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Prostate cancer focal brachytherapy: Improving treatment plan robustness using a convolved dose rate model

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Abstract

Low-risk prostate cancer can be treated by focal brachytherapy, in which small radioactive seeds are implanted directly into the prostate at targeted locations. Treatment planning is complicated by post-operative displacement of the seeds from their intended location. This reduces the actual dose received by the prostate and increases the dose to surrounding tissue such as the urethra and rectum, potentially causing harmful side-effects. Current treatment planning methods do not explicitly incorporate the effect of post-operative seed displacement. To address this, the radiation dose rate function used during planning is modified to reflect displacement using convolution. This new dose rate model enables plans to be produced automatically and efficiently. Simulation experiments show that treatment plans made using the convolved dose rate function are more robust to seed displacement than those using the original unconvolved dose, preserving treatment efficacy but giving increased protection to surrounding tissue.

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1 Introduction

Prostate cancer is the most common cancer diagnosed in Australia (excluding skin cancer) and the third most common cause of cancer death. Approximately one in five men will be diagnosed with prostate cancer by the age of 85. However, there is a greater than 94% chance of surviving this cancer 5 years from the time of diagnosis [1]. Prostate cancer treatments are therefore effective but side effects of treatment, which may include rectal, bladder and erectile dysfunction, can have an adverse impact on quality of life [20].

Common treatments for localised prostate cancer (i.e. confined to the prostate capsule) include surgical removal of the prostate, radiotherapy using high energy x-rays, or brachytherapy,

whereby small radioactive “seeds” are permanently or temporarily implanted into the prostate. These treatments typically target the entire prostate gland and may damage the urethra (which passes through the prostate), the rectum (which sits below the prostate) and/or the nerves that run alongside the prostate and are essential for erectile function.

This “whole gland” approach to treatment has been necessary because accurately localising and targeting tumours within the prostate has previously been very difficult. Advances in imaging and treatment delivery now make it possible to accurately treat sub-volumes of the prostate and thus limit damage to the healthy surrounding tissues [19]. This treatment approach is commonly referred to as “focal therapy”, and permanently implanting radioactive I-125 seeds into these sub-volumes has been proposed as an effective form of treatment to maintain high rates of tumour control whilst minimising treatment side effects [13].

Previous research by the authors has demonstrated that, with knowledge of the specific biology of the tumour, radiation dose distributions can be planned which optimise tumour control and minimise treatment side effects [11, 10]. Furthermore, these treatment plans can be generated using a fast optimisation algorithm [3, 12]. The plans generated describe precise locations within the prostate for radioactive seed implantation. These seeds are implanted under ultrasound guidance, however, whilst implantation may be precise, the seeds can migrate from their implanted position as a result of tissue swelling and bleeding. With this migration brings the risk of ineffective treatment due to underdosing of the tumour and/or overdosing of the healthy tissue. Accordingly, that original research is now extended. It is shown how, using a convolved dose model, robust focal therapy plans can be developed which preserve treatment efficacy and reduce radiation dose to organs at risk even under post-operative seed displacement. These can be rapidly generated, enabling them to be developed at the time the radioactive seeds are surgically implanted.

The following section describes the prostate brachytherapy procedure, and summarises the assumptions and constraints for automatic seed plan generation. Convolution of the dose rate function is outlined in Section 3. This is followed by computational experiments and discussion of the results, including their implication for clinicians.

2 Background

2.1 Prostate Brachytherapy

Transperineal implantation of radioactive seeds under ultrasound guidance is a common form of treatment for low risk prostate cancer [6]. The procedure requires an ultrasound probe to be placed in the rectum and needles, containing strands of radioactive seeds, are inserted through the holes of a template placed on the perineum, as shown in Figure 1. The ultrasound probe guides the depth of penetration into the prostate. Treatment planning, prior to implantation, requires capture of ultrasound images in 5mm increments, from the base of the prostate (which sits adjacent to the bladder) to the apex. These ultrasound images capture the size and shape of the prostate relative to the template grid which is used to guide needle insertion.

A treatment plan is generated such that radioactive seed placement meets local treatment planning objectives. These planning objectives define the minimum radiation dose that should be delivered to the target (commonly the whole prostate gland) that will also meet radiation dose constraints that will minimise the harm to normal tissues [6]. Using this technique, the radioactive seeds remain in place indefinitely and the radiation dose rate declines slowly as a result of the radioactive decay of the I-125 sources.

In conventional, whole gland brachytherapy, a safety margin is added to the prostate boundary to account for the likelihood of seed movement or migration after implantation. This margin,

which is typically 0 – 5 mm, creates a Planning Treatment Volume (PTV). This margin around the prostate results in irradiation of the normal surrounding tissue but is necessary to avoid the risk of underdosing the prostate if a seed migrates away from the prostate boundary. In practice, seeds typically migrate from their intended position in a random fashion and as such can equally move into normal tissues increasing the risk of toxicity.

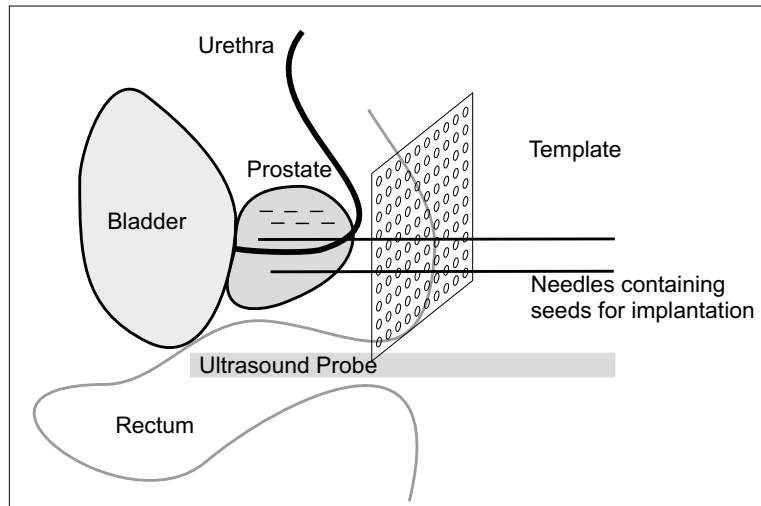


Figure 1: Prostate brachytherapy operation showing major relevant body structures, seeds implanted in prostate, seed containing needles and template

The approach presented in this publication considers the possibility of random displacement of each individual seed to minimise the risk of both underdosing the target volume (which is the prostate in whole gland therapy, or the tumour in focal therapy) and overdosing the organs at risk (the urethra and rectum). The treatment planning objectives are based on a biological model that takes into account the radiosensitivity of the tumour cells, the tumour cell density and other features of the tumour that may determine the need for high doses of radiation such as the aggressiveness of the tumour [11]. This biological model determines a Tumour Control Probability (TCP) value which is a relative measure of the likelihood of disease control following a given dose of radiation. Due to uncertainties in the model parameters, a TCP value can only be considered in a relative sense. However, it was shown by Haworth et al, that a TCP value of 0.62 results in a high likelihood of tumour control at 5 years post treatment [11]. This value was derived from the post-operative distribution of real seeds that were implanted at positions according to a treatment plan and then displaced due to normal tissue effects such as swelling and bleeding. To achieve a TCP value of 0.62, a treatment plan must be created that accounts for seed migration, and thus a target higher than this must be set during planning. It has been previously shown by the authors that seed displacements can be modelled and how treatment plans can be created that take into account seed migration [3, 12].

2.2 Automatic Treatment Planning

Prostate Structure and Dose Calculations:

- The prostate is modelled within a bounding volume (planning grid) consisting of voxels: $x = 5, y = 5, z = 5$ mm, labelled according to tissue type: prostate, rectum, urethra, PTV.

- The tumour cell density of each voxel is assigned one of five values according to tumour location statistics determined by Zeng et al. [10, 21].
- The objective function is TCP. The calculation is given in [3], using radiation dose rate function Equation 1, based on voxels of $x = 2, y = 2, z = 5\text{mm}$.

Seed Placement Constraints:

- Seed placement and radiation dose conform with the American Brachytherapy Society (ABS) recommendations [6].
- Seeds can only be placed at points spaced 5mm apart in each of the x, y and z axes, no two seeds can be on adjacent points, all seeds must be within the planning target volume (PTV), no seeds can be in the central column (which aligns with the urethra), no seeds can be placed between the PTV and rectum.
- The proportion of the urethra receiving a dose of more than 217Gy, (150% of the conventional dose of 145Gy) was constrained to 10% of the urethral volume. The rectal volume receiving 145 Gy was constrained to 2cc, as per AAPM recommendations [15].

3 Planning with Dose Convolution

3.1 Radiation Dose Calculation

The radiation dose rate R at a distance r from a single implanted seed is calculated as

$$R(r) = S_K \cdot \Lambda \cdot \frac{1}{r^2} g_p(r) \phi_{an}(r) \quad (1)$$

where S_K is air-kerma strength, Λ is the dose-rate constant in water, $g_p(r)$ is the radial dose function describing dose fall-off due to photon scattering and attenuation (excluding inverse square law fall-off) and $\phi_{an}(r)$ is the one dimensional anisotropy function [16]. Since the radioactive seeds are cylindrical with a radius of 1mm all dose rate calculations at distances of less than 1 mm are calculated at 1mm. The values $g_p(r)$ and $\phi_{an}(r)$ are obtained from the Amersham model 6711 dosimetry dataset [16] for the seeds used in this study.

3.2 Post-Operative Seed Displacement

The post-operative displacement of the implanted seeds from their intended location has the potential to significantly alter the actual radiation dose distribution throughout the prostate and surrounding region from that planned [18, 2, 4]. This may reduce treatment effectiveness and expose sensitive tissue to high levels of radiation, causing side effects such as urinary toxicity and rectal bleeding. Previous research by the authors [3, 12] evaluated the post-operative seed displacement for the patient data used in this study. This was found to be approximately normally distributed in each of the x, y and z axes having mean 0 and standard deviation of 3.8mm. This accords with results obtained or reported by other researchers [7, 2, 4].

In the modelling that follows it is assumed that the post-operative displacement of a seed is composed of three independent and normally distributed random variables, e_x, e_y and e_z , having mean 0 and standard deviation σ . Thus, the error in the post-operative distance between seed and target compared with the planned distance r (consisting of components r_x, r_y and r_z in each axis) for a given σ is

$$Err(r, \sigma) = \left| \sqrt{r_x^2 + r_y^2 + r_z^2} - \sqrt{(r_x + e_x)^2 + (r_y + e_y)^2 + (r_z + e_z)^2} \right|, \quad e_i \sim N(0, \sigma^2). \quad (2)$$

3.3 Planning Under Uncertainty

A planning model for prostate cancer brachytherapy that takes post-operative seed displacement into account could potentially be achieved using stochastic optimisation. This would require the expected TCP of a given seed configuration to be calculated by discrete-event simulation using randomly perturbed seeds [8]. The incorporation of this step at each iteration would make the calculation of the optimal expected TCP extremely computationally intensive. Although the efficiency of the stochastic optimisation may be improved by methods such as stochastic gradient-based approaches and metamodeling etc. [8, 17], the doubly exponential form of the output function [3] and dimensionality of the problem limits the utility of these approaches. As a consequence, stochastic modelling as it is traditionally performed is unsuitable in practical settings, where dose planning interactively or intra-operatively requires short solution times. For example, the non-stochastic method of [3] creates treatment plans in around 30 seconds; clearly, a stochastic implementation of this method would have a computation time increased proportionally to the number of trials pooled and evaluated at each iteration and even a small sample size would make the method infeasible.

Because of these practical time constraints, researchers and practitioners have typically used a deterministic approach for dose calculations during the planning process. This enables effective plans to be produced within a practical time frame. The effect of post-operative displacement on the actual treatment dose received by the patient can then be evaluated by simulation modelling in order to verify that plans meet treatment dose requirements with a certain reliability, for example [7, 18, 2, 4, 9, 12]. However, because these plans do not explicitly incorporate the effect of post-operative seed displacement during the planning phase they invariably over-estimate treatment dose, and under-estimate the radiation dose to organs at risk actually received by the patient.

To address this limitation, the effect of post-operative seed displacement is approximated during the optimisation by modelling the radiation dose distribution as though the seeds have been perturbed. Although this new method is not a stochastic optimisation in its strictest sense it reflects the effect of post-operative stochastic seed displacement on the actual radiation dose delivered to the patient, and enables plans to be constructed with the same efficiency as the original deterministic model.

3.4 Convolving The Radiation Dose Rate Function

The effect of post-operative seed displacement on the radiation dose received at a target is incorporated into the optimisation model by replacing the radiation dose function, Equation 1, by the convolution [5] of Equation 1 and the probability density function of the post-operative seed displacement function, $Err(r, \sigma)$, given by Equation 2. Because there is no tractable algebraic form for the convolved dose rate function, it is calculated by evaluating the expected dose rate for each combination of r and σ using simulation as described below.

Algorithm 1 works by first creating a point at random that is uniformly distributed over a sphere of radius r [14]. This is then perturbed randomly in the x , y and z axes, reflecting normally distributed post-operative seed displacement having standard deviation σ . The convolved dose corresponding to the original radius r is then calculated at this new point. Repeating this operation n times and averaging enables the expected convolved dose at a radius r to be calculated at a level of accuracy determined by n .

Algorithm 1 Convolved Radiation Dose Rate Function

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1: for  $r$  and  $\sigma > 0$  do
2:   for  $i = 1$  to  $n$  do
3:     Set random point on sphere  $\mathbf{P} = (p_x, p_y, p_z)$  where  $p_x, p_y, p_z \in N(0, 1)$ 
4:     and random post-operative seed displacement  $e_x, e_y, e_z \in N(0, \sigma)$ 
5:      $\mathbf{P}^* = (\frac{p_x r}{\|\mathbf{P}\|}, \frac{p_y r}{\|\mathbf{P}\|}, \frac{p_z r}{\|\mathbf{P}\|})$  is a point on sphere of radius  $r$ , i.e.  $\|\mathbf{P}^*\| = r$ 
6:      $\mathbf{P}^{**} = (\frac{p_x r}{\|\mathbf{P}\|} + e_x, \frac{p_y r}{\|\mathbf{P}\|} + e_y, \frac{p_z r}{\|\mathbf{P}\|} + e_z)$  is the perturbed point
7:      $R_{ci}(r, \sigma) = R(\|\mathbf{P}^{**}\|)$  the convolved dose at  $r$  is the calculated dose at  $\mathbf{P}^{**}$ 
8:    $R_c(r, \sigma) = \frac{1}{n} \sum_{i=1}^n R_{ci}(r, \sigma)$ 
9: return  $R_c(r, \sigma)$ 

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TCP calculations in the experiments that follow were made using tabulated convolved dose rate functions at discrete intervals of $r \in \{0, 0.1, 0.2, \dots, 10\}$ mm and $\sigma = 1, 2, 3, 4$ and 5mm. To create these, 1000 iterations of the algorithm were run at each parameter combination. Centered moving average smoothing over r was used to eliminate small deviations from monotonicity. Values of r between tabulated values were interpolated assuming a piecewise linearity. For notational simplicity in the following, R refers to the original (unconvolved) dose rate function in Equation 1, and $C1, \dots, C5$ refer to the convolved dose function at each value of σ .

Figure 2 shows the effect of the convolution on the original dose rate function evaluated at varying levels of σ . It can be seen that close to the seed, the radiation dose is highly attenuated due to the convolution, with larger values of σ resulting in a greater flattening of dose. Because seed planning constraints prevent two seeds being closer than $5\sqrt{2} \approx 7.1$ mm it is highly likely the attenuation of dose rate at r closer than this has little effect on actual seed placement. At values of r greater than ≈ 5 mm it can be seen that the convolved dose rate function curves cross, with those corresponding to larger values of σ becoming greater than those for smaller values of σ . In the following section it will be shown that the effect of this is to increase the distance between seeds slightly, on average, reducing the total number of needles required for treatment planning.

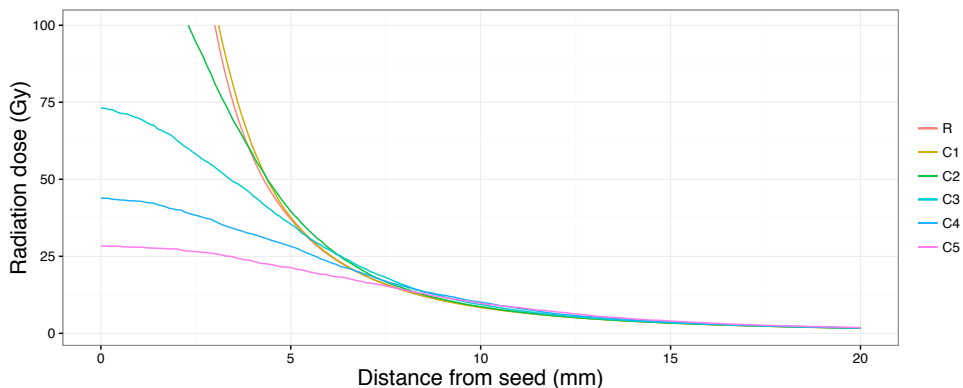


Figure 2: Dose rate for original and convolved dose rate function at varying levels of σ

4 Experiments and Results

4.1 Design of experiments

Patient Selection. Patient data used previously by the authors [3, 12], for which human ethics approval had been obtained, was used in this study. Patient data consisted of a voxel model of the prostate and surrounding tissue. Each voxel was classified according to tissue type (prostate, urethra, rectum, PTV) with tumour cell density identified for each voxel of the prostate.

Creation of Treatment Plans. To evaluate the effect of creating treatment plans using the convolved dose rate model, multiple treatment plans were created for each patient at each combination of: TCP Target Value: 0.85, 0.90 and 0.95, and Dose Rate Function: unconvolved (R) and convolved for $\sigma = 1, 2, 3, 4$ and 5mm.

The values of post-operative seed displacement (σ) encompass values likely to be encountered in practice [3, 4]. Target TCP values likewise represent those that could be realistically considered by a practitioner intending to achieve a treatment TCP > 0.62 post-operatively, as per [11]. Because the optimisation is non-deterministic, 10 plans were created for each patient at each parameter combination.

Evaluation of Treatment Plans. In order to measure the performance of the treatment plans under post-operative seed displacement, the seeds were perturbed, and the TCP and radiation dose received by the rectum and urethra of the perturbed seed plans were measured. σ values of 0, 1, 2, 3, 4 and 5mm were again used to perturb the seeds as described in Section 3.2. 50 perturbed seed plans were analysed at each parameter combination (TCP and Dose rate function) for each seed plan produced.

4.2 Properties of Convolved Dose Rate Plans

Table 1 shows the average number of seeds in each plan, the average distance of seeds from the centroid, and the average distance between each seed and its nearest neighbour as a function of TCP and dose distribution model used for optimisation. It can be seen that setting a higher target TCP increases the number of seeds in the treatment plan. This is to be expected, since additional radiation dose is required to increase TCP as a general principle. Using the convolved dose rate model reduces the number of seeds in a plan for a given TCP compared with the original (unconvolved) dose rate model. The number of seeds in each plan, on average, decreased as the amount of post-operative seed displacement (σ) increased, to a limit of $\sigma \approx 4$ mm. The reduction in seeds is explained by a small increase in the spread of seeds, shown by an increased average distance from the centroid, and an increased distance between closest pairs of seeds as σ increased.

Table 1: Seed count and spread as a function of dose rate model used for planning

	TCP	Dose Rate Model					
		R	C1	C2	C3	C4	C5
Average number of seeds in each plan	0.85	65.99	64.90	63.10	61.34	60.60	61.39
	0.90	69.39	68.25	66.51	64.63	63.74	64.97
	0.95	74.26	73.25	71.36	69.03	69.15	68.81
Average distance of seeds from centroid (mm)	0.85	18.79	18.83	18.82	18.85	18.85	18.99
	0.90	19.00	18.97	18.95	18.98	19.03	19.23
	0.95	19.19	19.17	19.23	19.20	19.34	19.43
Average distance between closest pairs of seeds (mm)	0.85	7.78	7.81	7.91	7.97	7.89	7.92
	0.90	7.75	7.74	7.80	7.85	7.83	7.84
	0.95	7.61	7.63	7.66	7.73	7.70	7.73

4.3 Treatment Efficacy of Convolved Dose Rate Plans

The effectiveness of treatment plans is now assessed. The criteria for effectiveness are (a) the potential to maintain a sufficiently high TCP, to treat the disease, even under post-operative seed displacement, and (b), the protection of organs at risk - namely the urethra and rectum - also under post-operative seed displacement.

Figure 3 shows TCP calculated for each planning target under each of the dose rate models, and evaluated under post-operative seed displacement for $\sigma = 0, 1, 2, 3, 4$ and 5mm. Each plot indicates TCP = 0.62 as Haworth et al. [10] identified this value as a predictor for treatment efficacy, whereby a TCP < 0.62 was associated with an unacceptably high probability of treatment failure.

Regardless of the dose rate model used for planning, the results show that a high target TCP needs to be chosen to preserve treatment reliability under post-operative seed displacement. Of the parameters chosen for the experiments, it is only trials with a target TCP of 0.95 that maintain sufficiently high TCP levels under post-operative seed displacement to warrant consideration for treatment planning. Increasing σ for the convolution model increases the variance of treatment TCP under post-operative displacement. However, the results show that when planning TCP = 0.95, all plans maintained lower quartile treatment TCP values greater than 0.62 even under the most extreme post-operative displacement.

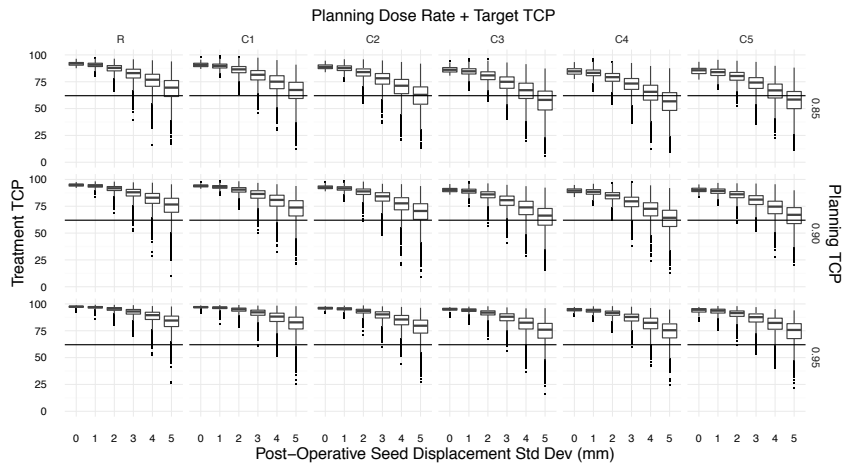


Figure 3: Treatment TCP as a function of Target TCP, dose rate model and post-operative seed displacement

Figures 4 and 5 show the volume of rectum receiving 100% of the planning dose and the proportion of the urethra receiving 150% of the planning dose respectively. These figures show that plans made using the convolved dose rate function at increasing values of σ reduce the radiation dose received by organs at risk under post-operative seed displacement. The figures also show that increasing the Target TCP has only a small effect on the dose received by the urethra and rectum. This means it is possible to aim for a high Target TCP without fear of exposing organs at risk to undue radiation using focal therapy. The results also show how a clinician could analyse the seed distribution, with and without the convolved dose-rate function, to observe the relative change in TCP and dose to organs at risk. This would enable an evaluation of implant quality in the individual patient prior to and during the treatment, leading to increased confidence in using a focal planning approach.

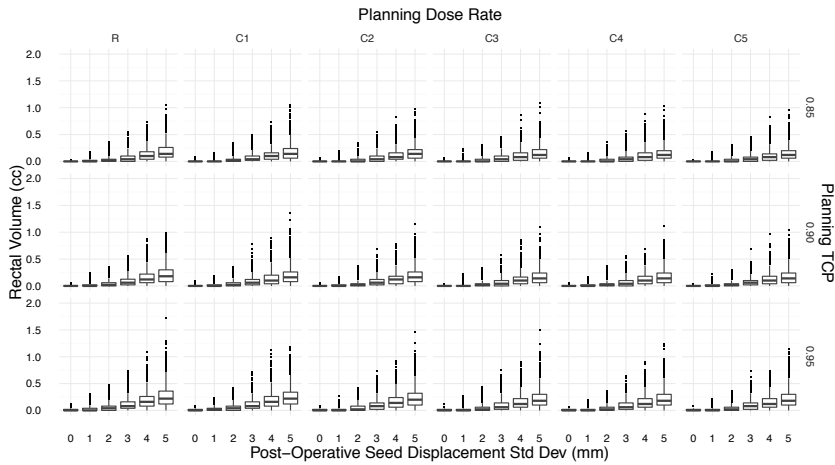


Figure 4: Rectal volume receiving 100% of planning dose as a function of Target TCP, dose rate model and post-operative seed displacement

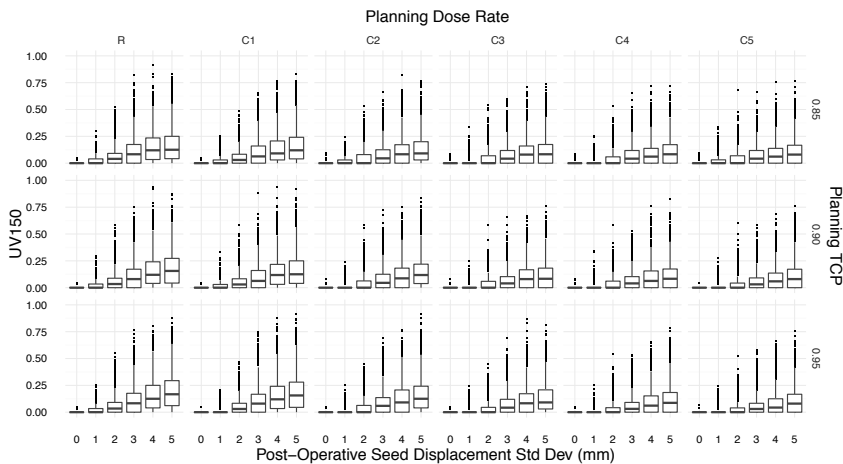


Figure 5: Proportion of urethra receiving 150% of planning dose as a function of Target TCP, dose rate model and post-operative seed displacement

5 Summary and Conclusion

This paper has presented a new radiation dose rate model for prostate cancer brachytherapy treatment planning. This new dose rate model is created by convolving the theoretical dose rate with the pdf of the function describing the post-operative displacement of the implanted radioactive seeds from their intended location.

This convolved dose rate model allows treatment plans to be created which achieve a high tumour control probability but result in reduced radiation dose to organs at risk. Furthermore, these plans are created quickly, allowing the method to be used intra-operatively.

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