Biological Effective Dose (BED) Distribution Matching for Obtaining Brachytherapy Prescription Doses & Dosimetric Optimization for Hybrid Seed Brachytherapy

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# Table of Contents

List of Tables                   ii  
List of Figures                  iii  
Abstract                      iv  

I. Introduction                          1  
  History on Interstitial Brachytherapy                      1  
  Prostate Cancer Treatment                         2  
  Derivation of BED                           6  

II. Model & Method of Calculation                 9  
  Treatment Plans                  9  
  BED Calculation                  11 

III. Hybrid Seeds vs. Single Isotope Seeds              18  
  Patient Parameters                18  
  Results                               19

IV. Discussion and Conclusions               23  
  Discussion                           23  
  Conclusions                         25  

V. Dosimetric Optimization for Hybrid Seed Brachytherapy           27  
  Introduction                         27  
  Materials & Methods                  29  
  Results                              32  
  Discussion                          36  
  Conclusions                         37  

References                  38  

Appendices                  44  
  Appendix A: Importing Files & Scaling Factor         45  
  Appendix B: Geometry Portion Calculation        47  
  Appendix C: BED Calculation                      50
List of Tables

| Table [1] | $\alpha/\beta$ values for various cell types | 7 |
| Table [2] | Biological parameters used in BED calculation | 13 |
| Table [3] | Construction parameters used in BED calculation | 15 |
| Table [4A] | Prostate volumes for the patients for patients who had $^{125}$I seeds | 18 |
| Table [4B] | Prostate volumes for the patients for patients who had $^{103}$Pd seeds | 18 |
| Table [5A] | Activities used for the $^{125}$I seeds implanted | 19 |
| Table [5B] | Activities used for the $^{103}$Pd seeds implanted | 19 |
| Table [6A] | Dose (Gy) to cover 90% of the prostate when BED coverage is the same ($^{125}$I treatment isotope) | 20 |
| Table [6B] | Dose (Gy) to cover 90% of the prostate when BED coverage is the same ($^{103}$Pd treatment isotope) | 20 |
| Table [7] | Air kerma strength of isotopes within the hybrid seed | 32 |
| Table [8] | Coefficients for equations of fit for BED vs. dose data sets | 36 |
List of Figures

Figure [1] How a TRUS is set up within the patient 2
Figure [2] Placement of the coordinate plate 3
Figure [3] CT slice of the prostate after implantation of brachytherapy seeds 5
Figure [4] Schematic of the Advantage Hybrid PdI source 10
Figure [5] Axial CT slice with a dose distribution overlain 12
Figure [6] Zoomed in slice of a three dimensional $^{125}\text{I}$ BED distribution 14
Figure [7] Calculation Flow Chart 17
Figure [8A] Prostate DVH for $^{125}\text{I}$ (treatment isotope), Hybrid, and $^{103}\text{Pd}$ seeds 21
Figure [8B] Prostate BEDDVH for $^{125}\text{I}$ (treatment isotope), Hybrid, and $^{103}\text{Pd}$ seeds 21
Figure [9a] Prostate DVH for $^{125}\text{I}$, Hybrid, and $^{103}\text{Pd}$ (treatment isotope) seeds 22
Figure [9b] Prostate BEDDVH for $^{125}\text{I}$, Hybrid, and $^{103}\text{Pd}$ seeds (treatment isotope) 22
Figure [10] Isodose Line for 2 hybrid seeds 30
Figure [11] Individual isotope contributions to total dose vs. BED relation for 49 seeds 33
Figure [12] Total dose vs. BED for differing number of seeds and distributions 34
Figure [13] Total dose vs. BED calculated for the rectum for hybrid seeds of ratio: 50/50, 25/75, 75/25 35
Abstract

Radioactive seed implant brachytherapy is a common radiotherapy treatment method for prostate cancer. In current clinical practice, a seed consists of a single isotope, such as $^{125}$I or $^{103}$Pd. A seed containing a mixture of two isotopes has been proposed for prostate cancer treatment. This study investigates a method for defining a prescription dose for new seed compositions based on matching the biological equivalent dose (BED) of a reference plan.

Ten prostate cancer cases previously treated using single isotope seeds (5 using $^{125}$I seeds and 5 using $^{103}$Pd seeds) were selected for this study. Verification of the method was done by calculating prescription doses for $^{103}$Pd and $^{125}$I seeds. A prescription dose for a 50/50 hybrid seed was calculated. Number and location of seeds remained invariant within each case. The BED distributions for hybrid and single isotope seed plans were generated and matched to the BED distribution generated off of the optimized plans.

For the $^{125}$I isotopes, the dose necessary to cover 90% of the prostate with a BED of 110 Gy is 145 Gy. For the same BED coverage, the dose for $^{103}$Pd and 50/50 hybrid seed is 120 Gy and 137 Gy respectively.
A method is introduced for obtaining prescription doses for new brachytherapy sources. The method was verified by obtaining doses for $^{125}$I and $^{103}$Pd isotopes which match clinical prescription doses. The method developed is robust enough to calculate prescription doses in any region of interest, for any seed type, and for any isotope as long as the BED coverage remains invariant with respect to the treatment plan.

Numerical calculations were performed to derive analytical conversions of total dose to BED for 50/50, 75/25 and 25/75 hybrid seeds. These analytical conversions are faster than the original numerical methods employed allowing for real-time BED optimization for hybrid seeds.

Varying seed distribution was seen not to influence the analytical conversions. It was observed that when total dose remained invariant while individual isotope contributions varied, the value of BED varied. The BED variance was seen to be the smaller at larger BED values (~2% at 100 Gy).

Using the conversions derived in this paper, BED based optimization for hybrid seeds are now performable. However, these conversions should only be used in high dose regions due to high uncertainty in the low regime.
I. Introduction

History on Interstitial Brachytherapy

Brachytherapy is defined by the treatment of a disease through use of radioactive sources placed within or on the body. Treatment of prostate cancer with brachytherapy began in 1914 when Pasteau and Degrais inserted radium into the prostate through the urethral catheter\textsuperscript{[1]}. Interstitial implantation of radium needles was first used in 1917 by Barringer\textsuperscript{[2]}. By the mid 1970’s, modern interstitial brachytherapy for the treatment of prostate cancer developed its formalism when in 1972 Whitmore et al. used $^{125}$I radionuclide seeds. The delivery of the radioactive isotopes was done through needles inserted retropubically. Depth coordinates for the needles were determined through palpation of the prostate through the rectal cavity.

Since 1972, several improvements have been made to the implantation process and radiation delivery of permanent seed implant brachytherapy\textsuperscript{[3]}. First, brachytherapy planning was optimized through use of patient images obtained either through transrectal ultrasound probes or CT scans. Using the patient images sets as well as dose calculation software (such as Variseed), better dose delivery by permanent seeds could be performed.

Another improvement to Whitmore’s technique was in streamlining the implanting procedure. Palpating the prostate gave way to ultrasound guidance in providing depth coordinates. Multi-channel grids, introduced in 1981 by Holm, et al.,
were constructed to guide interstitial needles during implant procedures to insure proper placement of the radioactive seeds in the lateral and posterior/anterior positions\[4\].

**Prostate Cancer Treatment**

Several criteria are used to determine which therapy modalities are available for treatment of a patient’s prostate cancer. The Gleason grade is a pathological grading system for measuring the degree of differentiation of prostate tumors\[5\]. A prostate specific antigen (PSA) test is also performed to find the concentration of the PSA protein within the patient’s blood. Finally, a digital rectal exam is also performed to check for any abnormalities. Patients eligible for prostate brachytherapy usually have the following criterion: a PSA level greater than 10, a Gleason grade of around 6, and minimal abnormalities found after the digital rectal exam.

**Figure [1]** how a TRUS is set up within the patient. [Image credit: http://www.strivewell.com/wiki/Image:TRUS.jpg ]
For early stage prostate cancer, several treatment options are available: permanent seed implant brachytherapy, external beam radiation therapy, prostectomy, or no treatment. Each form of treatment has its own associated risks and side effects. Urinary incontinence and impact on sexual function (impotence) may occur after prostatectomy\[^6\]. Sexual dysfunction and irritative gastrointestinal and genitourinary side effects are commonly reported following external radiation treatment for early stage prostate cancer\[^7\]. In permanent seed implant brachytherapy complications such as urinary retention, urinary incontinence, and radiation proctitis may arise\[^8\].

If the patient chooses to be treated with permanent seed implant brachytherapy then after diagnosis the patient is brought in so that a transrectal ultrasound (TRUS) probe (Figure [1]) can be used to image the patient’s prostate. These images are then imported into a treatment planning software so that a treatment plan may be developed.

**Figure [2]** Placement of the coordinate plate. The grid is used to ensure that brachytherapy seeds are correctly placed with regards to the LAT and AP coordinates.

Afterwards, the patient is brought back in for treatment. The TRUS is reinserted so depth coordinates can be obtained as brachytherapy seeds are implanted. For the anterior-posterior (AP) and lateral (LAT) coordinates, a coordinate plate (Figure [2]) is placed between the anus and scrotum.

Permanent implantation of sealed radioactive seeds within the target volume is a definitive or supplementary therapy used for early stage prostate cancer\cite{5,9,10} and has been used in the past for other sites such as treatment for head and neck tumors\cite{11-13}. (Figure [3] shows $^{125}$I seeds placed within a patient’s prostate.) The current technique of prostate seed implants (PSI) uses single isotope seeds to deliver the prescribed dose to the tumor\cite{14,15}. $^{125}$I and $^{103}$Pd are the most common radioactive isotopes used for PSI.

Based on their decay rates, $^{125}$I or $^{103}$Pd, has been prescribed to tumors considered slow-growing and fast-growing as designated by their Gleason grade, respectively\cite{16}. However, prescribing an isotope based on Gleason score has been criticized since no advantages have been observed\cite{15}. Nevertheless, differences in long-term complications between the two isotopes has been reported: a grade III-IV complication rate with $^{103}$Pd (0%) vs. $^{125}$I\cite{17} (6%), increased risk of proctitis when $^{125}$I used vs. $^{103}$Pd\cite{18}, and radiation prostatitis\cite{18}. Interest in use of new sources or a combination of sources for seed implants for use in brachytherapy remains\cite{19-21}. Since many isotope ratios are possible within hybrid seeds, a method of obtaining a prescription dose for new and novel seeds is warranted.
Figure [3] CT slice of the prostate after implantation of brachytherapy seeds. The white dots in the center of the image are the locations of $^{125}$I seeds used to treat the prostate of this patient. Pelvic bones can also be seen.

An effective treatment for prostate cancer is typically defined by chemical free survival (ASTRO guidelines: no three consecutive rising PSA tests$^{[22]}$). For early stage prostate cancer treatments using brachytherapy as monotherapy, the accepted standard for successful implants are that 90% of the prostate volume receives a dose of at least 145 Gy or 120 Gy for $^{125}$I or $^{103}$Pd isotopes, respectively$^{[23]}$. The effectiveness of the treatment is thus predicted by the dose coverage of the prostate. Prescribed doses for PSI using hybrid seeds or new isotopes have not been established. This paper will expand on the
biological effective dose (BED) methods previously used to calculate prescription doses for new brachytherapy sources\textsuperscript{[24]}.  

From the dose distribution one can calculate a BED distribution. The BED is used as a means to more accurately calculate the clinical expectation of different treatment modalities\textsuperscript{[25, 26]}. The conversion from dose distribution to BED distribution for brachytherapy plans that use seeds of a single isotope has been previously reported\textsuperscript{[27]}. However, for treatments using hybrid seeds, the calculation is complicated since no analytical expression for effective treatment time ($T_{\text{eff}}$) can be written. $T_{\text{eff}}$ is defined as the time at which the cell killing rate equals the proliferation rate\textsuperscript{[27, 28]} This is due to the different dose rates from the isotopes contained within each seed. Therefore, a system of equations is needed to solve the set of transcendental functions when calculating the BED and $T_{\text{eff}}$. This paper introduces a numerical method, to calculate BED distributions for PSI which then can be used to calculate prescription dose for new types of sources.

**Derivation of BED**

The best model for a cell survival curve is the linear quadratic model\textsuperscript{[29]}. This model in a very general way models the effectiveness of single and double strand DNA breaks. Taking into account the effect that dose has, the model characterizes the single and double strand breaks. Single strand breaks are proportional to dose, $D$, while double strand breaks are proportional to dose squared ($D^2$).

The relationship between cell survival and dose is given by:

$$S = e^{-\alpha D - \beta D^2}$$

Here, $S$ is the cell survival fraction for a given dose, $D$. The parameters $\alpha$ and $\beta$ describe the log of cell death per dose and dose squared, respectively\textsuperscript{[29]}. Specifically, $\alpha$ describes
the sensitivity of a cell line to single strand DNA breaks while $\beta$ describes the sensitivity to double strand breaks. The factors of $\alpha$ and $\beta$ are determined by cell lines and have been characterized by the early- and late- responding tissues\cite{30}. Table [1] shows a listing of $\alpha/\beta$ ratios for various cell lines.

**Table [1]** $\alpha/\beta$ values for various cell types. Note that cancer cells typically have higher $\alpha/\beta$ ratios indicating early responding tissues.

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>$\alpha/\beta$ (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>2.0$^{[31]}$</td>
</tr>
<tr>
<td>Eye lens</td>
<td>1.2$^{[31]}$</td>
</tr>
<tr>
<td>Liver</td>
<td>1.5$^{[31]}$</td>
</tr>
<tr>
<td>Brain</td>
<td>2.1$^{[31]}$</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>3.1$^{[27]}$</td>
</tr>
<tr>
<td>Rectal Cancer</td>
<td>5.06$^{[32]}$</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>10$^{[33]}$</td>
</tr>
</tbody>
</table>

The parameters $\alpha$ and $\beta$ establish a way of denoting the biological effect ($E$) that radiation has on cells.

$$E = -\log(S)$$ \hspace{1cm} (2)

$$E = \alpha D + \beta D^2$$ \hspace{1cm} (3)

Equation [3] is the biological effect for a single acute dose, $D$. However, for $n$ separated fractionations of dose, $d$, (where $nd = D$) the biological effect is:

$$E = n(\alpha d + n\beta d^2)$$ \hspace{1cm} (4)

$$E = \alpha nd(1 + \frac{\beta nd}{\alpha})$$ \hspace{1cm} (5)
Here the quantity, \( (1 + \frac{\beta nd}{\alpha}) \), is called the relative effectiveness (RE). Dividing Equation [5] by \( \alpha \) yields a quantity known as biologically effective dose (BED). This quantity of BED is used to compare different fractionation deliveries\(^{29}\).

\[
BED = \frac{E}{\alpha} = (nd)(1 + \frac{\beta nd}{\alpha})
\]  \hspace{1cm} (6)

The BED has been proposed as a way to establish the effectiveness of isotope selection\(^{17}\). The conversion from total dose to BED for brachytherapy plans that use seeds of a single isotope has been established\(^{27}\). In those plans, local dose rates as a function of time follow the decay formula of the corresponding isotope, making the conversion simple. However, for treatment plans using hybrid seeds, the calculation is complicated and no simple formula can be derived from the BED equations. This work introduces a method, using a numerical approach, to calculate the BED from dose distributions arising from these hybrid seeds.

Since the effectiveness of a treatment is denoted by prostate dose coverage, one can calculate an effective BED distribution from an effective dose distribution. Once this is done, BED distributions of new sources can be matched to those BED distributions calculated from effective dose distributions. After the BED distribution of the new isotope is matched to the BED distribution of an effective plan, a prescription dose can be calculated for the new source. This method is described in detail in subsequent chapters.
II. Model & Method of Calculation

Treatment plans

A total of ten prostate cancer cases previously treated using single isotopes, five $^{125}$I and five $^{103}$Pd, were selected for this study. Since TG-43 bases the prescription dose on post implant CTs, these image sets were used to calculate dose distributions from seed locations. The CT image sets also provided a means of obtaining the contours of the prostate, rectum and bladder. Because the post implant CT images were used for this study, the dose distribution was calculated for this seed arrangement and then the seed activity was adjusted to ensure that 90% of the prostate is covered by the prescription dose (145 Gy for $^{125}$I and 120 Gy for $^{103}$Pd).

These image sets also provided seed distribution information. After the BED and dose distributions were calculated for the treatment isotope, the treatment isotopes were removed and replaced with a new isotope or isotope mixture (using the same seed distribution). The method used in this paper requires the seed distribution to be the same between the treatment isotope and plans generated from the treatment isotope. Therefore, work done in this paper did not investigate optimizing the generated plans through varying seed number and location.

The hybrid seeds used in this study are a $^{125}$I and $^{103}$Pd combination. The total dose in water at 1 cm away from the seed has equal dose contributions from both isotopes. Figure [4] illustrates this concept. This is why the hybrid seed is considered a
50/50 mixture. Since the hybrid seed uses a 50/50 composition, it should be expected that the dose to generate the same BED for the hybrid seeds is between the doses of the two single isotopes.

**Figure [4]** schematic of the Advantage Hybrid PdI source. The 4.5 mm long seed is comprised of both $^{103}$Pd and $^{125}$I. The seed is designed so that at $r$ equal to 1 cm, the dose contributions from the $^{103}$Pd and $^{125}$I are equivalent.

Since the prescription dose for $^{103}$Pd and $^{125}$I are known, these isotopes can be used as a verification of the method introduced in this paper. If the reference plans used the $^{125}$I isotope, a generated plan will use the $^{103}$Pd isotope. The BED distributions between the two plans are then matched within the organ of interest and a prescription dose can be back calculated from the generated plan that used $^{103}$Pd. The verification is done vice versa for reference plans using $^{103}$Pd and whose generated plan uses $^{125}$I.

It is assumed that BED coverage for the prostate within the reference plans create an effective treatment. Therefore, the same BED coverage is needed when generating
plans for $^{103}$Pd and the hybrid seeds. Only the activities of the $^{103}$Pd and hybrid seeds were allowed to change since this is what influences dose distributions and subsequently BED distribution.

**BED calculation**

A computer program was developed to calculate the BED resulting from hybrid and single isotope seeds. The BED equations for a hybrid point source and single isotope point source take the form of Equations [7]$^{[19]}$ and [8]$^{[27]}$, respectively. (The source code is contained within Appendix [A].)

$$BED(t, D_{nth}, D_{nih}) = \sum_i^n \frac{D_{nthi}}{\lambda_i} (1 - e^{-\lambda t}) + 2\left(\frac{\beta}{\alpha}\right) \sum_j \sum_i D_{nihj} \left\{ \frac{1}{\mu - \lambda_i + \lambda_j} \left[ (1 - e^{-(\lambda_i + \lambda_j) t}) - \frac{1}{\mu + \lambda_j} (1 - e^{-(\mu + \lambda_j) t}) \right] \right\}$$

$$- \frac{0.693 T_{eff}}{\alpha T_p}$$

[7]

$$BED(t, D_{0i}) = \frac{D_{0i}}{\lambda_i} (1 - e^{-\lambda t}) + 2\left(\frac{\beta}{\alpha}\right) \frac{D_0^2}{\mu - \lambda} \left\{ \frac{1}{2\lambda} (1 - e^{-2\lambda t}) - \frac{1}{\mu + \lambda} (1 - e^{-(\mu + \lambda) t}) \right\}$$

$$- \frac{0.693 T_{eff}}{\alpha T_p}$$

[8]

Here $N$ is the number of different types of seeds, $\lambda_i$ is the respective decay constant, $t$ is time, and $\mu$ is the damage recovery constant (a biological parameter). The parameters, $\alpha$ and $\beta$, are radiobiological constants associated with dose and dose squared damage; $T_p$ is the tumor potential doubling time (in this study its value is roughly 40 days)$^{[19]}$. The parameter $D_0$ is the initial dose rate. The factor $T_{eff}$ is the effective treatment time, defined as the time at which the cell killing rate equals the proliferation rate$^{[27, 28]}$. 
Figure [5] an axial CT slice with a dose distribution overlain. Colors closer to the red spectrum indicate a higher dose relative to the blue colors. The high dose regions coincide with the $^{125}$I seeds.

The first step in the process was to calculate the BED for the previously planned treatment plans which use a single isotope, $^{125}$I. The treatment plans only had dose distribution and organ contour information. (Figure [5] shows a CT slice with the corresponding $^{125}$I dose distribution overlain.) Each voxel within the dose distribution contains the dose for that voxel. Calculations will be performed on a voxel by voxel basis. Typical dose distributions contain 512 by 512 voxels per slice. There are approximately 24 slices per dose distribution image set.

An inspection of Equation [8] reveals two unknowns, $BED$ and $t$. Therefore, a system of two equations is necessary in order to calculate the BED. Using the definition
of $T_{eff}$, evaluating time derivative of the single isotope BED equation when $t$ equals $T_{eff}$ will yield a zero result\cite{27}: Mathematically, this is:

$$\frac{\partial \text{BED}}{\partial t} \bigg|_{t=T_{eff}} = 0$$  \hspace{1cm} \text{[9]}$$

In addition to the system of equations, Equations [8 & 9], and the dose distribution, biological information is needed for each voxel. This information is provided by organ contours that are generated when the treatment plan for $^{125}$I is generated. As in the dose distributions, each voxel within the contour maps contain the information as to what kind of cell that voxel is. (In this study it is bladder, prostate, rectum, or other normal tissue. Table [2] provides the biological information used in this study.) With this information, a BED distribution, analogous to a dose distribution, can be generated for the single isotope $^{125}$I seed. Subsequently, the BED coverage for the prostate is now established per case for all seed modalities since it is a requirement of this study that the BED coverage be the same for all seed modalities.

**Table [2]** Biological parameters used in BED calculation. An $\alpha/\beta$ of 3 was assumed for late responding normal tissues, since this tissue is comparable to prostate cancer\cite{37-39}.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>$\alpha$ (Gy$^{-1}$)</th>
<th>$\beta$ (Gy$^{-2}$)</th>
<th>$\mu$ (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate Cancer</td>
<td>$0.15^{[27]}$</td>
<td>$0.048^{[27]}$</td>
<td>$0.0125^{[27]}$</td>
</tr>
<tr>
<td>Rectum</td>
<td>$0.0484^{[30]}$</td>
<td>$0.012^{[30]}$</td>
<td>$0.0164^{[34]}$</td>
</tr>
<tr>
<td>Bladder</td>
<td>$0.0774^{[30]}$</td>
<td>$0.02^{[30]}$</td>
<td>$0.0313^{[35]}$</td>
</tr>
<tr>
<td>Other normal Tissue</td>
<td>$0.2^{[37]}$</td>
<td>$0.067^{[36]}$</td>
<td>$0.0488^{[36]}$</td>
</tr>
</tbody>
</table>

The next step is to generate the dose distributions for $^{103}$Pd and the hybrid seed modalities. For $^{103}$Pd, the number of unknowns will be two just as in the $^{125}$I seed modality since it is a single isotope seed. To start, a voxel is selected from the $^{125}$I BED distribution so that the calculation to obtain the initial dose rate and $t$ can be performed.
Figure [6] a zoomed in slice of a three dimensional $^{125}$I BED distribution. The large red structure are contours for the prostate and rectum (from top to bottom respectively). The red colors within the prostate contours illustrate high BED regions. Lower BED values are illustrated by colors closer to the purple. The yellow arrow indicates the area where a voxel could be selected.

Using the isotope parameters for $^{103}$Pd, the system of Equations [8 & 9] will be used again to calculate the initial dose rate for the selected voxel. The voxel selected was required to lie on the prostate periphery where there was not a high dose gradient; however, the dose value within of the voxel is to be that of the prescribed dose for $^{125}$I. Figure [6] above illustrates a selection voxel.

Having this information ($D_0$ and $T_{eff}$) and coupling it with the seed number and location obtained from the $^{125}$I treatment plan, one can calculate the air kerma strength
needed to generate this initial dose rate. It is well established that for a set of radioactive seeds distributed three dimensionally, that the air kerma strength goes as\cite{20, 23}:

\[
S = \frac{D_0^{'}}{\Lambda \sum_i g(r)_i \Phi_{an}(r)_i / r_i^2}
\]  

\[10\]

\(S\) is the air kerma strength. The following parameters are seed construction and isotope dependent: \(\Lambda\) is the dose rate constant, \(g(r)_i\) is the radial dose function, and \(\Phi_{an}(r)_i\) is the anisotropy function. The radial dose function, \(g(r)\), accounts for dose fall due to scattering and attenuation. The anisotropy function, \(\Phi_{an}(r)\), takes into account the variation in dose as a function of polar angle. The seed construction parameters are given by the manufacturer and listed in Table [3].

**Table [3]** Construction parameters used in BED calculation. \(g(r)\) and \(\Phi_{an}(r)\) were linearly interpolated from data given\cite{20}. It should be noted that the activities listed give a dose of 144 Gy 1cm away from the seed (when measured in water); the ratio of these activities must remain the same (the values themselves can change).

<table>
<thead>
<tr>
<th>Isotope</th>
<th>(S) (U)</th>
<th>(\Lambda) (cGy/h/U)</th>
<th>(g(r)) (cm)</th>
<th>(\Phi_{an}(r)) (cm)</th>
<th>(\lambda) (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^{125})I</td>
<td>0.22</td>
<td>0.95</td>
<td>1.111 - 0.139r</td>
<td>0.212 + 0.075r</td>
<td>59.4</td>
</tr>
<tr>
<td>(^{103})Pd</td>
<td>1.42</td>
<td>0.69</td>
<td>1.135 – 0.186r</td>
<td>0.267 + 0.012r</td>
<td>17</td>
</tr>
</tbody>
</table>

In calculating the \(^{103}\)Pd BED distribution, another stipulation needs to be made: the air kerma strength for each seed is to be the same. With the activity of each seed known, Equation [10] can be rearranged and solved for initial dose rate distribution.

With the initial dose rate distribution known the total dose distribution can be calculated using:

\[
D = 1.44 T_{1/2} D_0^{'}
\]

\[11\]
Here $T_{1/2}$ is the half life for the isotope.

To obtain the BED distribution, the same process is implemented as was used for $^{125}$I. However, it needs to be stated that the BED coverage within the prostate for $^{103}$Pd be the same as for $^{125}$I. This is done by manually adjusting the air kerma strength and recalculating to obtain a similar BED coverage that matches the BED coverage calculated from the treatment plan.

In generating BED distributions for the hybrid seed modality, extra steps are required. Examining Equation [7] reveals three unknowns: two initial dose rates and time. Therefore, a third equation will be needed to solve for all three variables. Since Equation [10] is constructed from parameters given by the manufacturer, an initial dose rate ratio, Equation [12], can be constructed:

$$\frac{D_{01}}{D_{02}} = \frac{S_1 \lambda_1 \sum_i^n g(r)_i \Phi_{an}(r)_i}{S_2 \lambda_2 \sum_j^m g(r)_j \Phi_{an}(r)_j}$$

For the hybrid seed, the air kerma strengths values within Equation [12] will be given by the manufacturer of the Advantage Hybrid$^{\text{TM}}$ seed (Table 3). The same process is followed as performed for $^{103}$Pd but using three equation and solving for three unknowns. When adjusting the air kerma strengths of the hybrid seed, the ratio of the air kerma strengths must match the air kerma strength ratio given by the manufacturer.

Figure [7] gives a summarized view of the calculation process for this study.
A dose map is generated using prescription specifications provided by the doctor.

Using Equations [8 & 9], a BED map is generated. Contours are shown to note that different pixels have different $\alpha$, $\beta$, and $\mu$ values depending on the cell type.

Selected point on the edge of the prostate of the $^{125}$I BED map. Using this BED value and Equations [8 & 9], $T_{\text{eff}}$ and $\phi_{\text{Pd}}^0$ are calculated for the $^{103}$Pd isotope. For the hybrid seed, Equations [7, 9, & 10] are used to find $T_{\text{eff}}$, $\phi_{\text{Pd}}^0$, and $\phi_{\text{I}}^0$.

With $\phi_{\text{Pd}}^0$ known, Equation [11] is used to find the activity. The activity is assumed to be the same for each seed. Equation [12] is then used to generate dose maps for the respective isotope or mixture.

Equations [8 & 9] or Equations [7, 9, & 10], depending on the seed, are then applied to their respective dose maps to calculate the $^{103}$Pd or hybrid BED maps.

Figure [7] a calculation flow chart from the $^{125}$I dose map to the $^{103}$Pd or hybrid BED maps.
III. Hybrid Seeds vs. Single Isotope Seeds

Patient Parameters

All ten patients selected were diagnosed and treated for early stage prostate cancer. They were treated with either $^{125}$I or $^{103}$Pd brachytherapy with a prescription dose of 145 Gy or 120 Gy, respectively. Table [4A] shows that the prostate volumes treated using $^{125}$I isotopes; Table [4B] shows the prostate volumes treated using $^{103}$Pd isotopes. Tables [5A-B] show the activity selection for the $^{125}$I and $^{103}$Pd isotopes, respectively.

Table[4A] Prostate volumes for the patients for patients who had $^{125}$I seeds

<table>
<thead>
<tr>
<th>Patient</th>
<th>Prostate Volume (cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40.4</td>
</tr>
<tr>
<td>2</td>
<td>42.4</td>
</tr>
<tr>
<td>3</td>
<td>31.4</td>
</tr>
<tr>
<td>4</td>
<td>34.2</td>
</tr>
<tr>
<td>5</td>
<td>26.1</td>
</tr>
</tbody>
</table>

Table[4B] Prostate volumes for the patients for patients who had $^{103}$Pd seeds

<table>
<thead>
<tr>
<th>Patient</th>
<th>Prostate Volume (cc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>31.08</td>
</tr>
<tr>
<td>7</td>
<td>35.83</td>
</tr>
<tr>
<td>8</td>
<td>23.10</td>
</tr>
<tr>
<td>9</td>
<td>23.29</td>
</tr>
<tr>
<td>10</td>
<td>23.62</td>
</tr>
</tbody>
</table>
Table [5A] Activities used for the $^{125}$I seeds implanted

<table>
<thead>
<tr>
<th>Patient</th>
<th>$^{125}$I seed activity mCi</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.635</td>
</tr>
<tr>
<td>2</td>
<td>0.635</td>
</tr>
<tr>
<td>3</td>
<td>0.635</td>
</tr>
<tr>
<td>4</td>
<td>0.610</td>
</tr>
<tr>
<td>5</td>
<td>0.635</td>
</tr>
</tbody>
</table>

Table [5B] Activities used for the $^{103}$Pd seeds implanted

<table>
<thead>
<tr>
<th>Patient</th>
<th>$^{103}$Pd seed activity mCi</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>1.8</td>
</tr>
<tr>
<td>7</td>
<td>1.8</td>
</tr>
<tr>
<td>8</td>
<td>1.6</td>
</tr>
<tr>
<td>9</td>
<td>1.6</td>
</tr>
<tr>
<td>10</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Results

When solving the system of equations for the $^{125}$I isotope with a prescription dose of 145 Gy, the resulting BED is 110 Gy. This BED value was used to cover the same volume within the prostate for the $^{103}$Pd isotope and hybrid seed plans. Tables [6A-B] show the dose needed to achieve this coverage for each case. The average dose for the $^{125}$I isotope, hybrid seed, and $^{103}$Pd isotope is 145 Gy, 136 Gy ($\pm$ 2 Gy), and 120 Gy, respectively. The results in Table [6A-B] confirm the expectation that the dose for the 50/50 composition, when the BED coverage is the same in each seed, be between that of $^{125}$I and $^{103}$Pd. The calculation of 120 Gy for the $^{103}$Pd isotope and 145 Gy for $^{125}$I isotope coincides with the traditional prescription values, thus verifying the method used in this study.
Table[6A] Dose (Gy) to cover 90% of the prostate when BED coverage is the same ($^{125}$I treatment isotope).

<table>
<thead>
<tr>
<th>Patient</th>
<th>$^{125}$I</th>
<th>$^{103}$Pd</th>
<th>50/50</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>145</td>
<td>120</td>
<td>137</td>
</tr>
<tr>
<td>2</td>
<td>145</td>
<td>120</td>
<td>133</td>
</tr>
<tr>
<td>3</td>
<td>145</td>
<td>120</td>
<td>138</td>
</tr>
<tr>
<td>4</td>
<td>145</td>
<td>120</td>
<td>137</td>
</tr>
<tr>
<td>5</td>
<td>145</td>
<td>120</td>
<td>137</td>
</tr>
<tr>
<td>Average</td>
<td><strong>145</strong></td>
<td><strong>120</strong></td>
<td><strong>136</strong></td>
</tr>
<tr>
<td>$\sigma$</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Table[6B] Dose (Gy) to cover 90% of the prostate when BED coverage is the same ($^{103}$Pd treatment isotope).

<table>
<thead>
<tr>
<th>Patient</th>
<th>$^{103}$Pd</th>
<th>$^{125}$I</th>
<th>50/50</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>120</td>
<td>145</td>
<td>136</td>
</tr>
<tr>
<td>7</td>
<td>120</td>
<td>145</td>
<td>139</td>
</tr>
<tr>
<td>8</td>
<td>120</td>
<td>146</td>
<td>137</td>
</tr>
<tr>
<td>9</td>
<td>120</td>
<td>145</td>
<td>136</td>
</tr>
<tr>
<td>10</td>
<td>120</td>
<td>145</td>
<td>136</td>
</tr>
<tr>
<td>Average</td>
<td><strong>120</strong></td>
<td><strong>145</strong></td>
<td><strong>137</strong></td>
</tr>
<tr>
<td>$\sigma$</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

As an example, the dose-volume histogram (DVH) for one case is illustrated in Figure [8A]. The DVH curve for the hybrid seed initially mimics the $^{125}$I DVH curve; however, at higher dose, the hybrid DVH curve behaves like the $^{103}$Pd DVH curve. Examination of the slopes within Figure [8A] correlates the result obtained in Table [6A].

The corresponding comparison for BED-volume histogram (BED-DVH) for the same case is presented in Figure [8B]. The BED-DVH curves for the different seed modalities for this case are almost the same, indicating closer BED homogeneity within the prostate between the seed modalities as compared with the dose homogeneity in the DVH comparison.
Figures [9A-B] are the same types of graphs as Figures [8A-B]; however, the reference plans used $^{103}\text{Pd}$ isotopes unlike the $^{125}\text{I}$ reference plan isotopes used in Figures [8A-B].

**Figure** [8] (A) Prostate DVH for $^{125}\text{I}$ (treatment isotope), Hybrid, and $^{103}\text{Pd}$ seeds. The prescribed BED covers 90% of prostate in each case. (B) Prostate BEDDVH for $^{125}\text{I}$ (treatment isotope), Hybrid, and $^{103}\text{Pd}$ seeds.
Figure [9] (A) Prostate DVH for $^{125}$I, Hybrid, and $^{103}$Pd (treatment isotope) seeds. The prescribed BED covers 90% of prostate in each case. (B) Prostate BEDDVH for $^{125}$I, Hybrid, and $^{103}$Pd seeds (treatment isotope).
IV. Discussion and Conclusions

Discussion

Historically, recommended prescription doses for radiation therapy have been determined by treatment efficacy and normal tissue toxicity\(^5,40,41\). The method introduced in this paper provides a way of estimating a prescription dose based on the efficacy of isotopes already clinically implemented.

In a previous study done by Chen and Nath\(^{19}\), a generalized BED equation for multi-isotope source distributions was derived. They applied the equation to calculate the BED distribution for a mixture of \(^{125}\)I and \(^{103}\)Pd seeds. They found radiobiological “cold” spots arose depending on the prescription dose used. Since the plans developed use a mixture of different seeds and seed placement, the required prescription dose to achieve the same radiobiological effect will be unique to each plan. The method outlined in this paper provides a way of calculating a prescription dose for a mixed seed distribution.

In a recent study by Todor et al. investigated using dual-isotope permanent seed implants to create focal based brachytherapy treatments in prostate cancer\(^{21}\). A focal based brachytherapy treatment plan involves escalating the BED to the foci of the disease while reducing the prescription dose to the less involved prostate. The focal based brachytherapy treatment discussed by this work involved the use of different brachytherapy sources. For the general coverage of the prostate, the authors developed
plans using either $^{125}$I or $^{103}$Pd isotope. For boost to the foci of the disease, an isotope with a shorter half-life was used (such as $^{103}$Pd or $^{131}$Cs). Using this approach, they calculated dose distributions for plans that used $^{125}$I, $^{103}$Pd, or $^{131}$Cs as sole single isotope plans or in combination to generate a higher BED to the suspected foci. For both types of calculations, conventional prescription doses were used for the general prostate coverage; however, for plans that included a foci boost using a second isotope, the prostate volume covered by the prescription dose was smaller. The plans were then compared using the equivalent uniform BED (EUBED). The method developed by Todor et al. provides a way of designing focused based brachytherapy plans that use a combination of different brachytherapy seeds. Since their method delivers focused based treatment, each treatment plan developed will have its own prescription dose.

The work provided by Todor, et al. used an analytical expression for $T_{eff}$. When using this approach of a single isotope for general coverage and a different isotope for the suspected foci of disease, the distribution of sources allows one to approximate the $T_{eff}$ locally. So the effect of a long lived isotope on the $T_{eff}$ for a short lived isotope was ignored as a first approximation. When looking at a hybrid source or a more general mixture of sources, this approximation may not be appropriate.

The two studies mentioned above investigate the consequences of using a distribution of mixed brachytherapy sources. Calculating a prescription dose for plans that use a distribution of mixed sources would have to be done on a case by case basis since each mixed seed distribution results in a specific BED distribution. The method outlined in this paper can be used to calculate the prescription dose necessary for these
mixed seed plans; however, stating a general prescription dose (as one would do when using one type of seed) is not recommended.

The method developed in this paper provides a general way of studying various seed configurations. This study limited itself to three seed configurations: pure $^{125}$I, pure $^{103}$Pd, and a 50/50 combination of $^{125}$I and $^{103}$Pd. However, other seed configurations could easily be studied such as a 75/25 mixture, a composite seed distribution (where pure seeds of $^{125}$I are interspersed with pure $^{103}$Pd seeds), as well as other seed modalities.

It is important to notice that the above prescription doses are based on $\alpha$, $\beta$, and $\mu$ values listed in Table [2]. Different $\alpha$ and $\beta$ values have been reported by different groups\textsuperscript{[39, 42, 43]}. If different $\alpha$, $\beta$, and $\mu$ values are used, the prescription dose for each seed type will change accordingly. A different isotope ratio other than the 50/50 in the hybrid seed would require a different prescription dose to achieve the same BED coverage.

Since this method is essentially organ invariant, this study could also be applied to interstitial brachytherapy not intended for the prostate (such as in breast). The basic information needed to perform this study are: seed construction parameters, number and location of seeds, isotope parameters, and finally the biological information which is obtained via the organ contours.

**Conclusions**

The method introduced uses information taken from post-implant CT images. Since analysis of treatment efficacy can only take place after permanent seed implantation, prescription doses can only be determined from these image sets. However, because a prescription BED can be calculated for these image sets, prescription doses for new isotopes can be determined by setting the BED coverage of the new
isotope equal to the BED coverage calculated for the treatment isotope. This process was verified twice when clinical prescription doses were calculated for the $^{103}$Pd and $^{125}$I isotopes.

By matching BED coverage within the prostate, a way of obtaining a prescription dose for new and novel sources for use in brachytherapy is demonstrated within this paper. The method introduced is site and isotope invariant and only requires few knowns: the treatment dose distribution, isotope information, seed construction parameters, and biological information for the areas of interest. The method was then applied to a newly proposed source: the 50/50 Advantage Hybrid for which the prescription dose calculated was 136 Gy.
V. Dosimetric Optimization for Hybrid Seed Brachytherapy

Introduction

The linear-quadratic model is currently the most used model that quantitatively describes the survivability of a cell line for a given amount of radiation. Deriving from the linear quadratic model, the biological effective dose (BED) describes the biological effects of radiation\textsuperscript{[28, 29]}. Since BED provides a way of including radiobiological parameters, quantitative expectations can be obtained\textsuperscript{[44]}. It has been suggested that BED be used as a guide in clinical decision making\textsuperscript{[26, 44-47]}. This requires the calculation of BED from dose. Several papers have addressed the conversion of dose to BED for fractionated external beam radiation therapy\textsuperscript{[26, 28, 29, 45]}, in brachytherapy\textsuperscript{[19, 27, 46]}, and for composite modalities (external beam with brachytherapy)\textsuperscript{[36]}

With modern technologies, multiple radiotherapy treatment modalities are available to treat cancer. Even to treat the same lesion, multiple modalities may be involved. An example of such radiotherapy is prostate cancer being treated with external beam radiotherapy initially followed by seed implant brachytherapy as a boost treatment. Because of the dose rate differences between various treatment modalities, the radiation dose cannot be directly used to compare treatment outcomes of the various modalities. For a lesion treated with multiple modalities, the total dose from the treatments is not meaningful. To analyze these cases, BED needs to be used.
BED based optimization is thus necessary when multiple treatment modalities are involved. Currently, dose based optimization is common but BED based optimization is not available in commercial treatment planning systems. To make BED base optimization possible, a fast dose-BED conversion must be established. Since the relation between dose and BED is not linear, dose characteristics of each seed type do not necessary reflect the characteristics of BED. It was therefore necessary to set a standard by which various seeds can be compared (BED). Through this, one can set up a correlation between BED and dose.

Depending on the dose delivery mechanism, calculation of BED from radiation dose is relatively straight forward. For fractionated external beam radiation therapy, BED follows\[^{47}\]:

$$BED = n d (1 + \frac{d}{\alpha / \beta}) - \frac{\ln 2(T - T_k)}{\alpha \cdot T_p},$$  \hspace{1cm} (13)

where, \(n\) is the number of fractions, \(d\) is the dose per fraction, \(T\) is the overall treatment time, \(T_p\) is the cell number doubling time, \(T_k\) is time at which repopulation starts after treatment has started. The terms \(\alpha\) and \(\beta\) are standard radiobiological parameters that describe radiation effects on cells.

For brachytherapy using single isotope seeds, the BED equation can be approximated for clinical applications as\[^{46}\]:

$$BED = D \{1 + 2(D_0 \cdot \lambda) (\beta / \alpha) \cdot (\frac{\kappa}{\mu - \lambda}) \} - \frac{693 \cdot T}{\alpha \cdot T_p},$$  \hspace{1cm} (14)

where

$$\kappa = (\frac{1}{1 - e^{-\lambda T_{eff}}}) \{\frac{1 - e^{-2\lambda T_{eff}}}{2 \cdot \lambda} - \frac{1 - (e^{-\lambda T_{eff}} \cdot e^{-\mu T_{eff}})}{\mu + \lambda}\}$$  \hspace{1cm} (15)
Here, \( D \) is total dose, \( D_0 \) is the initial dose rate, \( \lambda \) is the isotope decay constant, and \( T_{\text{eff}} \) is the effective treatment time. Using the equations above, conversion from total dose to BED is straightforward.

Due to the mixture of dose rates, the calculation of BED becomes more complicated for multi-isotope seeds. The mixture of dose rate prevents an analytic expression of \( T_{\text{eff}} \) and so a system of equations is needed for calculating BED. The equations necessary for calculating the BED for the multi-isotope seeds are the BED equation (Equation [7]) \([19]\) and the time derivative of the BED equation (Equation [9]) \([27]\).

For hybrid brachytherapy the computation of BED is difficult because of the mixture of dose rates. Numerical computation of BED is possible; however, this process is time consuming \([48]\). Without an efficient way of computing BED in hybrid brachytherapy, dosimetric analysis of treatment plans becomes difficult. Thus, a fast dose - BED conversion method is desirable. The purpose of this paper is to introduce a fast dose – BED conversion so that possible BED based treatment plan optimization using hybrid brachytherapy seeds is feasible.

**Materials & Methods:**

A numerical approach was established to calculate BED distributions from initial dose rate distributions for hybrid seed implant brachytherapy. The 50/50 hybrid seed contains a mixture of \( ^{103}\text{Pd} \) and \( ^{125}\text{I} \) that contribute equal amounts of dose at 1 cm away from the seed \([20]\). Other hybrid ratios are possible and their name denotes the dose contributions by each isotope (i.e. a 75/25 hybrid seed has 75% dose contribution from...
$^{125}\text{I}$ and 25% from $^{103}\text{Pd}$). Dose distributions and initial dose rate distributions were calculated using Equation [10 & 11]⁻. In Equation [8] shows a unique correspondence between total dose and BED for a single isotope source. Therefore, a dose-BED conversion table can be easily established for single isotope seeds. However, for hybrid seeds it is possible that a total dose could have multiple corollary BED values due to the dependence of BED on the initial dose rates (This idea is illustrated in Figure [10]). Equation [10] shows the relation of initial dose rate with distance. Since each isotope has a different geometric function, the ratio of dose contributions from the isotopes will vary with distance. Therefore, to generate a dose-BED conversion table for hybrid seeds, the relation of individual dose contributions to BED, (while maintaining a constant total dose) needs to be established.

**Figure [10]** illustrates an isodose line for 2 hybrid seeds. Total dose remains the same along the isodose line; however, individual isotope dose contributions will vary. Areas in blue will have relatively equal isotope dose contributions from each seed. Areas in red will have isotope dose contributions that differ from each seed. The arrows are to indicate relative distances of the seeds to points on the isodose line.
To investigate how much effect varying individual dose contributions while total dose remains invariant has on the BED value, calculations were performed to see if the number of hybrid sources influenced the relation of total dose to BED. Three dimensional dose distributions were calculated for 2, 5, 10, and 49 planar seed distribution. From these dose distributions, the BED distributions were calculated. Finally, the total dose values were coupled with their corresponding BED values and a graph of dose component versus BED was constructed.

If the variance in BED values for a certain total dose was found to be large, then a dose-BED conversion table would not be useful clinically since there would be multiple BED values for one total dose. However, if the variance in the BED value is found to be small with respect to BED value, then practical applications of a dose-BED conversion table can be considered.

Finally a seed distribution and organ contours were taken from a post-implant CT image set in accordance with the TG-43 protocol. This image set came from a patient previously treated with single isotope (\(^{125}\text{I}\)) permanent seed implant brachytherapy. The image set also contained the information about the activity of the seeds. The sources used in this plan were replaced with hybrid seeds. A dose distribution was then calculated for this hybrid seed set; the BED distribution was then calculated.

In addition to calculating dose-BED graphs for a 50/50 hybrid seed, other ratios were investigated as well. Graphs were generated for a 75/25 and 25/75 hybrid seeds. (The ratio is presented as \(^{125}\text{I}/^{103}\text{Pd}\). Activities of the seeds were adjusted to reflect the isotope ratios investigated. These activities are given in Table [7]. Note that \(A_i\), \(g(r)_i\) and
\( \Phi_{an}(r) \) remained the same for these ratios. Once the activities were adjusted, dose distributions followed by BED distributions could be calculated.

**Table [7]** air kerma strength of isotopes within the hybrid seed that generate the appropriate dose contribution ratios to a total dose of 144 Gy 1 cm from the seed in water.

<table>
<thead>
<tr>
<th>Isotope</th>
<th>50/50 (U)</th>
<th>75/25 (U)</th>
<th>25/75 (U)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^{125})I</td>
<td>0.22</td>
<td>0.33</td>
<td>0.11</td>
</tr>
<tr>
<td>(^{103})Pd</td>
<td>1.42</td>
<td>0.71</td>
<td>2.13</td>
</tr>
</tbody>
</table>

Because BED can vary depending on the tissue medium, dose vs. BED figures were generated for multiple tissue types: normal tissue, prostate, bladder wall, and rectum. Values for the \( \alpha \), \( \beta \) and \( \mu \) used in this study are given in Table [2]. For each new set of biological parameters, the numerical method had to be applied.

For each total dose vs. BED graph, a line of best fit was determined using Excel’s polynomial fit. Since these equations are analytic, fast calculations can be performed with them. In optimization implementation these derived equations should be used.

**Results:**

Because a hybrid source contains multiple isotopes, the dependency of individual isotope dose contributions to BED needs to be investigated. The BED, total dose, and individual dose components were calculated for a 49 seed distribution within a prostate medium. The individual dose contributions for a given total dose leads to a BED variance seen in Figure [11].
Figure [11] the individual isotope contributions to total dose vs. BED relation for 49 seeds. This graph was calculated for prostate.

Figures [11] show that for a specific total dose value, multiple individual dose contribution combinations from each isotope exist. This causes a variance in BED value for a specific total dose. However, the variance in BED as compared to the variance in isotope dose contributions is small.

Next, an investigation as to whether the number of seeds influences the BED value was investigated. Figure [12] shows the total dose to BED conversions for a larger range of values. The data points for 2, 5, 10, and 49 seeds are seen to overlap suggesting that number of seeds does not influence the relation of total dose to BED.
Figure [12] total dose vs. BED for differing number of seeds and distributions. This graph was calculated for prostate.

Since the BED variance was seen to be small, generating total dose vs. BED graphs can be done. Figure [13] shows the total dose vs. BED graphs for rectal tissue for hybrid seed ratios of: 50/50, 75/25 and 25/75. From these graphs, polynomial equations can be fitted. These equations allow for a quick conversion of total dose to BED. For other tissues (prostate, bladder and normal tissue), the numerical technique was applied in order to obtain the total dose vs. BED data set. A polynomial equation was generated to fit each data set. For these tissues types, the three isotope ratios were investigated.
Figure [13] shows the total dose vs. BED calculated for the rectum for hybrid seeds of ratio: 25/75, 50/50 and 75/25.

A polynomial equation to the fourth power was generated by Excel for the following scenarios: rectal, prostate, bladder and normal tissues for hybrid seeds of ratio: 50/50, 25/75 and 75/25. Coefficients for these equations as well as the R² value are listed in Table [8]. The general form of the polynomial fit is given in Equation [17].

\[
BED (D) = AD^4 + BD^3 + CD^2 + ED + F
\]  

[17]
**Table [8]** Coefficients for equations of fit for BED vs. dose data sets. NT = Normal Tissue

<table>
<thead>
<tr>
<th>Hybrid Seed Type</th>
<th>Organ</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>E</th>
<th>F</th>
<th>(R^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50/50</td>
<td>Prostate</td>
<td>1.074×10^{-8}</td>
<td>-8.877×10^{-6}</td>
<td>2.802×10^{-3}</td>
<td>0.605</td>
<td>-4.765</td>
<td>0.999</td>
</tr>
<tr>
<td>50/50</td>
<td>Rectum</td>
<td>1.670×10^{-8}</td>
<td>-1.372×10^{-3}</td>
<td>4.489×10^{-2}</td>
<td>0.246</td>
<td>-7.792</td>
<td>0.999</td>
</tr>
<tr>
<td>50/50</td>
<td>Bladder</td>
<td>3.960×10^{-7}</td>
<td>-1.216×10^{-4}</td>
<td>1.520×10^{-2}</td>
<td>-0.038</td>
<td>-2.192</td>
<td>0.999</td>
</tr>
<tr>
<td>50/50</td>
<td>NT</td>
<td>9.729×10^{-9}</td>
<td>-8.023×10^{-6}</td>
<td>2.968×10^{-2}</td>
<td>0.661</td>
<td>-4.923</td>
<td>0.999</td>
</tr>
<tr>
<td>75/25</td>
<td>Prostate</td>
<td>2.000×10^{-8}</td>
<td>-1.000×10^{-3}</td>
<td>0.004</td>
<td>0.465</td>
<td>-4.160</td>
<td>0.999</td>
</tr>
<tr>
<td>75/25</td>
<td>Rectum</td>
<td>2.000×10^{-8}</td>
<td>-2.000×10^{-5}</td>
<td>0.006</td>
<td>0.015</td>
<td>-1.979</td>
<td>0.999</td>
</tr>
<tr>
<td>75/25</td>
<td>Bladder</td>
<td>1.917×10^{-8}</td>
<td>-1.643×10^{-3}</td>
<td>5.360×10^{-2}</td>
<td>0.205</td>
<td>-3.784</td>
<td>0.999</td>
</tr>
<tr>
<td>75/25</td>
<td>NT</td>
<td>1.171×10^{-8}</td>
<td>-9.750×10^{-6}</td>
<td>3.325×10^{-3}</td>
<td>0.594</td>
<td>-5.261</td>
<td>0.999</td>
</tr>
<tr>
<td>25/75</td>
<td>Prostate</td>
<td>9.056×10^{-9}</td>
<td>-7.186×10^{-6}</td>
<td>2.232×10^{-2}</td>
<td>0.708</td>
<td>-4.388</td>
<td>1</td>
</tr>
<tr>
<td>25/75</td>
<td>Rectum</td>
<td>2.222×10^{-9}</td>
<td>-1.713×10^{-3}</td>
<td>5.017×10^{-2}</td>
<td>0.321</td>
<td>-4.402</td>
<td>0.999</td>
</tr>
<tr>
<td>25/75</td>
<td>Bladder</td>
<td>1.418×10^{-8}</td>
<td>-1.714×10^{-3}</td>
<td>3.868×10^{-3}</td>
<td>0.494</td>
<td>-5.209</td>
<td>0.999</td>
</tr>
<tr>
<td>25/75</td>
<td>NT</td>
<td>7.586×10^{-9}</td>
<td>-6.170×10^{-6}</td>
<td>2.567×10^{-2}</td>
<td>0.744</td>
<td>-4.682</td>
<td>1</td>
</tr>
</tbody>
</table>

**Discussion:**

For specific total dose values, a variance in BED values was seen. This is due to BED being a function of individual isotope dose contributions and not the total dose. Since a number of possible combinations exist to give rise to a specific total dose, this was to be expected. However, the variance in BED was seen to be small. (The variance in BED value was seen to be ~2 Gy when BED is 100 Gy, an error of 2%.) The
explanation for this is that not all possible combinations of isotope dose contributions that add up to a specific total dose will be exist in the total isodose lines. Since multiple sources were used and the isotopes within each source lie within the same voxel, dose combinations along the same isodose line will vary although not all combinations will occur.

This fast conversion of total dose to BED for low total dose values is not as accurate as it for high dose values. The variance in BED values for total dose values around 30 Gy is roughly the same as in higher total dose values (~2 Gy). This results in an uncertainty of ~7%. Therefore, the uncertainty for low BED values when compared to large BED is bigger (even though the variance was seen to be the same). The uncertainty falls at larger total dose values since the variance remains the same.

**Conclusions:**

The work presented in this paper provides a fast calculation method of converting total dose to BED for 50/50, 75/25 and 25/75 isotope ratios within hybrid seeds. These conversions are calculated for specific organs: bladder, normal tissue, prostate and rectum. In providing a fast calculation method, the need for solving a series of transcendental equations was bypassed. This allows for BED based optimization of treatment plans using these novel brachytherapy sources.
References


_Euro. Urology_. 2002;41:427-433


recommendations for permanent prostate brachytherapy postimplant dosimetric 

for head and neck cancer with positive surgical margins. _Head Neck_ 1994;16:155-
157.

laryngopharyngoesophagectomy, and gastric transposition for patients with 
recurrent hypopharyngeal and cervical esophageal carcinoma. _The Laryngoscope_ 


[16] Ling CC, Li WX, Anderson LL. The relative biological effectiveness of I-125 and 


[29] Hall EJ and Giacca AJ. Radiobiology for the Radiologist (Lippincott Williams & Wilkins, USA, 2006)


Appendices

The following code is intended to be written as a generic version of the code used within the scope of this study. There will be individual differences in details if this code is to be implemented for in other similar studies.

The code was written using Mathematica 7. Descriptions of how the built in functions within Mathematica work will not be described; however, descriptions of how the functions are used. After each section, there will be a list of the definitions used within the purpose of that section. Following this, a separation bar of “*” will occur to denote the separation of definitions from code. A description of how the code works will be displayed as necessary.
Appendix A: Importing Files & Scaling Factor

**PROSTATE:** Prostate contour information; PROSTATE when defined has positional values of either 0 or 255  
**RECTUM:** Rectum contour information; RECTUM when defined has positional values of either 0 or 255  
**BLADDER:** Bladder contour information; BLADDER when defined has positional values of either 0 or 255  
**I125DOSE:** dose distribution information  
**scalingfactor:** factor multiplying the I125DOSE so that the prostate dose coverage is 145 Gy  
**PixelCoordinateRow:** Seed position information stored as a 1d list  
**ProstateDose:** selected portion of I125DOSE that coincides with the PROSTATE. When defined, the positional values will either be 0 or the values obtained from I125DOSE  
**SingleDoseValuesForProstate:** culled version of Prostate dose; the values within this definition are only that obtained from I125DOSE

```math
SetDirectory["Wherever the information is located "];

PROSTATE = Import["PatientNameProstateContour.raw", "Data Format"];
RECTUM = Import["PatientNameRectumContour", "Data Format"];  
BLADDER = Import["PatientNameBladderContour","Data Format"];  
I125DOSE = scalingfactor*Import["PatientName_I125_Dose_Information","Data Format"];  
PixelCoordinateRow = Import["PatientNamePixelCoordinatesRow","Data Format"]
```

The purpose of the scaling factor is to make sure that the dose distribution imported meets the prescription requirements. The prescription requirement for the I125 reference plan is that the prostate volume receive a 145 Gy over 90% of the volume. This scaling factor is the multiplied within the definition or I125DOSE (as already indicated).

```math
ProstateDose = Table[
   If[
      PROSTATE[[x]] == 0, 0, I125DOSE[[x]]
   ],
   {x,1, number of pixels within I125DOSE}]

SingleDoseValuesForProstate=Select[ProstateDose,>#0&];
```
Appendix A (continued)

N[
  Length[
    Select[
      potential_scaling_factor*SingleDoseValuesForProstate, # > 145 &
    ]
  ]
]/Length[SingleDoseValuesForProstate]]

When the potential_scaling_factor is 1, the output of the previous line will also be 1. The potential_scaling_factor is manually adjusted until the output of the previous line is .9. The value of the potential scaling factor is now the value of the scaling factor.
Appendix B: Geometry Portion Calculation

This part is intended to calculate the geometrical portions of the dose equation (Equation [11]) separately from the rest of the equation. Aside from the geometrical part, everything else can be reduce to a 1d list calculation (this reduces the calculation time considerably)

I125RadialDoseFunctionDATA: Radial Dose Function (RDF) Data for I125; The RDF data was given by the manufacturer in this study

RDF[r]: radial dose function for I125. Generated as a fit to I125RadialDoseFunctionDATA. A function of distance, r

I125ΦDATA: Anisotropy function data for I125. The anisotropy function data was given by the manufacturer in this study

Φ[r]: anisotropy function fitted to I125ΦDATA

pl_: pixel to length conversion factor for dimension _ (either x, y, or z)

PD103RDFDATA: Radial Dose Function (RDF) Data for Pd103; The RDF data was given by the manufacturer in this study

rdf[r]: radial dose function for Pd103. Generated as a fit to PD103RDFDATA. A function of distance, r

PD103φDATA: Anisotropy function data for Pd103. The anisotropy function data was given by the manufacturer in this study

φ[r]: anisotropy function fitted to PD103φDATA

g: number of seeds for the case being analyzed for

p: list of seed positions

c: local variable specifying the position of the seeds

GeometrySeedsRDFΦ[r]: Equation that calculates the geometrical portion for the \(^{125}\text{I}\) BED distribution

GeometrySeedsrdfφ[r]: Equation that calculates the geometrical portion for the \(^{103}\text{Pd}\) BED distribution

RDFMap: geometry function distribution for \(^{125}\text{I}\)

rdfMapPd: geometry function distribution for \(^{103}\text{Pd}\)

************************************************************************************************************************

Since geometrical considerations are required for this study, generation of the Radial Dose Functions and Anisotropy Functions are needed. Data for these functions are given as a function of distance by the manufacturer. A linear fit is conducted for this data for the respective functions. The functions are then coupled together within a function.

One should note that generally the data given for the anisotropy and radial dose functions are given in terms of length. The importing of dose distributions and subsequent distributions will be in terms of discrete points or pixels. Appropriate pixel to length conversion factors are needed for the respective dimensions. These parameters are not listed here since this may or may not be the case generally; however, this information can be added by simply multiplying each dimensional variable (x, y, z) within the anisotropy and radial dose functions by an appropriate \(pl_\).
Appendix B (continued)

I125RadialDoseFunctionDATA={List};

RDF[r_]:=Fit[
    I125RadialDoseFunctionDATA, {1,r},r
]

I125ΦDATA={List};

Φ[r_]:=Fit[
    I125ΦDATA, {1,r},r
]

Since the geometry dependence is 3 dimensional, we need to account for this in our variable.

Let \( r = \sqrt{(\text{With}\{c=p, c[[n, 3]]-x\})^2 + (\text{With}\{c=p, c[[n, 2]]-y\})^2 + (\text{With}\{c=p, c[[n, 1]]-z\})^2} \)

RDFΦ[z_,y_,x_]:=RDF[z,y,x]*Φ [z,y,x]

PD103RDFDATA={List};

rdf[r_]:=Fit[
    PD103RDFDATA, {1,r},r
]

PD103φDATA={List of data};

φ[r_]:=Fit[
    PD103φDATA, {1,r},r
]

Again, since the geometry dependence is 3 dimensional, we need to account for this in our variable.

Let \( r = \sqrt{(\text{With}\{c=p, c[[n, 3]]-x\})^2 + (\text{With}\{c=p, c[[n, 2]]-y\})^2 + (\text{With}\{c=p, c[[n, 1]]-z\})^2} \)

rdfφ[z_,y_,x_]:=rdf[z,y,x]*φ [z,y,x]

p = {List of seed positions in 3 dimensions}

g = Length[p];
Appendix B (continued)

\[
\text{RadiusSquared}[z_, y_, x_] := (x^2 + y^2 + z^2)
\]

\[
\text{GeometrySeedsRDF}[z_, y_, x_] := \text{If[}
\quad \text{FreeQ[p, \{z, y, x\}] == True,}
\quad \text{Sum}[\text{RDF}[z, y, x]/\text{RadiusSquared}[z, y, x],
\quad \{n, 1, g\}], 0
\]
\]

\[
\text{GeometrySeedsrdf}[z_, y_, x_] := \text{If[}
\quad \text{FreeQ[p, \{z, y, x\}] == True,}
\quad \text{Sum}[\text{rdf}[z, y, x]/\text{RadiusSquared}[z, y, x],
\quad \{n, 1, g\}], 0
\]
\]

\[
\text{RDFMap} = \text{Table[}
\quad \text{GeometrySeedsRDF}[z, y, x],
\quad \{z, 1, \text{number of slices}\}, \{y, 1, \text{number of pixels in y direction}\},
\quad \{x, 1, \text{number of pixels in x direction}\}
\]
\]

\[
\text{rdfMappd} = \text{Table[}
\quad \text{GeometrySeedsrdf}[z, y, x],
\quad \{z, 1, \text{number of slices}\}, \{y, 1, \text{number of pixels in y direction}\},
\quad \{x, 1, \text{number of pixels in x direction}\}
\]
\]

\[
d = \text{Flatten[RDFMap};
\]

\[
z = \text{Flatten[rdfMappd};
\]

\[
\text{Export["RDFMap", d, "Data Format"]}
\]

\[
\text{Export["rdfMappd", z, "Data Format"]}
\]
Appendix C: BED Calculation

\( \Delta \): initial dose rate for \( ^{125}\text{I} \)
\( \delta \): initial dose rate for \( ^{103}\text{Pd} \)
I125DOSE: dose distribution for \( ^{125}\text{I} \)
TH125: half life for \( ^{125}\text{I} \)

RECTUM: Rectum voxel positions
PROSTATE: Prostate voxel positions
BLADDER: Bladder voxel positions

\( \alpha \): coefficient for DNA damage proportional to dose
\( \beta \): coefficient for DNA damage proportional to dose\(^2 \)

\( \mu \): repair constant

\( \lambda_{125}\): \( ^{125}\text{I} \) decay constant
\( \lambda_{\text{Pd}}\): \( ^{103}\text{Pd} \) decay constant

TP: Tumor Potential doubling time

TR\_ = Tissue Repair constant; i.e. (NT = normal tissue):

PixelDesignation: Tells the code which biological parameters to use

d: local variable used to temporarily store the \( T_{\text{eff}} \) distribution.

\( t \): variable to temporarily store the \( T_{\text{eff}} \) distribution
Teffective-single-allslice: \( T_{\text{eff}} \) distribution file for \( ^{125}\text{I} \)
BEDSingle-allsllices: BED distribution for \( ^{125}\text{I} \)
BEDSSPD: BED value of the selected voxel

Equations: set of equations used to solve for the initial dose rates and \( T_{\text{eff}} \)

EffectiveTreatmentTimeSS: \( T_{\text{eff}} \) for the selected voxel for \( ^{103}\text{Pd} \)
PD103InitialDoseRateSS: \( \delta \) for the selected voxel for \( ^{103}\text{Pd} \)
TotalDosePD103SS: \( ^{103}\text{Pd} \) dose distribution
PDTDMSS: \( ^{103}\text{Pd} \) dose distribution but with seed positions taken into account; dose

values at seed position taken default to 2000

skPDss: air kerma strength for each seed for \( ^{103}\text{Pd} \)

Teffective-singlePD-allslice: \( T_{\text{eff}} \) distribution file for \( ^{103}\text{Pd} \)
BEDSingle-allsllicesPd: BED distribution for \( ^{103}\text{Pd} \)
PD103InitialDoseRatePd: \( \delta \) for the selected voxel for hybrid seed
EffectiveTreatmentTimePd: \( T_{\text{eff}} \) for the selected voxel for hybrid seed

I125InitialDoseRatePd: \( \Delta \) for the selected voxel for hybrid seed
SK: air kerma strength for \( ^{125}\text{I} \) portion of the hybrid seed

sk: air kerma strength for \( ^{103}\text{Pd} \) portion of the hybrid seed

SKI125: value of the air kerma strength for \( ^{125}\text{I} \) portion of the hybrid seed for a specified

position

TotalDoseI125: \( ^{125}\text{I} \) dose portion for the hybrid dose distribution
I125TDM: \( ^{125}\text{I} \) dose portion for the hybrid dose distribution with seed positions

skPD: value of the air kerma strength for \( ^{103}\text{Pd} \) portion of the hybrid seed for a specified

position

TotalDosePD103: \( ^{103}\text{Pd} \) dose portion for the hybrid dose distribution
PDTDM: \( ^{103}\text{Pd} \) dose portion for the hybrid dose distribution with seed positions

TD: dose distribution for hybrid seed
Appendix C (continued)

Teffective-mixed-allslice: \( T_{\text{eff}} \) distribution file for hybrid seeds
BEDHYBRID-allslices: BED distribution for hybrid seeds

*************************************************** *********************

The first thing that needs to be done is to convert the dose distribution file to an initial dose rate distribution file since the BED calculation uses initial dose rates. The BED calculation also requires to know the \( T_{\text{eff}} \) distribution. Therefore, calculation of \( T_{\text{eff}} \) prior to the BED calculation is needed.

For \(^{125}\text{I} \) BED Calculation:

\[
\Delta = \text{Table}\[
\text{If}[\text{I125DOSE[[x]]}<0, 0, \text{I125DOSE[[x]]}/(1.44\times \text{TH125})],
\{x,1, \text{number of pixels in dose distribution}\}\];
\]

\[
\text{PixelDesignation}[x_] := \\
\text{If}[\text{(RECTUM[[x]] + PROSTATE[[x]] + BLADDER[[x]])} == 0, \alpha = .20; \beta = \alpha / 3.00; \mu = \text{Log}[2]/\text{TRNT}, \\
\text{If}[\text{(RECTUM[[x]] + BLADDER[[x]])} == 0, \alpha = .15; \beta = \alpha / 3.10; \mu = \text{Log}[2]/\text{TRPROSTATE}, \\
\text{If}[\text{BLADDER[[x]]} == 0, \alpha = .0484; \beta = \alpha / 3.90; \mu = \text{Log}[2]/\text{TRRECTUM}, \\
\alpha = .0774; \beta = \alpha / 3.95, \mu = \text{Log}[2]/\text{TRBLADDER}]
\]
\]

\[
d = \text{Table}[\text{If}[\text{I125DOSE[[x]]} < 1, Q=0, \text{PixelDesignation}[x]; Q=\mu/\nu, \text{FindRoot}[\Delta[[x]] e^{2\lambda_125 t + 2(\beta/\alpha) \Delta[[x]]} - (\mu - \lambda_125 t) (e^{-2\lambda_125 t} - e^{-\mu - \lambda_125 t}) - 0.693/\alpha \times TP), \\
\{t,50\}]
\],
\{x, 1, \text{number of pixels in dose distribution}\}];
\]

\text{Export["Teffective-single-allslice", d, "Data Format"]}
Appendix C (continued)

t = Import["Teffective-single-allslice", "Data Format"];

d = Table[
   If[I125DOSE[[x]] < 1, Q = 0,
   PixelDesignation[x];
   ∆[[x]]/λ125 (1-e^{-λ125*t[[x]]}) + 2(β/α) ∆^2/(μ - λ125)*
   *(1/(2*λ125))(1-e^{-2λ125*t[[x]]}) - 1/(μ + λ125) (1-e^{-(μ+λ125)*t[[x]]}))
   - (.693* t[[x]])/(α *TP)
   ],
   {x, 1, number of pixels in dose distribution }];

Export["BEDSingle-allslices", d, "Data Format"]

For $^{103}$Pd BED Calculation

The BED distribution for $^{125}$I plans has now been calculated. As verification of
the method, a prescription dose will be calculated for $^{103}$Pd. First, a pixel must be
selected to provide a value for the BED. From this, the initial dose rate and $T_{eff}$ can be
calculated. After which, the activity of the each seed can be calculated allowing for the
initial dose rate distribution to be calculated.

BEDSingleallslices = Import["BEDSingle-allslices", "Data Format"];

BEDSSPD = BEDSingleallslices[[pixel position of selected voxel]]

The method for deriving the BED distribution is exactly the same for $^{103}$Pd as for
50/50 hybrid seeds. The only difference is the set of equations that are used to solve for
initial dose rates and $T_{eff}$.

Equations[t_, δ_]:= {
   δ e^{-λPd *t} + 2(β/α) δ^2/(μ - λPd)(e^{-2λPd*t} - e^{-(μ + λPd)*t}) - 0.693/(α × TP)==0,
   0 == δ/λPd (1-e^{-2λPd*t}) + 2(β/α) δ^2/(μ - λPd)*
   *(1/(2*λPd))(1-e^{-2λPd*t}) - 1/(μ + λPd)(1-e^{-(μ+λPd)*t}))
   - (.693* t)/(α *TP) - BEDSSPD
}

Block[{x = pixel position of selected voxel, α =.15, β = α /3.10, μ =
   Log[2]/TRPROSTATE},]
Appendix C (continued)

\[
d = \{Q, L\} = \{t, \delta\}./\text{FindRoot[ Equations}\[t, \delta\], \{\{t, \text{initial guess, min of range, max of range}\}, \{\delta, \text{initial guess, min of range, max of range}\}\}\];
\]

\[
w = \{\text{Part}[d,1],\text{Part}[d,2]\};
\]

\[
\{\text{EffectiveTreatmentTimeSS} = \text{Part}[w,1], \text{PD103InitialDoseRateSS} = \text{Part}[w,2]\}
\]

With the initial dose rate and \(T_{\text{eff}}\) for \(^{103}\text{Pd}\) for the selected voxel calculated, the air kerma strength needs to be calculated for each seed.

\[
\text{skPDss}[z_,y_,x_] := \frac{\text{PD103InitialDoseRateSS}}{\text{Sum}[\text{drc}*\phi[z, y, x]/\text{RadiusSquared}[z, y, x]], \{n, 1, g\}};
\]

Take note, when actually calculating \(skss\), the voxel position must be translated to 3d coordinates. With activity calculated, dose distribution can be calculated.

\[
\text{TotalDosePD103SS} = 1.44*\text{THPD}^*\text{drc}^*\text{skPDss}^*\text{Import["rdfMap pd","Real32"]};
\]

\[
\text{PDTDMSS} = \text{Table[ If[PixelCoordinatesRow[[x]] == 1, 2000, Q = TotalDosePD103SS[[x]]; If[Q<=0,0,Q]], \{x, 1, \text{number of pixels in dose distribution}\};}
\]

After the dose distribution is calculated, the remaining steps are the same as in the \(^{125}\text{I}\) BED calculation but parameters are appropriately changed.

\[
\delta = \text{Table[ If[ PDTDMSS[[x]]<0, 0, PDTDMSS[[x]]/(1.44*\text{THPD}) ], \{x, 1, \text{number of pixels in dose distribution}\};}
\]
Appendix C (continued)

d = Table[
  If[1125DOSE[[x]] < 1, Q = 0,
    PixelDesignation[[x]];
    Q = t/.
    FindRoot[δ[[x]] e^{-\lambda Pd t} + 2 (β/α) (\delta[[x]]^2/\mu - \lambda Pd) (1/e^{-(\mu + \lambda Pd) t} - (e^t)) - 0.693/(\alpha \times TP),
          {t, 50}]
    ],

  {x, 1, number of pixels in dose distribution}];

Export["Teffective-singlePD-allslice", d, "Data Format"]

t = Import["Teffective-singlePD-allslice", "Data Format"];

d = Table[
  If[1125DOSE[[x]] < 1, Q = 0,
    PixelDesignation[[x]];
    (\delta/\lambda Pd) (1/e^{-\lambda Pd t}) + 2 (β/α) ((\delta^2/\mu - \lambda Pd) (1/(2*\lambda Pd)) (1 - e^{-2 \lambda Pd t}) - (1/(\mu + \lambda Pd)) (1 - e^{-(\mu + \lambda Pd) t}) - (0.693 t)/(\alpha \times TP))
  ],

  {x, 1, number of pixels in dose distribution}];

Export["BEDSingle-allslicesPd", d, "Data Format"]

For 50/50 Hybrid Seed BED Calculation
Since there are 3 unknowns, t, δ, and Δ, there is a need to rewrite the Equations
Appendix C (continued)

Equations\[t, \delta, \Delta\] := 
\begin{align*}
0 &= \delta e^{-\gamma t} + \Delta e^{-\gamma t} + \\
&\quad 2(\beta/\alpha)
\left((\delta^2/(\mu - \lambda Pd))(1/2\lambda Pd t) - e^{-\gamma t} - e^-(\mu + \lambda Pd)t)\right) + \\
&\quad ((\delta \Delta)/(\mu - \lambda Pd)) \left(e^{-\gamma t}\lambda Pd + \lambda_{125} - e^{-\gamma t} + \lambda_{125}\right) \\
&\quad + ((\delta \Delta)/(\mu - \lambda_{125})) \left(e^{-\gamma t}\lambda Pd + \lambda_{125} - e^{-\gamma t} + \lambda_{125}\right) \\
&\quad - .693/(TP * \alpha),
\end{align*}

\begin{align*}
0 &= (\delta/\lambda Pd)(1 - e^{-\gamma t}) + (\Delta/\lambda_{125})(1 - e^{-\gamma t}) + \\
&\quad 2(\beta/\alpha)
\left((\delta^2/(\mu - \lambda Pd))(1/2\lambda Pd t) - (1/(\mu + \lambda Pd))(1 - e^{-\gamma t} - e^-(\mu + \lambda Pd)t)\right) + \\
&\quad ((\Delta^2/(\mu - \lambda_{125}))(1/(2\lambda_{125}))(1 - e^{-\gamma t} - e^-(\mu + \lambda_{125}))) + \\
&\quad ((\delta \Delta)/(\mu - \lambda Pd))(1/(\lambda Pd + \lambda_{125}))(1 - e^{-\gamma t}\lambda Pd + \lambda_{125}) - \\
&\quad \left(1/(\mu + \lambda_{125})(1 - e^{-\gamma t} + \lambda_{125})\right) \\
&\quad + ((\delta \Delta)/(\mu - \lambda_{125}))(1/(\lambda Pd + \lambda_{125}))(1 - e^{-\gamma t}\lambda Pd + \lambda_{125}) - (1/(\mu + \lambda Pd)) (1-e^{-\gamma t} + \lambda_{125}) \\
&\quad \right) - (.693*t)/(TP*\alpha) - BEDSSPD
\end{align*}

\[\Delta/\delta ==
\begin{align*}
&\quad .22*\text{DRC}*\text{Sum}[\text{RDF}\Phi(z, y, x)/\text{Radius}^2[z, y, x],\{n, 1, g}] \\
&\quad / (1.42*\text{drc}*\text{Sum}[\text{rdf}\varphi(z, y, x)/\text{Radius}^2[z, y, x],\{n, 1, g}]),
\end{align*}

Similar steps are taken as in calculation for $^{103}$Pd. First the initial dose rates need to be calculated first so that the air kerma strength of each seed can then be determined. With the air kerma strengths known, dose and BED distributions can be calculated. Please note the calculations for the initial dose rates and $T_{eff}$ are in three dimensions, so the Equations and PixelDesignation should change appropriately.

Block[\{\{z, y, x\} = \text{pixel position of selected voxel}, \alpha = .15, \beta = \alpha / 3.10, \\
\mu = \text{Log}[2]/\text{TRPROSTATE}\},
\begin{align*}
d &= \{Q, L, M\} = \{t, \delta, \Delta\}/.
\end{align*}

FindRoot[
\begin{align*}
\text{Equations}[t, \delta, \Delta, \{\{t, \text{initial guess, min of range, max of range}\}, \\
\{\delta, \text{initial guess, min of range, max of range}\}, \{\Delta, \text{initial guess, min of range, max of range}\}\}]
\end{align*}
];
Appendix C (continued)

\[ w = \{ \text{Part}[d,1], \text{Part}[d,2], \text{Part}[d,3] \}; \]

\{
\text{EffectiveTreatmentTime} = \text{Part}[w,1],
\text{PD103InitialDoseRate} = \text{Part}[w,2],
\text{I125InitialDoseRate} = \text{Part}[w,3]
\}

Dose distributions can be calculated from the determined initial dose rates.

\[ \text{SK}[z_,y_,x_] := \frac{\text{I125InitialDoseRate}}{\sum \text{DRC RDF} \Phi[z, y, x]/\text{RadiusSquared}[z, y, x], \{n,1,g\}}; \]

\[ \text{sk}[z_,y_,x_] := \frac{\text{PD103InitialDoseRate}}{\sum \text{drc RDF} \phi[z, y, x]/\text{RadiusSquared}[z, y, x], \{n,1,g\}}; \]

TotalDoseI125 = 1.44*TH125*DRC*SKI125*Import["RDFMap","Real32"]; 

I125TDM = Table[
If[ PixelCoordinatesRow[[x]] == 1, 2000, 
Q = TotalDoseI125[[x]]; 
If[Q<=0, 0, Q]
],
{x,1, number of pixels in dose distribution }];

Export["I125TDM", I125TDM, "Data Format"]; 

TotalDosePD103 = 1.44*THPD*drc*skPD*Import["rdfMappd","Real32"]; 

PDTDM = Table[
If[ PixelCoordinatesRow[[x]] == 1, 2000, 
Q = TotalDosePD103[[x]]; 
If[Q<=0, 0, Q]
],
{x,1, number of pixels in dose distribution }];

Export["PDTDM", PDTDM, " Data Format "]

TD = PDTDM + I125TD;
Appendix C (continued)

Export["TD", TD, "Real32"];

With the total dose distribution calculated, BED distribution calculation follows the same steps as in the previous calculations.

\[ \delta = \frac{PDTD}{1.44 \times THPD}; \]
\[ \Delta = \frac{1125TD}{1.44 \times TH125}; \]

\[ d = Table[ \]
\[ \text{If}[(\delta[[x]] + \Delta[[x]]) == 0, \]
\[ Q=0, \]
\[ \text{PixelDesignation}[[x]]; \]
\[ \text{Re}[Q=t/. \]
\[ \text{FindRoot}[\delta e^{-\lambda Pd t} + \Delta e^{-\lambda 125 t} + \]
\[ 2(\beta/\alpha) \left( ((\delta[[x]])^2/(\mu - \lambda Pd))(e^{2(\lambda Pd t)} - e^{-(\mu + \lambda Pd) t}) + \right. \]
\[ \left. + ((\Delta[[x]])^2/(\mu - \lambda 125))(e^{-2}\lambda 125 t - e^{-(\mu + \lambda 125) t}) + \right) \]
\[ + ((\delta[[x]] \Delta[[x]])/(\mu - \lambda Pd))(e^{t(\lambda Pd + \lambda 125)} - e^{-(\mu + \lambda 125) t}) + \]
\[ + ((\delta[[x]] \Delta[[x]])/(\mu - \lambda 125))(e^{t(\lambda Pd + \lambda 125)} - e^{-(\mu + \lambda Pd) t}) \}
\[ -.693/(TP \ast \alpha), \{t,100} \]
\[ ]; \]
\[ \text{If}[Q>0\&\&Q!=100., Q, Q=0], \]
\[ \{x, 1, \text{number of pixels in dose distribution} \}]; \]

Export["Teffective-mixed-allslice", d, "Data Format"];

t = Import["Teffective-mixed-allslice", "Data Format"];
Appendix C (continued)

d = Table[
   If[(\[\delta\][[x]] + \[\Delta\][[x]])==0,
      Q=0,
      PixelDesignation[[x]];
      
      (\[\delta\][[x]]/\[\lambda\]Pd)(1- e^{-\[\lambda\]Pd t}) + (\[\Delta\][[x]]/\[\lambda\]125)(1- e^{-\[\lambda\]125 t}) +
      2(\[\beta\]/\[\alpha\])
      
      ((\[\delta\][[x]]^2/(\[\mu\] - \[\lambda\]Pd))(1/(2*\[\lambda\]Pd))(1- e^{-\[\lambda\]Pd t}) - (1/(\[\mu\] + \[\lambda\]Pd))(1- e^{-\[\mu\]+(\[\lambda\]Pd) t}))
      + ((\[\Delta\][[x]]^2/(\[\mu\] - \[\lambda\]125))(1/(2*\[\lambda\]125))(1- e^{-2\[\lambda\]125 t}) - (1/(\[\mu\] + \[\lambda\]125))(1- e^{-\[\mu\]+(\[\lambda\]125) t}))
      + ((\[\delta\][[x]]*\[\Delta\][[x]])/(\[\mu\] - \[\lambda\]Pd))
      
      (1/(\[\lambda\]Pd + \[\lambda\]125)) (1 - e^{-\[\lambda\]Pd +\[\lambda\]125 t}) - (1/(\[\mu\] + \[\lambda\]125)) (1- e^{-\[\mu\]+(\[\lambda\]125) t})
      )
      + ((\[\delta\][[x]]*\[\Delta\][[x]])/(\[\mu\] - \[\lambda\]125))
      
      (1/(\[\lambda\]Pd + \[\lambda\]125)) (1 - e^{-\[\lambda\]Pd +\[\lambda\]125 t}) - (1/(\[\mu\] + \[\lambda\]125)) (1- e^{-\[\mu\]+(\[\lambda\]125) t})
      )
      
      ) - (.693*t)/(TP*\[\alpha\])
   ],
   {x, 1, number of pixels in dose distribution}];

Export["BEDHYBRID-allslices", d, "Data Format"]