RBE modelization: Present Status and Future Prospects

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Abstract

The main objective of this presentation is to review the RBE simulation models considered for application in hadrontherapy planning treatment. We focus on the two most advanced models for clinical application which are the Microdosimetric Kinetic Model and the Local effect Model. We present the formalism of the both models and a comparison of their basic concepts. Then we apply the MKM using the published data for HSG cell lines in order to compare our results with other published MKM results for the same cell line. Finally we apply the MKM for head and neck squamous cell carcinomas (SCC61 and SQ20B Cells) exposed to high LET ions. The results obtained with the Microdosimetric Kinetic model are analyzed and the model parameters of the SCC61 and SQ20B cell lines are compared in term of radiosensitivity to high-LET ions. We have seen that the parameters obtained in this study for both cell lines reflect the difference in their radiosensitivity. All these results are discussed in terms of parameter analysis and comparison between cell lines, benefits and limits of the MK model and leads to some prospects.

Introduction

Cell survival to ionizing radiations is a relevant biological endpoint to plan radiotherapy and hadrontherapy treatments since it can be linked to the probability of tumor control. Generally, cell survival is estimated by *in-vitro* measurements of cell-survival curves. To be integrated into a treatment planning system, experimental data have to be accurately reproduced by a model, which can predict survival values at any dose. In the field of radiotherapy with light ions (hadrontherapy), cell survival depends not only on dose, but also on ion species and ion energy. Consequently, a complex model is needed in order to take into account for the biological dependence of the radiation. Then, several models have been proposed to describe the biological efficiency of radiation on cells. The assumptions and formalisms of these models evolve with the development of knowledge in radiobiology. However the complexity of the radiochemical and radiobiological mechanisms involved in the formation of biological damages complicates the elaboration of such models. Consequently, some models, based on assumptions and approximations extrapolated from experimental results allow useful predictions. Most of the recent models are based on micrometric and nanometric scale calculation. Among others, two models have been the subject of study and development in the context of applications to hadrontherapy treatment planning. These models are the Local Effect Model (LEM) [1][2] and the Microdosimetric Kinetic Model (MKM) [3][4]. The LEM is already used in clinical routine in Germany [5] and the MKM is seriously considered by NIRS group, which has published several studies testing this model in order to adapt it to their treatment planning system [6][7]. Therefore, we focus in this paper on both these models and applied the MKM model to three cell lines.

Material and method

1. The LEM formalism

To predict cell survival, the Local Effect Model (LEM), considers that cell killing arises from the induction of lethal events by the ionizing radiation. Assuming that the distribution of lethal events obeys a Poisson distribution, the probability for the cell to survive reads:

$$S(D) = e^{-N_{lethal}(D)} \quad (1)$$

Where $N_{lethal}(D)$ is the mean number of lethal events induced in the cell after a dose *D*. The first key assumption of the LEM is to consider lethal events as point-like events generated by the local dose deposited by the radiation. Thus, the number of lethal events in the cell is the summation of the local lethal events over the cell sensitive volume:

$$N_{lethal}(D) = \iiint_{\text{Sensitive Volume}} \rho_{lethal}(\mathbf{r})d\mathbf{r} \quad (2)$$

Where the local density of lethal events is assumed to be a simple function of the local dose ***d(r)***:

$$\rho_{lethal}(\mathbf{r}) = \rho_{lethal}(d(\mathbf{r})) \quad (3)$$

In the LEM, the local dose is calculated by cumulative effects, superimposing the local dose deposited by each ion, which is represented by the radial dose d_R :

$$d(\mathbf{r}) = \sum_i d_R(r_i) \quad (4)$$

Where r_i is the radial distance of the point r to the trajectory of the i^{th} ion in the transversal plane to the beam axis.

The second key assumption of the LEM consists in extracting the relation between the density of lethal events and the local dose from survival measurements performed with *X-ray* radiation. Indeed, the local dose deposited by *X-ray* radiation is considered as uniform within the cell. Neglecting stochastic effects, it is therefore equal to the macroscopic dose D , which is delivered to the sample by the *X-ray* source:

$$d(\mathbf{r}) = D \quad (5)$$

Therefore for *X-ray* irradiation, Eq. (2) becomes simply:

$$N_{lethal}(D) \approx \rho_{lethal}(D).V_{sensitive} \quad (6)$$

According to equation (2), $N_{lethal}(D)$, and therefore $\rho_{lethal}(D)$ can be deduced from the measurement of cell survival to *X-ray* irradiation (described by the α and β parameters) and from an estimation of the cell sensitive volume $V_{sensitive}$. This latter is assumed to be uniformly distributed over the cell nucleus. The diameter of the sensitive volume depends on the cell and ranges from 5-20 µm. An explicit expression for the average number of lethal events can thus be obtained as:

$$N_{lethal} = \iiint_{\text{Sensitive Volume}} \frac{-\ln S_X(d(r))}{V_{sensitive}} d\mathbf{r} \quad (7)$$

The photon dose-effect relation is parameterized using an additional parameter, the threshold dose D_t, allowing extrapolating the radiation effect to very high dose. This special parameterization is presented in equation (8) :

$$-\ln S(D(r)) = \begin{cases} \alpha_X D(r) + \beta_X D^2(r) & \text{si} \quad D(r) \le D_{seuil} \\ (\alpha_X + 2\beta_X D_{seuil}) D(r) - \beta_X D_{seuil}^2 & \text{si} \quad D(r) > D_{seuil} \end{cases} \qquad (8)$$

Practically, the threshold dose cannot be measures and is fitted using experimental data measured for high-LET ions [8].

The LEM authors have changed their model by incorporating the effect of ionization clusters [9] and by modifying the parameterization of the radial dose in integrating an expression of the minimum radial distance r_{min} dependent on ion energy. However, the basic formalism of the LEM is still the same. The basic concepts of this model was extensively analyzed by *Beuve et al* [10][11].

2. The MKM formalism

The MK model is based on the statistical theory and the microdosimetric formalisms and quantities. In the MK model, the lesions are produced in sub-volumes of the cell nucleus called ”domains”. The dose deposited in these domains is quantified by the so-called “specific energy” stochastic variable z. The lesions are classified into two different types [12], Type I are lethal and non-repairable, type II are initially not lethal but may become lethal if they undergo some specific transformations. The probability of forming a type I lesion in a domain is proportional to the dose absorbed by the domain z. The non-lethal type II lesions may be repaired or transformed to lethal lesions. The processes that the type II lesions may undergo are 1°) a monomolecular-like process with first-order rate constant *a*. 2°) a pairwise combination with another type II lesion located in the same domain to form a lethal unrepairable lesion with second-order rate constant *b*. 3°) a repair process by a monomolecular-like process with first-order rate constant *c*.4°) a persistence for a period of time *tr*, after which it becomes lethal and not repairable. These possibilities are resumed in figure 1.

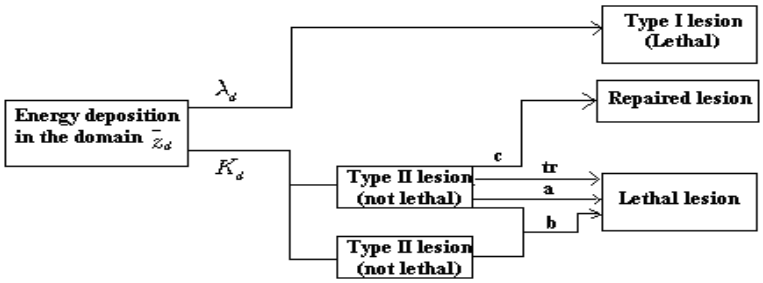

Figure 1: Schematic representation of the MKM formalism

For a short time irradiation and assuming a Poisson distribution of lethal lesions, the mean number of lesions in nucleus is expressed by:

$$\varepsilon(D) = \alpha_p D + \beta D^2 \qquad (9)$$

Where the index p indicates the Poisson distribution; $\alpha_p = (\alpha_0 + \beta \bar{z}_{1D})$ and α_0 and β are cell-dependent but LET independent parameters; $\bar{z}_{1D}$ is the single event dose mean specific energy in the domain. Therefore the expression of RBE_{1P} in the limit of the zero dose is given by:

$$RBE_{1p} = \frac{\alpha_0}{\alpha_R} + \frac{\beta}{\alpha_R} \bar{z}_{1D} \qquad (10)$$

Replacing $\bar{z}_{1D}$ by its expression versus the mean dose lineal energy $\bar{y}_D$ assuming spherical domain, equation (10) reads:

$$RBE_{1p} = \frac{\alpha_0}{\alpha_R} + \frac{\beta}{\alpha_R}\frac{0.2}{d^2}\bar{y}_D \qquad (11)$$

This expression allows deducing the two parameters α_0 and the domain diameter d by fitting experimental data for LET below the saturation effect. The value of β is deduced from the X rays radiation and assumed to be unchanged with changing LET or particle type.

However, for the very high-LET ions, the distribution of lethal lesions in the nucleus cannot be described by a Poisson distribution and the RBE value decreases with increasing LET. Then, Equation (10) requires a correction in order to take into account for this saturation effect in RBE. This correction was proposed by *R.B Hawkins* [12]:

$$RBE_1 = \frac{\alpha}{\alpha_R} = \frac{(1-\exp(-\alpha_p \bar{z}_{1Dn}))}{\alpha_p \bar{z}_{1Dn}} RBE_{1P} \qquad (12)$$

Where $\bar{z}_{1Dn}$ is the dose mean specific energy in the nucleus. It is expressed as a function of $\bar{y}_D$ by:

$$\bar{z}_{1Dn} = 0.16\frac{\bar{y}_D}{\sigma} \text{ Gy} \qquad (13)$$

Where σ is the cross sectional area of the sensitive nuclear volume expressed in µm²

If one replaces $\bar{z}_{1Dn}$, α_p and RBE_{1P} given respectively by equations (13), (9) and (11), in the equation (12), one can express the corrected linear coefficient of dose by equation (13).

$$\alpha^* = \sigma\frac{\left(1-\exp\left(\frac{-0.16(\alpha_0+\beta\frac{0.2}{d^2}\bar{y}_D)\bar{y}_D}{\sigma}\right)\right)}{0.16\bar{y}_D} \qquad (14)$$

Finally the equation (14) is fitted with experimental data for large LET range in order to deduce the value of σ.

3. The LEM vs MKM comparison

An interesting conceptual comparison was published by *Y. Kase et al 2008* [13]. In their work, *Kase et al* have adapted the MKM to amorphous track calculation in order to compare it to the LEM. We present here some conclusions of this comparison.

In the LEM, the biological effect is related to an energy deposition in infinitesimal small nuclear sub-volume assimilated to point-like target *(Scholz et al 1996* [1]*)*. Regarding the MKM, the biological effect is related to an energy deposition in nuclear sub-volumes with micrometric dimensions named "Domains". The domain is a small homogeneous reaction vessel with boundary that is impermeable to lesions. *(Hawkins 2003* [12]*)*. Both models need the photon dose-effect relation as an input parameter. In addition, the LEM needs the radial dose distribution of the incident ions. The LEM parameterization of this dose effect relation is presented in the equation (8). In the case of LEM the β parameter is considered as dependent of the LET and the particle type. For the MKM the photon dose-effect relation is parameterized by the linear quadratic model whatever the dose range and the β parameter is considered independent of the particle LET and type. In the case of the MKM the

additional input parameters are the lineal energy distribution in the domain and the experimental RBE-LET relation for at least two different LET values.

In the LEM the critical parameter is the threshold dose D_t , used in the parameterization of the experimental photon dose-effect relation for high dose. It is practically difficult to precisely determine the photon dose effect at very high dose. Then, D_t is kept as an adjustable parameter in order to allow the best representation of the experimental data [8]. In the case of the MKM, *Kase et al* [13] have reported that the model predictions are sensitive to relative variations of the domain size. Finally, both models provide a good description for different sets of experimental data. However, for some LET–energy combinations, the agreement with the experimental results is better with the MKM. Finally, *Kase et al* reported in their paper that there is a tendency for overestimation of RBE by the LEM model for high energetic ions at comparably low LET *(Kase et al* [13]*)* .

Results

Application of the MKM with experimental data of Furusawa et al[14]

The user needs to establish two experimental relations to calculate the necessary parameters of the MK model. These parameters are used later to characterize the cell radiosenstivity and predict the response of this cell to ion irradiation. These two experimental relations are 1°) the photon dose-effect relation of the cell. This relation is used to extract the domain diameter d. 2°) The RBE-LET relation which allow to calculate α_0 and σ . Then, we followed these steps to apply the MKM on experimental data published by *Furusawa et al* [14] for HSG cell line irradiated with carbon ion in aerobic conditions. The fitting of the photon dose-effect relation by the linear quadratic model resulted in the determination of the parameters: α_X =0,313Gy^{-1} and β =0,062 Gy^{-2}. The index x indicates that the alpha parameter is calculated for the X rays irradiation.

The second step of the MKM-parameter calculation is the determination of the domain diameter d and the effective area of the sensitive volume σ . These two parameters are extracted from the RBE-LET or RBE-lineal energy relation. Then we determine the domain diameter according to the equation (11) and the effective area of the HSG cells according to the equation (14). The result of these adjustments are shown in figure 2 .

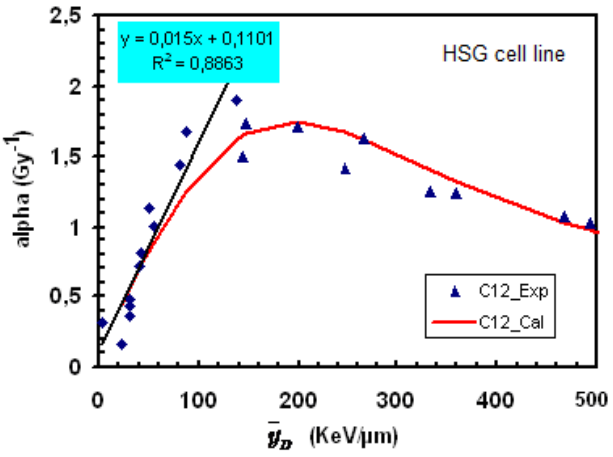

Figure 2: results of our MKM parameter calculation for HSG cell line irradiated with carbon ions of different energies. The experimental data are extracted from *Furusawa et al.* [14].

Therefore, the domain radius of the HSG cells is $r_d = 0,45\mu m$ and their effective nucleus area is $\sigma = 75\mu m^2$. If we assume that the nucleus sensitive volume has a cylindrical shape with radius R_n and

area σ . Therefore σ , can be expressed by: $\sigma = \pi R_n^2$. By replacing σ and π we obtain $R_n = 4,88\mu m$ for HSG cell line.

The MKM was also applied for HSG cell by *Kase et al (2006)* [15]. In their work *Kase et al.* have used the dose-effect of 200 KV X rays and of 290 MeV/n carbon ions to extract the domain diameter and α_0 parameter. However, they used another formula to correct the saturation effect and extract the nucleus effective area using the lineal energy saturation (details are presented in reference [15]). The table 1 resumes the MKM parameters obtained by our application of the original MKM and those obtained by *Kase et al* [15].

Table 1. *Comparison of our application of the MKM with those of Kase et al*[15] *on the HSG cell line*

MKM Parameters for HSG cell line	**Our application of the MKM**	***Y. Kase et al* results**
β (Gy^{-2})	0,0615	0,05
α_0 (Gy^{-1})	0,11 ± 0,02	0,13 ± 0,03
r_d (µm)	0,45 ± 0.05	0,42 ± 0,04
R_n (µm)	4,88 ± 0,4	4,1

The modified formulation used by *Kase and al* [15] can explain the difference between our calculation of R_n and that of *Kase et al* . Concerning r_d and α_0 , these parameters are extracted using the original formulation of the MKM in both cases. We note that *Kase et al* [15] used as input, the dose-effect relation based on two experimental relations determined by an irradiation with 200 kV photons and with 290 MeV /n carbon ions, in order to fit the linear equation expressed in equation (10). Instead we used a larger set of experimental data. Despite this, the differences between the both calculation results are acceptable taking into account the uncertainties associated to each calculation.

Application of the MKM to characterize two cell lines with different radio-sensitivities

The MK model is applied here to reproduce the experimental data of the irradiation of two cell lines. The cell lines used in this study are extracted from the same histological type of head and neck carcinoma. The first one is the radiosensitive SCC61 cells, extracted from a pharynx carcinoma. The second line is the radioresistant SQ20B cells, extracted from a neck carcinoma. These cells are prepared and cultured as described in reference [16]. The irradiation procedures and the results of theses irradiations was reported by *Beuve et al (2008)* [8]. The cells were irradiated with carbon ions of 72 MeV/n and with 85 MeV/n argon ions at GANIL facility in France. The energies mentioned above are the ion energies at the entrance of the cells. X-ray irradiations of both cell lines were performed using the same experimental protocols as used for ion irradiations. This is very important in order to compare the high-LET radiation results with the X rays ones. The approach used previously to calculate the MKM parameters for the HSG cell line is followed here in order to calculate the MKM parameters for SQ20B and SSC61 cell lines. The figure 3 below presents the data adjustment of the alpha parameter versus the dose mean lineal energy in the domain according to the equation (14). The calculated parameters, with this fit, are summarized in the Table 2. We note that in this case, we do an MKM application similar to that made by *Y Kase et al* [15]. This application is based on the use of two experimental dose-response relations obtained with photon irradiation and with low LET ion (72 MeV/n carbon ions), in order to estimate the domain size. However,

for the estimation of the effective nucleus area, we used the original formulation of the MKM with an additional experimental relation obtained using a very high LET (85 MeV/n argon ions).

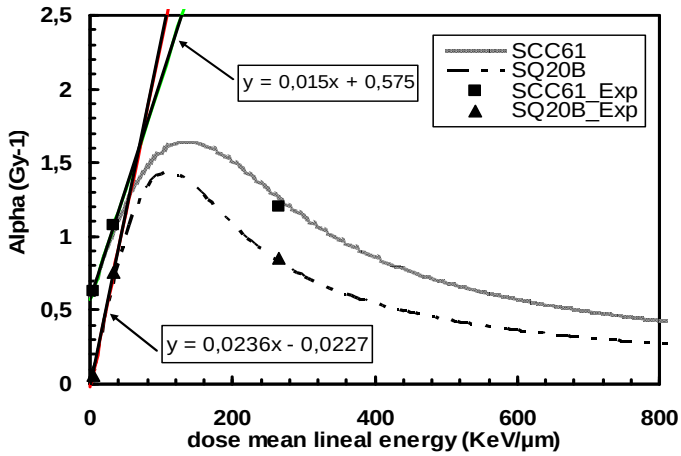

Table 2 : MKM parameters calculated for SCC61 and SQ20B cell lines

MK parameters	SCC61 cells	SQ20B cells
β (Gy^{-2})	0.02	0.0615
α_0 (Gy)	0.57	0.02
d (µm)	0.88	0.67
σ (µm²)	55	35

Figure 3: Results of MKM parameter calculation for SQ20B and SCC61 cell lines irradiated with carbon ions of 72 MeV/n and argon ions of 85MeV/n. The experimental data are extracted from *Beuve et al.* [8].

Discussion

The radiobiological significance of the MK model parameters allows an analysis of the biological response of the cells and comparison between different cell lines. In the case of SCC61 and SQ20B cell lines, the parameters obtained in this study reflect the difference in their radiosensitivity. The first difference consists in α_0. A mathematical description of this parameter is given by *Hawkins* [12]. It depend on the formation rate of non-reparable type I lesions, the formation rate of the lethal lesions by the monomolecular transformation of type II lesions and the transformation of the type II lesions to lethal lesion after a period t_r (see section 2 in method and result). Therefore, the cell lines which have low or zero value of α_0 are dominated by the formation of type I lesions or the monomolecular transformation of the type II lesions. In our case, the α_0 value for SCC61 cells is higher than for SQ20B. This implies that the lethal lesions produced in SCC61 cells are the result of the type I lesions or the monomolecular transformation of the type II lesions. The β parameter of the SQ20B cells is higher than those of SCC61, this means that the transformation rate of the type II lesions into lethal lesion by the bimolecular processes (interaction of two sublesions) is higher in the SQ20B cells. However, the MK model assumes that the production rate of type II lesions is constant regardless of the LET. While, the author of the MKM relay the type II lesions to the DSB lesions [12], consequently any change in the LET may affect the production rate of type II lesions and probably the β. Concerning the parameter σ, which reflects the nuclear sensitive volume, is more important in the SCC61 than in SQ20B cell.

Finally, this behavior of the MKM parameters can be exploited clinically to adapt the radiation depending on the degree of radiosensitivity tumor cells based on the model parameters. In this optic, it will be interesting to determine a common experimental protocol in order to calculate the MKM parameters and construct a parameter tables for each cell line considered in hadrontherapy treatement.

Conclusion

We have seen that the application of the MKM in its original version gives comparable results with the MKM version used by *Kase et al* [15] except for the determination of the effective nucleus area where *Kase et al* [15] included a new formula to correct the saturation effect using the lineal energy saturation. We have also seen that the MKM parameters allow characterizing the response mechanisms and the radiosensitivity of a cell lines. The MKM parameters calculated for the SCC61 and SQ20B cell lines reflect well their different radiosensitivity.

Then, this characteristic of the MKM parameters can be beneficial in clinical application of the MKM in order to improve treatments by adapting the radiation depending on radiosensitivity of tumor cells. The MK model still has some weaknesses especially regarding the change of beta parameter with LET since the MKM assumes that the β is independent of particle type and energy used. The α and β parameters are expressed in the MKM as a function of several other parameters related to production rates of type II and type I lesions and to their kinetic evolution in the cell. It assumes also that the production rate of type II lesions is constant regardless of the LET and is equal to 30 lesions / Gy. However, the MKM relay the type II lesions to the DSB lesions [12], consequently any change in the LET may affect the production rate of type II lesions and probably the β.

For the prospects of RBE modeling for hadrontherapy treatments, we adopted two approaches. The first approach is to continue the investigations of MKM in order to better understand the behavior of its parameters in different biological conditions. We are working on changing the expression given the production rate of type II lesions in order to include the influence of the LET. For this, we rely on the experimental data we are producing by irradiation with x-rays and carbon ions (at GANIL) of several types of cell lines following a well-defined protocol.

The second approach is to develop a new model, which in particular will include concept or element inspired from the models presently available in the literature and we considered as key points.

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RBE modelization: Present Status and Future Prospects

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Plan

. Introduction.

. Basic formulation of the MKM and the LEM

. Conceptual comparison of the MKM and the LEM.

. Application of the MKM to experimental data.

. Conclusions.

I. Introduction

•Radiobiological models are necessary to predict the biological effect of radiation in order to perform a rigorous treatment planning in hadrontherapy.

• There are several models, based on assumptions and approximations extrapolated from experimental results.

•There is two most advanced models for clinical application which are :

- The Microdosimetric Kinetic Model (MKM) *Hawkins 1994 and 1996*.

- The Local effect Model (LEM) *Scholz et al 1996*

Basic formulation of MKM and LEM

Scholz et al 1996

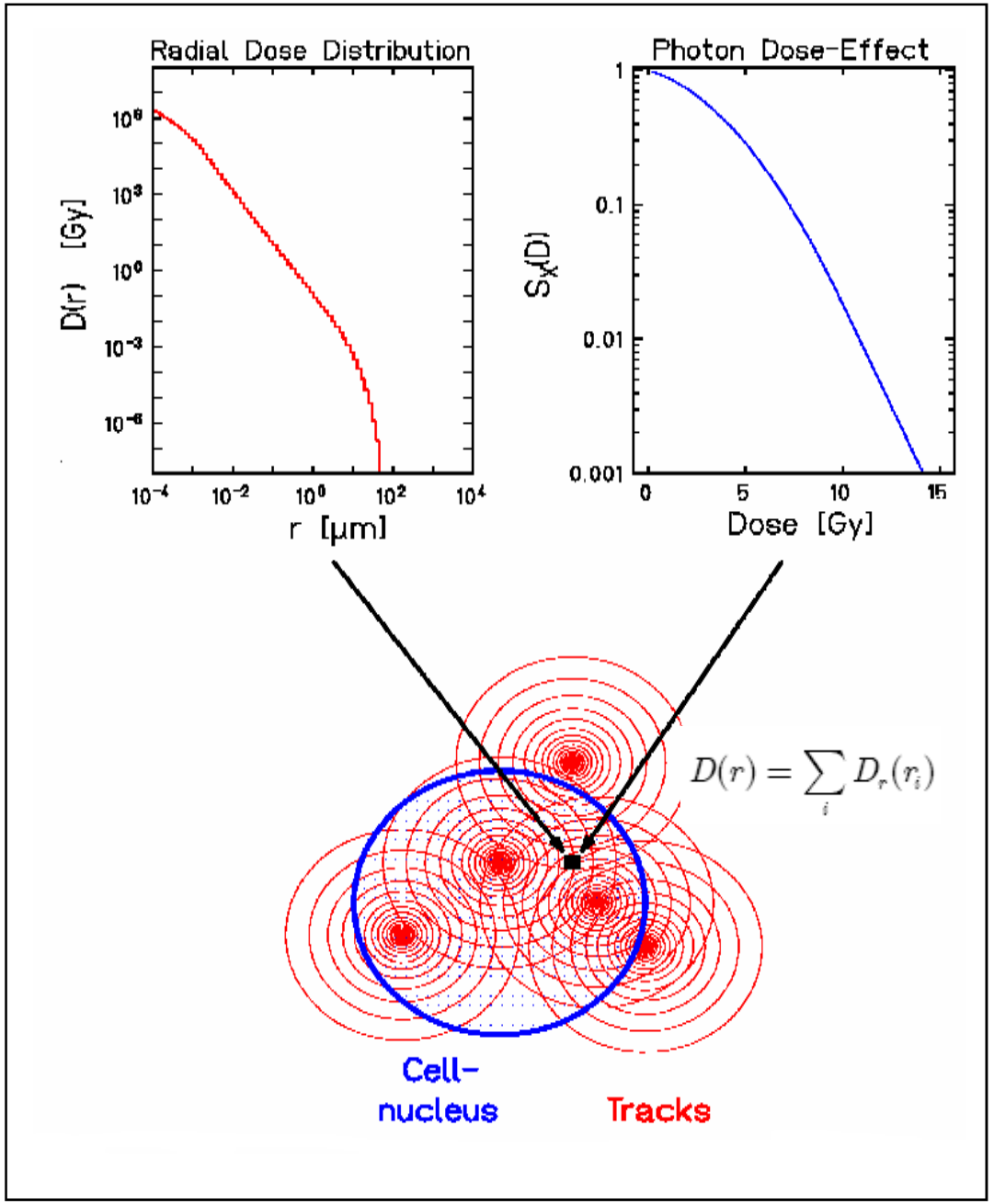
Mathematical formulation:

The total effect is obtained by summation of al local effects through total sensitive volume :

$$N_{létal}(D) = \iiint_V \frac{-\ln(S_X(D(r))}{V} dr$$

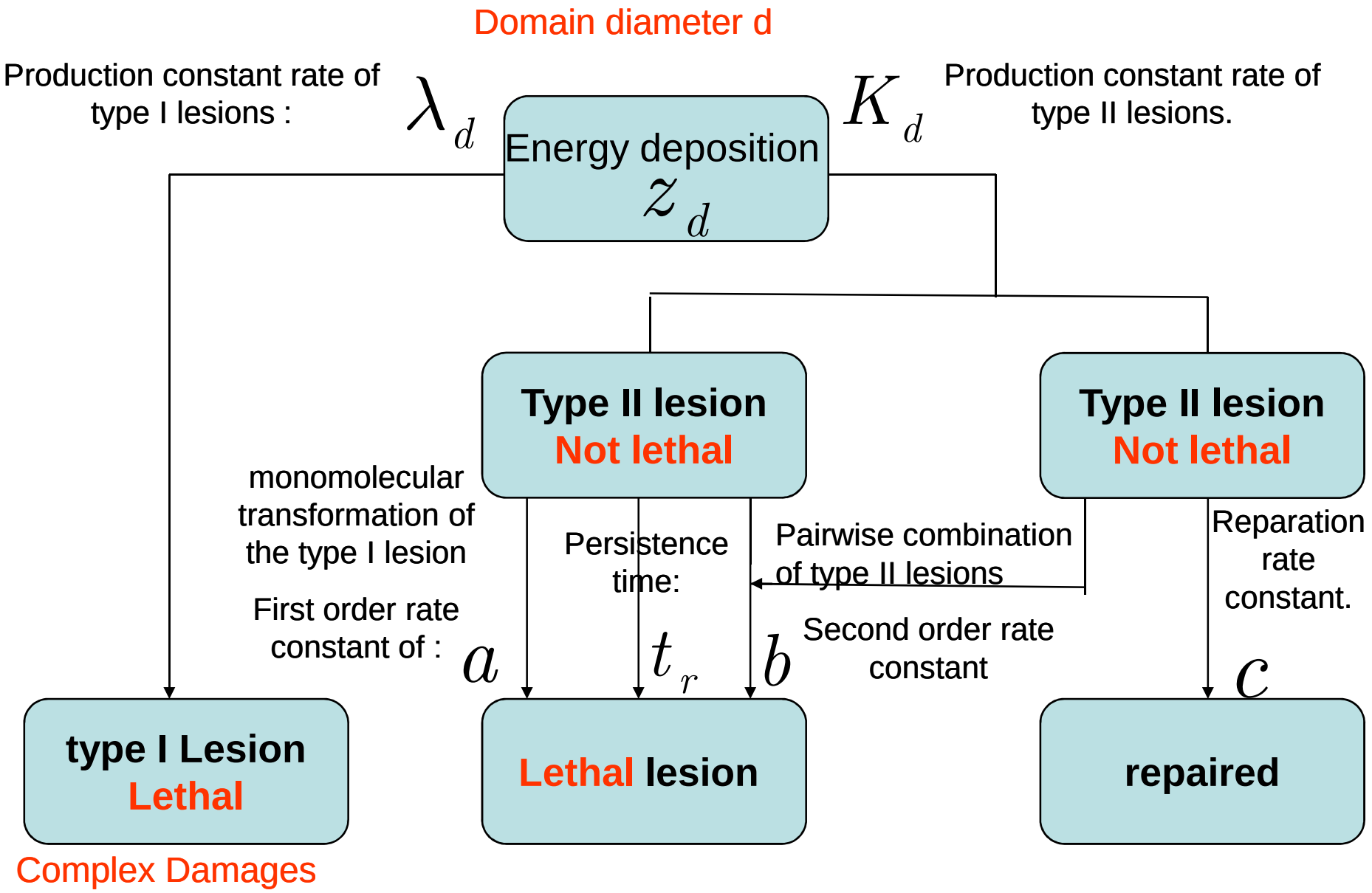
Poisson distribution of lethal lesions :

$$S_{ion}(D) = e^{-N_{letal}(D)}$$



2. MK Model

Hawkins et al 1996



Conceptual comparison of the MKM with LEM
(Y. Kase et al 2008)

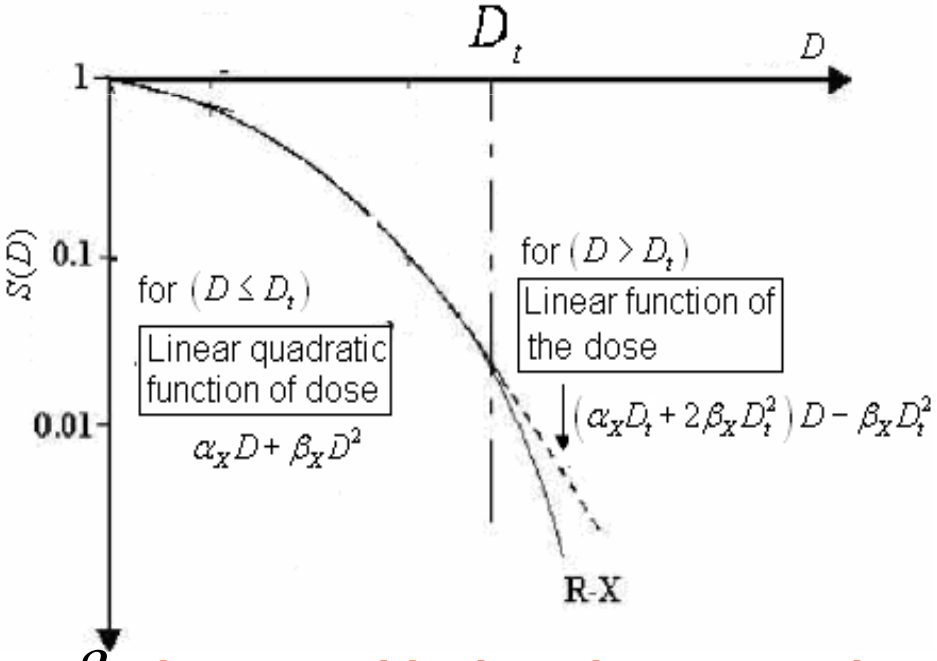
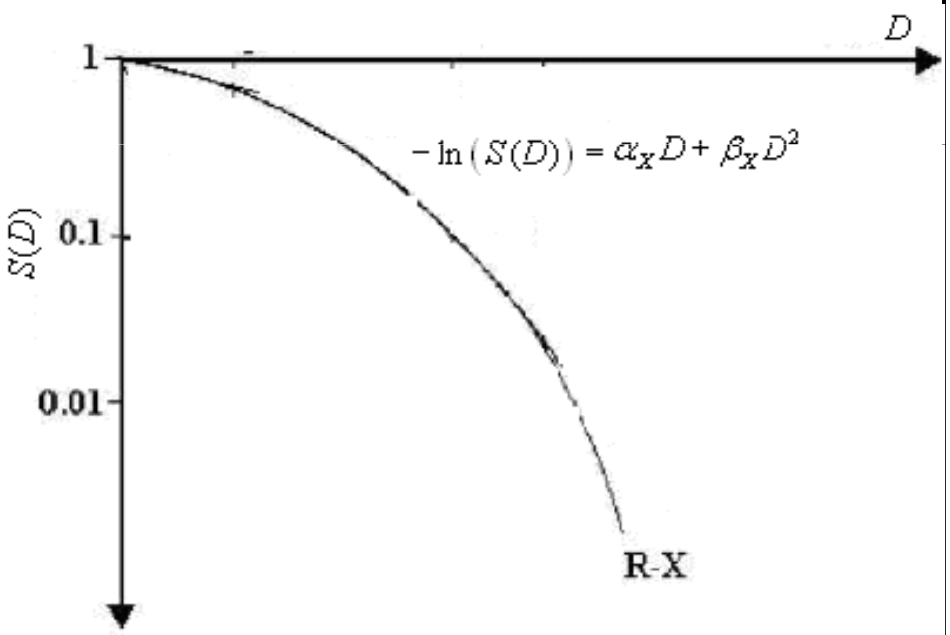
1. Radiosensitive sites

- Both models suppose that the radiosensitive structures are contained in the nucleus. These structures considered as the sub-volumes of the nucleus.

LEM	MKM
The biological effect is related to an energy deposition in infinitesimal small nuclear sub-volume ↓ Local effect ↓ Assimilated to point-like target *(Scholz et al 1996)*	The biological effect is related to an energy deposition in nuclear sub-volume with micrometric dimension ↓ Domain ↓ Small homogeneous reaction vessel with boundary that is impermeable to lesions. *(Hawkins 2003)*

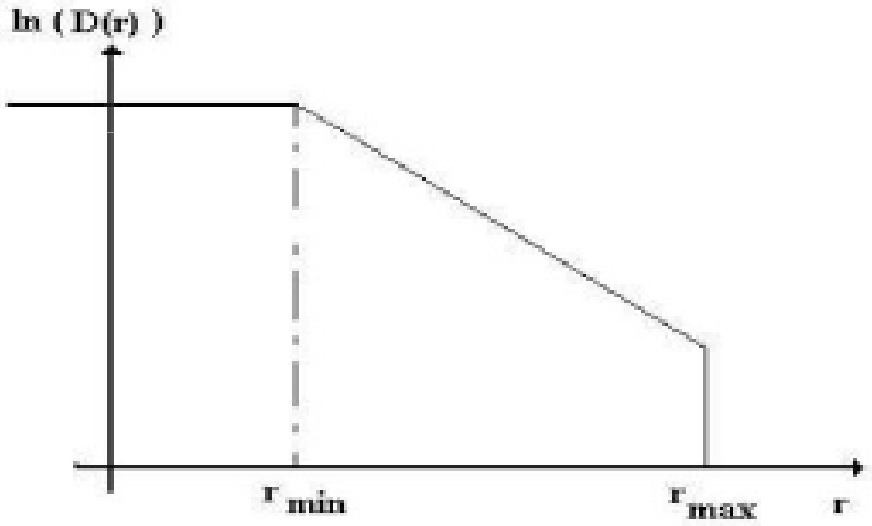
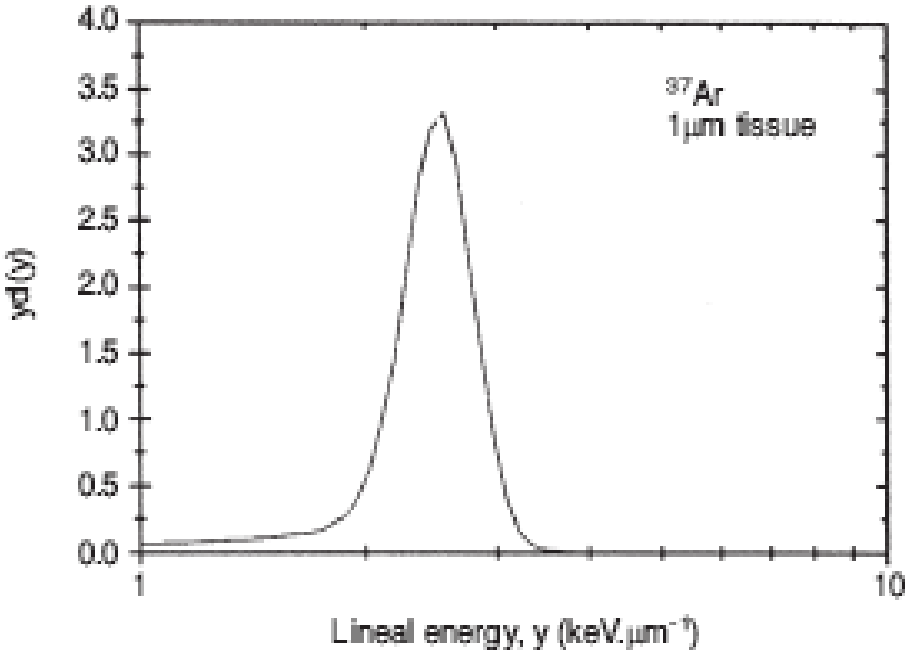
2. Photon dose-effect relation

• Both models use the photon dose-effect relation in the determination of the ion effect.

LEM	MKM
D_t : Threshold dose, obtained by adjusting the experimental data of The photon dose-effect relation.  β **changes with changing LET and particle type.**	The linear quadratic function of the dose is used for any value of dose.  β **is not dependent in LET and particle type**

3. The energy deposition

• Both models need physical input parameter to calculate the cell response.

LEM	MKM
The radial distribution of the dose: Distribution of the dose at distance r from the ion trajectory (In the LEM I).  $D_r(r) = \begin{cases} k(LET / r_{\min}^2) & \text{si} \quad r < r_{\min} \\ k(LET / r^2) & \text{si} \quad r_{\min} < r < r_{\max} \\ 0 & \text{si} \quad r > r_{\min} \end{cases}$	**Microdosimetric spectra** : Distribution of energy deposition in the domain ⟹ calculation of $\bar{y}_d$ or $\bar{z}_d$ 

4. Critical parameters

• Both models use parameters that could not be directly measured :

LEM	MKM
Threshold dose D_t : It is practically difficult to precisely determine the photon dose at very high dose. It's value depends on the LEM version considered. ⇩ D_t is kept as an adjustable parameter in order to allow the best representation of the experimental data.	**The domain size d :** Domain can not be identified with any known structure in the cell. ⇩ Obtained by fitting the RBE_1-LET relation at low LET range. ⇩ Linear approximation of the RBE_1-LET relation in this range of LET

5. Cell response

LEM	MKM
In the LEM, the biological response of the cell is taken into account by using the photon dose-effect relation. ↓ There are no parameters describing the formation and the kinetic evolution of lesions.	In the MKM, several parameters are used to describe the cell response and the kinetic evolution of the initial lesions. ↓ d σ α_0 β , al of these parameters are considered as independent from LET.

6. Application of models in treatment planning

• Both models provide a good description for different sets of experimental data.

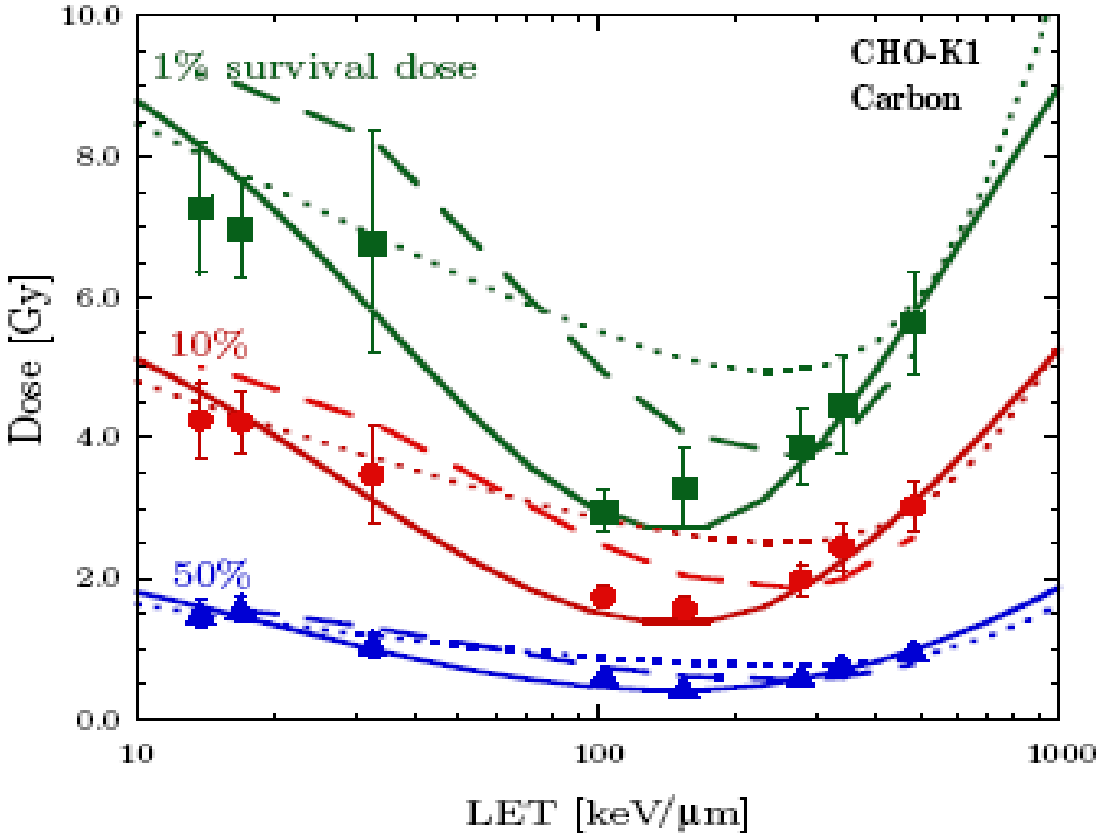
• However, For some LET–energy combinations, the agreement with the experimental results is better with the MKM.

Solid lines : MKM calculations

dotted lines : initial version LEM calculations.

dashed lines: Modified LEM calculations.

Y. Kase et al 2008



• There is a tendency for overestimation of RBE by the LEM model for high energetic ions.

Application of the MKM to experimental data

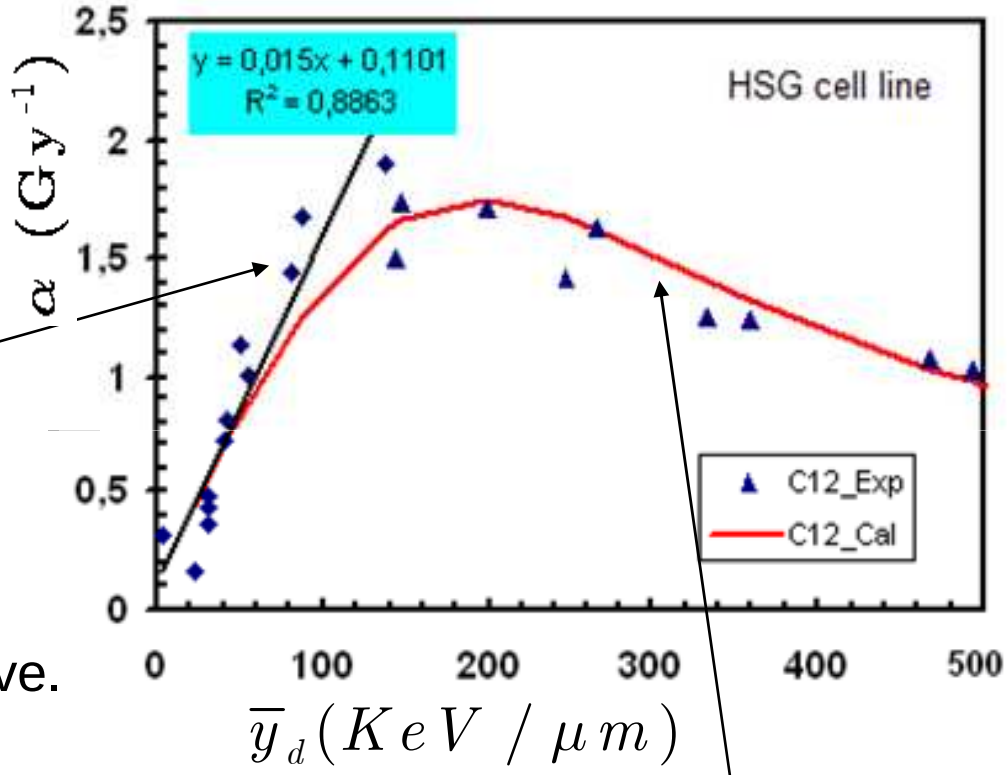
1. Calculation of the biological parameters for HSG cell line :

- experimental data extracted from ***Furusawa et al 2000,*** for HSG cell line irradiated with carbon ions in aerobic conditions

- **In the low LET range** :

Then the relation α_p vs $\bar{y}_d$ is linear

$$\alpha_p = \alpha_0 + \beta \frac{0.2}{d^2} \bar{y}_d$$



To deduce :

α_0 : initial slop of the survival curve.

d : domain's diameter.

- **In the high LET range** :

To deduce the effective area of the nuclear sensitive volume: σ

$$\alpha = \sigma \frac{\left(1 - \exp\left(\frac{-0.16(\alpha_0 + \beta \frac{0.2}{d^2} \bar{y}_D)\bar{y}_D}{\sigma}\right)\right)}{0.16\,\bar{y}_D}$$

2. Comparison of the parameters obtained by *Kase et al* for HSG cells:

• Calculation of the MKM parameters for HSG cell line by ***Kase et al (2006)*** using as input data de dose-effect relations obtained with:

• X rays of 200 KV and carbon ions of 290 MeV/n

The correction of the saturation effect is done using the lineal energy saturation in ***Kase et al 2006,*** calculation.

MKM Parameters for HSG cell line	Our application of the MKM	*Y. Kase et al* results
β (Gy^{-2})	0,0615	0,05
α_0 (Gy^{-1})	0,11 ± 0,02	0,13 ± 0,03
r_d (µm)	0,45 ± 0.05	0,42 ± 0,04
R_n (µm)	4,88 ± 0,4	4,1

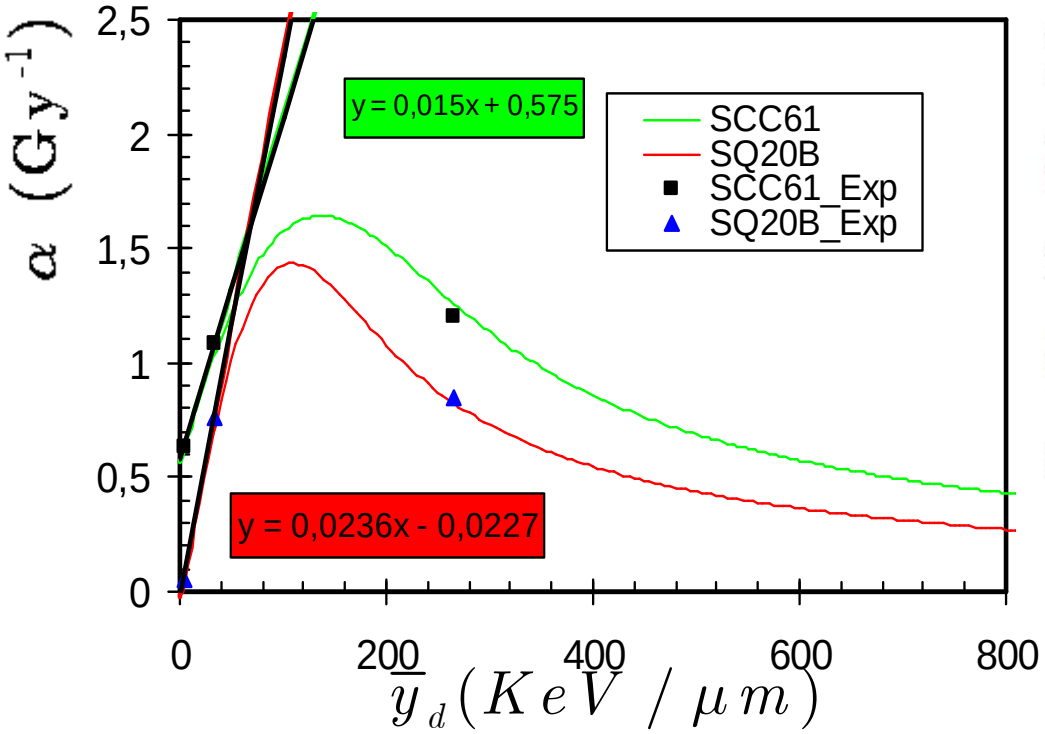
• The differences between the both calculation results are acceptable taking into account the uncertainties associated to each calculation.

• Except for R_n , where the difference can be explained by the modified formulation of the saturation effect used in *Kase et al* calculation.

3. Calculation of the biological parameters for SCC61 and SQ20B cell lines :

Beuve et al 2008

- **Cell lines :**
  - The radiosensitive cell line: SCC61,established from squamous cell carcinomas of the pharynx.
  - The radioresistant cell line: SQ20B,established from squamous cell carcinomas of the neck.
- **We used as input parameters :**
  - The experimental dose effect relation obtained with 250 KV X rays.
  - Experimental data obtained at GANIL with **72 MeV/n** carbon ions and **85 MeV/n** argon ions



MK parameters	SCC61 cells	SQ20B cells
β (Gy^{-2})	0.02	0.0615
α_0 (Gy)	0.57	0.02
d (µm)	0.88	0.67
σ (μm^2)	55	35

4. Discussion of the MKM parameters for SCC61 et SQ20B cells

Cell line	d (µm)	α_0 (Gy^{-1})	σ ($µm^2$)
SCC61	0.88	0.57	55
SQ20B	0.67	0.02	35

Domain's diameter d :

•Domain = distance a type II lesion can travel through the nucleus before it is removed by repair.

•The low difference of the domain size between the two cell lines can not explain the difference in radiosensitivity of the two cell lines.

Cell lines	d (µm)	α_0 (Gy^{-1})	σ (μm^2)
SCC61	0.88	0.57	55
SQ20B	0.67	0.02	35

α_0 *parameter (depends in K and λ parameters) :*

$$\alpha_0 = \frac{aK}{(a+c)} + \lambda + Ke^{-(a+c)t_r}$$

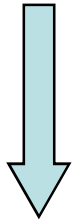
• The low value of α_0 indicates that the contribution of the monomolecular transformation of the type II lesions is weak ⟶ **SQ20B**

•The high value of α_0 indicates that the most lethal lesions are produced by the monomolecular transformation of the type II lesions ⟶ **SCC61**

Cell lines	d **(µm)**	α_0 **(G^{-1})**	σ **($µm^2$)**
SCC61	0.88	0.57	55
SQ20B	0.67	0.02	35

σ parameter :

The difference in σ value of both cell lines reflect probably

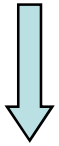


Difference in the distribution of the nuclear sensitive structures between the two cell lines.

Conclusions and prospects:

- A strength of both models is that due to the simplicity and the computational speed of the calculations, they are both applicable for treatment planning.

- the MKM and the LEM rely on the same three basic constituents of target geometry, photon survival curve and track structure.



however, their implementation of these constituents is significantly different.

- In both models, the photon dose-effect relation is not sufficient to calculate the ion response.

Additional information about the biological response to ion irradiation is necessary to determine the domain size in MKM or the threshold dose in LEM.

Conclusions and prospects :

- The MKM parameters calculated reflect the difference in cell radiosensitivity.

this characteristic can be beneficial in clinical application of the MKM in order to improve treatments.

- The MK model still has some weaknesses especially regarding the change of beta parameter with LET.
  - We are working on changing the expression given the production rate of type II lesions in order to include the influence of the LET on the β parameter.
  - To use Geant4 DNA to apply MKM in microdosimetrical context .
- Develop a new model, which in particular will include concept or element inspired from the models presently available in the literature and we considered as key points.