Bulg. J. Phys. **37** (2010) 123–131

Survival Curves Models of Neutron Irradiation Data and Evidence for Hypersensitivity Phenomena

F.A. Azooz, **H. Al-Taii**

University of Mosul, College of Education, Department of Physics, Mosul, IRAQ

Received *23 November 2009*; Revized *6 July 2010*

Abstract. In order to find out the most suitable model that describe neutron survival curves data, we used MAT-LAB facility programs to extract the neutron survival curves data from literature and fitting them to four survival curves models: The single-hit single-target (SHST) model and the linear quadratic equation (LQ) which both are classical models, and the inducible repair model (IR) and the Repairable Conditionally Repairable model (RCR) which both takes into account the recently discovered hypersensitivity phenomena. The classical models failed to describe neutron survival curves, whereas the Inducible Repair model (IR) was successful to a certain extent and the RCR was most successful in fitting the data Fitting analysis suggests that a hypersensitivity phenomena is present in old neutron data and needs to be investigated.

PACS number: 87.64.Aa, 87.56.bg

1 Background

Many mathematical and mechanistic models have been proposed to describe mammalian cell survival data and to interpret from the data possible molecular processes that are likely to bring about cell death. The first of these models was the single hit single target exponential equation [1]

$$S = \exp(-\alpha D) \tag{1}$$

Where S is the surviving fraction, D is the dose and α is the damage factor.

This equation was later replaced by multi-target single-hit and single-hit multi-target equations which were favored for fitting the shape of mammalian-cell survival curves in earlier decades. However they all give poor fit to the data, especially at low doses of radiations.

Although up to now no generally accepted hypothesis is available about the mechanism by which cellular responses are induced and expressed, the model involving a linear and quadratic (LQ) dependence on the dose is considered as adequate approximation for responses to doses of up to about 5Gy of low linear energy transfer (LET) radiation and equivalent doses of other radiations. It is given by [1]:

$$S = \exp(-\alpha D - \beta D^2) \tag{2}$$

This equation is a semi empirical in origin, but the fitting parameters α and β were interrupted later in terms of damage mechanism, where α is considered as the damage factor due to direct action mechanism and β as the damage factor due to indirect action.

However, in recent years, experimental evidence has shown that mammalian cells show a hypersensitivity to doses lower than 0.5 Gy. The hypersensitivity response occurs maximally at doses around 0.5 Gy, and the LQ model has been shown to significantly underestimate response in the dose range up to 1 Gy in these curves.

Many models have been suggested to describe the more complex shape of the survival curve if the hypersensitivity region is included. One of these models is a modified version of the LQ model and known as the Inducible Repair model (IR). It is assumed to be applicable to survival curves which show hypersensitivity phenomena as well as those which do not show it. It is based on a threshold dose D_c, below this dose (generally following up to ≈ 0.5 Gy) the tissue is hypersensitive, but when the dose has exceeded the threshold, repair mechanisms are induced in the tissue and the effective cell sensitivity reduces greatly. The IR model can be expressed in terms of effect on surviving fraction as [2]:

$$S = \exp\Big[-\alpha\Big\{1 + \Big(\frac{\alpha}{\alpha_S} - 1\Big)e^{-D/Dc}\Big\}D - \beta D^2\Big], \tag{3}$$

α_S is the steep initial slope at very low doses to describe the hypersensitivity region. It changes exponentially as the damage inflicted leads to the induction of more efficient repair, and transformed to a more resistant, shallower slope of the shoulder region after repair has fully induced (characterized by α in the LQ classical model. The quadratic β term takes over at progressively higher doses.

The IR model is so successful in describing survival curves in the low-dose region, however, it describes the high dose region poorly, and a new statistical model, the Repairable Conditionally Repairable model (RCR) was predicted by Linda Persson, in which the survival is given by [3]:

$$S = e^{-aD} + bDe^{-cD}, \tag{4}$$

where a, b and, c are fitting parameters

This recent model is assumed to be able to describe survival curves at low and high dose reasonably well.

2 Methods

Survival curves data for neutron irradiation of V79 cells were taken from references [4,5], scanned and fed to the computer as image files readable by MATLAB 7.0 (The Mathworks, Inc., Natick MA, USA) and transferred into figure files in pixel units. Calibration curves relating the pixel units and the real coordinates units were used to extract the real data points. Hence, a complete set of survival curves data points was obtained, the error bars were neglected. This was done for 12 survival curves ranging in energy between (0.11–15.0) MeV.

The survival curves data points were fitted to the four models described by equa-

Table 1. Statistical fitting parameters characterizing the goodness of fit

	SSE	ADJ	RMSE	SSE	ADJ	RMSE
	$E = 0.11$ MeV			$E = 0.176$ MeV		
SHST	0.002555	0.9974	0.0191	0.05934	0.8885	0.09945
LQ	0.003724	0.9955	0.02491	0.02329	0.9562	0.0623
IR	0.0006478	0.9992	0.01039	0.01569	0.9705	0.05114
RCR	8.466×10^{-5}	0.9999	0.004115	0.03451	0.9352	0.07584
	$E = 0.22$ MeV			$E = 0.34$ MeV		
SHST	0.001506	0.9984	0.01584	0.00214	0.9974	0.01888
LQ	0.0006669	0.9992	0.01155	0.0007805	0.9989	0.01249
IR	0.0004088	0.9994	0.01011	0.0007311	0.9989	0.01209
RCR	0.0007241	0.9989	0.01345	0.0002833	0.9995	0.008416
	$E = 0.43$ MeV			$E = 0.433$ MeV		
SHST	0.001264	0.9987	0.01344	0.006299	0.9909	0.03968
LQ	0.0003056	0.9996	0.007136	0.001414	0.9973	0.02171
IR	0.0001279	0.9998	0.005058	0.002457	0.9965	0.02479
RCR	0.0002147	0.9997	0.006553	0.02269	0.9564	0.08698
	$E = 0.583$ MeV			$E = 0.66$ MeV		
SHST	0.003142	0.9955	0.02507	0.001017	0.9989	0.01205
LQ	0.004047	0.9928	0.03181	0.0005081	0.9994	0.009203
IR	0.003196	0.9943	0.02827	5.266×10^{-6}	1	0.001147
RCR	0.0132	0.9765	0.05745	2.116×10^{-6}	1	0.0006505
	$E = 1.0$ MeV			$E = 2.0$ MeV		
SHST	0.004769	0.9953	0.0261	0.0001611	0.9998	0.004797
LQ	0.0004443	0.9995	0.008605	8.147×10^{-6}	1	0.001165
IR	0.0001203	0.9998	0.004906	9.281×10^{-7}	1	0.0004817
RCR	0.0002712	0.9996	0.007365	6.54×10^{-6}	1	0.001044
	$E = 6.0$ MeV			$E = 15.0$ MeV		
SHST	0.005787	0.9949	0.02875	0.001163	0.9985	0.01392
LQ	0.002585	0.9974	0.02076	6.149×10^{-5}	0.9999	0.003507
IR	0.002579	0.9974	0.02073	0.0001364	0.9997	0.00584
RCR	3.634×10^{-5}	1	0.002696	0.0001105	0.9998	0.005256

tions (1–4) using MATLAB fitting tools. The goodness of fit was measured depending on many statistical parameters or distributions; the first of these is the residual distribution which should be symmetric around zero; The second is the adjusted R-square value(ADJ), which takes into account the number of degrees of freedom in the fitted equation. R-square (the square of correlation) is defined as the ratio of the sum of squares of regression and the total sum of squares about the mean; it can take any value between 0 and 1, with a value closer to 1 indicating a better fit. R-square values obtained from the fit were very close to 1; The third criterion is that the sum of squares due to error (SSE) should be close to zero; And finally the root mean square error (RMSE) should be close to zero [6]. Table 1. shows the neutron energies used and the statistical parameters that describe the goodness of fit for each fitted model.

3 Results and Discussion

Data points used in this study were taken from two sources: The group with energies (0.11, 0.22, 0.34, 0.43, 0.66, 1.0, 2.0, 6.0 and 15.0) MeV represented by figures (1a, 1c, 1d, 1e, 1h, 1i, 1j, 1k, and 1l) belongs to Hall *et al.* [4]; and the group with energies (0.176, 0.433, and 0.583) MeV represented by figures (1b, 1f, and 1g) belongs to Leenhouts and Chadwick [5].

Although the neutron energies given by Leenhouts and Chadwick are close to some of those given by Hall et al, but the difference between corresponding curves is large. This is because of the difference in the dose range used in the two data sets in addition to accuracy of measurements. The most obvious about Leenhouts data (Figures 1b, 1f, and 1g) is that none of the four models can describe the data in any way. A careful inspection to these figures shows that there is a peculiar data point in each of them which occurs at about 0.32 Gy in Figure 1b, at 0.6 Gy in figure 1f and at about 0.4 Gy in Figure 1g. The other thing is that the data points in these figures are distributed over a small dose range (< 2.0 Gy), this helped to observe peculiar structure. We believe that this structure is a hypersensitivity phenomena which has been observed in recent years in alpha, proton and gamma irradiation data 7-9] which usually occurs at about 0.5 Gy, where the survival curves decreases sharply up to 0.5 Gy and then starts to increase again indicating the start of inducible repair [2]. The SHST model and the LQ model cannot describe the data points in these figures since they are not designed to take into account the hypersensitivity of the cells. The IR model and the RCR model also failed to describe the data precisely in this region simply because of the lack of data points in this sensitive region. This suggests that experiments on neutron irradiation should study this region with many additional data points nearby to look for a hypersensitivity phenomena.

The data points of the survival curves used by Hall *et al.* do not show such a structure, since larger fractional doses were used in their study, and the SHST

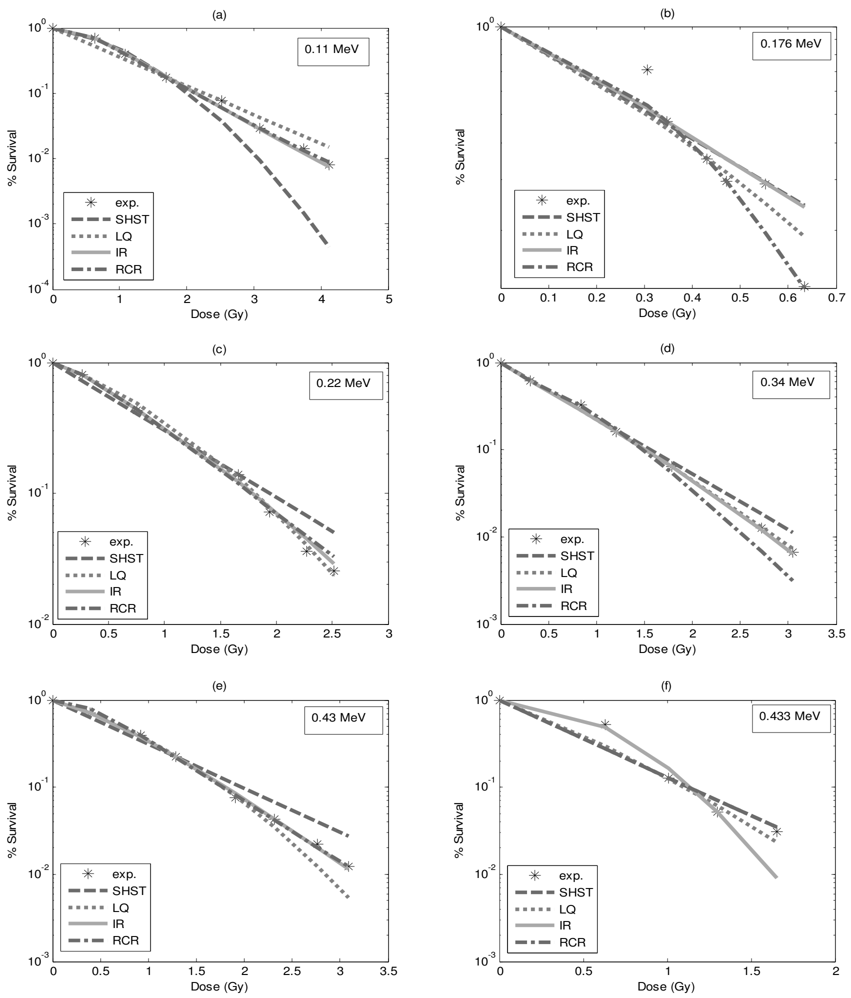

Figure 1. Survival curves for inactivation of V79 cells by neutrons fitted to: Single Hit Single Target (SHST), Linear Quadratic (LQ), Induced Repair (IR), and Repairable Conditionally Repairable (RCR) Models. The neutron energy appears at the top left side of the figure, the same type of line and the same color is used for each model in all figures.

model is unable to describe them, this is in contradiction to what has been thought before that the neutron data is usually described by the linear part of the LQ equation which is represented by the SHST model. The LQ model describes these data better at higher energies (> 1.0 MeV), than those at lower energies, however it is still unsuitable to be used for fitting neutron survival curves data. The IR model was successful to a certain extent to describe both Hall's data and

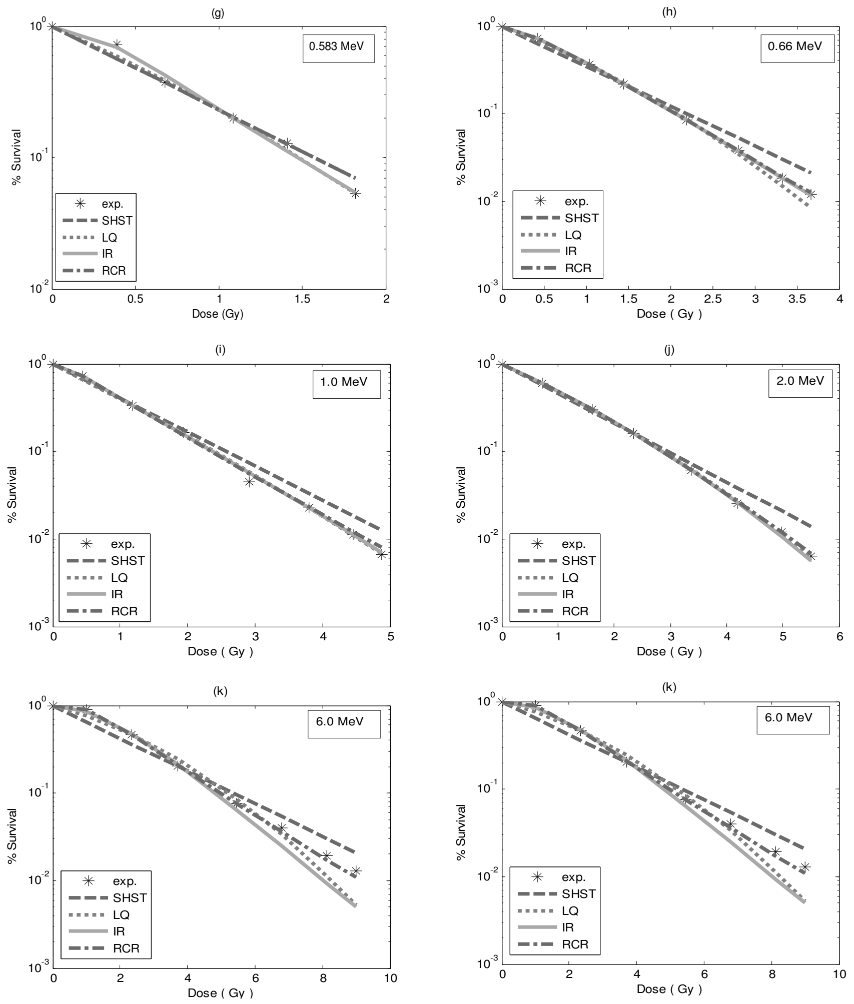

Figure 1. Continue.

Leenhouts data at low dose and high dose and at all the energy regions used in this study, but it needs more data points in the hypersensitivity region to give a better fit. The fitting process by the RCR model was most successful, the equation of this model is arranged in such a way as to take the maximum number of data points that describe the survival curve.

Although the fit results for the SHST model and the LQ model are not very reliable because they do not fit the survival curves quite well (Figures 1a–1f) but they give a close value to the damage factor (α) within errors at most of the energies used in this study (see Table 2). Also these values are typical for neutron

Table 2. The fitting parameters for the Single Hit Single Target (SHST) model and the Linear Quadratic (LQ) model

E	LET	Single Hit Single Target	Linear Quadratic Equation	
(MeV)	keV/μm	α (Gy^{-1})	α (Gy^{-1})	β (Gy^{-2})
0.11	51.585	1.023±0.32	0.3903±0.1	0.3609±0.035
0.176	55.327	2.221±0.27	2.221±0.19	1.0 fixed at bound
0.22	55.094	1.188±0.32	0.7086±0.048	0.3097±0.041
0.34	51.234	1.471±0.052	1.446±0.07	0.0546±0.075
0.43	48.076	1.167±0.052	0.7479±0.032	0.3042±0.029
0.433	48.076	2.036±0.18	1.72±0.34	0.3342±0.39
0.583	42.754	1.465±0.06	1.3±0.0186	0.1686±0.199
0.66	40.532	1.049±0.02	0.8376±0.036	0.1278±0.0268
1.0	32.193	0.8954±0.04	0.893±0.03	0.0266±0.018
2.0	20.439	0.7767±0.006	0.6712±0.003	0.0448±0.002
6.0	9.0351	0.4313±0.02	0.2394±0.018	0.0384±0.0096
15.0	4.2982	0.3437±0.0008	0.2831±0.006	0.01307±0.0013

irradiation (see for example Refs. [4,5]). The β-values are usually assumed to be zero when fitting neutron data or other densely ionizing radiations, but we found that we could obtain a better fit to the data when limiting the β-values between zero and one in the fit operation.

The damage factor (α) values in the IR model are close also to those in the SHST and the LQ models (Table 3) and the β-values in this model which are supposed to be the same β-values in the LQ-model are close to zero, but the two other parameters α_s and D_c in this model improved the fit very much, as said before, D_c is the dose at which the hypersensitivity phenomenon occurs

Table 3. The fitting parameters for the Inducible Repair Model (IR)

E	Inducible Repair Model (IR)			
(MeV)	α	α_s	β	D_c
0.11	1.2±0.069	0.0 fixed at bound	0.0 fixed at bound	0.9412±0.11
0.176	1.37±0.28	0.56±0.47	0.5 fixed at bound	0.3524±0.0635
0.22	0.977±0.079	0.0 fixed at bound	0.1716±0.053	0.1789± 0.044
0.34	1.3 fixed at bound	0.7 fixed at bound	0.1168±0.062	0.676±0.034
0.43	1.504±0.214	0.6575±0.0445	0.01573±0.078	1.5 fixed at bound
0.433	0.5478±0.1995	0.0 fixed at bound	1.5 fixed at bound	1.48 fixed at bound
0.583	1.626±0.184	0.0 fixed at bound	0.0 fixed at bound	0.446±0.132
0.66	1.075±0.068	0.4129±0.032	0.03898±0.022	0.7197±0.123
1.0	0.9236±0.034	0.0 fixed at bound	0.0189±0.0165	0.3148±0. 028
2.0	0.6527±0.012	0.747±0.16	0.0519±0.039	0.6089±0.305
6.0	0.637±0.13	0.0 fixed at bound	0.0 fixed at bound	3.481±2.143
15.0	0.2684±0.02	0.9±0.173	0.017±0.0038	0.4598±0.196

Table 4. The fitting parameters for the Repairable Conditionally Repairable Model (RCR)

E	Repairable Conditionally Repairable Model		
(MeV)	a	b	c
0.11	1.157±0.05	1.917±0.146	2.679 ± 0.157
0.176	2.0 fixed at bound	0.0 fixed at bound	2.0 fixed at bound
0.22	1.4±0.167	0.8721±0.168	2.585±0.745
0.34	6.694±1.376	3.563±0.55	2.67±0.149
0.43	1.463±0.099	1.674±0.094	2.672±0.227
0.433	2.036±0.426	0.0 fixed at bound	1.9 fixed at bound
0.583	1.465±0.143	0.0 fixed at bound	0.7 fixed at bound
0.66	1.219±0.008	0.8301±0.0075	2.192±0.029
1.0	0.9896±0.035	0.6719±0.1722	2.808±0.682
2.0	0.2432±0.013	0.0 fixed at bound	0.4145±0.0087
6.0	0.5069±0.0095	0.861±0.0173	1.083±0.026
15.0	0.8738±0.364	0.5897±0.2474	0.5842±0.0528

and α_s is the slope of the survival curve at the D_c value, we obtained some D_c values and corresponding α_s-values which improved the fit, but the lack of data points in the hypersensitivity region makes it difficult to trust the values of these parameters although the fitted curves for this model are moderate (see Figure 1)

The last of these models (the RCR) is a statistical in nature, it depends on Poisson distribution to describe the cell damage. The results of the fit to this model are shown in Table 4. It has three parameters a, b, and c, here the a-parameter is not the same as the α-parameter in the above three models, but our results show that the values of a are not very far from corresponding α-values in the other three models.

In fact the statistical RCR model fitted most of the data very well and we recommend to use this model in dose calculation for tumor therapy treatment by neutrons instead of the LQ model which is usually used for this purpose.

4 Conclusion

Fitting analysis suggests that a hypersensitivity phenomena is present in old neutron irradiation data and this phenomenon needs to be investigated experimentally .

The SHST model which is usually used to describe survival curves that belong to neutron irradiation is found to be unsuccessful. The LQ model also fails to describe these data. The IR model which is a modified version of the LQ equation gives a better fit than the LQ model, but the fitted parameters that are related to the hypersensitivity phenomenon are not very reliable because of the lack of data points in this region. The statistical RCR model fitted the data much better than the above three models and we recommend to use this model in the dose calculations for clinical purposes and disregard the LQ model.

References

[1] E.L. Alpen (1990) "*Radiation Biophysics*", Prentice-Hall International Inc.

[2] M.C. Joner, H. John (1988) *Radiat. Res.* **114** 385-398.

[3] B.K. Lind, L.M. Persson, M.R. Edgren, I. Hedlöf, A. Brahme (2003) *Radiat. Res.* **160** 366-375.

[4] E.J. Hall, J.K. Novak, A.M. Kelleher, H.H. Rossi, S. Marino, L.J. Goodman (1975) *Radiat. Res.* **64** 245-255.

[5] H.P. Leenhouts, K.H. Chadwick (1974) In: "*Biological Effects of Neutron Irradiation*", Vienna: International Atomic Energy Agency, p. 151.

[6] C. Danial, F.S. Wood (1980) "*Fitting Equations to Data*", John Wiley & Sons.

[7] X.-D. Jin, L. Qiang, W.-J. Li, J.-F. Wang, C.-L. Guo, J.-F. Hao (2006) *Nucl. Instrum. Methods Phys. Res., Sec. B* **245** 310-313.

[8] G. Schettino, M. Folkard, K.M. Prise, B. Vojnovic, A.G. Bowey, B.D. Michael (2001) *Radiat. Res*. **156** 526-534.

[9] E. Tsoulou, L. Baggio, R. Cherubini, C.A. (2002) *Radiat. Prot. Dosim*. **99** 237-240.

[10] B. Marples, K.A. Skov, M.C. Joiner (1994) *Radiat. Res.* **138** S81-S85.