons ($\psi_s$) and the mass energy absorption coefficient ($\mu_{ab}/\rho$) at the energy of source as below:

$$D_s(r) = \psi_s(r) \left( \frac{\mu_{ab}(r)}{\rho(r)} \right)$$

(2.A.6)

The scattered photon fluence in heterogeneous media ($\psi_{Het,s}$) as well as in homogenous water medium ($\psi_{w,s}$) can be obtained by substituting Eq. (2.A.6) in Eqs. (2.A.4) & (2.A.5) respectively:

$$\begin{align*}
\psi_{Het,s}(r) &= \frac{E}{4\pi r^2} \exp(-\int_0^r \mu(l).dl)k_a(r)(\int_0^r \mu(l).dl)^{k_b} \\
\psi_{w,s}(r) &= \frac{E}{4\pi r^2} \exp(-\mu_w r) \cdot k_a(\mu_w r)^{k_b}
\end{align*}$$

(2.A.7)

The scattered photon fluence is determined by the whole volume and since tissue contains high proportion of water, we make an assumption that $\psi_{Het,s}(r) = \psi_{w,s}(r)$ which leads to a solution for $k_a(r)$ as below:

$$k_a(r) = k_a \cdot \frac{\exp(-\mu_w r)(\mu_w r)^{k_b}}{\exp(-\int_0^r \mu(l).dl)(\int_0^r \mu(l).dl)^{k_b}}$$

(2.A.8)

$k_a(r)$ becomes equal to $k_a$ at each position where $\int_0^r \mu(l).dl = \mu_w \cdot r$. Therefore in a water-like medium where the volumetric average of linear attenuation coefficient is $\mu_w$, $k_a(r) \approx k_a$. 
2.8 Appendix 2.B

Calculating the dose around a line source in a heterogeneous medium

Dose surrounding a point source in a heterogeneous media can be expressed as (see Eq. (2.5)):

\[
D(\vec{r}) = \frac{E}{4\pi r^2} \frac{\mu_{ab}(\vec{r})}{\rho(\vec{r})} \exp\left(-\int_0^r \mu(l) dl\right) \times \left[1 + k_a \left(\int_0^r \mu(l) dl\right)^{k_b}\right] \quad (2.8.1)
\]

For simplification purposes we define:

\[
\begin{align*}
A(\vec{r}) &= \exp\left(-\int_0^r \mu(l) dl\right) \quad (2.8.2a) \\
B(\vec{r}) &= \left[1 + k_a \left(\int_0^r \mu(l) dl\right)^{k_b}\right] \quad (2.8.2b)
\end{align*}
\]

Thus:

\[
D(\vec{r}) = \frac{E}{4\pi r^2} \frac{\mu_{ab}(\vec{r})}{\rho(\vec{r})} A(\vec{r}) B(\vec{r}) \quad (2.8.3)
\]

A line source can be broken into series of smaller sources with length of \(\Delta l\) which can then be treated as point sources when \(\Delta l \to 0\). The total dose at each point of space can then be calculated by summing contributions of all point sources.

The dose at a field point \(P\) (see Fig. 2.8.1) due to a source with infinitesimal length of \(dl\) situated on a line source with length \(L\), can be expressed as:

\[
dD(\vec{r}) = \frac{E \times dl/L}{4\pi x^2} \times \frac{\mu_{ab}(\vec{x})}{\rho(\vec{x})} A(\vec{x}) B(\vec{x}) \quad (2.8.4)
\]

Where \(E\) is the total radiant energy and \(\vec{x}\) is the position vector of \(P\) with respect to the infinitesimal source. Since \(\frac{\mu_{ab}(\vec{x})}{\rho(\vec{x})}\) in Eq. (2.8.4) represents the value of mass energy absorption
coefficient at field point P, it can be replaced with \( \frac{\mu_{ab}(\vec{r})}{\rho(\vec{r})} \) where \( \vec{r} \) is the position vector connecting the middle of the line source to the field point P as below:

\[
dD(\vec{r}) = \frac{E \times dl/L}{4\pi x^2} \times \frac{\mu_{ab}(\vec{r})}{\rho(\vec{r})} A(\vec{x})B(\vec{x}) \quad (2.B.5)
\]

![Figure 2.B.1 - Calculation of dose surrounding a line source at a field point with radial distance \( r \) and polar angle \( \theta \). The line source is broken into infinite number of point sources and the accumulated dose is calculated by integration.](image)

If \( h \) is the height of the point P with respect to the line source and \( l \) is length between point H (projection of P) and the infinitesimal source and \( \beta \) is the angle subtended by the line \( l \) with respect to P (see Fig. 2.B.1), we can write:

\[
x = \frac{h}{\cos \beta} \quad (2.B.6)
\]
and

\[ l = h \tan \beta \]  
(2.B.7)

Differentiating Eq. (2.B.7) with respect to \( \beta \) yields:

\[ dl = h(1 + \tan^2 \beta) \, d\beta \]  
(2.B.8)

Substituting Eq. (2.B.6) and Eq. (2.B.8) into Eq. (2.B.5) yields:

\[ dD(\vec{r}) = \frac{E \times h (1 + \tan^2 \beta) \, d\beta / L}{4\pi \left( \frac{h}{\cos \beta} \right)^2} \times \frac{\mu_{ab}(\vec{r})}{\rho(\vec{r})} \, A(\vec{x})B(\vec{x}) \]  
(2.B.9)

This is simplified as:

\[ dD(\vec{r}) = \frac{E}{4\pi h L} \times \frac{\mu_{ab}(\vec{r})}{\rho(\vec{r})} \, A(\vec{x})B(\vec{x}) \, d\beta \]  
(2.B.10)

Integrating Eq. (2.B.10) over the entire length of the source results in:

\[ D(\vec{r}) = \int_{\beta_1}^{\beta_2} \frac{E}{4\pi h L} \times \frac{\mu_{ab}(\vec{r})}{\rho(\vec{r})} \, A(\vec{x})B(\vec{x}) \, d\beta \]  
(2.B.11)

Where \( \beta_1 \) and \( \beta_2 \) are the angles subtended by the start and end of the line source respectively.

Noting that \( E, h, L \) and \( \frac{\mu_{ab}(\vec{r})}{\rho(\vec{r})} \) do not vary with \( \beta \), Eq. (2.B.11) is simplified as:

\[ D(\vec{r}) = \frac{E}{4\pi h L} \times \frac{\mu_{ab}(\vec{r})}{\rho(\vec{r})} \int_{\beta_1}^{\beta_2} A(\vec{x})B(\vec{x}) \, d\beta \]  
(2.B.12)

Although Eq. (2.B.12) can be used directly to calculate the dose by integrating over \( \beta \), a more simplified format suffices in most practical applications. We can substitute:
\[
\int_{\beta_1}^{\beta_2} A(\vec{x}) B(\vec{x}) \, d\beta \equiv (\beta_2 - \beta_1) A(\vec{r}) B(\vec{r}) \tag{2.B.13}
\]

which is relatively accurate far from the source or on axial direction due to small variations in \(\beta\) and less accurate closer to the source and on transversal axis.

This yields

\[
D(\vec{r}) = \frac{E}{4\pi} \times \frac{\beta_2 - \beta_1}{hL} \times \frac{\mu_{ab}(\vec{r})}{\rho(\vec{r})} \times A(\vec{r}) B(\vec{r}) \tag{2.B.14}
\]

Substituting \(A(\vec{r})\) from Eq. (2.B.2a) and \(B(\vec{r})\) from Eq. (2.B.2b) and noting \(h = r \sin \theta\), Eq. (2.B.14) can be rewritten as:

\[
D(\vec{r}) = \frac{E}{4\pi} G_L(r, \theta) \frac{\mu_{ab}(r)}{\rho(r)} \exp \left( - \int_0^r \mu(l) \, dl \right) \times \left[ 1 + k_a \left( \int_0^r \mu(l) \, dl \right)^k h_b \right] \tag{2.B.15}
\]

Where \(G_L(r, \theta) = \frac{\beta_2 - \beta_1}{l r \sin \theta}\) is the geometry function of a line source as defined in TG-43 protocol.
References


Chapter 3

Dose Heterogeneity Correction for Low-Energy Brachytherapy Sources using Dual-energy CT Images
This chapter represents a reprint of "Mashouf S, Lechtman E, Lai P, Keller B, Karotki A, Beachey D and Pignol J 2014 Dose heterogeneity correction for low-energy brachytherapy sources using dual-energy CT images *Phys. Med. Biol.* 59 5305–5316" Copyright 2014 IOP Publishing Ltd. Minor formatting modifications have been made to maintain consistency throughout this thesis. The published article can be found online at:


3.1 Abstract

Permanent seed implant brachytherapy is currently used for adjuvant radiotherapy of early stage prostate and breast cancer patients. The current standard for calculation of dose around brachytherapy sources is based on the AAPM TG-43 formalism, which generates the dose in a homogeneous water medium. Recently, AAPM TG-186 emphasized the importance of accounting for tissue heterogeneities. We have previously reported on a methodology where the absorbed dose in tissue can be obtained by multiplying the dose, calculated by the TG-43 formalism, by an inhomogeneity correction factor (ICF). In this work we make use of dual energy CT (DECT) images to extract ICF parameters. The advantage of DECT over conventional CT is that it eliminates the need for tissue segmentation as well as assignment of population based atomic compositions. DECT images of a heterogeneous phantom were acquired and the dose was calculated using both TG-43 and TG-43×ICF formalisms. The results were compared to experimental measurements using Gafchromic films in the mid-plane of the phantom. For a seed implant configuration of 8 seeds spaced 1.5 cm apart in a cubic structure, the gamma passing score for 2% / 2 mm criteria improved from 40.8% to 90.5% when ICF was applied to TG-43 dose distributions.
3.2 Background

Seed brachytherapy is a standard treatment for patients with low risk prostate cancer [1-3]. It involves the permanent placement of radioactive seeds in the prostate under ultrasound guidance. Those seeds release low energy photons mostly from $^{125}$I as the source, and less frequently using $^{103}$Pd or $^{131}$Cs radioisotopes. In 2004 our group developed a permanent breast seed implant (PBSI) technique for early-stage cancer patients [4], selecting $^{103}$Pd as the isotope of choice for optimal radioprotection [5]. The advantage of seed brachytherapy over whole breast external radiation includes the enhanced dose distribution conformality as well as the convenience of a single treatment procedure.

Using a low energy photon source creates significant challenges in regards to treatment planning, since the photo-electric effect, which is a dominant interaction mechanism in this energy range is sensitive to the tissue atomic composition. Standard dose calculation algorithms are based on the American Association of Physicists in Medicine Task Group No. 43 report (AAPM TG-43 protocol) where the dose is generated in a homogenous water medium [6], ignoring the effect of heterogeneities present in the medium. Several recent studies have shown that using TG-43 results in significant errors in dose distributions for breast implants [7,8], due to the high fat content of breast. Errors in dose calculation as high as 40% have been reported at the skin which is a critical structure for PBSI.

We have previously proposed a heterogeneity correction methodology applying an Inhomogeneity Correction Factor (ICF) to the TG-43 formalism at each spatial voxel [9]. Unlike methods based on Monte Carlo or the radiation transport equation, this method does not require knowing the detailed internal structure of the source or the photon source phase-space,
and offers a fast calculation time. However the ICF method requires knowledge of bulk tissue properties such as attenuation coefficient ($\mu$) and mass energy absorption coefficient ($\mu_{ab}/\rho$).

In this paper we explored a methodology to extract the values of $\mu$ and $\mu_{ab}/\rho$ at the weighted mean photon energy of the radioisotope using dual energy CT imaging and compared dose distribution in a heterogeneous phantom using TG-43, the ICF method and experimental measurement using gafchromic films.

### 3.3 Material and methods

#### 3.3.1 ICF parameters extraction from dual energy CT

##### 3.3.1.1 ICF formulation

From Mashouf et al. [9], the dose absorbed in heterogeneous media surrounding a low energy brachytherapy seed can be calculated in each point of space as:

$$D_{\text{Het}}(\mathbf{r}) = D_{\text{TG-43}}(\mathbf{r}) \times \text{ICF}(\mathbf{r})$$  \hspace{1cm} (3.1)

Where $\mathbf{r}$ is the position vector with respect to the center of the seed, $D_{\text{TG-43}}(\mathbf{r})$ is the dose as calculated by TG-43 protocol and ICF($\mathbf{r}$) is the Inhomogeneity Correction Factor which is defined in terms of values of attenuation coefficient ($\mu$) and mass energy absorption coefficient ($\mu_{ab}/\rho$) of tissue and water at the weighted mean photon energy of the radioisotope.

##### 3.3.1.2 Extracting tissue parameters using dual energy CT

A CT scanner generates a map of linear attenuation coefficients ($\mu$) which are converted to Hounsfield Units ($HU$) by the following relation:

$$HU = 1000 \left( \frac{\mu}{\mu_w} - 1 \right) \hspace{1cm} (3.2)$$
where $\mu_w$ is the attenuation coefficient of water.

However, the linear attenuation coefficient ($\mu$) values are generated at an effective energy level that is generally different than the weighted mean photon energy of the radioisotope. Therefore the CT values need to be converted to the brachytherapy seed energy level. To resolve this we made use of a method previously described by Devic et al. using dual energy CT images [10].

The mass attenuation coefficient ($\frac{\mu}{\rho}$) and mass energy absorption coefficient ($\frac{\mu_{ab}}{\rho}$) of a study material $t$ can be expressed as a linear combination of two known basis materials, named here $m1$ and $m2$ as follow:

$$
\begin{align*}
\left( \frac{\mu}{\rho} \right)_t &= a \cdot \left( \frac{\mu}{\rho} \right)_{m1} + b \cdot \left( \frac{\mu}{\rho} \right)_{m2} \quad (3.3a) \\
\left( \frac{\mu_{ab}}{\rho} \right)_t &= a \cdot \left( \frac{\mu_{ab}}{\rho} \right)_{m1} + b \cdot \left( \frac{\mu_{ab}}{\rho} \right)_{m2} \quad (3.3b)
\end{align*}
$$

where $a$ and $b$ are energy independent coefficients specific for material $t$ (see Appendix A).

Multiplying by the density, Eq. (3.3a) becomes:

$$
\mu_t = A \cdot \mu_{m1} + B \cdot \mu_{m2} \quad (3.4)
$$

where $A = a \times \frac{\rho_t}{\rho_{m1}}$ and $B = b \times \frac{\rho_t}{\rho_{m2}}$ are constants.

Dividing by $\mu_w$ and replacing each ratio by $HU \times 10^{-3} + 1$, the following equation is obtained:

$$
HU_t \times 10^{-3} + 1 = A \cdot (HU_{m1} \times 10^{-3} + 1) + B \cdot (HU_{m2} \times 10^{-3} + 1) \quad (3.5)
$$

If a CT scan is performed at two different kVp (X-ray tube potentials) settings (Dual Energy CT or DECT), a system of equations are obtained as below:
\begin{align}
\begin{cases}
H_{U_{t,kVp1}} \times 10^{-3} + 1 &= A \cdot (H_{U_{m1,kVp1}} \times 10^{-3} + 1) + B \cdot (H_{U_{m2,kVp1}} \times 10^{-3} + 1) \\
H_{U_{t,kVp2}} \times 10^{-3} + 1 &= A \cdot (H_{U_{m1,kVp2}} \times 10^{-3} + 1) + B \cdot (H_{U_{m2,kVp2}} \times 10^{-3} + 1)
\end{cases}
\end{align}

(3.6a) \quad (3.6b)

Resolving this system allows calculation of the constants $A$ and $B$. Finally the values of $\mu_t$ and $\left( \frac{\mu_{en}}{\rho} \right)_t$ can be calculated using Eq. (3.4) and Eq. (3.3b) at the weighted mean energy of a brachytherapy seed to calculate the ICF.

3.3.1.3 Basis materials

Basis materials were selected to ensure that the materials had appreciable differences in the effective atomic numbers (see Appendix 3.A). This was to enable differentiation of coefficients $A$ and $B$ in (3.6a) and (3.6b) system of equations. For this work, water from a Super-Q® Plus water purification system (EMD Millipore, Billerica, MA) and a polyethylene rod from an RMI 465 electron density phantom (Gammax Inc., Middleton, WI) were chosen as basis materials. This is because polyethylene had the largest difference in effective $Z$ compared to water while their electron mass densities were relatively similar (see Table 3.1). The linear attenuation coefficients of the water and the polyethylene rod at 20.7 keV were calculated to be 0.76 cm$^{-1}$ and 0.38 cm$^{-1}$ respectively.

3.3.2 Phantom study

3.3.2.1 Heterogeneous phantom

Fig. 3.1 represents the 3D heterogeneous phantom used to perform the comparison between experimental and theoretical calculations of dose distribution. It was made of two acrylic cylinders (5 cm height, 5 cm radius) enabling the placement of a radiochromic film in between (Fig. 3.1(a)). Heterogeneities consisted of four 1.3 cm diameter cylindrical inserts made of polypropylene, Teflon, Virtual Water™ and acrylic (Fig. 3.1(b)). The center-to-center
Table 3.1 - Atomic composition, effective atomic number \((Z_{\text{eff}})\) and mass electron density \((N_g)\) of several materials. With water as a basis material, polyethylene scores the largest difference in effective atomic number with water.

<table>
<thead>
<tr>
<th>Materials</th>
<th>Atomic composition (% of mass)</th>
<th>(Z_{\text{eff}})</th>
<th>(N_g \times N_A)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H</td>
<td>C</td>
<td>O</td>
</tr>
<tr>
<td>Water</td>
<td>11.11</td>
<td>0.00</td>
<td>88.89</td>
</tr>
<tr>
<td>Polyethylene</td>
<td>14.37</td>
<td>85.63</td>
<td>0.00</td>
</tr>
<tr>
<td>Acrylic</td>
<td>8.05</td>
<td>59.99</td>
<td>31.96</td>
</tr>
<tr>
<td>Teflon</td>
<td>0.00</td>
<td>24.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Isopropyl alcohol</td>
<td>13.42</td>
<td>59.96</td>
<td>26.62</td>
</tr>
<tr>
<td>Ethanol</td>
<td>13.13</td>
<td>52.14</td>
<td>34.73</td>
</tr>
</tbody>
</table>

Distance of each insert was 1.5 cm (Fig. 3.1(c)). Each insert was drilled with a seed-loading compartment holding the seed 0.75 cm away from the film surface (Figs. 1(d), (e) & (f)).

Dose distributions were calculated and measured after loading alternatively each heterogeneity insert with two seeds (one in each top and bottom inserts). The dose was also calculated with seeds in all the inserts.

3.3.2.2 Dual energy CT of the heterogeneous phantom and basis material

Dual energy CT scans (Philips Brilliance CT scanner) of the phantom were obtained at 140 kVp and 90 kVp tube voltage settings. Two cylinders containing water and polyethylene basis materials were placed along the phantom and scanned concurrently. The CT images were imported and co-registered into MIM multimodality imaging platform (MIM Software Inc., Cleveland, OH). The average Hounsfield Unit (HU) was recorded in the middle of each basis material. For water the HU values were 2.7 and 14.1 for the 140 kVp and 90 kVp series respectively, and -86.1 and -105.2 in polyethylene respectively.
Figure 3.1 - (a) Heterogeneous phantom used in the experiments, (b) heterogeneity inserts, (c) position of inserts in the phantom, (d) seed loading assembly: 1. seed location, 2. heterogeneity, 3. filler piece. (e) seed compartment close-up, (f) position of Pd-103 seeds with respect to the Gafchromic film
3.3.3 Dose distributions

The relative dose distributions were determined on the mid-plane of phantom using (i) dosimetry by radiochromic films, (ii) TG-43 formalism [6], and (iii) TG-43 corrected by the ICF factor [9].

3.3.3.1 Film dosimetry

Measurements were performed using EBT2 Gafchromic™ film (Ashland Inc., Wayne, NJ). Two IsoAid Advantage™ Pd-103 seeds with air kerma strengths of 4.12±0.02 U and 4.09±0.02 U respectively (Capintec Inc. CRC-12 well chamber, Ramsey, NJ) were used to conduct all experiments. The seeds were loaded sequentially in acrylic inserts first, virtual water second, Teflon third, and polypropylene last for exposure times listed in Table 3.2. The red channel responses of the exposed films were used to calculate net optical density. The relative dose distributions were subsequently obtained by linearizing dose response of the film following Devic et al methodology [11].

<table>
<thead>
<tr>
<th>Film #</th>
<th>Active insert</th>
<th>Start time ($t_1$)</th>
<th>End time ($t_2$)</th>
<th>Exposure time ($t_2 - t_1$)</th>
<th>Full decay factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acrylic</td>
<td>0</td>
<td>4d</td>
<td>4d</td>
<td>6.6450</td>
</tr>
<tr>
<td>2</td>
<td>Virtual Water™</td>
<td>4d,20min</td>
<td>8d,20min</td>
<td>4d</td>
<td>7.8266</td>
</tr>
<tr>
<td>3</td>
<td>Teflon</td>
<td>8d,1hr</td>
<td>14d,45min</td>
<td>5d, 23hrs,45min</td>
<td>6.4059</td>
</tr>
<tr>
<td>4</td>
<td>Polypropylene</td>
<td>15d,2hr</td>
<td>21d,1hr,30min</td>
<td>5d,23hrs,30min</td>
<td>8.5494</td>
</tr>
</tbody>
</table>
3.3.3.2  **Dose calculation**

The TG-43 dose distributions were calculated assuming full decay on the mid-plane of the phantom where the films were placed, at pixel resolution of 0.5mm × 0.5mm. Eventually an ICF correction was applied to account for heterogeneity using Eq. (3.1). This was achieved by obtaining a 3D matrix of linear attenuation coefficient ($\mu_t$), and eventually calculating the ICF values for each pixel in the calculation domain. TG-43 dose value at each voxel was multiplied by the corresponding ICF value and the total dose was obtained by adding contributions of each seeds at each point.

3.3.3.3  **Dose distribution comparison**

To ensure accurate co-registration of experimental and theoretical dose distributions, the center of the film was identified in the scanned image as well as the point of highest dose, which corresponded to the center of an active insert. The film image was rotated around its centre to align the angular location of the rods on the film dose distributions with those on the CT image coordinate system in Fig. 3.2.

Dose distributions were compared calculating the Gamma Index (GI) at each pixel using equation below [12]:

$$GI = \min \left\{ \frac{(D_c(r) - D_M)^2}{(D_M \times \text{PDD})^2} + \frac{r^2}{(\text{DTA})^2} \right\} \forall \{r\}$$  \hspace{1cm} (3.7)

where $r$ is the position vector with respect to the middle of the pixel and $r$ is its magnitude, $D_M$ is the measured pixel dose, $D_c(r)$ is the calculated dose at point $r$ and PDD, and DTA defines a combined criteria for percentage dose difference and distance to agreement. In this study we report gamma passing rates for 2% (PDD) and 2mm (DTA) criteria following
recommendations of AAPM TG-186 report [13]. The relative dose distributions were used to calculate $G_I$ as the absolute dose at a normalization point is cancelled out in Eq. (3.7).

![Diagram](image.png)

Figure 3.2 - Position of heterogeneity rods in the CT image at the mid-plane. The centres of rods are located at 45, -45, 135 and -135 degrees in a polar coordinate system with the center of the phantom as origin with respect to $x$-axis. TF, PP, SW, AC represent Teflon, polypropylene, Virtual Water and acrylic rods respectively. The seed orientations have been identified with dotted rectangles as they are located out of plane.

### 3.4 Results

Fig. 3.3 displays relative dose distributions for the various seed inserts. In the case of seeds inserted in acrylic (Fig. 3.3(a)), the isodose lines for film measurements and ICF calculations are bent inward around the Teflon rod due to higher attenuation of Teflon compared to water. Conversely they bulge out around the polypropylene rod, which attenuates
less than water. The TG-43 dose distribution remains unaffected by the heterogeneities while the ICF isodose lines match well with the film measurements. The gamma index (GI) passing rate for 2% / 2 mm criteria is 22.0% for TG-43 and improves to 75.8% for the ICF dose distributions. In the case of seeds inserted in the Teflon rods (Fig. 3.3(b)), the GI passing rate for 2% / 2 mm criteria is 15.2% for TG-43 and increases to 69.2% for the ICF dose distribution. When seeds are inserted in polypropylene inserts (Fig. 3.3(c)), the TG-43 formalism underestimates the dose everywhere but in Teflon due to lower attenuation of polypropylene compared to water. The GI passing rate is improved from 28.6% in the case of TG-43 to 77.2% for the ICF formalism. In case of seeds loaded in Virtual Water (Fig. 3.3(d)) the GI passing rate improves from 21.2% for TG-43 to 71.9% for the ICF formalism.

Finally Fig. 3.3(e) displays the isodose lines when seeds are placed in all inserts. TG-43 calculations suggest that the area underneath the Teflon rod receives the same dose compared to other rods, while on the film dose distribution the isodose lines bulge in around the Teflon rod indicating a cold spot. The GI passing rate increased from 40.8% for TG-43 to 90.5% for the ICF formalism, suggesting very good agreement with film measurements.
(a)

(b)
Figure 3.3 - Iso-dose lines for the case of seeds loaded in the pair of (a) acrylic, (b) Teflon, (c) polypropylene and (d) Virtual Water inserts. (e) Total dose when all inserts are loaded with seeds. Blue, green and red contours represent film dosimetry measurements, TG-43 and TG-43×ICF dose distributions respectively. All doses have been normalized to the corresponding value at the centre of each insert with exception of (e) which has been normalized to the center of phantom. All values are in percentage.
3.5 Discussion

In this study we demonstrated that ICF parameters can efficiently and accurately be determined at each voxel using dual energy CT (DECT) images. To evaluate the methodology, we used a tissue equivalent phantom with materials mimicking muscle (acrylic), fat (polypropylene), water (Virtual Water™) and bone (Teflon) [14] for dose calculations as well as measurements. The ICF formalism generated better agreement with measurements when compared to TG-43. The agreement improved further when multiple seeds were inserted due to smoothing effects and cross coverage of other seeds. This is of practical importance as clinical implants involve multiple seeds to deliver dose.

When seeds were loaded in the phantom, slight deviations in seed orientation occurred due to misalignment of the seed compartment. In each case, the seed orientation was checked and appropriate correction was made to TG-43 dose distributions. We chose to validate DECT results with experiments rather than Monte Carlo methods in order to avoid errors associated with assigning atomic compositions. Many plastics contain trace elements including high atomic number impurities that are introduced during various manufacturing processes [15,16]. The presence or lack of these trace elements could lead to significant dosimetry variations for low energy sources using Monte Carlo simulations [17]. Similarly in Gafchromic films, the active layer atomic composition could vary from lot to lot [18] which renders Monte Carlo simulations less accurate for such low energies if the composition is not exactly known. On the other hand, in our study the basis materials were selected so that the atomic compositions and densities are accurately known. Water is always preferred as a basis material as it has known physical properties and is available in a highly pure form. Moreover it results in convergence
of TG-43×ICF dose distributions into TG-43 dose distributions in a homogenous water phantom using DECT.

In theory, ICF parameters can be obtained in any material using DECT without any limitations. In practice, however, resolving low-density materials could result in large errors due to smaller difference between HU numbers at two different energies. This is because the influence of CT noise and other artifacts could result in comparable variations in HU numbers when the density is too low. In human body, air and lung comprise materials with lower densities. In this case the tissue parameters required to calculate ICF (i.e. $\mu_t$, $(\frac{\mu_{ph}}{\rho})_t$) can be assigned manually to equal to air or lung depending on the density.

Another potential issue relates to the need for image co-registration between DECT images captured at different energies for analysis. While in solid phantoms rigid registration yields accurate overlapping volumes, this is harder to achieve in soft tissues (such as breast) due to patient movement between scans. However, the recent emergence of multi-detector and rapid kVp-switching dual energy CT scanners enable simultaneous capturing of CT images, which are already co-registered and therefore do not suffer from this shortcoming [19,20].

Effects of tissue heterogeneity become more important for low energy x-ray sources due to dominance of the photoelectric effect [21] which has an interaction cross section proportional to $\frac{Z^4}{\varepsilon^2}$. Tissue heterogeneity correction algorithms in scholarly articles include analytical models with primary/scatter separation, Monte Carlo simulations, and methods based on solving the radiation transport equation [22]. The proposed analytical method offers a computationally efficient alternative as it involves a combination of TG-43 dose calculations and a closed form formula to calculate the ICF, which can be accelerated further by parallel processing. In
addition, the use of TG-43 protocol streamlines integration into a clinical setting as standard TG-43 seed parameters are already published and well defined. Using the ICF methodology, the source is described by its TG-43 parameters and there is no need for detailed internal source structure or the photon phase space of the source [9]. Furthermore using dual energy CT images (DECT), tissue parameters in ICF formulation \( (\mu_t, \left(\frac{\nu_{ab}}{\rho}\right)_t) \) can be extracted directly from CT images without the need to segment and assign population based atomic compositions. In addition to a high degree of automation afforded by DECT, it would also help to eliminate inherent errors associated with assigning average composition of body tissues [21,23].

### 3.6 Conclusion

We used dual energy CT images captured using a commercial CT scanner to calculate the dose in a tissue equivalent phantom. Our results indicate TG-43× ICF in combination with DECT using a commercial CT scanner is a viable option for dosimetry in heterogeneous media. The possible path of integration of DECT into a clinical workflow for dosimetry purposes entail scanning a calibration phantom made of solid water with several inserts (including pair of base materials) at two different kVp settings and entering the values. The recorded data for each CT scanner in clinical use will be subsequently entered into the treatment planning system along with CT number to density conversion charts.

The advantage of DECT over conventional CT is that it eliminates the need for tissue segmentation, which streamlines the planning process. It also does not suffer from errors associated with assigning population based atomic compositions.
3.7 Appendix 3.A

Basis materials for tissue characterization

In this appendix, we demonstrate the mass attenuation coefficient as well as mass energy absorption coefficients of a material can be expressed as a linear combination of two base materials providing base materials meet a certain condition.

Using the compound law, the mass attenuation coefficient of any material can be expressed as a linear combination of mass attenuation coefficient of its elemental constituents as below:

\[
\frac{\mu}{\rho} = \sum_i \left( \frac{\mu}{\rho} \right)_{E_i} w_i \quad (3.A.1)
\]

where \( w_i \) is the mass fraction of the element \( E_i \).

Assuming Compton and photoelectric effects are the dominant mechanisms of photon interactions, the mass attenuation coefficient of an element can be broken into two components as below [24]:

\[
\left( \frac{\mu}{\rho} \right)_{E_i} = \left( \frac{\sigma}{\rho} \right)_{E_i} + \left( \frac{\tau}{\rho} \right)_{E_i} = \sigma_e N_A \frac{Z_i}{A_i} + C \frac{Z_i^{3.5}}{(\hbar \nu)^3} \quad (3.A.2)
\]

where \( N_A \) is the Avogadro's number, \( Z_i \) is the element's atomic number, \( A_i \) is the atomic weight, \( \sigma_e \) is the electron cross section, \( C \) is a constant and \( \hbar \nu \) is the photon energy.

Substituting Eq. (3.A.2) into Eq. (3.A.1), the mass attenuation coefficient can be expressed as:

\[
\frac{\mu}{\rho} = \sigma_e N_A \sum_i \frac{Z_i}{A_i} w_i + \frac{C}{(\hbar \nu)^3} \sum_i Z_i^{3.5} w_i \quad (3.A.3)
\]
Noting that \( N_A \sum_i \frac{Z_i}{A_i} w_i \) is the mass electron density \( (N_g) \) and \( \left( \sum_i Z_i^{3.5} w_i \right)^{1/3.5} \) is the effective atomic number \( (Z_{\text{eff}}) \), Eq. (3.A.3) is simplified as below:

\[
\frac{\mu}{\rho} = \sigma_e N_g + \frac{c}{(h\nu)^3} Z_{\text{eff}}^{3.5}
\]  

(3.A.4)

We want to explore the possibility of expressing the tissue mass attenuation coefficient as a linear combination of two base materials as below:

\[
\left( \frac{\mu}{\rho} \right)_t = a \cdot \left( \frac{\mu}{\rho} \right)_a + b \cdot \left( \frac{\mu}{\rho} \right)_b
\]  

(3.A.5)

where subscripts \( t, a \) and \( b \) indicate the corresponding values for tissue, base material 'a' and base material 'b' respectively.

Expanding Eq. (3.A.5) by substituting Eq. (3.A.4) for each term, yields:

\[
\sigma_e N_g + \frac{c}{(h\nu)^3} (Z_{\text{eff}})_t^{3.5} = \sigma_e \left[ a N_{ga} + b N_{gb} \right] + \frac{c}{(h\nu)^3} \left[ a (Z_{\text{eff}})_a^{3.5} + b (Z_{\text{eff}})_b^{3.5} \right]
\]  

(3.A.6)

For Eq. (3.A.6) to hold true at all energies it is sufficient that the coefficients of the energy dependant terms (\( \sigma_e \) as well as \( \frac{c}{(h\nu)^3} \)) be equal on both sides which results in a system of equations as below:

\[
\begin{aligned}
&\begin{cases} 
  a N_{ga} + b N_{gb} = N_{gt} \\
  a (Z_{\text{eff}})_a^{3.5} + b (Z_{\text{eff}})_b^{3.5} = (Z_{\text{eff}})_t^{3.5}
\end{cases}
\end{aligned}
\]  

(3.A.7a/b)

which can be solved for \( a \) , \( b \). For this system of equations to have a solution, the following condition should be met:

\[
\frac{(Z_{\text{eff}})_a^{3.5}}{N_{ga}} \neq \frac{(Z_{\text{eff}})_b^{3.5}}{N_{gb}}
\]  

(3.A.8)
which sets a condition for the base materials.

Since mass electron density ($N_e$ in $\#e/g$) differs little in various materials, a more practical and simplified criterion for the selection of base materials is obtained as:

$$(Z_{\text{eff}})_a \neq (Z_{\text{eff}})_b \quad (3.A.9)$$

The same approach can be used to determine the coefficients $a$ and $b$ for the mass energy absorption coefficient ($\frac{\mu_{ab}}{\rho}$) as a linear combination of the mass energy absorption coefficients of two base materials by expanding the equation below:

$$(\frac{\mu_{ab}}{\rho})_t = a \cdot (\frac{\mu_{ab}}{\rho})_a + b \cdot (\frac{\mu_{ab}}{\rho})_b \quad (3.A.10)$$

Assuming that radiative losses are small leads to the same set of equations as obtained previously except that the electron cross section ($\sigma_e$) is replaced by the electron energy-transfer cross section ($\sigma_e^{tr}$) in all equations. Since electronic cross sections are cancelled out, the same pair of equations is obtained for $a$ and $b$ as in Eqs. (3.A.7a) & (3.A.7b). This is of practical importance since the same $a$ and $b$ coefficients obtained for mass energy attenuation of a material can be used to calculate the mass energy absorption of the same material as well.
References


Chapter 4

Effect of Accounting for Tissue Heterogeneity in Prediction of Skin Toxicities for Permanent Breast Seeds Implant Brachytherapy
4.1 Abstract

**Purpose:** The Inhomogeneity Correction Factor (ICF) method provides heterogeneity correction for the TG43 formalism in seeds brachytherapy. Due to the use of standard TG43 dose distributions as input and fast calculation, ICF method enables an easy integration into the clinical workflow. This study compared ICF corrected plans to their standard TG43 counterparts looking at their capacity to predict skin toxicities for patients who received breast permanent seed implant (PBSI).

**Methods and Materials:** The 2 month post implant CT and plans of 140 PBSI patients were used to calculate dose distributions using the TG43 formalism and the ICF method. Short term (erythema and desquamation) and long term (telangiectasia) skin toxicity data were available on 125 and 110 of the patients, respectively, at the time of study. Multiple DVH parameters of skin were extracted for both ICF and TG43 dose distributions. The predictive value of each parameter was evaluated using area under the curve in the associated ROC curve for each toxicity endpoint. The two methods were also compared with regards to DVH parameters of the CTV dose distribution.

**Results:** The ICF methodology show higher predictive value for toxicity compared to TG43 for 90.9% of the skin dosimetry parameters. However the ICF method only led to a small increase in the prediction of desquamation, telangiectasia and erythema. The DVH parameters of skin calculated using the ICF method showed an overall increase compared to TG43 while those of CTV showed a decrease confirming previously reported findings on the impact of heterogeneity with low energy sources.
Conclusions: The use of the ICF correction led to an increase in prediction accuracy of skin toxicities in majority of cases. This difference, however, was not statistically significant to demonstrate the advantage of a heterogeneity corrected dose over TG-43 protocol.

Keywords: Breast seed implant, dosimetry, heterogeneity correction, skin toxicity

4.2 Background

Breast cancer is the most frequent cancer diagnosed among women in developed countries [1]. Since the generalization of breast screening about two thirds of all new cases in North America are diagnosed at early stage [2,3]. The treatment of early stage breast cancer has gone progressively through de-escalation from mastectomy to breast conservation treatment involving a lumpectomy followed by whole-breast irradiation (WBI) [4,5]. Recently for selected cases, accelerated Partial Breast Irradiation (APBI) has been suggested as an alternative to whole breast irradiation [6]. The use of APBI is supported by the fact that majority of failures after breast conservation surgery happens in the vicinity of the resected tumor [7]. The theoretical advantages of APBI over WBI include a decrease in dose to healthy breast tissue and adjacent organs as well as shorter treatment times. APBI can be delivered using different modalities including interstitial brachytherapy, 3D conformal external-beam and intra-operative irradiation [8-10]. In 2004, our team initiated a Permanent Breast Seed Implant (PBSI) technique involving the permanent implantation of Pd-103 brachytherapy seeds [11]. PBSI is realized in a single one-hour procedure under light sedation and has a good tolerance profile [12]. In the 6 weeks following PBSI 42% of the patients presented some
redness, 16.5% moist desquamation, and in the 2 years following the implant 22% presented small area of telangiectasia, ranging from a single vessel to a 1.5 cm$^2$ skin patch and 23% some induration.

A review of post-implant QAs have shown that dose to skin is significantly associated with skin side effects at 6 months in patients receiving PBSI [12]. However in 30% of patients presenting moist desquamation, the dose to the skin fails to explain the acute toxicity. For these patients, the skin dose was below threshold for 5% incidence risk of Grade 2 toxicity [13]. This suggests that either other parameters are at play, or the dose calculated to the skin was not accurate.

Our team also reported recently the use of a new correction factor to the AAPM TG43 formalism, the inhomogeneity correction factor (ICF), to account for the tissue heterogeneity in the calculation of dose [14]. In this work we explore whether those skin side effects could be better predicted using dose heterogeneity corrections that are not accounted for in the AAPM-TG43 formalism.

### 4.3 Methods and Materials

#### 4.3.1 Patients and treatment

Early stage invasive or in-situ breast cancer patients referred to a single cancer centre for adjuvant radiotherapy after conserving surgery were prospectively included into three PBSI clinical trials. The trials involve a Phase I/II trial of adjuvant PBSI for low risk infiltrating ductal carcinoma, a Phase I/II study of PBSI for DCIS, and a multicenter prospective Registry study of PBSI for infiltrating ductal carcinoma. The short term (6-8 weeks) and long term (2
years) skin toxicity results were available on 125 and 110 of these patients respectively at the time of study. The skin toxicities which were studied included erythema and desquamation for short term and telangiectasia for long term.

4.3.2 Post-implant Quality Assurance

All patients had a 2 month post-implant CT scan as part of the standard Quality Assurance (QA) procedure [13]. The QA process involved contouring the Seroma. The Seroma was expanded into a Clinical Target Volume (CTV) corresponding to the seroma plus a margin of 1 cm, limited 5 mm below the skin surface and on the fascia pectoralis. Individual seed positions were identified on CT images and the dose distribution calculated.

4.3.3 TG43 formalism and ICF

All post-op CT images, contours and DICOM RT plans were imported into MIM Symphony™ (MIM Software Inc., Cleveland, OH), which is a multi-modality LDR brachytherapy treatment planning system. The skin was contoured as a 1 mm inner ring to the patient external body contour. This thickness includes the epidermal shell, the dermal shell and the full length of the associated microvessel functional unit defined by Archambeau et al. [15]. TG-43 dose distributions were generated using the standard MIM Symphony™ algorithm. For the ICF formalism, from Mashouf et al. [14], the dose absorbed in heterogeneous media surrounding a low energy brachytherapy seed can be calculated in each point of space as:

\[ D_{\text{Het}}(\mathbf{r}) = D_{\text{TG-43}}(\mathbf{r}) \times ICF(\mathbf{r}) \]  

(4.1)

where \( \mathbf{r} \) is the position vector with respect to the center of the seed, \( D_{\text{TG-43}}(\mathbf{r}) \) is the dose as calculated by TG-43 protocol and \( ICF(\mathbf{r}) \) is the Inhomogeneity Correction Factor which is
defined in terms of linear attenuation coefficient \( (\mu_t) \) and mass energy absorption coefficient \( \left( \frac{\mu_{ab}}{\rho} \right)_t \) of tissue and water at the weighted mean photon energy of the radioisotope.

In order to calculate the values of ICF, the effective energy of the CT scanner was determined following Millner et al. [16]. Using the effective energy, theoretical Hounsfield Unit (HU), \( \mu_t \) and \( \left( \frac{\mu_{ab}}{\rho} \right)_t \) values of various tissues of breast (adipose, fibroglandular, skin) as well as surrounding structures (air, lung, ribs) were calculated. HU to \( \mu_t \) and HU to \( \left( \frac{\mu_{ab}}{\rho} \right)_t \) conversion graphs were created by interpolating between the points which were used to extract the values of \( \mu_t \) and \( \left( \frac{\mu_{ab}}{\rho} \right)_t \) from the associated CT image. Presence of seeds on post-op CT images introduce artifacts which were mitigated by overriding \( \mu_t \) and \( \left( \frac{\mu_{ab}}{\rho} \right)_t \) matrices with values of average breast tissue at location of seeds. The dose distribution was recalculated in Matlab\textsuperscript{®} using the ICF methodology. The results were exported back into MIM Symphony\textsuperscript{TM} where DVH parameters of skin contour and CTV were obtained for both TG-43×ICF and TG-43 dose distributions. The extracted DVH parameters of skin included \( D_{10cc} \), \( D_{5cc} \), \( D_{2cc} \), \( D_{1cc} \), \( D_{0.5cc} \), \( D_{0.2cc} \), \( D_{0.1cc} \), \( D_{0.05cc} \), \( D_{0.01cc} \) and \( D_{0.005cc} \). The DVH parameters of CTV were also extracted in order to make comparisons between TG-43 and the ICF method. These included \( V_{200\%} \), \( V_{100\%} \), \( V_{90\%} \), \( D_{100\%} \), \( D_{90\%} \) and \( D_{50\%} \). The percentage difference (PD) between DVH parameters of TG-43 and ICF method was calculated for each patient using the formula below:

\[
PD = \frac{DVH(TG43×ICF)-DVH(TG43)}{DVH(TG43)} \times 100\% \quad (4.2)
\]

The mean percentage difference (\( \overline{PD} \)) was obtained by averaging the values of PD over all patients.
4.3.4 Statistical Analysis

Outcomes were expressed into a dichotomous variable depending on the presence or not of a given skin toxicity. The predictive value of each DVH parameter of skin was obtained by establishing a Receiver Operating Characteristic (ROC) curve and calculating the area under the curve (IBM® SPSS® Statistics 21). Area under the curve (AUV) assumes values between 0.5 and 1 with higher values indicating higher accuracy in predicting an outcome [17]. Logistic regression analysis (IBM® SPSS® Statistics 21) was used to establish a dose to outcome relation as below:

$$\pi(x) = \frac{1}{1 + \exp[-(\beta_0 + \beta_1 x)]} \quad (4.3)$$

where $\pi(x)$ is the probability of $Y = 1$ as a function of a DVH parameter ($x$).

4.4 Results

4.4.1 DVH parameters of skin and CTV

The total number of patients who received PBSI by the end of July 2014 accounted for 140 patients. Table 4.1 displays the mean percentage difference ($\overline{PD}$) of several DVH parameters of skin between ICF methodology and TG43. Positive values of ($\overline{PD}$) in table 4.1 indicate an overall increase of DVH values of skin in heterogeneous model of breast in comparison to TG43.

Table 4.2 displays the mean of important DVH parameters of CTV obtained using TG43 as well as ICF methodology and the mean percentage difference ($\overline{PD}$). In contrast to skin, the
DVH parameters of CTV in heterogeneous model of breast display an overall reduction when compared to TG43.

Table 4.1 - Mean percentage difference in several DVH parameters of skin in heterogeneous model of breast versus simple homogeneous water model for a cohort of 140 patients.

<table>
<thead>
<tr>
<th>Skin DV</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>D_{10cc}</td>
<td>31.92%</td>
</tr>
<tr>
<td>D_{5cc}</td>
<td>27.07%</td>
</tr>
<tr>
<td>D_{2cc}</td>
<td>20.75%</td>
</tr>
<tr>
<td>D_{1cc}</td>
<td>17.61%</td>
</tr>
<tr>
<td>D_{0.5cc}</td>
<td>15.27%</td>
</tr>
<tr>
<td>D_{0.2cc}</td>
<td>12.31%</td>
</tr>
<tr>
<td>D_{0.1cc}</td>
<td>10.74%</td>
</tr>
<tr>
<td>D_{0.05cc}</td>
<td>9.44%</td>
</tr>
<tr>
<td>D_{0.02cc}</td>
<td>8.77%</td>
</tr>
<tr>
<td>D_{0.01cc}</td>
<td>16.58%</td>
</tr>
<tr>
<td>D_{0.005cc}</td>
<td>19.80%</td>
</tr>
</tbody>
</table>
Table 4.2 - Average DVH parameters of CTV obtained using TG43 and TG43×ICF dose calculations in a cohort of 140 patients. Negative values of $P\bar{D}$ indicate an overall decrease in the values of DVH parameters in heterogeneous model of breast compared to simple homogeneous water model.

<table>
<thead>
<tr>
<th>CTV</th>
<th>TG43</th>
<th>TG43×ICF</th>
<th>$P\bar{D}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_{100%}$</td>
<td>35.90%</td>
<td>32.70%</td>
<td>-3.60%</td>
</tr>
<tr>
<td>$D_{90%}$</td>
<td>91.40%</td>
<td>82.40%</td>
<td>-6.20%</td>
</tr>
<tr>
<td>$D_{50%}$</td>
<td>187.50%</td>
<td>172.90%</td>
<td>-7.30%</td>
</tr>
<tr>
<td>$V_{200%}$</td>
<td>44.50%</td>
<td>40.20%</td>
<td>-7.60%</td>
</tr>
<tr>
<td>$V_{100%}$</td>
<td>84.80%</td>
<td>80.60%</td>
<td>-4.70%</td>
</tr>
<tr>
<td>$V_{90%}$</td>
<td>88.00%</td>
<td>84.70%</td>
<td>-3.40%</td>
</tr>
</tbody>
</table>

Fig. 4.1 represents a typical TG43 and TG43×ICF dose distributions for a breast patient displaying elevation of dose at the skin, retraction of 200% iso-dose lines in breast and expansion of 20%, 10%, 2% iso-dose lines in lung and air.
Figure 4.1 - Side by side comparison of TG43 (top) and TG43×ICF (bottom) dose distributions in a PBSI patient. A dose elevation from 37.9 Gy (using simple water model) to 42.5 Gy in heterogeneous model of breast has been illustrated at the same anatomical point on the skin.
4.4.2  Prediction of skin toxicities

Table 4.3 lists area under the curve (AUC) of ROC curves of several dose metrics of skin obtained using TG43 (left panel) as well as TG43×ICF methodology (right panel). Study of AUC values listed in table 4.3 demonstrate dose metrics based on heterogeneous model of breast offer an improvement over those obtained by simple water model in regards to prediction of skin toxicities. In 30 out of 33 (90.9%) cases, skin dose metrics offer higher predictive value when calculated using TG43×ICF methodology.

The values of AUC assist in identifying skin dose metrics which offer highest predictive values. Based on tables 4.3(a), 4.3(b) and 4.3(c), D_{0.5cc} is identified as the skin dose metric with highest predictive value for desquamation and D_{0.05cc} for erythema and telangiectasia. Fig. 4.2 compares ROC curves generated using highest predictive skin dose metrics calculated by ICF method versus TG43 formalism. ROC curves using ICF dose metrics locates above and left of TG43 for most part indicating higher sensitivity and specificity in prediction of skin toxicities. This difference, however, is not significant with p-values of 0.286, 0.444, 0.118 for desquamation, erythema and telangiectasia respectively.

Table 4.3 - Predictive value (AUC) of several dosimetry parameters of skin for (a) desquamation (6-8 wks) (b) erythema (6-8 wks) and (c) telangiectasia (2 yrs). Left panel: TG43, right panel: TG43×ICF. P-value is the significance under null hypothesis: AUC= 0.5.

(a) Desquamation (6-8 wks)

<table>
<thead>
<tr>
<th>Skin D_v (TG43)</th>
<th>AUC</th>
<th>p-value</th>
<th>Skin D_v (TG43×ICF)</th>
<th>AUC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>D_{10cc}</td>
<td>.653</td>
<td>.030</td>
<td>D_{10cc}</td>
<td>.664</td>
<td>.021</td>
</tr>
<tr>
<td>Skin Dv (TG43)</td>
<td>AUC</td>
<td>p-value</td>
<td>Skin Dv (TG43xICF)</td>
<td>AUC</td>
<td>p-value</td>
</tr>
<tr>
<td>---------------</td>
<td>-----</td>
<td>---------</td>
<td>---------------------</td>
<td>-----</td>
<td>---------</td>
</tr>
<tr>
<td>D_{10cc}</td>
<td>.537</td>
<td>.482</td>
<td>D_{10cc}</td>
<td>.542</td>
<td>.427</td>
</tr>
<tr>
<td>D_{5cc}</td>
<td>.590</td>
<td>.089</td>
<td>D_{5cc}</td>
<td>.601</td>
<td>.055</td>
</tr>
<tr>
<td>D_{2cc}</td>
<td>.649</td>
<td>.005</td>
<td>D_{2cc}</td>
<td>.666</td>
<td>.002</td>
</tr>
<tr>
<td>D_{1cc}</td>
<td>.673</td>
<td>.001</td>
<td>D_{1cc}</td>
<td>.681</td>
<td>.001</td>
</tr>
<tr>
<td>D_{0.5cc}</td>
<td>.688</td>
<td>.000</td>
<td>D_{0.5cc}</td>
<td>.691</td>
<td>.000</td>
</tr>
<tr>
<td>D_{0.2cc}</td>
<td>.694</td>
<td>.000</td>
<td>D_{0.2cc}</td>
<td>.697</td>
<td>.000</td>
</tr>
<tr>
<td>D_{0.1cc}</td>
<td>.704</td>
<td>.000</td>
<td>D_{0.1cc}</td>
<td>.706</td>
<td>.000</td>
</tr>
<tr>
<td>D_{0.05cc}</td>
<td>.703</td>
<td>.000</td>
<td>D_{0.05cc}</td>
<td>.707</td>
<td>.000</td>
</tr>
<tr>
<td>D_{0.02cc}</td>
<td>.699</td>
<td>.000</td>
<td>D_{0.02cc}</td>
<td>.706</td>
<td>.000</td>
</tr>
<tr>
<td>D_{0.01cc}</td>
<td>.697</td>
<td>.000</td>
<td>D_{0.01cc}</td>
<td>.705</td>
<td>.000</td>
</tr>
<tr>
<td>D_{0.005cc}</td>
<td>.696</td>
<td>.000</td>
<td>D_{0.005cc}</td>
<td>.700</td>
<td>.000</td>
</tr>
</tbody>
</table>

(b) Erythema (6-8 wks)
### Telangiectasia (2 yrs)

<table>
<thead>
<tr>
<th>Skin Dv (TG43)</th>
<th>AUC</th>
<th>p-value</th>
<th>Skin Dv (TG43*ICF)</th>
<th>AUC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>D&lt;sub&gt;10cc&lt;/sub&gt;</td>
<td>.609</td>
<td>.105</td>
<td>D&lt;sub&gt;10cc&lt;/sub&gt;</td>
<td>.619</td>
<td>.076</td>
</tr>
<tr>
<td>D&lt;sub&gt;5cc&lt;/sub&gt;</td>
<td>.613</td>
<td>.090</td>
<td>D&lt;sub&gt;5cc&lt;/sub&gt;</td>
<td>.649</td>
<td>.026</td>
</tr>
<tr>
<td>D&lt;sub&gt;2cc&lt;/sub&gt;</td>
<td>.703</td>
<td>.002</td>
<td>D&lt;sub&gt;2cc&lt;/sub&gt;</td>
<td>.716</td>
<td>.001</td>
</tr>
<tr>
<td>D&lt;sub&gt;1cc&lt;/sub&gt;</td>
<td>.749</td>
<td>.000</td>
<td>D&lt;sub&gt;1cc&lt;/sub&gt;</td>
<td>.760</td>
<td>.000</td>
</tr>
<tr>
<td>D&lt;sub&gt;0.5cc&lt;/sub&gt;</td>
<td>.774</td>
<td>.000</td>
<td>D&lt;sub&gt;0.5cc&lt;/sub&gt;</td>
<td>.784</td>
<td>.000</td>
</tr>
<tr>
<td>D&lt;sub&gt;0.2cc&lt;/sub&gt;</td>
<td>.791</td>
<td>.000</td>
<td>D&lt;sub&gt;0.2cc&lt;/sub&gt;</td>
<td>.797</td>
<td>.000</td>
</tr>
<tr>
<td>D&lt;sub&gt;0.1cc&lt;/sub&gt;</td>
<td>.802</td>
<td>.000</td>
<td>D&lt;sub&gt;0.1cc&lt;/sub&gt;</td>
<td>.806</td>
<td>.000</td>
</tr>
<tr>
<td>D&lt;sub&gt;0.05cc&lt;/sub&gt;</td>
<td>.801</td>
<td>.000</td>
<td>D&lt;sub&gt;0.05cc&lt;/sub&gt;</td>
<td>.809</td>
<td>.000</td>
</tr>
<tr>
<td>D&lt;sub&gt;0.02cc&lt;/sub&gt;</td>
<td>.800</td>
<td>.000</td>
<td>D&lt;sub&gt;0.02cc&lt;/sub&gt;</td>
<td>.803</td>
<td>.000</td>
</tr>
<tr>
<td>D&lt;sub&gt;0.01cc&lt;/sub&gt;</td>
<td>.799</td>
<td>.000</td>
<td>D&lt;sub&gt;0.01cc&lt;/sub&gt;</td>
<td>.804</td>
<td>.000</td>
</tr>
<tr>
<td>D&lt;sub&gt;0.005cc&lt;/sub&gt;</td>
<td>.794</td>
<td>.000</td>
<td>D&lt;sub&gt;0.005cc&lt;/sub&gt;</td>
<td>.800</td>
<td>.000</td>
</tr>
</tbody>
</table>
TG43xICF (D_{0.5cc})

TG43 (D_{0.5cc})

TG43xICF (D_{0.05cc})

TG43 (D_{0.05cc})
Figure 4.2 - ROC curves for (a) desquamation (b) erythema and (c) telangiectasias generated by skin dose metric calculated by ICF (solid lines) versus TG43 (dotted line). ICF method displays a modest advantage over TG-43 in terms of predicting skin toxicities.

4.4.3 Dose-outcome relation

In order to establish a relationship between dose to skin and skin toxicities, a logistic regression analysis was performed for each skin toxicity, with $D_{0.5cc}$ as a predictor for desquamation and $D_{0.05cc}$ as a predictor for erythema and telangiectasia. Fig. 4.3 illustrates the probability curves of logistic regression model for each skin toxicity as a function of the associated skin dose metric. The values of constant and the coefficient of the logistic regression model ($\beta_0$ and $\beta_1$ in Eq. (4.3)) have been included within each graph. The relative shift of the ICF curves to the right with respect to TG43, is consistent with an overall increase in dose metrics of skin in heterogeneous model of breast.
(a) Odds ratio (Desquamation)

- ICF: \( \beta_0 = -4.809, \beta_1 = 0.063 \)
- TG-43: \( \beta_0 = -4.514, \beta_1 = 0.064 \)

(b) Odds ratio (Erythema)

- ICF: \( \beta_0 = -1.837, \beta_1 = 0.024 \)
- TG-43: \( \beta_0 = -1.715, \beta_1 = 0.024 \)
4.5 Discussion

The current standard for calculation of dose in permanent seed implants is based on TG-43 protocol which assumes that the energy is absorbed into homogeneous water medium [18]. Breast, however, is a very heterogeneous organ containing mixes of adipose and fibroglandular tissues and surrounded by air, ribs and lung. Monte Carlo simulations in heterogeneous models of breast have shown that dose metrics of the breast skin are underestimated by up to 40% using TG-43 protocol and this error increases by the fraction of adipose tissue in breast [19]. An average breast contains a higher adipose content than previously thought (80% vs. 50%) and this ratio varies significantly between patients [20]. As
a result, low energy photons may travel further away in the tissue, reducing the dose absorbed into the target volume and increasing the dose received by organs at risks. In addition, TG-43 formalism does not account for inter-seeds attenuation which reduces the dose absorbed both in the target volume and the surrounding critical structures. TG-43 based TPSs do not reflect these variations of dose due to the heterogeneities which renders dose-outcome relationships less accurate.

Heterogeneity corrections algorithms have long been implemented in treatment planning systems for external beam radiotherapy using megavoltage X-rays [21]. In brachytherapy, however, TG43 formalism based on dose calculations in homogenous water has been the mainstay, even though the interaction physics of low energy photons is much more dependent on tissue composition compared to external beam radiation [22]. Permanent seed implants, in particular, are more sensitive to tissue heterogeneities as they make use of radioisotopes which emit at a lower range of photon energies for radio protection purposes. Earlier studies using Monte Carlo simulation have demonstrated the effect of heterogeneities are particularly significant in PBSI patients due to a high carbon content of breast and use of Pd-103 which emits lower energy photons than I-125 and Cs-131[23].

We have already reported on a dose heterogeneity correction algorithm which involves applying an Inhomogeneity Correction Factor (ICF) to TG-43 formalism at each point in calculation domain. Since this formalism is based on a correction factor which is extracted using Hounsfield Units, it is easy to implement clinically.

In this study we have evaluated using the ICF formalism the effect of heterogeneities in several dose metrics of CTV and skin in patients who received PBSI at our institution. Our results are
in agreement with earlier studies using Monte Carlo simulations for breast implants using Pd-103 sources [19,23]. Similar to Afsharpour et al. [19] our results indicate CTV $V_{100\%}$ and $D_{90\%}$ are less affected by heterogeneities compared to $V_{200\%}$ and $D_{50\%}$ which are decreased (table 4.3). This means that the dose conformality is relatively maintained while the implant high dose sleeves are smaller in breast tissue. This could be explained by the fact that less energy are deposited around a seed in breast tissue in comparison to water due to the lower effective atomic number of breast tissue. This effect is gradually compensated by an increase in photon fluence farther from the seed due to less attenuation of photons in breast tissue [14] which explains why $V_{100\%}$ and $D_{90\%}$ are less affected in breast tissue.

Afsharpour et al. [19] used a 5 mm thickness for skin definition for Monte Carlo simulations and assigned the atomic composition and density of skin to the defined volume. In our methodology, however, tissue parameters are assigned using CT images and hence it is important to contour only the skin. In order to avoid contouring subcutaneous fat layer we chose to contour the skin with 1mm thickness. Furthermore the skin sensitive volume which contains microvessel tufts and the associated epidermis and dermis (skin functional units) are situated within 1mm depth of the skin [15].

Logistic regression model was used to establish correlation between skin dose and toxicities as it is well established that the probability of normal tissue complication have a sigmoidal dependence on radiation dose [24-26].

ROC curves were utilized to determine which skin dose metric is a better predictor of skin toxicity. The prediction accuracy was significantly higher for desquamation and telangiectasia compared to erythema (table 4.3). This indicates erythema is influenced more than desquamation and telangiectasia by factors other than radiation dose such as systemic
therapies, patient age, etc. [27,28]. This can be also seen in Fig. 4.3 where for no exposure, the probability of erythema is 13.7% compared to 0.8% and 1.8% for desquamation and telangiectasia respectively. Using Pearson chi-square test for association, telangiectasia was found to be highly correlated with desquamation ($p < 0.001$). ROC curves in Fig. 4.2 show only modest improvement is gained by using ICF over TG-43 in terms of predicting a skin toxicity.

In this study we made use of population based atomic compositions and densities to calculate HU number, $\mu_t$ and $\left(\frac{\mu_{ab}}{\rho}\right)_t$ for breast and surrounding tissues [29]. This would limit the application of the associated conversion curves to the breast site only. Using dual energy CT images, however, $\mu_t$ and $\left(\frac{\mu_{ab}}{\rho}\right)_t$ can be extracted directly without the need to assign population based atomic compositions [30]. Besides eliminating errors associated with population based data, DECT method can be also readily applied to other sites such as prostate.

### 4.6 Conclusion

Due to the significance of heterogeneity effects in brachytherapy, the use of model-based dose calculation algorithms which account for heterogeneities in parallel with TG43 formalism has been recommended by several radiation oncology societies [22]. In order to make a successful transition from TG-43 to model-based dose calculation algorithms, there is a need for retrospective studies to establish updated dose constraints for each treatment modality and target site [31]. Our preliminary results show there is a clinical advantage in implementing ICF method for PBSI patient in terms of prediction of skin toxicities which can be verified further by future randomized trials.
Even in the absence of prospective randomized trials, our recommendations is that heterogeneity corrections should become an essential part of the treatment of patients receiving PBSI due to the higher accuracy in calculating dose.
References


Chapter 5

Summary and conclusions
5.1 Thesis summary

Since the planning for PBSI is slightly different than the one done for prostate implant, we designed, implemented and validated a dedicated treatment planning system for PBSI patients (MIM Symphony™), which has received FDA and Health Canada accreditation. Prior to the introduction of MIM Symphony, the planning process was a multi-step process through different platforms, one for contouring, one for re-slicing, and one for planning. MIM Symphony consolidates this process so that the planning tasks could be done on a single platform. The advantages include reduction of errors, the possibility to correct previous steps more easily, and a more efficient overall process running clinical trials.

A new tissue heterogeneity correction algorithm (ICF method) for LDR brachytherapy sources was also developed and validated. We also implemented the algorithm into our clinical treatment planning system (MIM Symphony) using both dual and mono energy CT images. We obtained dosimetry parameters of the clinical target volume for a cohort of PBSI patients using TG-43 as well as the ICF method. At the end we explored whether using a heterogeneity corrected dose results in better prediction of skin toxicities in PBSI patients.

5.2 Significance of the work

There is a general trend towards implementing model-based dose calculation algorithms (MBDCAs) in brachytherapy to account for medium heterogeneities [1]. This is supported by the fact that dose distributions can be significantly affected by the heterogeneities [2]. There is, however, no commercial treatment planning system currently available to account for tissue heterogeneities in permanent seed implants. Our work introduces a new methodology (ICF method) which can be easily integrated into the existing TG-43 based treatment planning
systems to correct the dose for heterogeneities present in the medium. There are several reasons which make the ICF an ideal method for clinical implementation. First, it makes use of the standard TG-43 protocol which is well established in clinic. Second, the ICF method is computationally efficient. Third the correction factor is extracted directly from Hounsfield Units without the need for tissue segmentation and forth the scanning of a CT calibration phantom (which is required as part of the process) is already part of the regular QA of CT scanners in a radiotherapy department. All of these features enable seamless introduction of the methodology into the fast paced clinical environment.

As mentioned above computational efficiency is one of the advantages of the ICF method. A typical run time on a PC with an Intel-i7 processor and 8GB of RAM for a post-op plan containing an average number of 80 seeds is about 3 minutes. This should be compared with run times of several days obtained using MCNP5 code in phantom 3 discussed in chapter 2. This is due to several reasons: first, the ICF method takes in TG-43 dose distributions as an input which is already calculated in a TPS or fast to calculate. Second, it makes use of a closed form analytical formula to calculate the ICF factor. And lastly, our preliminary results show that the voxel size of the linear attenuation matrix can be increased by several folds without affecting the calculation accuracy. Using larger voxel sizes with dual energy CT images has the added benefit of minimizing registration errors. A typical run time on a PC

Other MBDCA methods such as those based on Monte Carlo or radiation transfer equations can be computationally intensive [3,4]. Monte Carlo (MC) methods use random number generation to simulate physical events occurring during particle transport through the medium. With sufficient particle histories, an estimate of the quantity of interest like the absorbed dose can be calculated. The MC calculation time is specially augmented in brachytherapy
applications due to the inverse-square law fall off of primary photons [2]. Furthermore at relatively low energies a photon may undergo multiple elastic scattering (Thomson and Rayleigh) scattering before being absorbed by a photoelectric event, adding to the calculation time.

Another MBDCA method involves solving the Boltzmann linear radiation transport equation by discretization in space and energy [5]. Resolving this equation produces several photon fluence maps of various energy bins. The dose can then be derived by multiplying the photon energy fluence by the appropriate mass energy absorption coefficient, at each point. They are generally considered more computationally intensive than MC methods [4]. The accuracy of the solution is also dependent upon how fine the discretization is which rapidly adds to the computation burden of the method [2]. Another advantage of the ICF method in comparison to MC and methods based on solving the radiation transport equation is that there is no need for tissue segmentation. Tissue parameters can be extracted using the CT images without the need to delineate various tissues/organisms.

In this thesis we also explored the clinical benefit of using a heterogeneity corrected dose in terms of predicting skin side effects. Studies exploring advantages of a heterogeneity corrected dose in seed brachytherapy are scarce. The reasons for lack of such studies include unavailability of new dose constraints using MBDCAs for various clinical sites and slow calculation time preventing real-time planning. In this thesis we have addressed both of these issues by offering a computationally efficient algorithm and extracting dosimetry parameters of the target volume for a cohort of PBSI patients. Comparison of the new dose metrics obtained by a MBDCA (e.g. ICF method) with those of standard TG-43 protocol enables to identify new dose constraints when planning using MBDCA [1].
5.3 Future directions

The effect of heterogeneity in prostate implants is another topic to be explored more in future. Since non-calcified prostate is almost water equivalent [1,6], the effect of medium heterogeneity is mainly due to seed interseed attenuation or any possible calcifications.

Computational efficiency is one of the main advantages of the ICF method. Our preliminary results show that the voxel size of the linear attenuation coefficient matrix (μ) can be increased by several folds without affecting the overall dose calculation accuracy. Increasing the voxel size will significantly enhance the computation time as it speeds up the calculation of the line integral in the ICF formulation. The error introduced by lowering the resolution of μ should be quantified as a function of the voxel size. A potential future work involves testing the robustness of the ICF method with regards to this expansion and setting an upper limit for the resolution of μ matrix.

Another potential area of research relates to extending the concept of ICF into higher energy sources such as HDR Ir-192 brachytherapy. The first step will be to establish a proper correction factor. Any such factor should be able to account for applicator heterogeneities as well as tissue/air interfaces as they are the dominant source of dosimetry effects [1]. This is in contrast to permanent seed brachytherapy where tissue heterogeneities are the major contributor to dose variations from TG43 [7]. This difference between higher versus lower energy sources are best reflected in dosimetry of breast cancer patients. For example it has been shown that dose to the breast skin is decreased using high energy sources due to the lack of backscatter at skin-air interface in comparison to TG-43 [8,9]. Conversely skin dose experience an overall increase using low energy sources due to the dominance of tissue
heterogeneity effect in breast despite lack of backscatter from air which counteracts the former [7].

Finally efforts are underway to make the ICF method commercially available. A beta version of the code is already available in MIM Symphony. Future work includes 510k validation tasks for regulatory purposes. These tasks should include reproduction of TG-43 dose distributions in a homogenous water phantom [1]. One advantage of the ICF method is that the formulation converges to TG-43 dose distributions in a homogeneous water phantom by default. The second level of validation involves comparison of dose distributions in a heterogeneous phantom. The dose distributions produced by the ICF should be verified against benchmark dose distributions in the same phantom. The benchmark dose distributions are obtained independently using a well-documented MC code or experiments. These reference datasets are going to be available to medical physics community in DICOM-RT format through a registry [10].

Accounting for heterogeneities in the medium serves as a step towards personalized cancer treatment, where dose distributions are tailored for each individual based on their unique anatomy. As personalized cancer treatment advances in other modalities, effect of all these modalities can be combined into a single composite index which will determine the overall chance of local control in cancer treatment.
References


