Biological Effective Dose and Tumor Control Probability Modeling using the MIM® Software Suite

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Introduction

Biological Effective Dose (BED) modeling is an important tool in understanding tumor and normal tissue response across different treatment modalities and fractionation schemes. Calculating BED allows a physical dose to be converted into a dose that describes the biological effect of the radiation on tumor or normal tissue. BED analysis can inform therapy decisions such as adaptive therapy replanning or evaluation of life-time dose limits when performing treatment planning for tumor recurrence.

MIM provides BED-scaling and tumor control probability (TCP) modeling tools using several common dose response models based on the linear-quadratic (LQ) formalism.

MIM Features

MIM can be used to scale doses from multiple treatment modalities into Gy-BED units using several variants on the LQ-model. Doses can also be converted to standard 2 Gy equivalent dose fractions (EQD2). Additionally, TCP calculations can be performed based on any of the available models.

MIM's comprehensive suite of tools for performing dose summation for adaptive-therapy replanning and multi-modality therapy can also be extended through the use of the BED tools. For example, the change in predicted tumor control probability can be calculated to help guide adaptive replanning decisions. Additionally a better understanding of the effect from combined modality therapy, such as permanent seed implants and external beam, can be achieved by scaling each dose to BED and then summing the doses.

Dose Response Models

MIM's BED features are based on the linear-quadratic cell survival model. The cell survival fraction after a fractionated course of radiotherapy is given by (SF)

$$SF = exp\left(-\alpha nd - \beta nd^2\right) = exp\left(-(\alpha nd + \beta nd^2)\right) \quad [1]$$

where,

- n is the number of fractions,
- d is dose per fraction, in Gy,
- α and β are model parameters that govern the linear and quadratic elements of the dose response,
- the quantity ($\alpha nd + \beta nd^2$) is the biological effect, E.

BED is a quantity with unit Gy defined as

$$BED = \frac{E}{\alpha} = nd\left(1 + \frac{d}{\alpha/\beta}\right)$$

MIM provides the basic LQ model and three variations:

Variation 1 – LQ model with time factor

This model takes into account tumor repopulation during the treatment course.

$$BED = nd\left(1 + \frac{d}{\alpha/\beta}\right) - \frac{0.693(T - T_k)}{\alpha T_{eff}} \quad [2]$$

where,

- n is the number of fractions,
- d is dose per fraction, in Gy,
- α and β are the linear and quadratic coefficients,
- T is the total treatment time, in days,
- T_k is the "kick-off time," the period in days between the start of radiation therapy and the onset of tumor repopulation,
- T_{eff} is the effective tumor doubling time.

A modified version of this formula has been used for HDR brachytherapy where T_k is set to 0. This would result in the equation:

$$BED = nd\left(1 + \frac{d}{\alpha/\beta}\right) - \frac{0.693(T)}{\alpha T_{eff}} \quad [3]$$

Variation 2 – LQ-L model

It has been observed that at high dose fractions, the survival curve exhibits linear-quadratic-linear behavior [4]. MIM follows the bipartite method proposed by [5], in which below a transition dose per fraction, d_t, LQ behavior is observed and above which a final linear portion to the survival curve is observable.

If $d < d_t$:

$$BED = nd\left(1 + \frac{d}{\alpha/\beta}\right)$$

If $d > d_t$:

$$BED = nd_t\left(1 + \frac{d}{\alpha/\beta}\right) + n\frac{\gamma}{\alpha}(d - d_t) \quad [5]$$

where,

- n is the number of fractions,
- d is dose per fraction, in Gy,
- α and β are the linear and quadratic coefficients for the initial LQ portion of the cell survival curve,
- γ is the linear coefficient for the final linear portion of the survival curve,
- d_t is the transition dose at which LQ-L behavior begins.

If an estimate of the ratio $\frac{\gamma}{\alpha}$ is unavailable, it can be estimated by using the tangent of the cell survival curve at the point d_t. If this approximation is used,

$$\frac{\gamma}{\alpha} = 1 + \left(\frac{2d_t}{\alpha/\beta}\right) \quad [5]$$

Variation 3 – LQ model for Low-Dose Rate Brachytherapy

A model specifically for permanent-seed brachytherapy applications is provided, as specified by [6].

$$BED = D\left\{1 + 2(d_0 * \lambda)(\beta/\alpha) * \frac{\kappa}{\mu - \lambda}\right\} - \frac{0.693T}{\alpha T_P}$$

with

$$\kappa = \frac{1}{1-\varepsilon}\left\{\left(\frac{1-\varepsilon^2}{2\lambda}\right) - \left[\frac{1 - \varepsilon * e^{-\mu Teff}}{\mu + \lambda}\right]\right\}$$

and

$$T_{eff} = \frac{1}{\lambda}\ln\left((1.44 * d_0) * (\alpha * T_p)\right)$$

where,

- D is the total dose in Gy,
- d_0 is the initial dose rate in Gy/h,
- $\lambda = 0.693/t_{1/2}$, where $t_{1/2}$ is the half-life of the radioisotope,
- $\mu = 0.693/t_{1/2(repair)}$, where $t_{1/2(repair)}$ is the cell repair constant,
- α and β are the linear and quadratic coefficients,
- T_p is the potential tumor doubling time,
- T_{eff} is the effective treatment time,
- $\varepsilon = e^{-\lambda T_{eff}}$.

Tumor Control Probability

MIM uses a Poisson model compatible with any LQ formalism that models the cell survival fraction. Hence, MIM will calculate TCP predictions using any of the four models that are supported for BED. The formula for TCP is given by:

$$\begin{aligned} TCP &= exp(-N * SF) \\ &= exp(-N * exp(-E)) \\ &= exp(-D_c * V * exp(-\alpha * BED)) \end{aligned} \quad [7]$$

where,

- N is the number of tumor clonogens,
- D_c is the density of clonogens per cm^3,
- V is the volume of the tumor.

Aggregate TCPs for tumor volumes are calculated by computing the product of the individual TCP's for each dose voxel within the tumor volume.

Model Parameters

MIM provides a library with default parameter values for the supplied models that were derived from the literature [2], [5], [6]. New parameters can also be added by users to meet their specific needs.

Discussion

The needs for treatment planning have extended past physical dose assessment alone and methods to incorporate information about the radiobiological effect of dose have taken on additional importance. MIM's suite for tools for BED and TCP calculations have addressed this need and provide the opportunity to more effectively incorporate radiobiology into the treatment planning and evaluation process.

References

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