

Web-Based Bioeffect Equations Software for use with the book Applied Radiobiology and Bioeffect Planning†

Download from www.boldenterprise.com.au/bio/bioeffect.html If there any problems with downloading feedback to this address would be welcome. It is suggested that the user downloads and prints a hardcopy of the text so it can be read while operating the graphs. For convenience the text contains references to selected pages in the book for additional information. A CD version of the software will soon be available through www.medicalphysics.org

Introduction

The purpose of this software is to make many of the interactive graphs in the book† accessible to users who may have little or no knowledge of mathematics. The variables may be changed and the effects of such changes seen. No equations are visible and no special mathematical software is required. The mathematical foundations of the procedures used may be examined in the book. Source code will be made available on request so the mathematical rigour of the equations may be scrutinised.

In the past radiotherapy has tended to progress in an irregular manner with long periods of gradual change interrupted by developments that significantly altered the practice of radiotherapy. These changes necessarily precipitated changes in attitudes and thinking in all the related disciplines. Examples of these seminal developments include the transition from orthovoltage to megavoltage beam qualities, the introduction of computer planning and then CT based computer planning. More recently there has been progress in a number of areas which collectively converge on 3D planning systems and modern linear accelerators. Examples are multileaf collimators, intensity modulation, beam optimisation and inverse planning. These greatly enhance the capacity to deliver the “dose” where it is required (dose painting). Improvements in CT imaging and the increasing availability of MRI, PET and Ultrasound enhance the capacity to define target volumes and dose limiting normal tissues. These are exciting developments which collectively offer the potential to substantially improve the quality of radiotherapy, but they come at a price.

Anybody who has practiced radiotherapy in recent decades and who has had to adapt to current developments is aware that one of the prices to be paid is that planning is now far more complicated and time consuming. Gone are the days when relatively standard field arrangements with simple shielding of rather ill defined target volumes sufficed. Now the scope for much more individualised treatment is at hand. All these changes present a substantial intellectual challenge but perhaps the greatest challenge for radiation oncologists is that posed by the increasing clinical relevance of applied radiobiology.

The mathematics of radiobiological modelling is a particular problem for most clinicians. Most of the graphs in the book are driven by equations but only static examples can be presented. The purpose of this download is to make a number of models and graphs available in an interactive form.

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One of the difficulties in appreciating the clinical relevance of radiobiological models is to derive a “feel” for how the equations behave. How much are the predicted effects influenced by changes in parameter values? What is the relative importance of different parameters? By altering parameter values and seeing the response a better appreciation of the behaviour of the models and their clinical relevance may be derived.

There is growing realisation that biologically based planning has a place and is likely to become increasingly relevant but there is justified concern about its application to the treatment of individual patients. Models to describe very complicated physiological and pathological processes are, at best, a compromise and uncertainties about parameter values are a real concern. For these good reasons opinions range from deep suspicion to cautious enthusiasm for inclusion of elements of biological modelling into planning and treatment decisions. The dilemma is that unless biologically based planning is attempted as a means of providing comparisons with traditional isodose plans then there is no means of demonstrating the differences and radiotherapy will remain locked into traditional isodose planning which is shown in the book to sometimes have serious deficiencies.

The way out is to develop biologically based options in 3D computers with the capacity to display the predicted effects for comparison with standard isodose plans. This should be on an experimental basis as isodose planning remains the gold standard on which all prescriptions should be based.

The availability of biologically based plans is an important step in developing an awareness of the relevance of evolving clinical radiobiology applied to patients. Familiarity with clinically useful models, such as in this download, is a necessary foundation for biologically based planning. It is hoped that these few examples are a useful teaching tool to help gain insights into applied radiobiology. The reader is invited to cross check the predictions using this software against published clinical data because it is only by doing this that the usefulness of the equations and the parameters chosen by the user can be evaluated and improved.

Four tables are provided to assist the user. Table 1 lists the Interactive Graphs and page references. Table 2 provides guidelines to the location of parameter values in the book. Table 3 provides guidelines to tables of parameter values and figures particularly for the EFFECT and P+PUTCOBE models and table 4 provides sample parameter values for these figures. For further reading references to page numbers of equations and text in the book are provided. On the screen a cursor has been provided to read the X and Y co-ordinates.

Feedback via the web-site will be very welcome. I am particularly interested if there are any errors of any type so they can be corrected.

It is most important to stress that any predictions are at best approximations. The author cannot accept any responsibility for prescriptions based on the contents of the book or the download.

PLOTTING AND PRINTING

The graphs are plotted by clicking on [Plot!] and then may be printed by clicking on the gnuplot graph icon. Gnuplot provides several options including choosing Line Style (useful for black and white printing) then click on the Print button.



Guidelines to the use of Figure 1.3 (FDFVEST) pp 14 and Figure 4.5 (HTPCOS1ST) pp 127

Purpose

To derive biologically equivalent number of fractions as the dose per fraction, number of fractions, volume and dose limiting normal tissues are changed. Figure 1.3 applies to daily fractions and figure 4.5 applies to twice daily fractions.

Variables

For Figure 1.3. N, Number of fractions: d_g , Dose per fraction which may be varied in steps of δ : L_t Length of side of cubic treatment volume (cm): L_r , Length of side of cubic reference volume (cm): d_s , Specified dose per fraction (Gy): r , α/β value of dose limiting normal tissue (Gy): ϕ , Tissue specific volume exponent.

For Figure 4.5 the corresponding variables are N_h : d_{gh} : L_c Length of side of cubic target volume (conventional daily treatment): L_h , Length of side of cubic target volume (hyperfractionated treatment): d_{sc} , Specified dose per fraction given daily: h_m , Incomplete repair factor: r and ϕ as above for daily treatment.

In chapter 1 a series of graphs are presented which may be used to determine the biological equivalence of fractionated treatment given to normal dose limiting tissues in which the dose is normalised to an equivalent number of fractions of a specified dose per fraction, such as 2.0 Gy. These graphs may be used to compare different fractionation schedules and to sum partial treatments as described on pp 12 in reference to figure 1.3. They may also be used for bioeffect planning if the standard isodose plans are presented as dose per fraction plans (“rad displays”) which is usually possible in radiotherapy planning computers, an example of which is presented in figure 10.3 (pp 376). This simple procedure (pp 11, 374) introduces the concept of inverse planning. Even if bioeffect plans incorporating the models are not reproduced but only “rad display” contours are available the look-up charts may be used to check the biologically effective dose in terms of the number of fractions of a specified dose per fraction, for example 2.0 Gy, that has been given to a point and tissue of interest.

The variables for daily and twice daily treatments may be changed to reproduce figure 1.3, 1.4 and 1.5 (pp 14, 15) for daily treatments and figures 4.5 (pp 127) for twice daily treatments. The variable values may be changed for alternative doses volumes and tissues. Note that ϕ is inactive when $L_t = L_r$ and $L_c = L_k$.

Figure 1.3 may be used for dose limiting normal tissues other than *stroma* with α/β (r) = 3.0 Gy and $\phi = 0.12$. For example figure 1.12 (pp 18) is used for large volumes of *brain* with α/β (r) = 1.78 and $\phi = 0.116$. By using an appropriate α/β (r) value and its companion tissue specific volume exponent ϕ , isoeffective doses for other late reacting tissues may be explored. Tables 2 and 4 provide access to more complete information on useful parameter values.

In chapter 4 figure 4.5 (pp 127) is a similar look-up graph that has been derived for hyperfractionated treatments of *stroma* ($\alpha/\beta = 3.0$ Gy $\phi = 0.12$). This method is described by equation 4.8 (pp 126) and includes an incomplete repair factor h_m the value of which depends on the interval between fractions as discussed in 4.2 (pp 122). Values for 6, 4 and 8 hourly intervals used in the examples for 4.5, 4.6 and 4.7 were 0.0625, 0.158 and 0.0248 assuming a repair half time of 1.5 hours. It is acknowledged that in recent times bi-exponential repair processes are being described and also second order repair (Reciprocal repair) in which the repair rate decreases with

time¹. As the data are scanty for these, for simplicity, the mono-exponential repair process has been used for figure 4.5. The number of fractions used is defined as N_h (N for daily fractions in figure 1.3) and the dose per fraction is defined as d_{gh} (d_g in figure 1.3). As in figure 1.3 each of the variables may be changed and there biological equivalence shown on the X – axis is expressed as the number of daily fractions of d_s Gy per fraction which, in the examples shown, is 2.0 Gy. The late reacting tissues may be changed by changing to an appropriate value of α/β (r) and its tissue specific volume exponent ϕ . Figure 4.5 will give the same results as figure 1.3 for daily fractions if $h_m = 0$.

Spinal cord is a dose limiting tissue of particular interest. This is described in figures 1.10 and 1.11 (pp 17, 18) in which no volume or length effect has been included. Figure 4.5 (HYPCO1ST) may be used for spinal cord effects for either daily or twice daily treatments by choosing and appropriate α/β value (r) and by defining $L_c, L_h \phi$ each = 0. An α/β value of 2.0 Gy was used for spinal cord in figures 1.10 and 1.11 (table 8.7 pp 253). For daily treatments h_m must also = 0. For twice daily treatments and incomplete repair factor is required. Assuming a repair half time of 1.5 hours, incomplete repair factors of 0.0248, 0.0625 and 0.158 apply for intervals between two fractions of 8, 6 and 4 hours.



Guidelines to the use of Figure 2.15 (IVFDFSTT) to demonstrate the Volume Effect.

Purpose

To demonstrate the change in biological effect in dose limiting normal tissue within the Boost Volume as the number of fractions, dose per fraction, volumes treated and tissue types are changed.

Variables

d_s , Specified dose per fraction (Gy) with variable lower and upper limits in steps of δ ; d_{g1} , Dose per fraction in the initial volume (Gy); d_{g2} , Dose per fraction in the reduced volume (Gy); N_1 , Number of fractions to the initial volume; N_2 , Number of fractions to the reduced volume; L_1 and L_2 , Length (cm) of side of initial and reduced volumes respectively; ϕ , Tissues specific volume exponent; r , α/β value of dose limiting normal tissue (Gy).

Developments in modelling of the volume effect continue at a rapid rate and are becoming increasingly relevant to the application of 3D computer planning and optimisation. These issues are briefly reviewed in section 2.4.1 (pp 65 – 67) but given the complexity and rapidity of developments this section is by no means a complete review. Models are available for non-uniform dose distributions. Other models are based on the functional organisation of normal tissues but for simplicity the power law model has been used here which depends on the tissue specific volume exponent derived from clinical data. This method provides a reasonable approximation provided the dose is uniform, the complication probabilities are low and the partial volume is greater than approximately 0.15.

As shrinking field techniques are widely used in clinical practice it is important to have some appreciation of the significance of volume changes and for this reason, despite the limitations of the power law model (pp 32, 48) the simple Integral FDF (I.F.D.F.) model, equation 2.21 (pp 47) figure 2.15 (pp 53) is included.

This model may be used to show the effects of using a shrinking field technique on normal tissues treating an initial volume equivalent to a cube of $L_1 \times L_1 \times L_1$ cm ($L_1 = 10$ cm in figure 2.15) with N_1 fractions and then reducing the volume to $L_2 \times L_2 \times L_2$ cm ($L_2 = 4 - 10$ cm in figure 2.15) and treating with N_2 fractions. The options include altering the dose per fraction to the initial volume (d_{g1}) and to the reduced volume (d_{g2}). The late reacting tissues may be changed by changing the $\alpha\beta$ (r) value and its tissue specific volume exponent ϕ .

It is important to note that this integral volume effect model predicts the biologically effective dose in the *reduced volume* (V_2 in figure 2.6 pp 40) following treatment to both the initial and the reduced volume. The biologically effective dose in this reduced volume is shown on the X – axis in units of the equivalent number of fractions of d_s Gy per fraction.

Compared with the use of the non-integral volume models, which consider only the reduced (boost) volume, the integral model is “safer to use” as it predicts higher biologically effective doses in the reduced (boost) volume leading to prescription of lower doses.

Although figure 2.15 shows three values of d_s it is likely to be more useful using one value such as $d_s = 2.0$ Gy.



Guidelines to the use of Figure 3.3 (GYGY2S2)

Purpose

To describe the relationship between dose rate of continuous low dose rate irradiation and the biologically equivalent dose per fraction of fractionated treatment

Variables

R_a , Dose rate of continuous irradiation in Gy per hour ranging between > 0 and 5.0 in steps of δ :
 D_c , Total dose of continuous irradiation: $T_{0.5}$, Tissue repair half time (h).

It is convenient to keep in mind that for each dose per fraction in fractionated treatment there is a corresponding dose rate of continuous irradiation that has an equivalent biological effect. This is discussed in pp 77 – 82 and shown in figure 3.2 and 3.3 (pp 81-92). In these figures it can be seen that dose rates of approximately 0.5 Gy per hour have similar biological effects as 2.0 Gy per fraction. It is for this reason that when low dose rate radium/radon brachytherapy was used the total doses of continuous irradiation and fractionated radiotherapy of 1.8 – 2.0 Gy per fraction were commonly simply added together. However, as figure 3.3 (pp 81) shows, this total dose equivalence does not apply to larger dose rates or fraction sizes. For example a dose rate of 1.0 Gy per hour equates to approximately 4.0 Gy per fraction when the Repair half time is 1.5 hours, as can be read from the X-axis.

Figure 3.3 (pp 81) includes low dose rates ranging from 0.2 to 1.6 Gy per hour. In figure 3.3 (GYGY2S2) the dose rate may be varied from 0.1 to 5.0 Gy per hour and the Repair half time may be varied. It is suggested that a Repair half time of 1.5 hours is a convenient choice but see tables 3.1 (pp 74 – 75) for more detail. See also the comments in the Guidelines to the use of Figures 1.3 and 4.5. It is suggested that the total dose D_c is left at the Default value of 60.0 Gy.

The dose per fraction which corresponds approximately to a chosen dose rate of continuous irradiation at a given repair half time may be read from the X-axis.



Guidelines to the use of Figure 3.5 (LQ5PRO)

Purpose

To show Survival Fraction curves following continuous irradiation. These curves show α cell and β cell kill separately and α plus β cell kill combined. The total dose, dose rate, repair constant, α and β values of the tissues may be changed and the survival fraction curves redrawn.

Variables

α and β , Radiosensitivity parameters of tissues irradiated (The α/β ratio is automatically recalculated): R_a , Dose rate in Gy per hour: t , Treatment time in hours: μ , Repair constant. The value of μ may be calculated by entering the repair half time $T_{.5}$ and μ is recalculated ($0.693/T_{.5}$). The new value of μ may be entered into the button above and a new set of survival curves calculated.

Figure 3.5 (pp 84) has been derived using equation 3.21 (pp 84). This figure shows the shape of the *dose response curve of continuous irradiation* when the radiosensitivity parameters α and β , dose rate (R_a Gy h^{-1}), duration of treatment (t hours) or the repair constant μ are changed. Alpha cell kill, beta cell kill and combined alpha + beta cell kill are shown separately. α and β values and repair rates are discussed in section 3.4 of the text (pp 82). α and β values are shown in tables 8.4, (pp 245) (tumour in-vitro values), 8.5 (pp 247) (tumour in-vitro values), 8.6 (pp 252) (tumour in-vivo values), 8.7 (pp 253) (late reacting tissues). Repair constant values μ are shown in table 3.1 pp 74 and also briefly discussed under Figure 1.3 (FDFVEST) and Figure 4.5 (HYPCO1ST).

For example when $\alpha = 0.1$, $\beta = 0.024$, $R_a = 0.4$ Gy h^{-1} , $t = 150$ and $\mu = 0.355$ the survival curves as shown in figure 3.5 (pp 84) are produced. If R_a is increased to 120 Gy h^{-1} and $t = 0.5$ h the survival curves are as in figure 3.6 (pp 85) although comparison is easier with $t = 0.2$ h. The overall treatment time t needs to be adjusted to give an appropriate total dose for the defined dose rate R_a .

Each of the variables may be changed. In addition, if required, the value of μ for any value of $T_{.5}$ may be recalculated and entered in the button for μ above.



Guidelines to the use of Figure 3.15 (CONR2ST)

Purpose

To compare the biological equivalence of continuous and fractionated irradiation as the dose rate, dose per fraction and dose limiting normal tissues are varied. No volume effect is included.

Variables

d_s , Specified dose per fraction: t , Overall treatment time of continuous irradiation (h) in steps of δ : r , α/β value of dose limiting normal tissue: μ , Repair constant per hour of dose limiting normal tissue: R_a , Dose rate of continuous irradiation in Gy per hour.

The predicted equivalent biological effect of continuous irradiation described in terms of fractionated radiation in fractions of d_s Gy per fraction is described by equation 3.24 (pp 93). This equation has been used to produce figures 3.14 and 3.15 (pp 94 – 95) using dose rates of 0.8 and 0.5 Gy per hour.

Figure 3.15 (CONFR2ST) uses the same equation 3.24 in which the dose per fraction, the dose rate and total dose of continuous irradiation, the α/β value and repair half time of the dose limiting normal tissues may be varied.

The total dose of continuous irradiation may be defined in steps for example 10, 20.....70 Gy. These steps are derived by defining the overall treatment time t (h) in appropriate intervals δ . For example for a total dose of 10 Gy at 0.8 Gy per hour $t = 10/0.8 = 12.5$ (h) and for 20 Gy at 0.8 Gy per hour $t = 20/0.8 = 25$ (h) and $\delta = 25 - 12.5 = 12.5$ (h). For a total dose of 70 Gy $t = 70/0.8 = 87.5$ (h).

Other examples with different dose rates, dose per fraction and tissues may be explored using figure 3.15 (CONFR2ST).



Guidelines to the use of Figure 3.21(CONEXTAS)

Purpose

A means of describing the biological equivalence of combined continuous and fractionated (including hyperfractionated) treatment in terms of a number of daily fractions of a specified dose per fraction. This may also be used for continuous irradiation alone.

Variables

r , α/β value of tissue: R_a , Dose rate of continuous irradiation (Gy per hour) which may be increased in steps of δ : t , Duration of continuous irradiation (h): $T_{.5}$ Repair half time (h): d_s , Specified dose per fraction (Gy): d_{gh} , Dose per fraction given (Gy): n_h , Number of fractions given: h_m , Incomplete repair factor to be used for twice daily treatments.

Figure 3.21 (CONEXTAS) is derived from equation 3.26 (pp 96) and is used for figure 3.21 (pp 101) and figure 10.67 (pp 424). Figure 10.67 is derived using the same equation 3.26 but has been written to show a large range of dose rates between 0.5 and 125.0 Gy per hour. This expanded model is not reproduced here but figure 3.21 (CONEXTAS) may be used to generate biologically equivalent doses for any dose rate chosen by changing R_a and t .

With figure 3.21 (CONEXTAS) for *continuous irradiation* a range of dose rates may be defined, in steps of δ , to a total dose defined by the duration of treatment t (h). The repair half time $T_{.5}$ of the tissue of interest must also be defined (Table 3.1 pp 74 – 75). If continuous irradiation alone is used then d_{gh} , n_h and h_m should each = 0.

In the Default values of figure 3.21 (CONEXTAS) no fractionated treatment is given but *Fractionated daily irradiation* may be added by entering values for n_h and d_{gh} . If twice daily treatment is used then a value for the incomplete repair factor h_m should be included (see pp 122 – 126). As shown in figures 4.6, 4.5 and 4.7 (pp 127 -129) h_m values of 0.158, 0.0625 and 0.0248

were used assuming tissue repair half times of 1.5 hours and intervals between treatments of 4, 6 and 8 hours respectively.

The Default Specified dose per fraction d_s is 2.0 Gy but may be of any value of interest, in which case the biologically effective dose of the treatment given is expressed as a number of fractions of the chosen value of d_s .

This model has been used for bioeffect planning of combined continuous and fractionated irradiation and is described in Chapter 10 (pp 415 – 427) figures 10.61, 10.62, 10.63, 10.64, 10.65, 10.66 10.68 and 10.69.



Guidelines to the use of Figure 3.29 (CONEX7Bt)

Purpose

For the summation of two different schedules of continuous irradiation with the biological effect expressed as the equivalent number of fractions of a specified dose per fraction.

Variables

r , α/β value of tissue irradiated: Ra_1 , Dose rate of continuous irradiation schedule 1 (Gy per hour): Ra_2 , Dose rate of the second schedule (Gy per hour) in steps of δ : t_1 , Duration of schedule 1 treatment (h): t_2 , Duration of the second schedule (h) which may be varied by the lower and upper values: μ , Repair constant per hour: Values of μ other than the Default value 0.462 may be calculated by entering an alternative repair half time ($T_{.5}$) and click on Plot! The new value of μ appears in the box next to $0.693/T_{.5}$. d_s , Specified dose per fraction (Gy).

A means of summation of two schedules of continuous irradiation is described by equation 3.34 (pp 112) and shown in figure 3.29 (pp 113). Depending on the values of the variables used it may be necessary to adjust the upper limits of t_1 and t_2 to generate a convenient scaling of the X-axis.

In the examples shown in figure 3.29 (pp 113) a specified dose per fraction of $d_s = 2.4$ Gy was used as explained in the text (pp 114). A more familiar value of d_s would be 2.0 Gy but any value of choice may be used in which case the biological effect of the two schedules is defined as the number of fractions of d_s Gy shown on the X-axis.



Guidelines to the use of Figure 9.8 (OPTIMCD)

Purpose

To explore the interactions between tumour and normal tissue variables and derive guidelines to the optimum fractionation for both daily and twice daily treatments.

Variables

α_m , Mean value α for clonogens: β_m , Mean value β of clonogens: h_{mcl} , Incomplete repair factor for clonogens: h_{mst} Incomplete repair factor for stroma: T_{pm} , Mean repopulation rate of clonogens: ϕ , Tissue specific volume exponent: K_{tol1} , K_{tlx} are numbers that define the assumed tolerance levels

of dose limiting tissues for daily and twice (or more = x) fractions per day treatment. These numbers act like a “Thermostat” defining tolerance. The derivation of these values are described below: r , Normal tissue α/β value: M_m , Clonogen number: d_{gm} , Mean dose per fraction (Gy) for which a range needs to be defined: L , Length of side of cubic target volume (cm): FW1, Fractions per week when only 1 fraction is given daily: FWX, Fractions per week when X fractions given daily, (eg 2 fractions per day 5 days per week FWX = 10): T_s , Extra days in split course: T_k Kick off time in days.

Derivations button. Click on the Derivations button and two sets of derivations are displayed.

The first set of derivations is a means of deriving K_{tol1} and K_{tolx} to be included in Figure 9.8 (OPTIMCD): r , Normal tissue α/β value: d_{gm} and N_k , Dose per fraction and Number of fractions for deriving K_{tol1} : d_{gmh} and N_{hk} , Dose per fraction and Number of fractions for deriving K_{tolx} : L_k and ϕ , Length of side of cubic volume and Tissue specific volume exponent both applied to K_{tol1} and K_{tolx} . Having entered the chosen parameter values click on [Calculate K_{tol1} and K_{tolx} values] and the new values are displayed.

Alternative “Thermostat” tolerance settings for both daily and twice daily (K_{tolx}) treatments may be used. Figure 4.5 (HYPCO1ST) (pp 127) may be used to calculate alternative values of N_k , d_{gm} and N_{hk} , d_{gmh} for different assumed tolerance doses.

The second set of derivations refer to the application of Equations 9.30 (pp 296) and 9.31 (pp 297) to calculate the OPTIMUM number of fractions and OPTIMUM dose per fraction following entry of the [DAYS] button. The [DAYS] button refers to the TREATMENT TIME [DAYS] on the X-axis of the graph at the point where the peak of the Daily or BD fractions curves start to decline. The cursor may be used to define the X and Y coordinates. Click on [Calculate] to recalculate N and Optimum Doses Per Fraction.

Operating the Graph

The OPTIMUM model shown in Figure 9.8 (OPTIMCD) is shown in Figure 9.8 (pp 298) and is described in section 9.8 (pp 293 – 299). Its applications are described in pp 316 – 322, pp 323 – 327. Figure 9.8 (OPTIMCD) does not incorporate the option of including inhomogeneities of α , β , T_{pm} and d_{gm} and only mean parameter values of α , β , T_{pm} and d_{gm} are used. If the effect of including inhomogeneities of α , β , T_{pm} and d_{gm} tumour control probability at optimum fractionation are required the EFFECT model (P+, PUTCObe) may be used.

Having determined the tolerance settings K_{tol1} or K_{tolx} the other variables may be changed to generate curves such as in figure 9.8 (pp 298). Other examples are shown on pp 319 - 320 and 323 - 325.

The next step is to adjust the clonogen numbers M_m to bring the curves comfortably within the TUMOUR CONTROL PROBABILITY scale on the Y-axis. Then the TREATMENT TIME (DAYS) is read from the X-axis under the peak of the TCP curve where it starts to drop. This procedure is done for both daily and hyperfractionated curves as the peaks may differ. Click on the [Derivation] button to display the [DAYS] button for calculation of the OPTIMUM Fraction Number and DOSE PER FRACTION for Daily and X Daily Dose Per Fraction.

The Default values show that from the graph for Daily Fractions at the peak the OPTIMUM TREATMENT TIME [DAYS] is approximately 28 days and for BD Fractions approximately 35

days. These values correspond to 20 fractions of 2.9 Gy at 5 per week and 50 fractions of 1.49 Gy twice daily fractions at 10 fractions per week.

This model is useful to explore the factors that determine the OPTIMUM overall treatment time and hence fractionation. Figure 9.25 (pp 323) gives examples in which the mean repopulation rate is varied and demonstrates how important this may be in determining the optimum fractionation. A summary of the general guidelines to optimum treatment time and hence fractionation derived by application of the OPTIMUM model to clinical data is shown in pp 337- 338.

For optimum treatments there is a trend towards shorter treatment times and larger doses per fraction for tumours with rapid repopulation rates. Resistant tumours with low α values require fewer larger fractions and tumours with low β values require more and smaller fractions. An increase in the α/β value of stroma requires shorter treatment times and larger fractions.

Examples To demonstrate the sensitivity of optimum fractionation to tumour repopulation rate enter T_{pm} values in steps from 3 to 15 days, adjust clonogen numbers (M_m) as necessary to keep the curves within the Tumour Control Probability scale. Click [Derivation] button and derive the optimum number of fractions and dose per fraction. Compare these results with figure 9.25 (pp 323) and table 9.4 (pp 321). Try changing other variables to test sensitivity of optimum fractionation to these alterations.



**Guidelines to the use of Figure 9.6 (EFFECTB) (pp 291), 9.7 (pp 292), 9.11 (pp 306).
Guidelines also to use of Figure 9.6 (P+PUTCOBE)**

Purpose

To examine the effects of changes in tumour, normal tissue and fractionated treatment variables on tumour control probabilities and the probability of late normal tissues effects. These models have the option of including inhomogeneity effects of tumour and treatment variables. The figure 9.6 (P+PUTCOBE) version has the addition of presenting effects as Uncomplicated Tumour Control Probabilities.

Variables

α_m , Mean value of α : α_σ , Standard deviation of α : β_m , Mean value of β : β_σ , Standard deviation of β : D_{Mn} , Dose modifying effect of cytotoxic drugs on normal tissue: D_{Mcl} , Dose modifying effect of cytotoxic drugs on clonogens: N , Number of fractions with range option: K , Number of random samples calculated: i , range of variable of K : d_{gm} , Mean dose per fraction: $d_{g\sigma}$, Standard deviation of dose per fraction: T_{pm} , Mean repopulation rate of tumour: $T_{p\sigma}$, Standard deviation of repopulation rate of tumour: L_t , Length of side of cubic target volume in cm: L_r , Length of side of cubic reference volume in cm: ϕ , Tissue specific volume exponent: N_{def} , Number of fractions of d_s at $D_{.5}$ (dose at 50% complication probability): d_s , Dose per fraction of $D_{.5}$: T_o , Overall treatment time in days: T_s , Time of rest in a split course (days): T_k , Kick-off time (days): h_{mt} , Incomplete repair factor for tumour and normal tissue: r , Normal tissue α/β : M_m , Number of clonogens:

In this section the EFFECT model as shown in figures 9.6, 9.7 and 9.11 is described but attention is drawn to the fact that the figure 9.6 (P+PUTCOBE), which is based on the EFFECT model, has two extra curves showing Uncomplicated Tumour Control Probability for tumours in which either

mean parameter values only are used or in which the inhomogeneity effects of α_σ , β_σ , $T_{p\sigma}$ and $d_{g\sigma}$ are included. This form of presentation of uncomplicated tumour control is sometimes described as a P+ model.

$$\text{Uncomplicated Tumour Control} = \text{TCP} \cdot (1 - \text{NTCP})$$

where TCP = Tumour Control Probability from the EFFECT equation
 NTCP = Normal Tissue Complication Probability from the EFFECT equation

The two uncomplicated tumour control probability curves in Figure 9.6 (P+PUTCOBE) model show an initial rise which peaks at the optimum dose and then declines as the biologically effective dose increases. The biologically effective dose on the X - axis is described in terms of the number of fractions N of d_{gm} Gy per fraction. As the biologically effective dose increases the probability of complications increase and a point is reached beyond the peak of the uncomplicated TCP curve when complications become increasingly harmful and beyond tolerance. Tolerance is set by the “Thermostat” (N_{def} and d_s).

All the parameter values listed above the plot are interactive and tables 3 and 4 have been prepared to assist in the choice of parameter values.

N_{def} combined with d_s defines the chosen tolerance level and is like a “Thermostat setting”. Once these values are chosen there is no need to change them when any of the other parameters including d_{gm} are altered. For example if twice daily hyperfractionated treatment is used then d_{gm} (and its standard deviation $d_{g\sigma}$ table 8.18 pp 274) can be changed, overall treatment time T_o adjusted and the incomplete repair factor h_{mt} added, its value depending on the interval between treatments. N_{def} and d_s need not be changed unless a different level of tolerance is required. The effect curves for differing normal tissues may be changed by changing the α/β value (r) and the tissues specific volume exponent ϕ .

K defines the number of random samples calculated. Each recalculation produces a slightly different result due to variations in sampling but with the Default value of 500 these differences are small.

The number clonogens M_m consists of 2 boxes [3.5^3] and [10^7]. The first box approximates to a tumour diameter, for example 3.5 cm, but if 10 is raised to a power > 9 the equation calculation overloads. The way around this is to enter 10^3 or 100^3 in the first box and 10^x in the second box. For example $10^3 \times 10^7 = 10^{10}$ and $100^3 \times 10^7 = 10^{13}$.

Figure 9.6 (EFFECTB) has the option of calculating Normalised Dose-Response Gradients (γ slopes) of late effects and tumour control probability curves as shown in figure 9.11 (pp 306) and described pp 310 - 311.

To activate this option click on the [Derivation] button and alter the default parameter values as required. At the bottom there are two sections for γ for Late Effects and γ for Tumour Control Probability. Enter N for each. N is the number of fractions at which a 50% effect occurs for the particular example used. The value of N may be read from the Normal Tissue Effects and TCP curves at the 50% effect level. Click on the [Calculate] button and the slope derivatives and $\gamma_{.50}$ slopes are calculated.

Attention is drawn to *two particularly important applications*.

1. Figure 9.6 (EFFECTB) and figure 9.6 (P+PUTCOMBE) show how the TCP curves become flatter as *inhomogeneities of parameter values* are introduced, as occurs when populations rather than individuals are treated. As the standard deviations of the parameter values decrease the curves become steeper. This has many implications for example on the estimates of statistical power and sample sizes required for clinical trials (pp 343 – 351).
2. In Chapter 5 it is emphasised how almost no quantitative data are available defining the Dose Modifying Effects of cytotoxic drugs on normal tissue tolerance. This is an extraordinary state of affairs given the widespread use of combined chemo/radiotherapy for several decades. Some indication of the magnitude of these effects may be seen by entering assumed values of D_{Mn} (or D_{mcl}) and see how the TCP curves in equation 9.6 (P+PUTCOMBE) are affected. Of particular concern is the potential but unquantified magnitude of the effects of cytotoxic drugs on the tolerance of dose limiting tissue. *For example* using Default values of Figure 9.6 (P+PUTCOBE) if there is no Dose modifying effect on the tissues ($D_{Mn} = 1.0$) the tolerance dose shown in the X-axis at the apex of the Uncomplicated TCP with inhomogeneity effects curve is approximately 33 fractions of 2.0 Gy if the dose modifying effect D_{Mn} is increased 10% ($D_{Mn} = 1.1$) tolerance drops to approximately 30 fractions of 2.0 Gy and TCP falls. Failure to make this adjustment may have serious consequences. 10% may well be a conservative figure as figures higher than this have been observed in animal experiments (pp 143) but the essential point is that human D_{mn} values are virtually unknown. Alternatively if D_{Mn} values were known then the biologically effective dose may be increased.

The fall in TCP occurring at tolerance may be compensated for by the effect of the Dose modifying effect on the clonogens as can be seen by increasing D_{Mcl} from the Default value of no effect ($D_{Mcl} = 1.0$). This model may therefore be useful to at least highlight the magnitude of the uncertainties when combined chemo/radiotherapy is used.

Tables 3 and 4 have been prepared to assist in the choice of parameter values for figure 9.6 (EFFECTB) and (P+PUTCOBE) models.



Guidelines to the use of Figure 9.4 (LOGISTPB)

Purpose

To derive the number of fractions N_{def} which may be chosen to define the total dose D_{50} given at d_s Gy per fraction which has a 50% complication probability.

Variables

d_g , Dose per fraction for D_{50} dose with range options in steps of δ : ϕ , Tissue specific volume exponent: h_m , Incomplete repair factor for twice daily treatments: L_t and L_r , Length of side in cm of cubic target and reference volume respectively: r , Normal tissue α/β value: d_s , Dose per fraction for D_{50} total dose: N_{def} , Number of fractions of d_s that defines the D_{50} dose with a range option.

In the variants of the EFFECT model Figure 9.6 (EFFECTB and P+PUTCOBE) it is necessary to define a value of N_{def} which is the number of fractions of d_s Gy per fractions that defines the total

dose ($N_{\text{def}} \times d_s = D_{50}$) at D_{50} . D_{50} is the total dose with a 50% complication probability in the late reacting dose limiting normal tissues.

Figure 9.4 (pp 288) is a means of deriving N_{def} values and its corresponding D_{50} dose when differing values of the dose per fraction d_g are used. Equation 9.14 (pp 287) is used in figure 9.4 and is described pp 287 - 290. Each of the variables may be changed so it may be used for hyperfractionated or standard daily treatments. An incomplete repair factor needs to be included for hyperfractionated treatments. The late reacting normal tissue may be changed by using the appropriate α/β value (r) and its companion tissue specific volume exponent ϕ and the target volume may also be changed by redefining L_t .



Guidelines to the use of Figure 9.43 (CONFCHTb)

Purpose

To describe the biological effect of continuous irradiation, with or without fractionated irradiation, in terms of Percent of Tolerance when tolerance is defined by a scaling factor K_{cont} for continuous irradiation. Also to derive K_{cont} .

Variables for Figure 9.43 (CONFCHTb)

d_g , Dose per fraction for fractionated treatment: N , Number of fractions: R_a , Dose rate of continuous irradiation in Gy per hour with a range in steps of δ : t , Duration in hours of continuous irradiation with a range: K_{cont} , Scaling factor to normalise tolerance to 100%: r , α/β value of normal tissue: $T_{5,5}$, Repair half time of tissue in hours.

Variables for derivation of K_{cont}

r , α/β value for normal tissue: R_{ak} , Dose rate of continuous irradiation in Gy per hour: $Tk_{5,5}$, Repair half time from which μ is derived: ϕ , Tissue specific volume exponent: tk , Duration of continuous irradiation: μ , Repair constant, calculated from $Tk_{5,5}$, L_K , Length of side of cubic target volume.

Figure 9.43 (CONFCHTb) (pp 353) is derived from equation 9.39 (pp 352) and discussed in pp 351 - 354. This figure provides a means of calculating the treatment time of continuous irradiation at a defined dose rate that is required to reach a tolerance dose in late reacting dose limiting normal tissues. This requires specifying a value of K_{cont} for continuous irradiation that sets the "Thermostat" at a tolerance level.

K_{cont} values may be derived by clicking on the [Derivation] button then entering the required variable values and click on the [Calculate] button. To alter the Default value of μ (0.693) change $Tk_{5,5}$ from the Default value of 1.5 hours then click on [Calculate] and the new value of μ and K_{cont} are then evaluated. These new values of K_{cont} and μ then need to be entered into the appropriate buttons in the Equation: Figure 9.43 (CONFCHTb) then click on [Plot!]. In figure 9.43 (CONFCHTb) no fractionated irradiation is used and the Default value of both d_g and $N = 0$. Fractionated irradiation may be added by entering the required values of d_g and N and click on [Plot].



Guidelines to the use of Figure 9.44 (The CONFRACT MODEL)

Purpose

Figure 9.44 The CONFRACT MODEL pp 356 provides a means of deriving the tumour control probability of continuous irradiation alone or continuous irradiation combined with fractionated irradiation. The fractionated irradiation may be conventional daily treatments or hyperfractionated twice daily treatments. There are four curves produced.

Variables

α_m , α_σ , β_m , β_σ , Mean and standard deviations of α and β values of tumour: K, Number of random samples calculated with range variable i: t_m , Duration of continuous irradiation in minutes with range: $T_{c.5}$, Clonogen repair half time in hours: h_{mc} , Incomplete repair factor for hyperfractionated treatment: T_{pm} , $T_{p\sigma}$, Mean and standard deviations of doubling time of tumour in days: M_m , M_σ , Mean and standard deviation of number of clonogens: R_a , Dose rate of continuous irradiation in Gy per hour: N, Number of fractions of fractionated treatment: T_k , Kick-off time in days: nd, Number of fractions per day: d_g , Dose per fraction.

To operate figure 9.43 and 9.44 several steps are required.

- A. Define a tolerance level of continuous irradiation by first deriving an appropriate value of K_{cont} using the [Derivation] button in equation figure 9.43 (CONFRACTb).
- B. From figure 9.43 (CONFRACTb) derive the treatment time t in hours from the Y-axis required to reach 100% of Tolerance shown on the X-axis corresponding to the variables used in this figure. Then for figure 9.44, convert time t in hours to t_m minutes (in the example figure 9.44 pp 356 $t_m = 8160$ minutes) and derive an appropriate range of t_m values for the X-axis of figure 9.44.

Figure 9.44 (pp 356) is an example of worked values showing a TCP of 0.7 at tolerance dose of brachytherapy as defined at 8160 minutes (136 hours) using a clonogen population of $10^{8.4} \times 3.5^3$ (approximately 10^{10}).

- C. In figure 9.44 (pp 356) no fractionated irradiation has been used. If daily fractionated treatment is to be added then a single value of N should be entered together with $nd = 1$ and the dose per fraction d_g entered and $h_{mc} = 0$. If twice daily hyperfractionated treatment is added $nd = 2$, the dose per fraction is changed appropriately an appropriate repair half time added. The Default value $h_{mc} = 0.063$ which is the value for a repair half time of 1.5 hours. All other parameter values may be changed as required. The dose rate R_a in figure 9.44 may be changed, for example to 0.8 Gy per hour, in which case the treatment time at tolerance (h) shown in figure 9.43 must be read from the same dose rate line $R_a = 0.8$ ($t = 68 \text{ h} = 4,800 \text{ min}$).

There are four curves produced in figure 9.44 but as no fractionated treatment is used (Default values N, $nd = d_g = 0$) there are apparently only 2 curves because the continuous irradiation curves are superimposed on the combined treatment curves. 4 curves are generated if fractionated treatment is added. The names of the curves demonstrated in the book are shown below in parentheses.

1. Continuous irradiation alone ($TCP_{cont\sigma m}$) in which inhomogeneities of the parameter values α_σ , β_σ , $T_{p\sigma}$, and M_σ are included. In the graph Figure (The CONFRACT MODEL) this TCP curve is labelled Cont + inhomogeneities.

2. Continuous irradiation alone (TCP_{cont} , equation 9.41 pp 354). Inhomogeneities of parameter values are not included so the mean values only are used. Consequently the curve is steeper than 1 and is labelled Cont mean values only.
3. Continuous irradiation combined with fractionated treatment excluding inhomogeneities of parameter values (Fract/cont mean only, equation 9.42 pp 355). The curve is labelled Fract/Cont mean only.
4. Continuous irradiation combined with fractionated treatment including inhomogeneities of parameter values ($TCP_{cf\sigma_{tm}}$). This curve is flatter than 3 and is labelled Fract/Cont + inhomogeneities.

This model is useful to explore the general relationships between the variables known to affect continuous and fractionated irradiation in terms of tumour control probability when treating to defined tolerance doses. For more details see pp 351-365.



SUMMARY

It is hoped that these interactive models when used in conjunction with the book are found to be useful as a learning and teaching tool. A further extension, as described in the book, is the introduction of useful biological models into a bioeffect planning system. Once again it is stressed that biological planning should be considered a teaching and experimental tool and that all prescriptions must be ultimately determined following consideration of conventional isodose planning which remains the gold standard. The author cannot accept any responsibility for prescriptions based on the contents of the book or this software.

Have fun!

GUIDELINES TO THE SELECTED INTERACTIVE GRAPHS

Table 1 showing the interactive graphs used

Figure number in book	Page Number in Book	Description (Equation name in BIOEFFECT EQUATIONS SOFTWARE)
1.3	14	A modified FDF model for daily fractionated treatment. The biological effect is expressed as the equivalent number of fractions of d_s Gy per fraction. (FDFVEST)
4.5	127	Similar to figure 1.3 except that it is written to include hyperfractionation. (HYPCO1ST)
2.15	53	An integral volume effect model to examine the biologically effective dose in the reduced “boost” volume following treatment to the whole target volume when using a shrinking field technique. (IVDFSTT)
3.3	81	A graph to show the relationship between isoeffect dose per fraction and dose rate of continuous irradiation. (GYGY2S2)
3.5	84	Survival fraction dose response curves of continuous irradiation showing α cell kill, β cell kill and $\alpha + \beta$ cell kill combined. (LQ5PRO)
3.15	95	Predicted effects of continuous irradiation expressed in terms of the biological equivalence of fractionated treatment. (CONFR2ST)
3.21	101	Predicted effects of combined fractionated, or hyperfractionated treatment and continuous irradiation expressed in terms of the biological equivalence of fractionated treatment. (CONEXTAS)
3.29	113	Predicted effects of summation of two schedules of continuous irradiation expressed in terms of the biological equivalence of fractionated treatment. (CONEXBt)
9.8	298	The OPTIMUM model to explore the relationships between optimum treatment time and hence fractionation as normal tissue and tumour parameter values vary. (OPTIMCD)
9.6, 9.7, 9.11	291, 292, 306	The EFFECT model to explore the relationships between normal tissues and tumour variables and their effect on tumour control and late effect probabilities. To derive Normalised Dose – Response Gradient (γ_{50} slopes). (EFFECTB)
		Modification of the EFFECT model to include Uncomplicated Tumour Control Probability Curves. (P+Model) (P+PUTCOBE)
9.4	288	For the derivation of D_{50} doses for late reacting normal tissues. This value is required to set the “thermostat” for the EFFECT model. (LOGISTPB)
9.43	353	For the derivation of the treatment time of continuous irradiation at various dose rates to give a tolerance dose. This value is necessary for figure 9.44. (CONFCHTb)
9.44	356	The CONFRAC model used to show the predicted tumour control probability when treating with continuous irradiation alone or combined with fractionated irradiation. Inhomogeneities of parameter values may also be used. (CONFRAC)

THE CHOICE OF PARAMETER VALUES

Parameter values and their uncertainties have been discussed extensively in the book especially in chapter 8. For convenience table 2 is a reference to descriptions of parameters. It is inevitable that additional or improved data is or will become available and these may then be used in the models. In the meantime it is stressed again that the user must be fully aware of the hazards associated with the use of biological models and parameter values which are usually, at best, only approximations.

Table 2 showing the location of parameter values

Parameters	Tables in book	Pages in book
$\alpha\beta$ (r) values of late reacting normal human tissues	8.7	253
ϕ Tissue specific volume exponents for late reacting normal tissues	8.8	255-257
D_{05} and D_{50} values for late reacting normal tissues	8.8	255-257
Calculations of D_{50} dose		287-288 and figure 9.4
In vitro α and β values for tumours (grouped data)	8.4	245
In vitro α and β values for tumours	8.5	247-249
Tissue repair constants (μ) and repair half times ($T_{1/2}$)	3.1	74-75
h_m (h_{mst} , h_{mcl} in figure 9.8) Incomplete repair factor		Values shown in figures 3.21, 4.5, 9.8, 9.11, 9.4, 9.44. Models and discussion pp 122 - 126
$d_{g\sigma}$ Standard deviation of dose per fraction	8.18	274
D_{Mt} Dose modifying effect on clonogens D_{Mn} Dose modifying effect on normal tissues		Discussion in chapter 5. Inadequacies of data stressed pp 137 - 153
T_{pm} (T_{pot}) Mean tumour repopulation rates	8.12	262 – 263
T_k Kick-off time		264 – 265 Figure 9.19 pp 314
M_m Clonogen numbers	8.15	269
K_1 , K_{tol} , K_{tolx} , K_{cont} . Scaling factors to define tolerance (Thermostat)		These values may be derived from equations in figure 9.8 pp 298
Plausible parameter values (radiosensitivity, tumours, treatment variables)		274 - 276

Table 3 Guidelines to the use of the EFFECTB (P+PUTCObe) model

Parameters and models	Figures in book	Tables in book	Pages in book
EFFECT model	9.6, 9.7, 9.11		291, 292,306
In vitro α and β values for tumours		8.5	247-249
In vitro α and β values for tumours (grouped data)		8.4	245
T_{pm} (T_{pot}) mean repopulation rate		8.12	262-263
$d_{g\sigma}$ Standard deviation of dose per fraction		8.18	274
M_m Clonogen numbers		8.15	269
T_k Kick-off time	9.19		264-265 314
α/β (r) values of normal tissue		8.7	253
ϕ Tissue specific volume exponent		8.8	255-257
h_{mt} Incomplete repair factor	4.1, 4.2, 4.3		122-126
D_{mn} Dose modifying effect of chemotherapy on normal tissue D_{mcl} Dose modifying effect of chemotherapy on clonogens			Discussed in Chapter 5 pp 137 – 153. Inadequacies of data stressed
Normalised dose-response gradient (γ_{50} Late effects)	8.9		257
Normalised dose-response gradient (γ_{50} Tumour control probability)	8.10		258
Derivation of normalised dose-response gradients. Late effects and TCP	9.11		306
Normalised dose-response gradients derivation			310
Calculations of N_{def} and D_{50} dose	9.4		287- 290
Plausible Parameter Values (radiosensitivity, tumours, treatment variables)			274 - 276

Table 4. Sample Parameter Values for use in Figures 9.6 (EFFECTB and P +PUTCOBE)

Daily Treatments								
Tissue and volume	α/β (r) Gy (1)	Volume exponent (ϕ) (2)	D_{05} Gy (2)	N_k (4)	d_{gm}	D_{50} Gy (2)	N_{def} with $d_s =$ 2.0 Gy	Ktol1
Stroma 10cm ³	3.0	0.081	60	30	2.0	76	38	0.330
	3.0	0.081	66	33	2.0	84	42	0.303
Brain 2/3 volume	2.0	0.089	50	25	2.0	65	32.5	0.5
Brainstem	2.0	0.089	50	25	2.0	65	32.5	0.5
Lung whole Acute pneumonitis	3.3	0.114	17.5	8.75	2.0	24.5	12.25	1.078
Liver whole ² Liver failure	2.5	0.098	30	15	2.0	40	20	0.741
Bone. Femoral neck necrosis	2.27	0.076	52	26	2.0	65	32.5	0.45
Rectum small volume conformal treatments	3.0	0.056	65	32.5	2.0	76.6	38.3	0.308
Twice Daily Treatments								
	α/β (r)	ϕ	D_{05}	N_{hk}	d_{gmh}	D_{50}	N_{def}	Ktolx
Head and Neck EORTC 22719 ³	3	0.081	80.5	70	1.15			0.294
RTOG 90-03 ³	3	0.081	81.6	68	1.2			0.0287
Bladder (3)	3	0.081	60	60	1.0			0.410
	3	0.081	70	70	1.0			0.352
	3	0.081	67.2	56	1.2			0.348

(1) See table 8.7 for details. (2) See table 8.8 for details. (3) See table 9.1 for details.

(4) Used in [Derivation] for OPTIMUM

References

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3. Fowler JF. Confirmation of improved local-regional control with altered fractionation in head and neck cancer. Int J Radiat Oncol Biol Phys 48;1;3-6, 2000.