The Henryk Niewodniczański INSTITUTE OF NUCLEAR PHYSICS, Polish Academy of Sciences

A STUDY OF V79 CELL SURVIVAL AFTER PROTON AND CARBON ION BEAMS AS REPRESENTED BY THE PARAMETERS OF KATZ' TRACK STRUCTURE MODEL

Leszek Grzanka[1,2]*, Michael P.R. Waligórski[1,3], Niels Bassler[4]

[1] Institute of Nuclear Physics (IFJ PAN), Kraków, Poland, [2] University of Science and Technology (AGH), Kraków, Poland,
[3] The Marie-Skłodowska-Curie Centre of Oncology, Kraków Division, Kraków, Poland, [4] Aarhus University, Aarhus, Denmark

* Leszek.Grzanka@ifj.edu.pl

AIM OF STUDY

Carbon ion beam radiotherapy planning requires accurate knowledge of cellular survival and of RBE along the beam and within the target volume. RBE depends on ion species, ion fluence, ion LET and on the survival level itself. Representative sets of survival curves of several cell lines irradiated by a variety of ions have been gathered in two data bases: PIDE (by GSI) [1] and by Sorensen [2]. We found no systematic survival data for a single cell line irradiated by protons and by heavier ions, measured within one laboratory. From the GSI database [1] we chose V79 Chinese hamster cell survival data measured by Wouters et al [3] for proton beams, and by Furusawa et al [4] for carbon beams of different energies or LET, assuming track-segment irradiation.

Our aim was to study the consistency between predictions of the Katz model [5] and experimental data. Katz's phenomenological model introduces four radiosensitivity parameters to characterise a cell line and is able to predict cellular survival after irradiation by different ion species. Over twenty years ago Katz applied his model to systematically study cellular radiosensitivity parameters of several mammalian cell lines [6,7], which provided us with guidance as to the range of parameter values to represent V79 cells.

We wished to verify whether a single set of four parameters of the Katz model: m, D_0, σ_0 and κ could be found to consistently represent survival of V79 cells after their irradiation by protons and by carbon ions.

We therefore obtained three sets of radiosensitivity parameters representing V79 cells survival: best-fitted to the data set of Wouters et al.[3] for protons alone, best-fitted to the data set of Furusawa et al.[4] for carbon ions alone, and best-fitted to both these data sets combined.

CONCLUSIONS

- We were unable to find a unique set of m, D_0, σ_0 and κ parameters of the Katz model to satisfactorily predict RBE-LET dependences for V79 cells after proton and carbon ion irradiation.
- When applying the Katz model in ion therapy planning it would be possible, in a pragmatic approach, to apply a different set of radiosensitivity parameters for proton beams from those for heavier ions. This approach needs to be tested also for helium and lithium beams, against available radiobiological data.
- Systematic measurements of survival curves reported in databases for cell lines representative to ion radiotherapy, should cover a broad range of ions, including protons, through carbon and heavier species, measured in the same laboratory. Co-60 or Cs-137 should be used as reference radiation rather than 250 kVp X-rays.
- Due to the analytical formulation of the Katz model, the calculation algorithms and optimisation routines are fast and efficient, making them very suitable for application in a future inverse-planning 3-D TPS for ion radiotherapy.
- All codes developed in this work are available through the libamtrack open source platform http://libamtrack.dkfz.org

THE KATZ MODEL

The Katz model radiosensitivity parameters characterising *in vitro* survival of a given cell line may be loosely interpreted as follows: m and D_0 represent (via the m-target formula) survival vs. dose of reference radiation; σ_0 may be related to the size of the radiosensitive site (cell nucleus). The value of κ may represent the sizes of m 1-hit "sub-targets" within the volume σ_0. The value of κ (or $z^{*2}/\kappa\beta^2$) determines the LET value at which maximum of RBE obtains, while the maximum value of RBE is also related to σ_0 (Korcyl [9])

Single ion inactivation cross section:

- dose averaged over site (target) with radius a_0

$$D_{av}(r) = \frac{1}{\pi a_0^2}\int_{t_{min}}^{a_0+r} D(t)\Phi(t,a_0,r)dt$$

- inactivation probability (m-target formula)

$$P(t) = (1-\exp(-D_{av}(t)/D_0))^m$$

- direct calculation (double integration)

$$\sigma = \int_0^{t_{max}+a_0} P(t)2\pi t dt$$

- analytical approximation (based on scaling of $D(r)$):

$$\sigma = \sigma_0 \begin{cases} (1-\exp(-z_{eff}^2/(\kappa\beta^2)))^m & \text{if } \sigma < 0.98\sigma_0 \\ f(m, z_{eff}^2/(\kappa\beta^2)) & \text{elsewhere} \end{cases}$$

Ion kill component:

$$\Pi_i(D) = \exp(-\sigma F) = \exp\left(-\frac{\sigma\rho}{L}D\right)$$

Gamma kill component:

$$\Pi_\gamma(D) = 1-\left(1-\exp\left(-\frac{(1-p)D}{D_0}\right)\right)^m$$

Cell survival:

$$S(D) = \Pi_i(D)\cdot\Pi_\gamma(D)$$

THE FITTING PROCEDURE

The goal of the optimization procedure is to find a set of four parameter values for which discrepancy between model predictions and experimental data is minimal. Experimental data includes error-weighted data points of survival curves after reference and after ion irradiation. Model predictions of ion data are based on the Katz model, while reference radiation data are described by the m-target formula.

The in-house developed optimization routine is included in the *libamtrack* library as a python code and uses the L-BFGS-B minimization algorithm (Grzanka [8]).

$$\chi^2 = \chi^2_{ion} + \chi^2_{Xrays}$$

$$\chi^2_{ion} = \sum_E\sum_D(\ln(S_{Katz,ion}(D,E)) - \ln(S_{experiment,ion}(D,E)))^2$$

$$\chi^2_{Xrays} = \sum_D(\ln(S_{model,Xrays}(D)) - \ln(S_{experiment,Xrays}(D)))^2$$

$$S_{model,Xrays}(D) = 1-(1-\exp(-D/D_0))^m$$

RBE PREDICTIONS

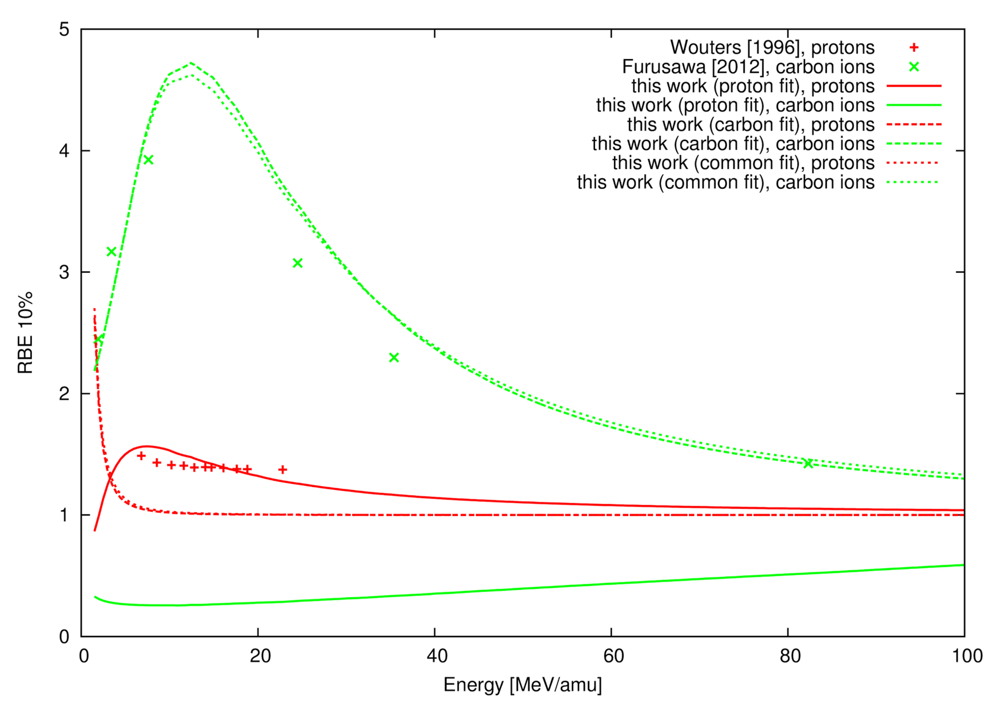

Figure 3. RBE at 10% survival vs. ion energy, calculated using the Katz model, with radiosensitivity parameters listed in Table 1. Solid lines – using parameters best fitted to proton data; dashed lines - using parameters best fitted to carbon data; dotted lines – using parameters best-fitted to combined proton and carbon data.

To analyse the data of Wouters et al. [3] we took track-segment LET values for protons of different energies, as listed in the PIDE database [1]. To analyse the carbon ion data we used original experimental data reported by Furusawa et al. [4], kindly supplied to one of us by Dr. Yoshiya Furusawa.

Applying the above-described fitting procedure, all four parameters of the model were simultaneously fitted to the respective sets of survival data: separately for the proton and carbon data, and for the proton and carbon data set combined. The resulting three sets of values of best-fitted radiosensitivity parameters are given in **Table 1**.

Table 1. Values of radiosensitivity parameters best-fitted to V79 survival data sets

Data sets	m	D_0 [Gy]	σ_0 [m^2]	κ
Proton	**2.73**	**2.86**	**0.06*10^{-11}**	**45**
Carbon	**3.45**	**1.94**	**5.01*10^{-11}**	**588**
Combined	**3.27**	**1.96**	**5.06*10^{-11}**	**620**

Using the respective best-fitted radiosensitivity parameter sets, we calculated the resulting survival curves and compared them with experimental proton data (**Fig. 1 below, left panel**), and carbon data (**Fig. 1 below, right panel**). The difference between V79 cell response after reference radiation data obtained by Wouters et al.[3] and Furusawa et al. [4] is shown in **Fig. 2, below**.

We next calculated RBE dependences at 10% survival, for protons and carbon ions, versus ion energy (**Fig. 3**), and ion LET (**Fig. 4**) using each set of radiosensitivity parameters listed in Table 1.

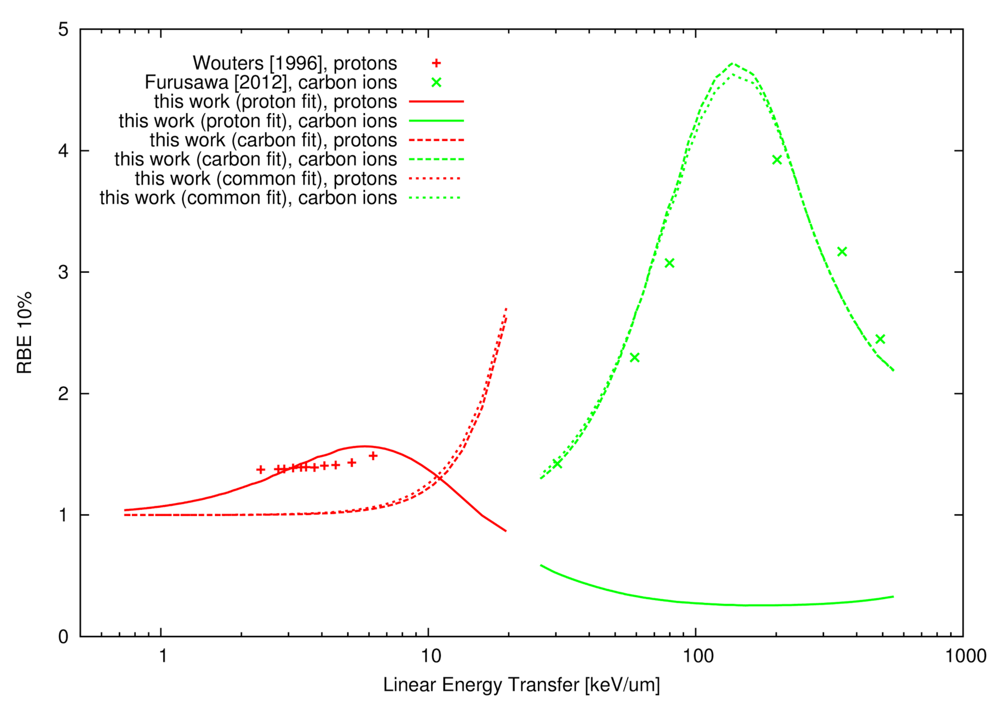

Figure 4. RBE at 10% survival vs. ion LET, calculated using the Katz model, with radiosensitivity parameters listed in Table 1. Solid lines – using parameters best fitted to proton data; dashed lines - using parameters best fitted to carbon data; dotted lines – using parameters best-fitted to combined proton and carbon data.

CELL SURVIVAL

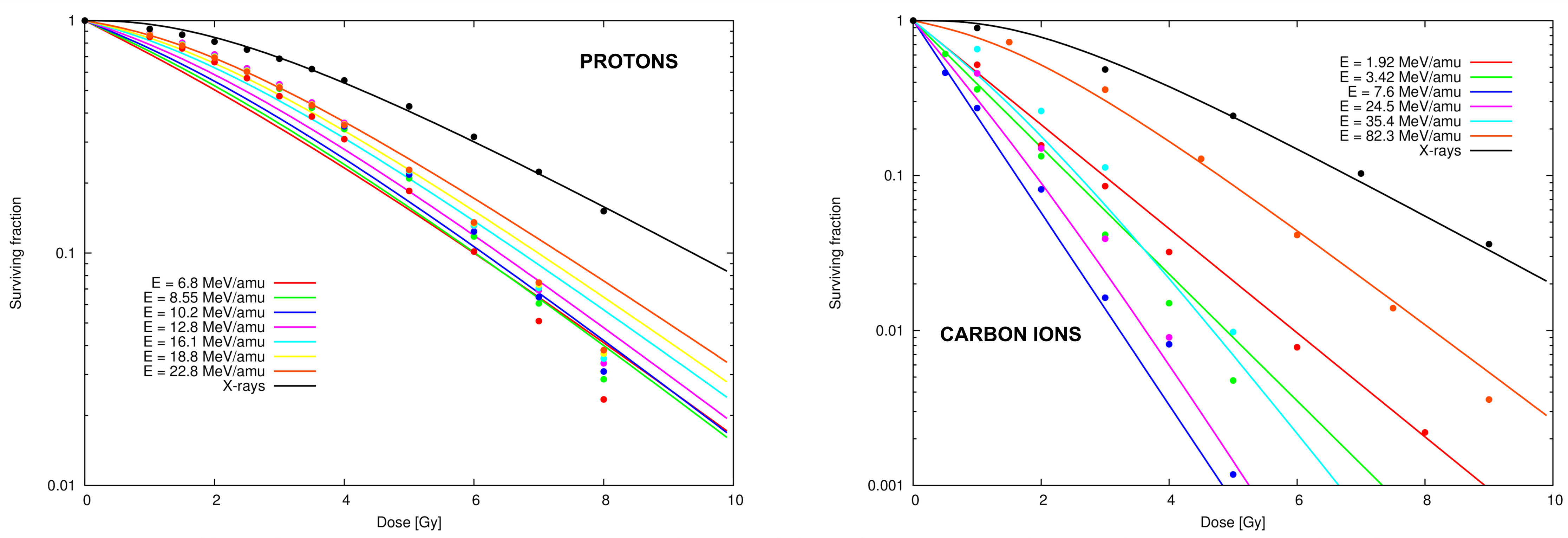

Figure 1. Results of fitting of Katz model parameters to survival curves after proton (left panel) and carbon ions (right panel) irradiation. Values of best-fitted parameters are listed in Table 1. Full lines represent model calculations, experimental data points are from Wouters et al. [3] (left panel) and from Furusawa et al. [4] (right panel) and correspond to projectiles of different energies (colour-coded in this figure). The reference radiation is 250 kVp X-rays (black).

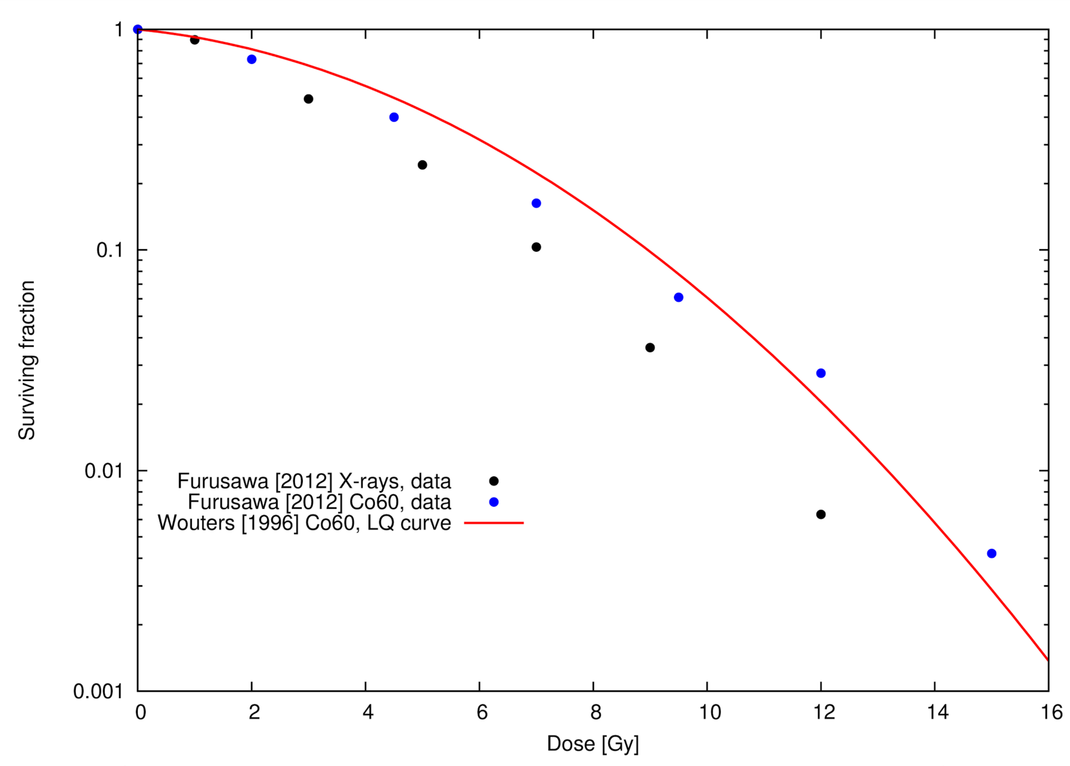

Figure 2. Comparison between data points representing V79 cell survival after doses of reference radiation: Co-60 and 250 kVp X-rays, data of Furusawa et al. [4] and Co-60, reproduced using alpha and beta values given by Wouters et al. [3] (full line).

DISCUSSION

While satisfactory representations of measured survival curves was found using best-fitted values of radiosensitivity parameters for proton and carbon survival data separately (**Fig. 3**), the best-fitted parameter values for these data sets differed considerably, especially with respect to σ_0 (0.06*10^{-11} m^2 vs. 5.01*10^{-11} m^2) and to κ (45 vs. 588) for the proton and carbon data sets, respectively (**Table 1**). Fitting the combined proton and carbon data sets yielded model parameter values close to those obtained for the carbon data set only (**Table 1**). As shown in **Fig. 3** and **Fig. 4**, application of the "proton" radiosensitivity parameters does not satisfactorily reproduce the carbon RBE-LET or RBE-ion energy dependences. Likewise, introduction of the "carbon" radiosensitivity parameters (and of the "combined" parameters) in model calculations does not correctly predict the proton RBE-LET or RBE-ion energy dependences.

The observed discrepancy between the measured V79 survival curves after doses of reference radiation in the data sets of Wouters et al. and Furusawa et al. (**Fig. 2**) does not explain these differences. More likely is the lack of "response saturation" in the survival of V79 cells after proton irradiation (in Katz model parlance – lack of transition between "grain count" and "track width" regimes in the case of proton irradiation), due to the much lower LET values of protons than those of carbon ions , which presumably forces the minimising procedure to seek much lower best fitting values of σ_0 and κ than those obtained for the "carbon" data set.

Values of "carbon" and "combined" radiosensitivity parameters are compatible with those found in the systematic evaluations of Katz et al. [6, 7].

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