IOP Publishing *Phys. Med. Biol.* **66** (2021) 045028 https://doi.org/10.1088/1361-6560/abddd0

Physics in Medicine & Biology

IPEM Institute of Physics and Engineering in Medicine

OPEN ACCESS

RECEIVED
6 October 2020

REVISED
15 January 2021

ACCEPTED FOR PUBLICATION
20 January 2021

PUBLISHED
11 February 2021

PAPER

Fast neutron energy based modelling of biological effectiveness with implications for proton and ion beams

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Keywords: neutron, proton, RBE, LET

Abstract

A practical neutron energy dependent RBE model has been developed, based on the relationship between a mono-energetic neutron energy and its likely recoil proton energy. Essentially, the linear energy transfer (LET) values of the most appropriate recoil proton energies are then used to modify the linear quadratic model radiosensitivities (α and β) from their reference LET radiation values to provide the RBE estimates. Experimental neutron studies published by Hall (including some mono-energetic beams ranging from 0.2 to 15 MeV), Broerse, Berry, and data from the Clatterbridge and Detroit clinical neutron beams, which all contain some data from a spectrum of neutron energies, are used to derive single effective neutron energies ($\mathrm{NE_{eff}}$) for each spectral beam. These energies yield a recoil proton spectrum, but with an effective mean proton energy (being around 50% of $\mathrm{NE_{eff}}$). The fractional increase in LET is given by the recoil proton LET divided by the proton ($\mathrm{LET_U}$) value which provides the highest RBE. This ratio is then used to determine the change in the linear-quadratic model α and β parameters, from those of the reference radiation, to estimate the RBE. The predicted proton recoil RBE is then reasonably close to the experimental neutron RBE values found when taking into account the variation inherent in biological experiments. The work has some important consequences. The data of Hall *et al* (1975 *Radiat. Res.* **64** 245–55) shows that the highest RBE values are found with neutron energies around 0.3–0.4 MeV, but this energy cannot possibly generate recoil proton energies which are higher, as necessary for a 0.68 MeV proton with a 30.5 keV $\mu\mathrm{m}^{-1}$ $\mathrm{LET_U}$ (the LET value which provides the maximum obtainable RBE for a specified ion). For 0.4 MeV neutrons with proton recoil energies of around 0.2 MeV, the latter have a LET of around 62.88 keV $\mu\mathrm{m}^{-1}$. This could have an impact on proton beam RBE modelling. However, this is compensated by finding that the maximum radiosensitivity for mono-energetic neutrons was around 1.7 times larger than previously suggested from experimental ion beam studies, probably due to the necessary spreading out of Bragg peaks for ion beam experimental purposes, sampling errors and particle range considerations. This semi-empirical model can be used with minimal computer support and could have applications in ionic beams and in radioprotection.

Introduction

There are many published models designed to estimate the relationship between linear energy transfer (LET) and proton and ion beam relative biological effectiveness (RBE) (Elsässer *et al* 2008, Jones 2015, Chen *et al* 2017, Rørvik *et al* 2018, Paganetti *et al* 2019). In contrast, there are fewer models of the LET and RBE relationship for fast neutron beams of different energies, probably because of the inherent complexity of the neutron interactions resulting in many different ionising products. Consequently, there are a large number of resulting variables, which can be studied by use of Geant4 Monte Carlo and other simulation programmes (Baiocco *et al* 2016, Zabihi *et al* 2020).

It is known that around 50% of the absorbed dose imparted by neutron collisions (between 0.1 and 70 MeV) is due the ionising effect of elastically scattered recoil protons, mainly from hydrogen atoms present in water contained in living cells. The remaining 50% consists of 10%–35% from nuclear recoils (elastic neutron scattering) and up to 35%–40% from neutron-generated light ions (including deuterons, tritons, ^{3}He and alpha particles (Bewley 1989, Blomgren and Olsson 2003, Pomp 2010, Jones 2020). Chemical bond energies are much smaller in magnitude than the kinetic energies and can be neglected for radiobiological purposes. Each of these ionic species will have their own LET–RBE relationship. Furthermore, the neutron energies in most beams form part of a spectrum, and consequently the neutron products will also have their own related energy distributions.

The present report describes a tentative and approximate method for estimating fast neutron RBE values by considering elastically scattered recoil proton energies and their LET values and assumes a proportional averaged high LET contribution from all other ionic products including non-elastic (nuclear) scattering in the initial model, although these are later found to be unnecessary within the calculation process, as described below.

A relatively simple neutron RBE model, even if exploratory, and accurate to a first/second order of magnitude may be useful in medical applications and more generally in radioprotection. At the present time, it seems to be the case that neutron contamination within proton and ion beams are not included in routine treatment planning systems and in associated RBE estimates.

The present article describes such a model for predicting mono-energetic fast neutron RBE values by identifying the proton recoil energies and their LET values which determine the RBE. The estimated results are then compared with several published neutron RBE data sets containing neutron spectra with a maximum energy of 62.5 MeV and mono-energetic neutrons from 0.2 to 15 MeV. In the case of neutron energy spectra, a single effective neutron energy ($\mathrm{NE_{eff}}$) which determines RBE is used.

Methods and description of model

The method is based on previously published work for protons and ions which uses a semi-empirical or phenomenological approach coupled with scientific concepts based on the energy efficiency of cell killing (Jones 2015a, 2015b), which is further adapted to include neutron energy and proton recoil LET. A broad qualitative overview of the model is given in figures 1(a) and (b). More detailed descriptions of the processes are provided in tables 1 and 2 where the specific equation numbers given in the text are referred to, and which will allow users to generate their own computer programmes.

Physical assumptions

An operative value of LET for a neutron beam is assumed to be the sum of LET values obtained from:

(1) Elastically scattered recoil protons will on average have around half the energy of the incident neutron, and such protons provide a 50% overall contribution to the total ionisation as (Blomgren and Olsson 2003, Pomp 2010).

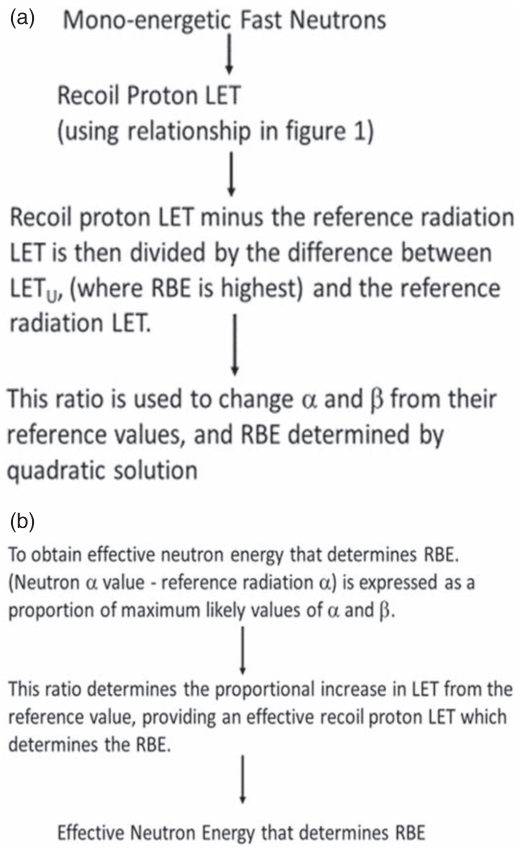
(2) Other neutron-generated products, as listed in the introduction, are assumed to have an average LET larger than in category (1) by a factor *m*. This is justified by the similarity of RBE values between carbon ions and fast neutrons which was used for many years in providing estimates of RBE with LET for carbon ion therapy in Japan (Kanai *et al* 1997). This *m* factor could be between 2 and 6 or more in order to be consistent with respective LET values associated with the maximum obtainable RBE values, which have been estimated to be between 30.4 keV.μm^{-1} and 70 keVμm^{-1} for protons and around 157 keV.μm^{-1}for carbon ions (Belli *et al* 2000, Jones 2015, 2017, Jones and Hill 2019, 2020) where each ion species has an unique LET–RBE turnover point rather than sharing common turnover at around 100–110 keV.μm^{-1} (Friedrich *et al* 2013).

(3) The link between neutron energy, proton recoil energy and LET is obtained by listing outputs of LET for proton kinetic energies (assumed on average to be half those of the neutrons as suggested by Bewley 1989) in liquid water by using the SRIM software package (SRIM *et al* 2008). The recoil proton LET (represented by F[Pr]LET) with changes in neutron kinetic energy (NKE), is given by the sum of three-exponential functions as:

$$\mathrm{F[Pr]LET} = 73.55\, e^{-1.64\mathrm{NKE}} + 21.05\, e^{-0.165\mathrm{NKE}} + 5.04\, e^{-0.016\mathrm{NKE}}. \tag{1}$$

This function was found by least squares fitting to SRIM produced proton recoil energies that have 50% of the energy of the neutron, as shown in figure 2. Essentially, this function will be linked to the LET–RBE relationships considered further below, and its overall form will influence the RBE changes seen when neutron energies increase above energies of around 0.4 MeV.

Then, it is assumed that all the ion products other than recoil protons can be represented by an averaged LET expressed as *m*.F[Pr] LET.


(a) Mono-energetic Fast Neutrons

Recoil Proton LET (using relationship in figure 1)

Recoil proton LET minus the reference radiation LET is then divided by the difference between LET_U, (where RBE is highest) and the reference radiation LET.

This ratio is used to change α and β from their reference values, and RBE determined by quadratic solution

(b) To obtain effective neutron energy that determines RBE. (Neutron α value - reference radiation α) is expressed as a proportion of maximum likely values of α and β.

This ratio determines the proportional increase in LET from the reference value, providing an effective recoil proton LET which determines the RBE.

Effective Neutron Energy that determines RBE

Figure 1. Summary of the overall approaches used in the Model to determine (a) the RBE for mono-energetic neutrons and (b) the effective neutron energy when the beam has a spectrum of neutron energies. For further information in tables 2 and 3 should be used for specific equations.

Table 1. Procedure for estimating RBE of a neutron source with known mono-energetic energy.

1. Use α and β values either from experiments, or choose relevant α and β values for the reference radiation and ensure their ratio is appropriate for a particular tissue. Some suggested values and combinations are available in Jones (2017) as a supplementary file and also in pages 9–8 to 9–10 in Practical Radiobiology for Proton Therapy Planning, Series in Physics and Engineering in Medicine and Biology, IOP ebooks ISBN 978-0-7503-1338-4]. These reference values are designated as α_C and β_C.
2. Choose the reference radiation (either 1 keV.μm^{-1} for orthovoltage x-rays, or 0.2–0.6 keV.μm^{-1} for megavoltage radiations).
3. The specified mono-energetic neutron value is used to find the average proton LET using equation (1).
4. The neutron LET_U is set as 157 keV.μm^{-1} for the full model (recoil protons and other ion products), but in the simplified form for recoil protons only as 62.8 keV.μm^{-1} (derived on page 7).
5. Equations (9) and (10) are used to determine α_U and β_u (the values of α and β at LET_U where the RBE is highest).
6. Equations (11) and (12) are used to find α_N and β_N (the neutron values of α and β at the specified energy).
7. The neutron exposure dose is known, then equation (14) is used to find the dose of the reference radiation for the same effect.
8. Equation (16) is used to provide the RBE, with or without the option of adding 0.2 to the result.

Table 2. Procedures to determine the effective neutron (NE_{eff}) energy from a spectrum of energies.

1. If using radiobiological data, use only the α radiosensitivity values of the reference and neutron irradiations (α_C and α_N respectively) and apply in equation (20) to give the effective proton recoil LET.
2. Use equation (1) iteratively to find the neutron energy that will produce the result obtained in 1, or use computer software such as SRIM.
3. Alternatively, without radiobiological data estimate the NE_{eff} value from the maximum neutron energy by using equation (21). The RBE is then estimated using the procedures in table 1.

Biophysical assumptions

The total LET produced by the proton recoils and the other ions can then be

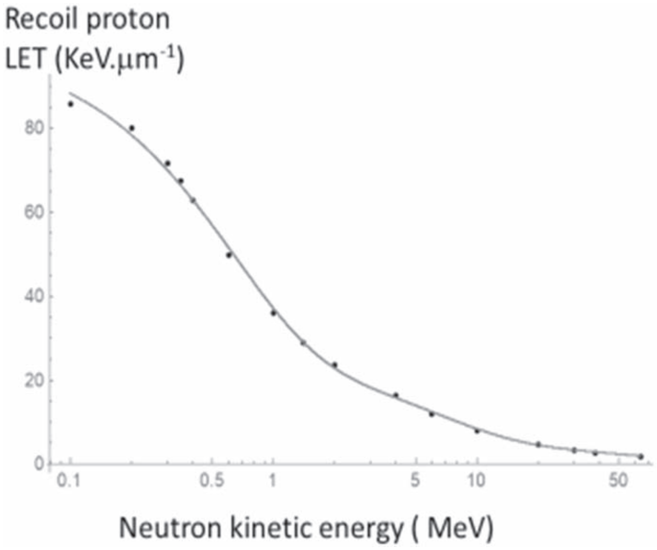


Figure 2. The curve given by equation (1), which expresses recoil proton LET as a function of neutron kinetic energy, is plotted with data points obtained using the SRIM software for protons in water.

written as:

$$0.5\ \mathrm{F[Pr]LET} + 0.5m.\mathrm{F[Pr]LET}. \quad (2)$$

Hall *et al* (1975) showed that for quasi mono-energetic neutrons, the maximum neutron RBE was around 0.3–0.4 MeV. The use of equation (1) for an energy of 0.4 MeV produces a recoil proton $\mathrm{LET_U}$ value of 62.88 keV $\mu\mathrm{m}^{-1}$. The total LET given in equation (2), using equation (1) to input the neutron energy and find the proton and ionic LET contributions at the maximum biological effect, is obtained when all the ionic contributions and the proton recoils provide an LET that is equal to $\mathrm{LET_U}$ obtained using equation (1). This allows the estimate of $\mathrm{LET_U}$ to be done will be equation (2) when it contains LET values which satisfy:

$$0.5\ \mathrm{F[Pr]LET} + 0.5 \times 4\ \mathrm{F[Pr]LET} = \mathrm{LET_U}. \quad (3)$$

In this way where m is assumed to be 5, the solution for $\mathrm{LET_U}$ is around 157.2 keV.$\mu\mathrm{m}^{-1}$ for a value of neutron kinetic energy of 0.4 MeV (the ultimate RBE found by Hall *et al*), and which is close to the published estimate carbon ion $\mathrm{LET_U}$ value around 157 keV.$\mu\mathrm{m}^{-1}$ (Kanai *et al* 1997). This value is used in all subsequent estimations which use the full model (as in equation (5) below).

Since there is no evidence of a bimodal peak of biological effect in the mammalian cell data sets in the region of the maximum RBE at around 0.4 MeV, it can be assumed that the maximum biological effect is obtained by the combined effect of the elastic scattered protons and the other ionic products. It then follows that the first part of equation (2) can be used to estimate the influence of the recoil protons alone on $\mathrm{LET_U}$ and then the 0.5 reduction factor is no longer required, since only recoil protons are being considered. In this way the proton $\mathrm{LET_U}$ for energies around 0.2 MeV (half of the neutron energy) can be estimated from:

$$\mathrm{F[Pr]LET} = \mathrm{LET_U}. \quad (4)$$

Thus the proton $\mathrm{LET_U}$ value is estimated to be approximately 62.88 keV.$\mu\mathrm{m}^{-1}$ by using the SRIM software. This $\mathrm{LET_U}$ value can be used for if using the simplified form of the model (as in equation (6) below).

The proton $\mathrm{LET_{U,}}$ previously estimated to be 30.4 keV.$\mu\mathrm{m}^{-1}$, with a proton kinetic energy of 0.68 MeV (Kanai *et al* 1997, Jones 2017, Jones and Hill 2019), produces an immediate problem in that for a neutron beam of 0.3–0.4 MeV, recoil proton energies of 0.68 MeV cannot occur. This revised estimate of the value of the proton $\mathrm{LET_U}$, the possible reasons for this difference, and the potential implications are discussed in greater detail within the discussion section below.

It is then necessary to scale this value of combined neutron products LET as a fraction of the neutron $\mathrm{LET_U}$ (which provides a maximum RBE at around 0.3–0.4 MeV) to the maximum possible value of the linear quadratic model radiosensitivity parameters α (designated as α_U) and β (designated as β_U), which occur at the LET–RBE turnover points where overkill commences.

If the proportion of total LET at any energy of, say, x MeV is given by equation (2) divided by the LET at the energy of the maximum RBE (around 0.4 MeV neutrons), and reverting here to the full form of the equation which includes recoil protons and other ionic products with a 50% split, then

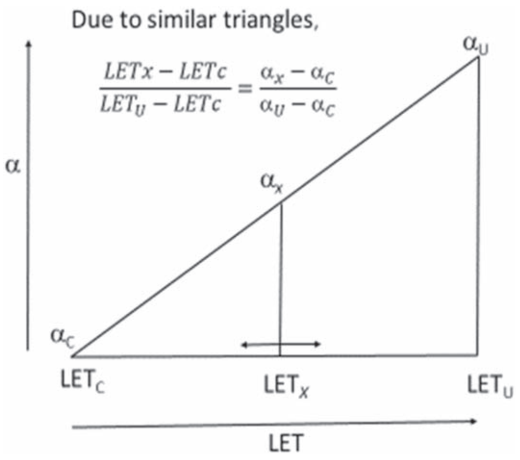


Figure 3. Schematic diagram of the fractional LET method.

$$\text{LET proportion} = \frac{0.5\ \text{F[Pr]LET}(x\text{MeV}) + 0.5 \times 4\ \text{F[Pr]LET}(x\text{MeV})}{0.5\ \text{F[Pr]LET}(0.4\ \text{MeV}) + \ 0.5 \times 4\ \text{F[Pr]LET}(0.4\ \text{MeV})}. \tag{5}$$

$$\text{This reduces to be LET proportion} = \frac{\text{F[Pr]LET}}{\text{LET}_\text{U}\text{[Pr]}}. \tag{6}$$

This result can be obtained with simpler symbolism as shown in appendix C. The value of the denominator (the LET_U value) in equation (5) is 157 keV.μm^{-1} (since all ion products are assumed to contribute) but in equation (6) the denominator (LET_U) is 62.8 keV.μm^{-1}, being that of the proton recoils.

Thus it is only the ratio of the proton recoil LET values, at any energy, divided by the proton recoil energies at LET_U that is necessary to consider in order to map any neutron energy onto the recoil proton LET curve shown in figure 2, which can then be used for estimating the changes in radiosensitivities described below. The relative proportions of proton recoils and the other ions, as well as their higher LET are not necessary within these scaling procedures.

Separate simulations have confirmed that the factors *m* and the relative proportions of other ions have no influence on the RBE obtained by scaling the proportion of LET to the LET_U on to radiosensitivities: the simple ratio is sufficient.

Thus the fractional increment in LET relative to the reference radiation LET value is the recoil proton LET minus the reference radiation LET (LET_C), divided by the difference between the proton LET_U and LET_C, as in:

$$\text{fractional proton recoil LET} = \frac{\text{F[Pr]LET} - \text{LET}_\text{C}}{\text{LET}_\text{U}\text{[Pr]} - \text{LET}_\text{C}}, \tag{7}$$

where LET_U will be the specific value for recoil protons, estimated above to be around 62.88 kev.μm^{-1}.

Use of the fractional proton recoil LET to determine RBE

This fractional LET method has been used in previous publications for proton and ion beam modelling (Jones 2015a, 2015b). Essentially it can be visualised in the form of similar triangles, since there is also a linear increment of α and β radiosensitivity with LET (see figure 3). The α and β parameters are assumed to have the same LET_U value, since there is perfect symmetry in the published LET–RBE relationships when dose (and surviving fraction) is changed, since the surviving fraction is controlled mostly by the α parameter at low dose, and by the β parameter at higher doses. In the following sections α_C is that for the reference (or control) radiation, with an LET designated by LET_C; α_x refers to the α value at any LET designated by LET_x; and α_U refers to the α value at any the LET designated by $\text{LET}_{\text{U},}$ where the biological effect is highest.

Previous work with ion beams (Jones 2015a) identified a saturation-type relationship of the form

$$\alpha_\text{U} = 2.7(1 - e^{-j.\alpha_\text{C}}) \tag{8}$$

with parameters $j = 3.6$–3.9 in two different analyses (Jones 2015a, 2015b), and a value of 3.9 was used in the present study. The 2.7 number represents the maximum attainable α value and was obtained from data that used fully electron-stripped ions which were not monoenergetic, due to the use of spread out Bragg peaks, kinetic energy spreads per bunch in the accelerators, and ion straggling. It is possible that the value of α_U is then underestimated and will be further influenced by sampling error since ion beam data sets contain relatively few biological data points (Jones and Hill 2019). The method may need a correction for neutrons where mono-energetic conditions are assumed, or (as shown later) a single effective energy is derived from a spectrum of energies, e.g. by using a multiplication factor, g, to give to a value g x α_U, where g is around 1.7. This aspect will be discussed further in Results and the Discussion sections below. Accordingly α_U was modified to be

$$\alpha_U = 1.7 \times 2.7(1 - e^{-j.\alpha_C}) \,. \tag{9}$$

The similar function for β is:

$$\beta_U = 0.5(1 - e^{-50.j.\beta_C}). \tag{10}$$

There is a much smaller increment in β with LET, which is well established for neutrons and probably for other ions (Jones 2015a, 2015b, Baiocco *et al* 2016). Further modest increases in β has only minor effects on the estimation of RBE.

Consequently the neutron α parameter (α_N) will be given by consideration of the proportional geometry in figure 3, so that the proportional increase in LET is the same as for α, and where α_C is the reference-radiation α value, as

$$\alpha_N = \frac{\mathrm{LET}x - \mathrm{LET_C}}{\mathrm{LET_U} - \mathrm{LET_C}}(\alpha_U - \alpha_C), \;\; \text{or alternatively as } \alpha_N = \frac{\mathrm{F[Pr]LET} - \mathrm{LET_C}}{\mathrm{LET_U[Pr]} - \mathrm{LET_C}}(\alpha_U - \alpha_C) \tag{11}$$

for neutron energies above 0.4 MeV (i.e. where LET values are below $\mathrm{LET_U}$, and above which overkill occurs for even lower neutron energies).

The same form of equation is used for β, with similar symbolism, namely

$$\beta_N = \frac{\mathrm{F[Pr]\,LET} - \mathrm{LET_C}}{\mathrm{LET_U[Pr]} - \mathrm{LET_C}}(\beta_U - \beta_C) \text{ or } \beta_N = \frac{\mathrm{LET}x - \mathrm{LET_C}}{\mathrm{LET_U} - \mathrm{LET_C}}(\beta_U - \beta_C). \tag{12}$$

In order to provide RBE estimates for different neutron radiation doses (and cell surviving fractions), it is then necessary to solve the quadratic equation which links the reference radiation and the neutron equation for a biological isoeffect for either d_C (the dose when using the reference radiation) or d_N (the neutron dose) in the simplest form of the linear quadratic model. If the number of treatments are the same in both reference radiation, such that:

$$\alpha_C d_C + \beta_C d_C^2 = \alpha_N d_C + \beta_N d_N^2, \tag{13}$$

and from which RBE is obtained by using one of the two following equations and the known dose either depending on whether the reference radiation or the neutron dose needs to be found, as in:

$$d_C = \frac{-\alpha_C + \sqrt{{\alpha_C}^2 + 4\alpha_N\,\beta_C\,d_N + 4\beta_C\,\beta_N\,{d_N}^2}}{2\,\beta_C}, \tag{14}$$

$$d_N = \frac{-\alpha_N + \sqrt{{\alpha_N}^2 + 4\alpha_C\,\beta_N\,d_C + 4\beta_L\,\beta_N\,{d_C}^2}}{2\,\beta_N}. \tag{15}$$

From which the RBE is then, by definition, the ratio

$$\frac{d_C}{d_N}. \tag{16}$$

A neutron radiation beam RBE lower limit of 1.2, rather than 1, is applied by adding 0.2 to the estimated RBE on an arbitrary basis. Various data sets show the minimum values appear to be around 1.2 (Fowler 1981, Bewley 1989). This is because RBE levels do not approach 1 in fast neutron beams, due to their high LET. This should be regarded as an option, although this addition has been used in the present study because it does to some extent compensate for the greater uncertainties associated with the increase in β (when compared to α) with LET. It should be noted here that the minimum RBE at high dose per fraction is controlled by a term called $\mathrm{RBE_{min}}$, which is defined as

$$\mathrm{RBE_{min}} = \frac{\sqrt{\beta_N}}{\sqrt{\beta_C}}. \tag{17}$$

The above equations can be used to model the increment in RBE with reductions in neutron energy. Below a value of around 0.4 MeV, the RBE reduces in the data of Hall *et al* (1975) due to overkill. The radiosensitivity reduction responsible for the reduced RBE values can be found using an inefficiency function to represent wasted energy (and where the resulting efficiency will be expressed by (one-inefficiency). The inefficiency is the excess energy released beyond the $\mathrm{LET_U}$ value (i.e. LETx–$\mathrm{LET_U}$) divided by the total energy released expressed by LETx–$\mathrm{LET_C}$, as in the erratum to (Jones 2015). The fall in α is then proportional to the wasted energy, as follows:

$$\alpha_N = a_C + \left(1 - \frac{\mathrm{F[Pr]LET} - \mathrm{LETu}}{\mathrm{F[Pr]LET} - \mathrm{LETc}}\right)(\alpha_U - \alpha_C). \tag{18}$$

And similarly for the β parameter

$$\beta_{\mathrm{N}} = \beta_{\mathrm{C}} + \left(1 - \frac{\mathrm{F[Pr]LET} - \mathrm{LETu}}{\mathrm{F[Pr]LET} - \mathrm{LETc}}\right)(\beta_{\mathrm{U}} - \beta_{\mathrm{C}}). \tag{19}$$

In this way α and β values fall with increasing LET values when greater than $\mathrm{LET_U}$ at energies below 0.4 MeV in the present model.

The experimental data sets

A summary of the experimental data sets is shown in table 3.

The data set of Hall *et al* (1975) for CHO cells is used because it provides reasonably mono-energetic neutrons on a scale between 0.11 and 15 MeV only but with neutron energy spectra with maximum energies of 0.11, 35 and 50 MeV. For these three beams a derived effective neutron energy ($\mathrm{NE_{eff}}$) is used using the radiobiological method given in table 2 and this concept is described further below.

Also, the more limited T1 human cell survival data of Broerse *et al* 1967 (Broerse *et al* 1968) has been analysed to obtain the reference radiation radiosensitivity parameters α and β and the RBEs for the different neutron energies. The fission energy spectrum (0–18 MeV) beam is noted as a 1 MeV beam by Broerse *et al* (1968) (1 MeV was the 'most intensive energy' within the beam) and two other beams contained an energy spectrum. Consequently, the method noted in table 2 (point 3) was used to provide an effective neutron energy for the fission data (max energy 18 MeV, $\mathrm{NE_{eff}} = 1.57$ meV), and the two beams which had a neutron energy spectrum (16 MeV, NEeff = 1.39 MeV; 20 MeV, Neff = 1.74) by using equation (21). In the publication of Broerse *et al* (1968), their figure 6 provides RBE uncertainties which are consistent with a coefficient of variation (CV, which is the ratio of the standard deviation divided by the mean) of 24% if four data points were used for each surviving fraction and 30% if five had been used. The use of RBE error bars is unusual: to estimate confidence limits formally the use of Fieller's theorem (Fieller 1954) is required and many published studies have not used this method. It allows the RBE ratio to express the confidence limits of the surviving fractions of the reference and test irradiations. For the graphics concerned with the Hall *et al* data, a standard deviation value of 30% of the mean has been used to show a potentially acceptable degree of dispersion, and which would far exceed the conventional uncertainty values in many biological experiments.

The fast neutron cell survival experiments at Clatterbridge (Warenius and Britten 1994, Warenius *et al* 1994) are also used to investigate some potential applications of the model. In such a large group of cell lines, it is important to select lines which have lower to moderate radiosensitivities, and exclude highly radiosensitive lines (including repair deficient mutants) since they may not exhibit so large an RBE. Figure 4 shows the reference radiation α and β values for all the cell lines and their subdivision into three phase space zones; only the lowermost in Group C were used for the estimations in this report. In these experiments the most relevant neutron energy for increasing RBE from the entire energy spectrum was not known. The model can be adapted to deduce the effective LET of recoiled protons (as in figure 1(b) and table 3), which gives the same change in the α radiosensitivity parameter, when both equations (7) and (18) are equated and then solved for the proton LET, so that the effective proton recoil $\mathrm{LET_{pr}}$ is given by:

$$\mathrm{LET_{pr}} = \frac{\alpha_{\mathrm{U}-}\alpha_{\mathrm{N}+}\mathrm{LET_U}(\alpha_{\mathrm{N}} - \alpha_{\mathrm{C}})}{\alpha_{\mathrm{U}} - \alpha_{\mathrm{C}}}. \tag{20}$$

This effective LET value is then related to the proton energy using SRIM software, or by iterations of equation (1) to give the neutron energy.

Further analysis of the data of Berry who used P388 leukaemia cells with other authors (Berry 1970, 1973, Berry and Bewley 1976) have also been used to determine effective neutron energies in the same way as with the clinical Clatterbridge beam and also for the Detroit beam (Joiner *et al* 2010). In the latter case only the PC-3 line could be used and with exclusion of the negative β parameter value found for neutrons, the α parameter being modified to be 0.826 $\mathrm{Gy^{-1}}$ by subtracting the neutron $\sqrt{\beta}$ value. This neutron α value yields an LET of 14.87 $\mathrm{keV.\mu m^{-1}}$, and an effective neutron energy of around 4.6 MeV, lower than the higher energy Clatterbridge beam.

For the Uranium fission spectra (0–18 MeV), the energy ranges are from two (Watt 1952, Grundl 1971), including the plate method which could have a highest energy of between 6 and 8 MeV, although the lowest was assumed.

A summary of the order of procedures and equations to be used within a computer programme to estimate RBE and the effective neutron energy from a spectrum are given in tables 1 and 2.

Apart from the use of the SRIM software, all graphics and programming was performed using *Mathematica* (Wolfram, Champagne Illinois) software. An example for determination of neutron RBE is given in appendix B.

Table 3. Summary of experimental data sets.

First author	Reference numbers	Reference radiation α_C (Gy^{-1})	Clonogenic cell lines	Neutron source(s)	Neutron energies (MeV)
Hall	19	0.11 (pooled data average)	Chinese Hamster Ovary (CHO) cells	d-T, d-D d-T, d-Be	0.11–50
Berry	25–27	0.8	P388 leukaemia cells	U Fission spectrum + Cyclotron	0.5–50
Broerse	21	0.14	Human kidney T1cells	U Fission spectrum; d-D & d-T Neutrons	0–18; 3–15
Joiner	28	0.24	PC-3 cell line	p-Be	48.5
Warenius	23, 24	0.26 (pooled data average)	12 tumour cell lines	d-Be	62.5

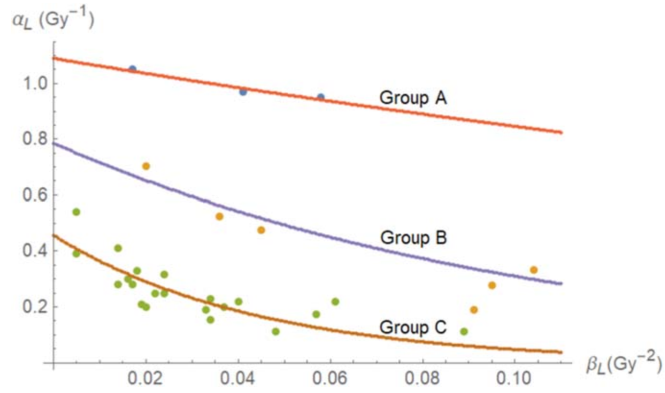


Figure 4. Plots of the control (reference radiation) low LET αL and β_L data for the Clatterbridge data set. These are divided into three groups according to their intrinsic radiosensitivities.

Results

RBE estimations superimposed on the data of Hall *et al* (1975) are shown for three levels of surviving fraction in figures 5(a)–(d), and also with assumed standard deviation curves for a coefficient of variation of 30%. The biological data shows considerable variation and it is not surprising that the predictions are also variable. It was necessary to assume an incremental factor of 1.7 for the α_U parameter for each neutron energy.

The original data of Hall (1975) is reproduced in figure 6, where it can be seen that the highest two energies which contain a spectrum of energies but plotted with their maximum value appear to have higher RBE's than would be expected from the overall trends. This is particularly marked for the 35 MeV beam. The survivals at the 0.8% level are somewhat erratic, probably due to the influence of use of very low doses on the neutron dose deposition and the proximity of the cell survival curves at low doses.

The RBE data of Broerse *et al* (1968) is shown with accompanying model predictions in figures 7(a)–(c). The Fission source (labelled F) uses a 1 MeV effective energy. Reasonable agreements occur in many instances although less so for the 16 MeV spectrum source produced from D on Be, which probably has a higher NE$_{\mathrm{eff}}$ than allocated; the agreement is better for the ^{3}He on Be 20 MeV spectrum. The predictions are not as good as those for the data of Hall *et al* (1975), but there is great diversity in the radiation sources used and considerable experimental measurement variations.

For the two clinical centres, the energies are always quoted as the maximum neutron energies which are the incident proton energies on beryllium targets. Figure 8 summarises the important (averaged) energy exchanges, as explained lower in this paragraph. Following the suggestion of Bewley (1989), the working value for the neutron energy is half of the maximum energy and the elastically scattered recoil proton energies around half of that. Thus for the Clatterbridge cyclotron, 62.5 MeV protons on to the beryllium target becomes a spectrum based on a mean energy of around 30 MeV neutrons with recoil protons having a spectrum with a mean of energy of around 15 MeV, although it was anticipated that lower energy protons are more likely to determine the RBE, since lower energies will have higher LET values. Equation (21) was then used to determine the effective recoil proton LET considered to be most likely to govern the RBE, based on the LET value which would provide the same change in α radiosensitivity found, on average, in the experimental data set. Equation (1) can then be used to find the effective energy. In this way the effective recoil proton energy was found to be 2.5 MeV, with an approximate LET value of 13.87 keV.μm^{-1}, and which is a 0.22 of the predicted LET$_U$ value of around 62.8 keV.μm^{-1}.

For the other ionic species, the energies that provide the same proportion of the average α radiosensitivity increments found in the experiments, as might a 50% combination of 12.5 MeV alpha particles and 12.5 MeV deuterons: the LET values are respectively around $47/121 = 0.39$, and $7.75/84.6 = 0.08$, which provides an estimated mean LET which is 0.23 of the combined LET$_U$. These particle energies are present in the beam and although such estimates only suggest (rather than prove) which energy predominantly determines the RBE, the model appears to be sufficiently robust to predict the range of RBE with allowance for biological uncertainties.

The data published by Berry and colleagues at different times and laboratories (Berry 1970, 1973, Berry and Bewley 1976) used radiosensitive P388 leukaemia cells. The only mono-energetic neutron data was at 14 MeV: further analysis reveals a probable neutron α value of 1.19, with 1.13 Gy^{-1} predicted by the present model. The other data are neutron spectra, which are used (with the other spectral neutron data already considered above) to provide the effective neutron energies shown in figure 9. There is but one anomaly, Hall's TAMVEC study (Hall *et al* 1975) using a 50 MeV maximum neutron energy spectrum. The higher effective neutron energy in this case,

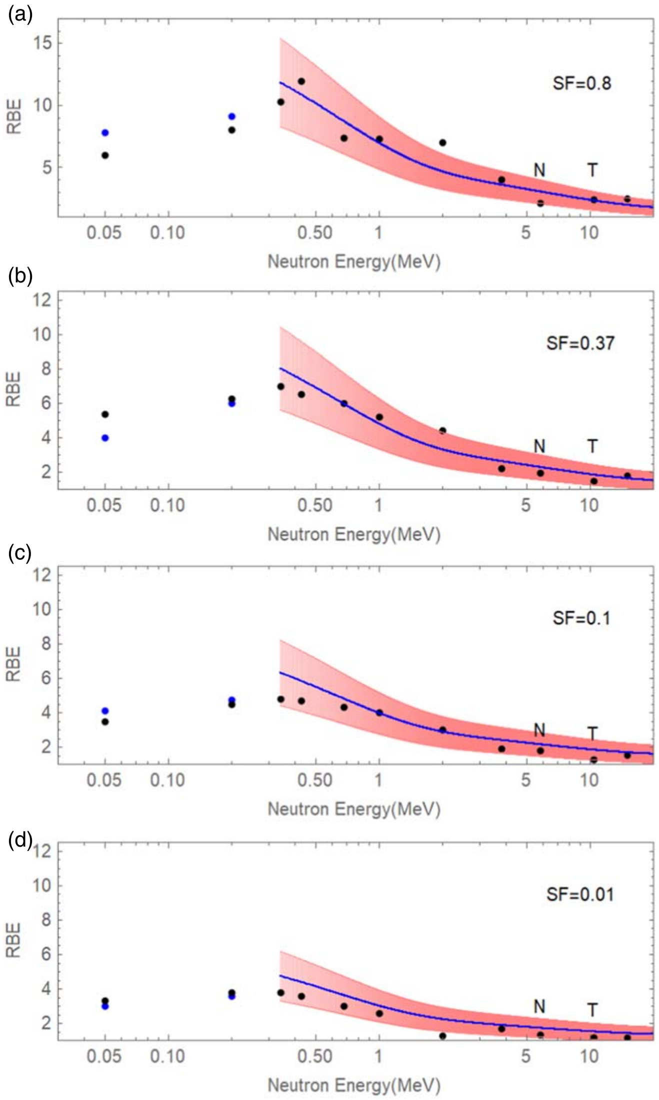


Figure 5. Data of Hall *et al* (1975) for CHO cells exposed to different neutron beams. Note that where beams had a spectrum of neutrons the effective energy was found by estimating NE_{eff}. The blue curve indicates the estimated RBE using the full model. The pink shaded area signifies the allowance of a coefficient of variation of 30% above and below the mean, indicating one standard deviation. For the lowest two energies (those below 0.4 MeV), where overkill occurs, a different in-efficiency function is used, the experimental data points (black) can be compared with the blue points which are those predicted by the model. No standard deviations are used in this region for better visualisation purposes since the exact position of the discontinuity may not be adequately captured by the data (a) Surviving fraction of 0.8. (b) Surviving fraction of 0.37. (c) Surviving fraction of 0.1. (d) Survival fraction of 0.01.

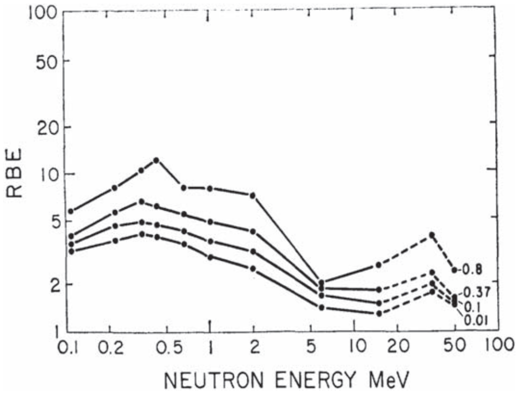


Figure 6. Reproduced from Hall *et al* (1975, Radiation Research with permission), which shows the RBE for different neutron energies for 0.8 (80% survival), 0.37 (37% survival), 0.1(10% survival) and 0.01 (1% survival) for V-79 cells. The 35 MeV and 50 MeV points are from experiments using the NRL and TAMVEC accelerators respectively.

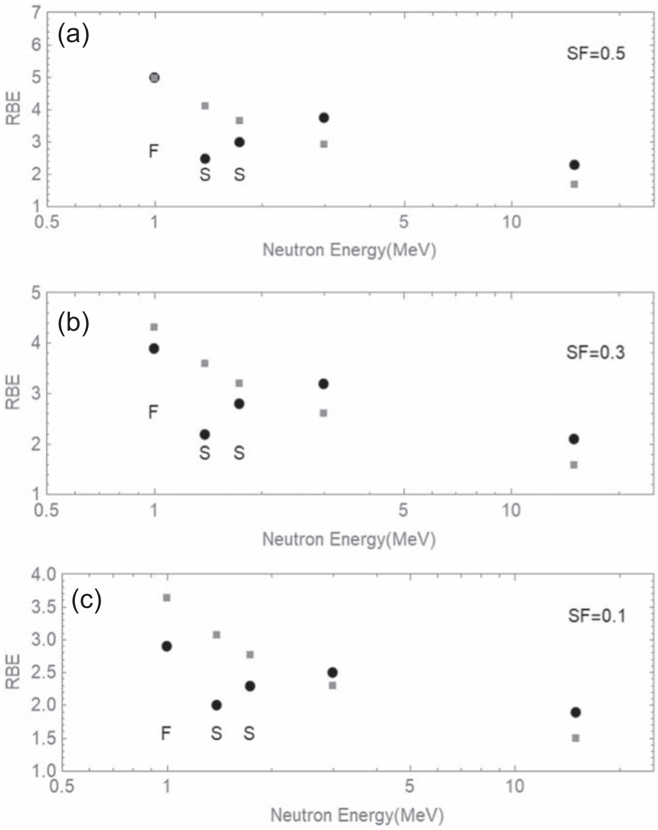


Figure 7. Approximated RBE Data of Broerse *et al* (1968) plotted with neutron kinetic energy as black points, with modelled estimates as grey squares for three survival fractions. The energies of the three beams which contained a neutron energy spectrum are indicted by F for the fission beam and S for each neutron beam from accelerators with beryllium targets.

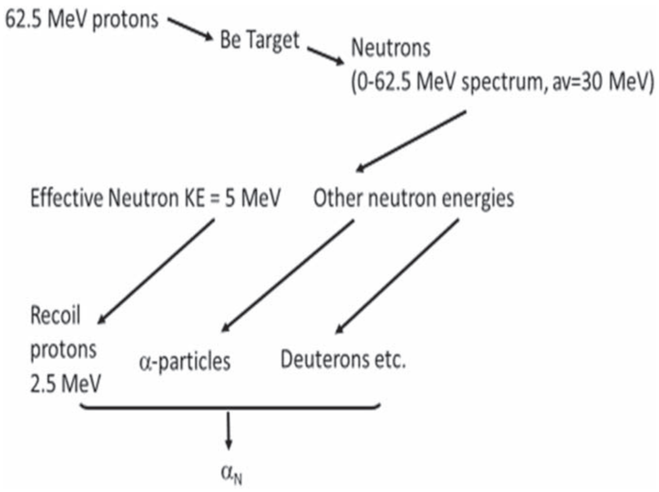


Figure 8. Schematic diagram which summarises the typical energy relationships that dominate the biological effectiveness.

which exceeds the 5 MeV N_{eff} found for the 62.5 MeV Clatterbridge beam, could be due to additional beam hardening due to tissue equivalent plastic sufficient to stop most recoil protons placed in front of the cell capsule and/or other unknown experimental factors. A smaller tissue equivalent plastic medium was used for the 35 MeV NRL beam by Hall *et al* (1975), which corresponds better to the linear fit obtained. The relationship between the maximum neutron energy NE_{max} (within an energy spectrum) and the effective neutron energy (NE_{eff}) can be fitted by a linear function ($R^2 = 0.97; p < 0.01$, standard error of gradient = 0.006) as:

$$NE_{eff} = 0.087\ NE_{max} \tag{21}$$

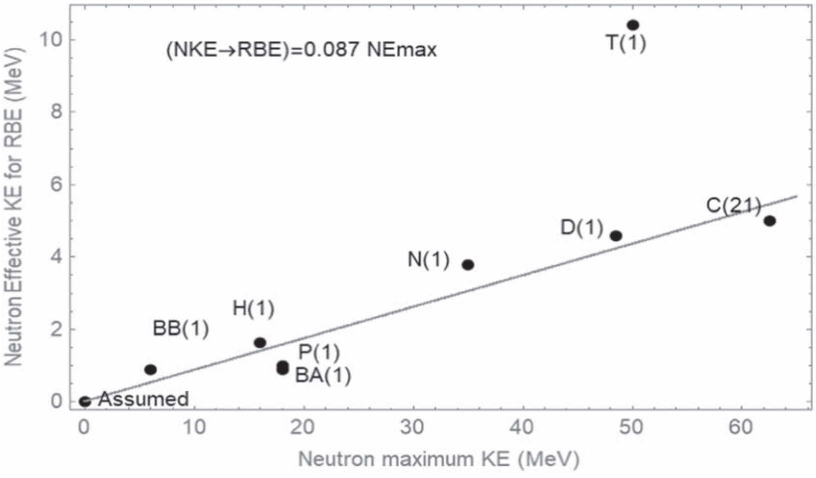


Figure 9. Data plots which show the relationship between neutron maximum kinetic energy in a beam and the effective neutron energy for bio-effectiveness. The individual beam codes are, for the cyclotrons: T = TAMVEC (Hall *et al* 1975), C = Clatterbridge (Warenius and Britten 1994, Warenius *et al* 1994), D = Detroit (Joiner *et al* 2010), N = NRL (Hall *et al* 1975), H = Hammersmith (Berry 1973, Berry and Bewley 1976), followed by the fission sources at P = Petten (Hall *et al* 1975), B(A) = Brookhaven (full spectrum) (Hall *et al* 1975), B(B) = Brookhaven (using plate converter assumed to have max energy of 6 MeV) (Hall *et al* 1975). An assumed zero–zero coordinate point was also used to obtain the slope. The numbers given in parentheses are the numbers of cell types used on each beam.

Discussion

The model presented provides a relatively simple and highly practical way of quickly estimating the RBE for neutron beams ranging from 0.1 to 64 MeV. It is intended to be a first/second order method for the estimation of RBE. Essentially, the model assumes that, from a spectrum of neutrons and recoil protons, a single effective recoil proton energy will determine the increase in RBE. The interesting finding that the elastic recoil proton LET as a proportion of its $\mathrm{LET_U}$ value, probably reflects all the other ionic species generated, even though the relative intensities of such ions may vary with energy, although perhaps in a way that does not significantly contribute to the overall RBE. It can be regarded as a phenomenological model, although semi-empirical would be a better description since rational physical and biological assumptions values have been used. The model has suggested that there is a real peak of RBE for recoil protons at around 62.8 keV.$\mu\mathrm{m}^{-1}$, and assumes linear increments in the linear quadratic cell kill parameters α and β, and of RBE, with LET. Also, that each ion has a unique turnover $\mathrm{LET_U}$ value, dependent on its nuclear charge (Z) number, rather than a common turnover at around 110 keV.$\mu\mathrm{m}^{-1}$, as found in the analysis of many ion beam data sets (Jones 2015, Jones and Hill 2019, 2020).

Bewley (1989) had reasoned that since the maximum possible proton LET of around 100 keV.$\mu\mathrm{m}^{-1}$ occurs when the proton energy is around 70 keV, then if this energy occurs half way along their tracks, their initial energy should be around 140 keV. This latter value indicates that the mean neutron energy prior to collision would be around 280 keV. Consequently, the highest RBE should occur with neutrons close to 300 keV which is reasonably close to the value of 0.4 MeV found in the experiments of Hall *et al* (1975) However, the maximum biological effect is known not to coincide with the maximum possible LET, but at lower LET values (Jones and Hill 2020), which is self-evident from the well-established turnover relationship found between LET and RBE in a large number of published experiments (Jones 2015, Jones and Hill 2019). Thus, the maximum RBE should occur at an energy which exceeds 0.3 MeV, which again is more compatible with the findings of Hall *et al* (1975).

Other authors have published descriptions of far more complex models, for example using GEANT 4 and other simulations, with multiple assumptions regarding biophysical events such as DNA double strand break (DSB) production density etc, and over much more limited energy ranges than the present study (Chen *et al* 2017, Zabihi *et al* 2020). The DSB end point, although better than single strand breaks, may not adequately reflect cell killing for RBE determination, since DSB are normally repaired efficiently. Cell death is better correlated with lethal chromosome breaks (Cornforth and Bedford 1987). For example, the advanced models of Boccacio and colleagues (Zabihi *et al* 2020) consider the relative proportions of other ion species produced within a neutron beam using fundamental and phenomenological approaches, but there is no validation with extant biological data sets. This group did predict a second peak of RBE between 20 and 40 MeV, as appeared to be the case for the experimental data of Hall *et al* (1975) as shown in figure 6, but when the NEeff correction is applied for Hall's 35 and 50 MeV beams effective neutron energy this peak at 35 MeV cannot be found, since much lower energies in the spectrum dominate the RBE. In figures 5(a)–(d) the energies plotted are the effective energies for the three beams with neutron energy spectra (0.11, 35 and 50 MeV). To confirm the predictions of Boccacio *et al* using their simulations, radiobiological experiments using mono-energetic neutrons are indicted; the data sets presented in the present paper cannot be used to verify their findings.

Zahibi and colleagues (Chen *et al* 2017) find good approximations to data and a peak RBE at 0.4 MeV is predicted, but the model is not valid for neutron energies above 5 MeV due to the current limitations of Geant 4-DNA for the tracking of heavy ions below 0.5 MeV/u. Further examples can obtained in other publications (Alloni *et al* 2013, de la Fuente Rosales *et al* 2018, Lampe *et al* 2018, Tang *et al* 2019). These show the progress being made but are not discussed further in the present article and there is a clear need for a more unified approach using perhaps top down and bottom up models.

The difficulties of producing a model that exactly fits biological data are well known. Biological heterogeneity is substantial often with coefficients of variation (CV) of between 10% and 30% or higher. In Hall's study (Hall *et al* 1975), for example, both reference radiations and specific neutron energy experiments were performed for each cell batch, and the range of reference radiation α and β values are considerable (for energies of 0.3–15 MeV they are: mean $\alpha = 0.106\ \mathrm{Gy}^{-1}$, median $\alpha = 0.096\ \mathrm{Gy}^{-1}$ and Standard Deviation 0.05, so the CV is around $0.05/0.106$, or 47%); for the β parameter the CV is $0.0041/0.0236 = 17\%$. Thus for each energy these key bio-parameters vary, and any linear based model as in figure 3 will use the mean overall parameters rather than a specific value for α and β for each energy. If this is done for say 37% survival, then better approximations are made.

The Broerse *et al* data (1968) set is also informative, but has considerable variation in the survival curves, especially for the 16 MeV spectrum (with a predicted NEeff of 1.4 MeV), and suggests that the most numerous neutrons with around 1 MeV neutrons provide the main determinant of RBE in a 0–18 MeV neutron fission source. Again, the RBE is broadly predicted to an accuracy compatible with biological variations with the exception of the 16 MeV spectrum source.

The Clatterbridge data set (Warenius and Britten 1994, Warenius *et al* 1994) has provided data from which it is possible to speculate the determining recoil proton energy is as low as 2.5 MeV from 5 MeV neutrons (from a peak value of 62.5 meV), which effectively determine the RBE because these energies will, on average, give the same increment in α radiosensitivity as would a 2.5 MeV proton beam, regardless of the other ionic products present. These energies are available in the beam and appear to be reasonable estimates. It is also suggested that all the ions released will be close to their maximum possible RBE effect.

The present study suggests that the $\mathrm{LET_U}$ value of protons is around 62–63 $\mathrm{keV.\mu m^{-1}}$, which is considerably larger that the value of 30.4 $\mathrm{keV.\mu m^{-1}}$ derived from the data of Belli *et al* (2000), Jones and Hill (2019), and upon which some proton models are based (Jones 2015, Rørvik *et al* 2018, Paganetti *et al* 2019). Various authors did suggest higher values around 60–80 $\mathrm{keV.\mu m^{-1}}$ or higher as reviewed by Friedrich *et al* [ ] and the later discussion in Jones and Hill (2019), but the experiments included an increasing proportion of deuterons in order to maintain particle range; deuterons probably have a higher $\mathrm{LET_U}$ value. The Belli data set (Belli *et al* 2000) contained protons only and it is possible that their range was limited in comparison with the average cellular thicknesses of 6–7 μm found using confocal microscopy, whereas when the experiments took place a thickness of 4 μm was measured using older optical methods (Dr O'Neill, personal communication). Thus if proton energies increase beyond 30.4 $\mathrm{keV.\mu m^{-1}}$ they may fail to reach cellular nuclei, so the RBE is likely to reduce with further increases in LET. This may now explain the Belli *et al* results (2000) where a linear increase is not maintained beyond 30.4 $\mathrm{keV.\mu m^{-1}}$. In contrast, fast neutrons can release recoil protons at any distance, so there would be no physical consequences to the limited tissue range, since the recoil could be released very close to or within a cell. This also implies that proton experiments will always have this limitation, so that a direct demonstration of the true LET–RBE turnover point may not be possible, but only inferred indirectly by using recoil protons. However, for clinical RBE estimations the data of Belli *et al* (2000) should still be used as it reflects the reality of a proton beam.

What are the implications for proton therapy? Would predictions of RBE need to be lowered? This may not be necessary, since in the course of the present study it was found necessary to assume a much higher value of α_U than in previous studies, which results in the predicted proton RBE values being similar. For example, a 30.4 $\mathrm{keV.\mu m^{-1}}$ $\mathrm{LET_U}$ value with LET values of 1, 2, 3, 5 and 10 $\mathrm{keV.\mu m^{-1}}$ respectively gives estimated RBE values of 1.08, 1.18, 1.27, 1.44, 1.82, whereas a 62.88 $\mathrm{keV.\mu m^{-1}}$ $\mathrm{LET_U}$ value, with a larger α_U value by a factor of 1.7 gives RBE values of 1.07, 1.15, 1.23, 1.38 and 1.7 RBE estimates. These are based on the conditions where a high RBE can be expected using 1.8 Gy per fraction of protons and reference-radiation radiosensitivities given by $\alpha = 0.06\ \mathrm{Gy}^{-1}$ with $\alpha/\beta = 2$ Gy as used elsewhere (Jones 2017). Although these are reasonably similar results, this higher value of $\mathrm{LET_U}$ may not be appropriate for a proton beam, since protons with energies corresponding to a LET of around 60–70 $\mathrm{keV.\mu m^{-1}}$ cannot reliably penetrate most V-79 mammalian cells, but neutrons of 0.4 MeV will do so, releasing their recoil proton within a cell. Thus, the 30.4 $\mathrm{keV.\mu m^{-1}}$ proton $\mathrm{LET_U}$, found by experiment, should continue to be the value used for a proton beam and with this value it is not necessary to apply the 1.7 times correction to $\langle_{\mathrm{U}}$, since there will inevitably be a mix of energies, for reasons mentioned above, which will modify pristine Bragg peaks to become spread out peaks with lower averaged LET values.

Although fast neutron radiotherapy has been in decline, because of inadequate evidence of therapeutic benefit (Jones 2020), neutron production in proton and other ion beams are potentially important (whether produced from interactions with collimators, filters etc, or arising within the patient due to interactions mainly with water). The use of raster scanned pencil beams have reduced the former effect but cannot eliminate the latter.

Neutron exposures are of greater concern not only in the nuclear industry for workers radioprotection purposes, but also in high altitude and trans-polar air travel, as well as outer space travel exposures of cosmic rays with secondary neutron production.

Conclusions

It is possible to estimate neutron beam effective energies in terms of recoil proton energies, which are sufficient to determine the RBE with reasonable accuracy when compared with experimental neutron RBE data obtained using a wide range of fast neutron energies and energy spectra. Considerable theoretical Monte Carlo simulation work would be required to implement these seemingly useful neutron RBE values into present proton and ion beam treatment planning systems, taking into account all the necessary physical interactions, to provide LET and dose maps. Further experimental studies are also indicated since some of the available data sets considered above contain a limited number of cell lines and neutron energies and the non-linear effects found by McNally for neutron and photon mixtures may apply (McNally *et al* 1984, Jones 2020). Studies that use multiple cell lines with a wide range of mono-energetic fast neutrons obtained are indicated to confirm possible higher RBEs predicted to occur at energies beyond the range of mono-energetic (0.2–15 MeV) and effective energies obtained from beams (with maximum energies as high as 62.5 MeV) which are considered in the present work. Also, experiments where proton/ion beams can also be delivered simultaneously would be ideal, at some advanced physics laboratory with sufficient beam time.

Acknowledgments

To Professor JW Hopewell for digitising the mono-energetic neutron results obtained by Hall, some technical conversations with Drs Peter O'Neill, Mark Hill, Boris Vojnovic, and to Andrzej Kacperek and Kirsten Hopkins (IAEA) for some literature sources.

There are no financial conflicts of interest within this work.

Appendix A. Table of symbols and definitions

Table A1.

Symbol	Definition	Code used in *Mathematica* programme (where relevant) in appendix C
NKE	Neutron kinetic energy	nke
NEmax	The maximum neutron energy in a spectrum	(not applicable)
$\mathrm{NE}_{\mathrm{eff}}$	Effective neutron energy (from a neutron energy spectrum) that determines RBE	(not applicable)
$\mathrm{LET}_{\mathrm{C}}$	Linear energy transfer for the reference radiation	letc
LETx	Linear energy transfer for the proton under consideration	letx
$\mathrm{LET}_{\mathrm{U}}$	Linear energy transfer for the highest possible RBE in the range of interest	letu
α_{C}	Reference radiation α parameter	ac
α_{N}	Neutron α parameter	an
α_{U}	α radiosensitivity at $\mathrm{LET}_{\mathrm{U}}$	au
β_{C}	Reference radiation β parameter	bc
β_{N}	Neutron β parameter	bn
β_{U}	β radiosensitivity at $\mathrm{LET}_{\mathrm{U}}$	bu
F[Pr]LET	The function which provides the recoil proton LET	letx
$\mathrm{LET}_{\mathrm{U}}$[Pr]	The $\mathrm{LET}_{\mathrm{U}}$ value of a proton	letu
d_{C}	Isoeffective dose of the reference radiation	dc
d_{N}	Isoeffective dose of the neutron radiation	dn
RBE	Relative Biological Effectiveness	rbe

Appendix B

Brief *Mathematica* Code for estimation of RBE for mono-energetic neutrons (between 0.4 MeV to a limit of around 20 MeV) when the reference low LET dose is known.

(Where letc is reference LET, nke is the neutron kinetic energy, au and bu is α_U and β_U, prlet = proton recoil LET; letu is $\mathrm{LET_U}$, dc is the reference radiation dose and dn the neutron dose; an and bn are α_N and β_N.)

letc = 1;ac = 0.106; bc = 0.0236;
au = 1.7 10.57/3.92 (1-Exp[−3.92 alow]);
bu = 0.05 (1-Exp[-50 blow]);
prlet = 73.55 Exp[−1.64 nke] + 21.05 Exp[−0.165 nke] + 5.04 Exp[−0.016 nke]
letu = 157;dlow = insert dose of reference radiation;
an = ac+(prlet-letref)/(letu-letref)(au-ac);
bn = bc+(prlet-letref)/(letu-letref)(bu-bc);
dn = 1/(2 bn) (−an + $\sqrt{}$(an^2 + 4ac.bn.dc+4 bn bc dc^2)
rbe = 0.2+dc/dn

If the neutron dose is known, then use equation (14) to obtain the iso-effective reference radiation dose at the penultimate step.

Appendix C

Simplified algebraic symbolism for obtaining equation (6)

Equation (Chen *et al* 2017) can be represented in simpler form by the terms:

$$p = \frac{ax + amx}{ay + amy}, \tag{C1}$$

where a and m replace 0.5 and 4 respectively, with x being the proton recoil LET values from a specified neutron energy and y is the proton recoil LET values for 0.4 MeV neutrons where bio-effects are maximal.

Equation (6) can be further simplified as:

$$p = \frac{x}{y}. \tag{C2}$$

It also follows for multiple ionic products from neutron collisions, each with respectively proportions $a, b, c\ldots n$, and relative magnitudes of LET given by $m_1x, m_2x, \ldots .m_nx$, that

$$p = \frac{ax + bm_1x + cm_2x \ldots \ + nm_nx}{ay + bm_1y + cm_2x \ldots \ + nm_ny} = \frac{x}{y}. \tag{C3}$$

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