

# Paradigm Shift in Radiation Treatment Planning Over Multiple Treatment Modalities

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## Abstract

The inverse planning simulated annealing optimization engine was used to develop a new method of incorporating biological parameters into radiation treatment planning. This method integrates optimization of a radiation schedule over multiple types of delivery methods into a single algorithm. We demonstrate a general procedure of incorporating a functional biological dose model into the calculation of physical dose prescriptions. This paradigm differs from current practice in that it combines biology-informed dose constraints with a physical dose optimizer allowing for the comparison of treatment plans across multiple different radiation types and fractionation schemes.

**Keywords:** Biological dose models, inverse planning, treatment planning

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## INTRODUCTION

Current radiation treatment planning follows a greedy algorithm based on experience and intuition. The physician will apply a certain primary treatment, usually external beam radiation therapy (EBRT), and then subsequently plan the secondary treatment, usually brachytherapy, as a means of filling in the rest of the prescription or escalating the dose.<sup>[1-3]</sup>

EBRT can be delivered to large areas of the body with no invasive procedures, but its dose uniformity is generally not as conformal to the target cancerous tissue as brachytherapy. Thus, the dose delivered to a tumor is constrained by the sensitivity of nearby normal tissues and organs. Brachytherapy, on the other hand, involves the surgical implantation of catheters directly into the target tissue. Brachytherapy, therefore, allows a higher dose gradient outside the target which leads to more conformal treatment planning.<sup>[4]</sup> The difficulties of the surgical procedures necessary for brachytherapy and the heterogeneity of its dose distribution tend to dissuade practitioners from weighing it equally against EBRT.<sup>[1]</sup>

By planning the use of each modality separately, the strengths of each treatment type cannot be fully utilized. Instead of following sequential planning methodology, an integrated planning system would allow for optimization of both parts (EBRT and brachytherapy) concurrently to find an

optimal plan. This includes adjusting fractionation schemes and/or modification of the ratio of EBRT dose to brachytherapy dose.

To take advantage of different fractionation schemes, the treatment planning algorithm needs to incorporate the biological response to radiation into its calculation. Several attempts have been made at describing how different proliferation rates and DNA repair mechanisms affect the damage radiation imparts to a cell. Popular models include the linear-quadratic model, biological effective dose, equivalent dose in 2 Gy fractions (EQD2), equivalent uniform dose, the Lyman–Kutcher–Burman model, the Poisson model, tumor control probability, and normal tissue complication probability.<sup>[5-12]</sup> These models map a physical dose onto a space that accounts for cell type, DNA repair capabilities, cell proliferation rates, and fractionation scheme. In this way, constraints on the dose delivered to organs at risk (OARs) can be tabulated independent of fractionation scheme and delivery type. Current treatment plans optimize based on physical dose and thus cannot compare alternate fractionation plans. This

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paper explores how biological models can be implemented into the current inverse planning simulated annealing (IPSA) algorithm to allow physicians to explore more treatment options.

### THEORY

We assume that a model that maps total physical dose,  $D$ , to biological dose,  $B$ , for a given number of fractions,  $n$ , exists as a one-to-one function for the domain  $D \geq 0$  and  $n > 0$ , i.e.,  $B = f_n(D)$ . Because this model is one to one in the region of interest, an inverse function exists that maps biological dose back to physical dose,  $D = f_n^{-1}(B)$ .

Brachytherapy regulatory committees such as GEC-ESTRO and American Brachytherapy Society give their treatment recommendation in biological doses such that they can be fit for different fractionation schemes and cancer types. Given a constraint on biological dose (either a maximum or minimum), the physical dose constraint for fractions is given by  $D_{max/min} = f_n^{-1}(B_{max/min})$ .

In most treatment plans, EBRT is given prior to brachytherapy. In this analysis, we assume two different treatment modalities are used, each with their own independent fractionation schemes. We also assume that if a dose constraint exists, the first treatment does not exceed this constraint (i.e., the second treatment is unable to provide negative dose).

If a physical dose,  $D_1$  is given using the first treatment method (say EBRT) in  $n_1$  fractions, we denote the equivalent biological dose as  $B_1 = f_{n_1}(D_1)$ . The biological dose constraint is given as  $B_{max/min}$ . The amount of physical dose you can apply in  $n_2$  fractions before reaching this constraint is then given as:

$$D_2 = f_{(n_2)}^{(-1)}(B_{(max/min)}) - f_{(n_2)}^{(-1)}(B_1) \tag{1}$$

$$= f_{n_2}^{-1}(B_{max/min}) - f_{n_2}^{-1}(f_{n_1}(D_1))$$

Since this function is non-linear, we cannot simply plug  $\{B_{max/min} - B_1\}$  into the inverse to calculate the remaining physical dose - that would neglect the dose-dependent radiosensitivity predicted by the linear quadratic model. This is a common mistake. Because the two treatments are different, you must map the first treatment onto the curve of the second treatment. Then, you can calculate the difference between the constraint and the current dose.

$D_2$  is thus the prescription that IPSA uses for planning. If you have  $D_2$  left to give to a location, IPSA determines the correct treatment geometry to match these prescriptions. These functions  $f_{n_1}$ , and  $f_{n_2}$ , account for number of fractions and cell type. If you adjust the number of fractions, you adjust the value of  $D_2$ . Similarly, changing  $D_1$  or  $n_1$  also adjusts  $D_2$ . Whereas before a clinician would set  $D_1$  independently, we can now use the power of inverse planning to weigh different fractionation options and different modality weights.

To illustrate this point, we consider the well-defined EQD2 model. EQD2 is given as:<sup>[5]</sup>

$$EQD2 = f_n(D) = \frac{D(1 + \frac{D}{n(\alpha/\beta)})}{1 + \frac{2}{\alpha/\beta}} \tag{3}$$

$D$  is the total physical dose,  $n$  is the number of fractions, and  $\frac{\alpha}{\beta}$  is a radiobiological parameter that describes a cell's response to radiation. To simplify notation, let's denote  $A = \frac{\alpha}{\beta}$  and  $k = \frac{1}{1 + \frac{2}{\frac{\alpha}{\beta}}}$ .

Using the quadratic formula and only taking the positive root (since dose must be positive), the inverse of this function is given as:

$$D = f_n^{-1}(EQD2) = (\frac{A \times n}{2})(-1 + \sqrt{1 + (\frac{4}{k})(\frac{EQD2}{A \times n})}) \tag{4}$$

Say EBRT is performed first for a total dose of  $D_E$  over  $n_E$  fractions. The EQD2 equivalent of this is given as:

$$f_{n_E}(D_E) = EQD2_E = kD_E(1 + \frac{D_E}{A \times n_E}) \tag{5}$$

If you then perform brachytherapy, the amount of physical dose  $D_B$ , you can supply in  $n_B$  fractions to reach a total constraint of  $EQD2_{con}$  is given as:

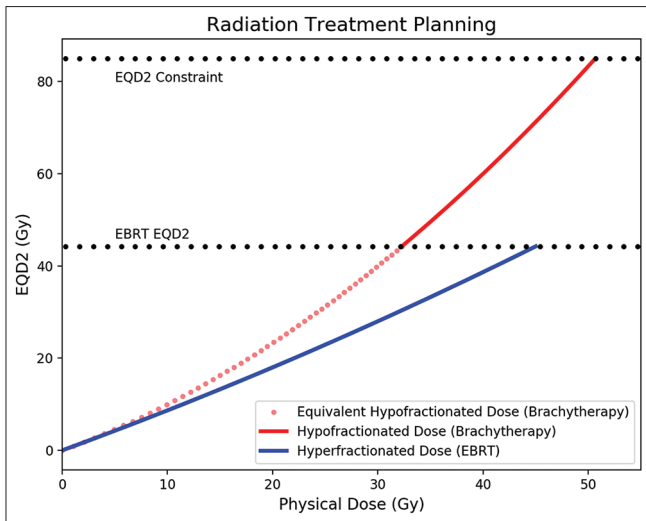
$$D_B = f_{n_B}^{-1}(EQD2_{con}) - f_{n_B}^{-1}(EQD2_E) \tag{6}$$

$$= (\frac{A \times n_B}{2})(-1 + \sqrt{1 + (\frac{4}{k})(\frac{EQD2_{con}}{A \times n_B})}) - (\frac{A \times n_B}{2})(-1 + \sqrt{1 + (\frac{4}{k})(\frac{EQD2_E}{A \times n_B})}) \tag{7}$$

When performing IPSA optimization for this brachytherapy treatment,  $D_B$  then informs what you set for the constraints. If this is an OAR,  $D_B$  is the maximum dose it can receive. If this is a tumor,  $D_B$  is the minimum dose it should receive. Some physicians avoid "hot spots" near dwell locations. In that case,  $D_B$  informs the maximum dose for those volumes. Figure 1 provides a graphical representation of this constraint paradigm, and Table 1 gives some sample values for cervical cancer.

### METHODS

With this model for testing different fractionation schemes and treatment spreads, we used the IPSA treatment planning algorithm to test how altering these hyperparameters can impact our treatment goals such as tumor coverage and normal tissue sparing. We performed these experiments using previous cervical cancer cases from the UCSF Medical Center Radiation Oncology Department. Five cases of varying degrees of



**Figure 1:** Treatment plan visualization. This graph highlights the impact of traversing the biological dose function.  $\alpha/\beta = 10$ , minimum equivalent dose in 2 Gy fractions = 85 Gy,  $n_E = 25$ ,  $D_E = 45$  Gy, and  $n_B = 5$ . The constraint is given in equivalent dose in 2 Gy fractions and represented by the top horizontal dotted line. The lower dotted line represents the equivalent dose in 2 Gy fractions at which the first treatment method stops and the second method begins. The blue solid line represents the dose trajectory of external beam radiation therapy. The dotted red line shows what the equivalent brachytherapy trajectory would be. This is a phantom trajectory in that it is just used in this graphic to track where brachytherapy starts. Once the external beam radiation therapy treatment is done, the organ is left at the equivalent dose in 2 Gy fractions marked by the first dotted line. Brachytherapy picks up along the solid red line. The difference between the x-values of the endpoints of this solid red line gives the brachytherapy dose constraints we plug into inverse planning simulated annealing

**Table 1: Example cervical cancer parameters and results. Using Eq. 7 outlined in the theory section as well as EQD2 constraints and biological parameters that we selected for the actual study, this table displays some physical dose constraints that a physician could use in brachytherapy planning. Note that all dose values are given in Gy.**

Organ	$\alpha/\beta$	EQD2 <sub>con</sub>	$D_E$	$n_E$	$n_B$	$D_B$
Bladder	3.85	70	45	25	5	9.33
			45	25	4	8.39
			36	20	5	12.95
Rectum	4.00	65	45	25	5	7.79
			45	25	4	7.01
			36	20	5	11.45
Bowel	2.99	65	45	25	5	7.29
			45	25	4	6.54
			36	20	5	10.65
CTV	10.00	85	45	25	5	18.39
			45	25	4	16.69
			36	20	5	23.23

EQD2: Equivalent dose in 2 Gy fractions, CTV: Clinical target volume

anatomical complexity were chosen to demonstrate how our procedure affects treatment plan quality in different patients.

Treatment plans were assessed using the dose guidelines outlined in Table 1 under “EQD2<sub>con</sub>”.

Specifically, the two parameters we varied independently were number of brachytherapy fractions and number of EBRT 1.8 Gy fractions. Plans were evaluated using two metrics: V85 and D2cc. V85 is the fraction of the organ volume that received at least 85 Gy. This number was used to assess how effective the treatment was at delivering the 85 Gy EQD2 dose prescription to the tumor. V85 is ignored for OARs. D2cc is the highest dose delivered to a 2-cm-cubed volume of the organ. This was used to ensure that organs were properly spared. To focus the scope of this manuscript, and since there is active debate that they can be beneficial, tumor hot spots were not explicitly constrained. Thus, D2cc is not important for tumor dose evaluation. This problem can thus be formulated as defining the IPSA potentials and penalties to maximize the V85 of the tumor while maintaining the D2cc of each OAR under the maximum dose guidelines.

The brachytherapy fractionation experiment was carried out by adjusting the number of brachytherapy fractions from 5 to 1 for each case. Each patient received an initial EBRT treatment of 45 Gy in 25 fractions.

The EBRT fractionation experiment was performed by adjusting the number of 1.8 Gy fractions the patient received prior to 5 fractions of brachytherapy. EBRT fractions were reduced from 25 to 5 in increments of 5. The brachytherapy fractions were kept at 5, so we could assess these variables separately.

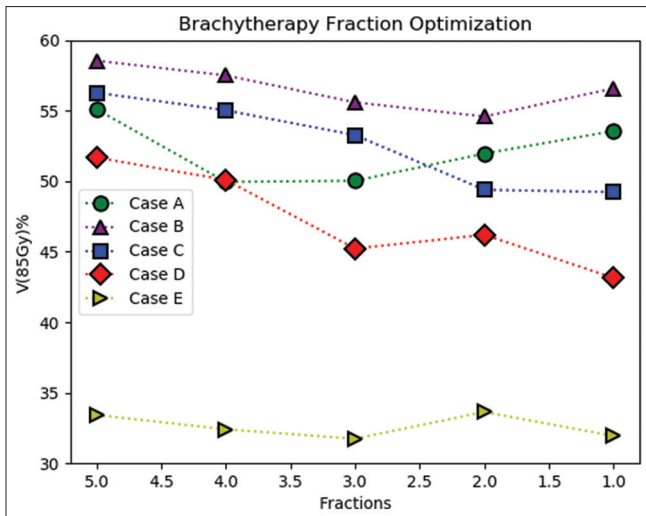
For each trial, we calculated the corresponding dose constraints using equation 6 and then tuned the potentials to maximize the tumor V85 while keeping the D2cc of each organ under said constraints. Thus, the potentials plugged into IPSA for each organ were not kept constant when adjusting the number of brachytherapy fractions or initial EBRT dose. Instead, we looked for the best possible outcome of each treatment plan, just as a dosimetrist would do in practice.

## RESULTS

Figures 2 and 3 display the results of the brachytherapy fractionation study and the EBRT fractionation study, respectively. In both figures, the x-axis is presented in descending order to show how the study began with hyperfractionation and then tracked the outcomes as treatment was hypofractionated. All five subjects are shown on the same graph, and each subject is assigned the same symbol for both graphs.

## DISCUSSION

This treatment optimization exercise exhibits some interesting trends that only become quantifiable and comparable when biological dose models are implemented into the treatment planning software. First, Figure 2 exhibits the lack of freedom



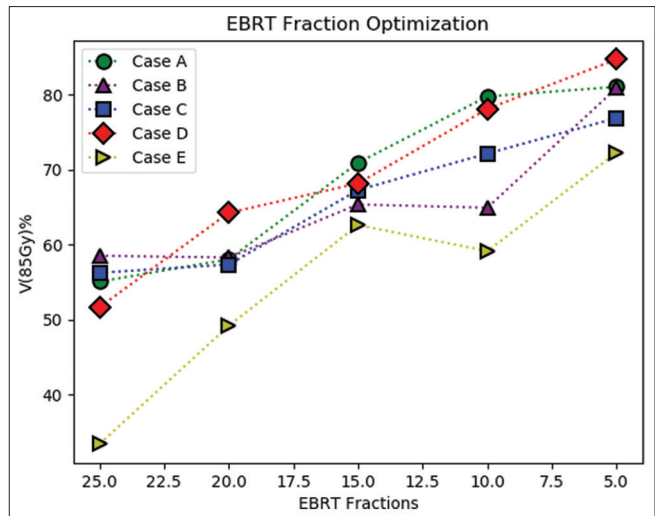
**Figure 2:** Brachytherapy fractionation study. The x-axis is the number of brachytherapy fractions in reverse order. The y-axis contains the percent of the tumor volume that received at least 85 Gy (V85). This study was done with an initial external beam radiation therapy treatment of 45 Gy in 25 fractions

brachytherapy has when EBRT is planned independently. Each treatment began by delivering a standard 45 Gy EBRT dose in 25 fractions to the pelvis. No matter the fractionation scheme, V85 remained below 60% for every case. There is a weak downward trend for some of the cases where reducing the number of fractions reduced the treatment efficacy. This is most likely due to the increased damage on normal tissue without proper repair time. However, this downward trend only spans a few percentage points and is not present for every case (specifically case A).

Overall, treatment efficacy appears to remain stagnant during hypofractionation. This is an important finding for a treatment planner. If radiation delivery can be reduced to very few treatments, perhaps this brachytherapy boost can be converted to an outpatient procedure. This would lead to a reduction in the cost of treatment and a reduction in the waiting times for treatment.

In Figure 3, treatment efficacy takes a vastly different trend as fractionation is varied. There is an overwhelmingly positive trend in V85 as EBRT fractions are reduced. Dose coverage begins as low as 33% for Case E in 25 fractions but reaches as high as 85% for Case D. Each case’s V85 spans 20–30 percentage points between 25 fractions and 5 fractions. Case E was the most difficult case explored here; it also shows the largest improvement in coverage. Each plan demonstrates a much more significant increase in tumor coverage than what was seen in the brachytherapy fractionation study.

The EBRT variation test differs from the brachytherapy variation test in that the EBRT dose is being reduced with the number of fractions. For the brachytherapy experiment, the same dose was spread over different numbers of fractions. In this study, the full treatment was



**Figure 3:** External beam radiation therapy fractionation study. The x-axis is the number of fractions of 1.8 Gy external beam radiation therapy, which precedes 5 fractions of brachytherapy treatment. The y-axis again contains the V85 as percent of the target volume

differentially split between EBRT and brachytherapy. As EBRT fractions were reduced, brachytherapy was given more of the treatment load. As described in the introduction, brachytherapy is a much more conformal treatment modality. Although brachytherapy has a lot of practical disadvantages to EBRT, it can be seen, theoretically, that by giving the more precise treatment a larger role, tumor coverage increases greatly.

### CONCLUSION

There are many different considerations in treatment planning that are not addressed in this example exercise – EBRT does not necessarily have to bathe the entire region in a uniform dose, brachytherapy may be unmanageable for certain patients, and hot spots within the tumor may be undesirable. However, the focus of this manuscript is simply to demonstrate the feasibility of integrating biological parameters into dose optimization using the current treatment planning software. From these exercises, it is seen that treatment plan metrics improve when dose planning is integrated for the entire course of treatment (EBRT and brachytherapy). Biological dose models provide the necessary degrees of freedom to optimize fractionation schemes between multiple treatment modalities. As these models become more accurate and as increased effort is put into automating optimization over complex, discontinuous, multivariate parameter spaces, this research provides the necessary framework for implementing new theory into the clinic today.

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### Conflicts of interest

There are no conflicts of interest.

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