Uncertainty analysis for relative biological effectiveness derived from different dose-effect curve model fits

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INTRODUCTION

The relative biological effectiveness (RBE) of the radiation field is used to scale the physical dose of treatment in charged particle beam therapy. The RBE is defined as the ratio of a reference radiation dose to a corresponding test radiation dose under the condition that both radiation types yield an equivalent biologic effect. RBE values of high-LET particles depend on several factors including particle type, energy, dose, tissue type, and biologic endpoint. Calculating the effective dose from novel charged particle therapy modalities rests on the prediction of RBE using biophysical models. Methods to quantify and visualize the uncertainty in RBE values could offer valuable insight to clinicians using particle therapy.

AIM

To demonstrate the derivation of RBE and its uncertainty for biologic dose response data using various curve fitting models.

METHOD

The RBE and its uncertainty were analytically derived for three dose-effect curve models with increasing complexity: the Linear Model fit, the Linear Quadratic General Model fit, and the Modified Error Function Model fit as commonly used in NTCP analysis.

The uncertainty in the RBE was estimated for each model as a function of dose and uncertainties in corresponding fit parameters estimated during the numerical curve fitting and using error propagation methods.

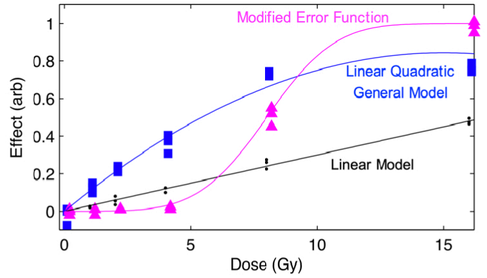

Fig. 1. Example of curve fitting for 3 possible dose response relations. Gnuplot (V5.2) allows a fit of a user-defined function using the nonlinear least-squares Marquardt-Levenber algorithm, solves for the model fit parameters, and reports the uncertainty of individual fit parameters.

RESULTS

The derived solutions demonstrate the relation between curve fit parameters for dose-response data of three models, the analytical expression of RBE, and the estimation of uncertainty in RBE as a function of dose.

Linear Model Fit

This model assumes the biologic effect is directly proportional to the radiation dose. Also, the slope of the dose-effect curve likely depends on the LET and biologic endpoint. It is the simplest relation tested, with the advantage of possibly being the most robust to noise in biologic data.

RBE

Assuming the relation of biologic effect (E) to dose (D) is linear with fitting parameters (free variables) a and b as

$$E = aD + b.$$

Considering the definition of RBE, which is the ratio of doses for a reference (r) radiation type (*e.g.*, x-ray) and a test (t) radiation (*e.g.*, high-LET)

$$RBE = D_r/D_t,$$

under the condition that they produce an equivalent biologic effect,

$$E_t = E_r.$$

We then substitute to express

$$a_t D_t + b_t = a_r D_r + b_r.$$

Solving for D_r and by substitution, we find

$$RBE(D_t) = \frac{a_t D_t + b_t - b_r}{a_r D_t}.$$

σ_{RBE}

Using propagation of error to estimate the uncertainty in the RBE values as a function of dose, $\sigma_{RBE}(D_t)$, and the uncertainties in the fit parameters, and by taking the partial derivatives of the RBE:

$$\sigma^2_{RBE}(D_t) = \sigma^2_{a_t}\left(\frac{\partial RBE}{\partial a_t}\right)^2 + \sigma^2_{b_t}\left(\frac{\partial RBE}{\partial b_t}\right)^2 + \sigma^2_{a_r}\left(\frac{\partial RBE}{\partial a_r}\right)^2 + \sigma^2_{b_r}\left(\frac{\partial RBE}{\partial b_r}\right)^2.$$

Solving for $\sigma^2_{RBE}(D_t)$, we find

$$\sigma^2_{RBE}(D_t) = \sigma^2_{a_t}\left(\frac{1}{a_r}\right)^2 + \sigma^2_{b_t}\left(\frac{1}{a_r D_t}\right)^2 + \sigma^2_{a_r}\left(\frac{b_r - b_t - a_t D_t}{a_r^2 D_t}\right)^2 + \sigma^2_{b_r}\left(\frac{-1}{a_r^2 D_t^2}\right)^2.$$

Linear Quadratic General Model Fit

This model allows for a sub-/super- linear transition from the initial slope. The term "General" distinguishes this model from the Linear-Quadratic (LQ) Model typically used in radiobiology and denotes that this General fit is simply a second-order polynomial fit without any underlying theoretical basis regarding radiation effect. This model allows for detection of a more complex radiation dose response than the linear model.

RBE

Assuming the relation of the biologic effect (E) to dose (D) may have a linear and quadratic component with fitting parameters a, b, and c as

$$E = aD^2 + bD + c.$$

If experiments are appropriately controlled, we can assume that at zero dose, $c_t = c_r$.

Using the definition of RBE we can express

$$RBE(D_t) = \frac{-b_r \pm \sqrt{b_r^2 + 4a_r(a_t D_t^2 + b_t D_t)}}{2a_r D_t}.$$

σ_{RBE}

Again, using propagation of error to estimate σ_{RBE} we find

$$\begin{aligned}\sigma^2_{RBE}(D_t) &= \sigma^2_{a_t}\left(\frac{D_t}{\sqrt{b_r^2 + 4a_r(a_t D_t^2 + b_t D_t)}}\right)^2 + \sigma^2_{b_t}\left(\frac{1}{\sqrt{b_r^2 + 4a_r(a_t D_t^2 + b_t D_t)}}\right)^2 \\ &+ \sigma^2_{a_r}\left(\frac{-b_r + \sqrt{b_r^2 + 4a_r(a_t D_t^2 + b_t D_t)}}{2a_r D_t} + \frac{4D_t^3 a_r^3 a_t}{\sqrt{b_r^2 + 4a_r(a_t D_t^2 + b_t D_t)}}\right)^2 \\ &+ \sigma^2_{b_r}\left(\frac{b_r}{2a_r D_t\sqrt{b_r^2 + 4a_r(a_t D_t^2 + b_t D_t)}} - \frac{1}{a_r D_t}\right)^2.\end{aligned}$$

Modified Error Function Fit

This model is appropriate for data exhibiting a binary response, *e.g.*, normal (0) or abnormal (1) and for which the normal fraction generally changes with dose, especially about a threshold dose D_T. Assuming the dose at which data reach abnormal status is normally distributed about D_T, with standard deviation, σ_{D_T}, fitting the error function allows characterization of D_T and the variance in dose response about the threshold. The RBE derivations in the framework of the Modified Error Function quantify the shift in D_T for toxicity that occurs for different LET ranges.

RBE

We first define the standard error function (erf) as

$$\text{erf}(x) = \frac{2}{\sqrt{\pi}}\int_0^x e^{-t^2}dt.$$

For the Modified Error Function, assuming the relation of biologic effect (E) to dose (D) transitions from normal ($E = 0$) to abnormal ($E = 1$) at D_T, with a normal distribution to account for subject-to-subject variation (σ_{D_T}), as

$$E = \left[\text{erf}\left(\frac{D - D_t}{\sqrt{2}\sigma_{D_t}}\right) + 1\right]/2.$$

Substituting to express equivalence of biologic effect for the test (t) and reference (r) radiation types, which simplifies as

$$\frac{D_t - D_{T,t}}{\sigma_{D_{T,t}}} = \frac{D_r - D_{T,r}}{\sigma_{D_{T,r}}}.$$

Solving for D_r and by substitution into the definition of RBE, we find

$$\text{RBE}(D_t) = \left[\left(D_t - D_{T,t}\right)\left(\sigma_{D_{T,r}}/\sigma_{D_{T,t}}\right) + D_{T,r}\right]/D_t.$$

σ_{RBE}

Using propagation of error considering the uncertainties in the fit parameters ($D_{T,t}$,$\sigma_{D_{T,t}}$, $D_{T,r}$,and $\sigma_{D_{T,r}}$) and taking the partial derivatives we find

$$\sigma^2_{RBE}(D_t) = \sigma^2_{D_{T,t}}\left(\frac{\sigma_{D_{T,r}}}{D_{T,t}D_t}\right)^2 + \sigma^2_{\sigma_{D_{T,t}}}\left(\frac{D_{T,t}\sigma_{D_{T,r}}}{D_t\sigma^2_{D_{T,t}}}\right)^2 + \sigma^2_{D_{T,r}}\left(\frac{1}{D_t}\right)^2 + \sigma^2_{\sigma_{D_{T,r}}}\left(\frac{-D_{T,t}}{\sigma_{D_{T,t}}D_t}\right)^2.$$

CONCLUSIONS

These methods allow for handling of confidence intervals and estimation of the uncertainties in RBE, for example for high LET radiations, for various types of biologic response data. The methods rely on the assumption that underlying fit parameter uncertainties are Gaussian and independent. If correlations are found between parameters in the model fits, a more complex handling of uncertainties, e.g., by numerical analysis[1], should be considered.

REFERENCES

1. Friedrich T, Weyrather W, Elsässer T, Durante M, Scholz M. Accuracy of RBE: experimental and theoretical considerations. *Radiat Environ Biophys.* 2010;49(3):345-349. doi:10.1007/s00411-010-0298-9

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