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LPA2: support to radiobiology activities.

Cell holder design and MC analysis of radiobiological effectiveness of ultra-high dose rates pulses

LPA2-Project
04/02/2021
Bologna

IDEA OVERVIEW

The flash sources will probably be the next generation radiotherapy devices.

The usual models (e.g. the Modified Linear Quadratic Model), used for describing the surviving fraction of irradiated cells are required to be upgraded for such field of application.

$$S = e^{-\alpha D - G\beta D^2}$$

"S" is usually interpreted as indicating that cell killing results from the interaction of two elementary damaged species-perhaps DNA double-strand breaks- to produce a species-perhaps a dicentric chromosomal aberration-which may cause lethality.

The two terms, α, β, in Equation indicate that the two elementary damaged species may be produced by the passage of the same track of radiation (linear term in dose) or by two different tracks (quadratic term). Clearly, if some time elapses between the passage of the first and second tracks, there exists the possibility of the first damaged site being repaired before interacting with the second. This repair will result in a reduction of the second, quadratic term by a factor denoted "G". The factor G will depend on the details of the temporal distribution of the dose, as well as on the time dependence of the function describing the repair of the elementary damaged species.

A strategy for predicting the RBE of flash devices and, consequently, the α and β terms have been investigated.

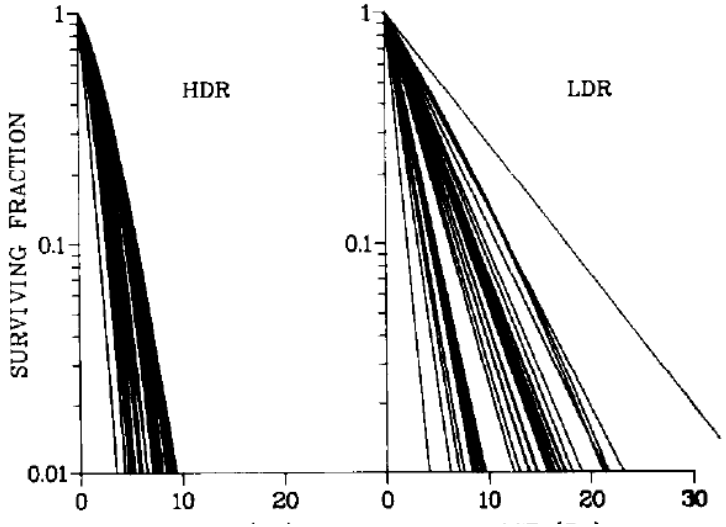
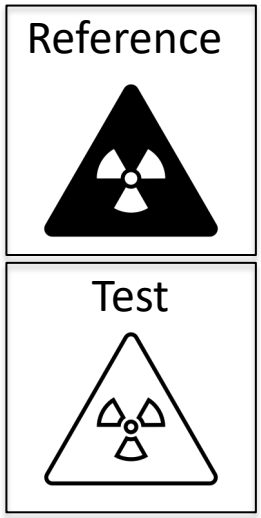


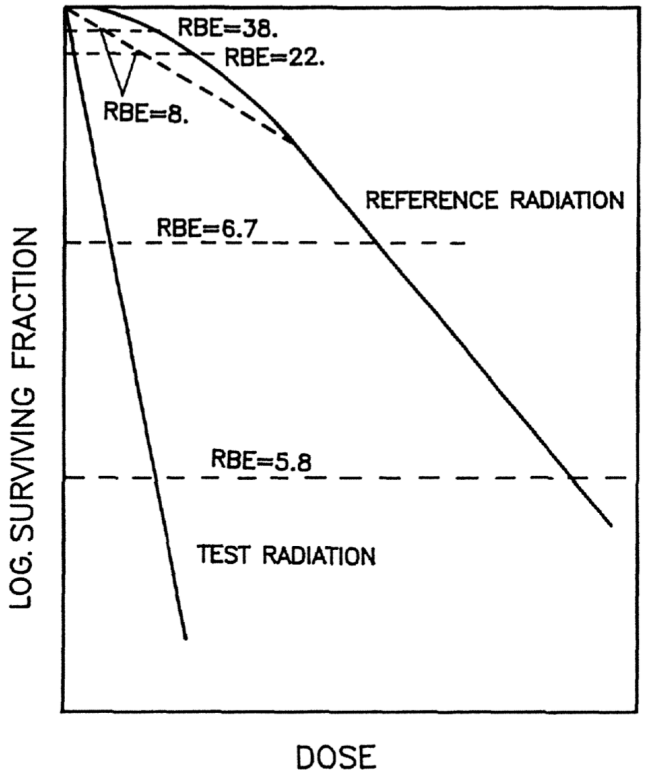
Table 1. *In-vitro* cell lines of human origin analyzed, and LQ parameters

Cell line	Cell type	Protocol	α (Gy^{-1})	β (Gy^{-2})	α/β (Gy)	$T_{1/2}$ (min.)
HX-34	Melanoma	Ldr	0.27	4.21×10^{-2}	6.4	8
HX-32	Pancreatic Ca	Ldr	0.51	4.84×10^{-2}	10.5	316
HX-58	Pancreatic Ca	Ldr	0.47	5.20×10^{-2}	9.0	48
HX-99	Breast Ca	Ldr	0.50	3.05×10^{-2}	16.4	3
HX-118	Melanoma	Ldr	0.33	3.80×10^{-2}	8.7	14
HX-151c	Cervical Ca	Ldr	0.74	3.54×10^{-2}	20.9	26
HX-155c	Cervical Ca	Ldr	0.29	2.35×10^{-2}	12.4	22
HX-156c	Cervical Ca	Ldr	0.31	2.46×10^{-2}	12.6	22
HX-160c	Cervical Ca	Ldr	0.46	7.73×10^{-2}	5.9	129
HX-171c	Cervical Ca	Ldr	0.33	1.69×10^{-2}	19.4	9
SK-N-SH	Neuroblastoma	Ldr	0.26	2.63×10^{-2}	9.9	21
U-20S	Osteosarcoma	Ldr	0.28	5.15×10^{-2}	5.4	24
SK-MEL28	Melanoma	Ldr	0.13	11.3×10^{-2}	1.2	1
RPMI-7951	Melanoma	Ldr	0.27	4.68×10^{-2}	5.8	12
MDAMB-231	Breast Ca	Ldr	0.52	9.10×10^{-2}	5.7	1
SW-620	Colon Ca	Ldr	0.23	4.80×10^{-2}	4.8	37
AG-1522	Skin Fibroblast	Ldr	0.21	3.97×10^{-2}	5.3	16
CCD-18LU	Lung Fibroblast	Ldr	0.24	3.45×10^{-2}	6.9	66
Hs-88LU	Lung Fibroblast	Ldr	0.28	2.76×10^{-2}	10.1	20
KM-101	Bone marrow stroma	Ldr	0.17	10.8×10^{-2}	1.6	62
KM-102	Bone marrow stroma	Ldr	0.27	11.8×10^{-2}	2.3	16
KM-103	Bone marrow stroma	Ldr	0.07	14.5×10^{-2}	0.5	57
KM-104	Bone marrow stroma	Ldr	0.06	14.2×10^{-2}	0.4	52
KM-105	Bone marrow stroma	Ldr	0.17	16.8×10^{-2}	1.0	34
HL-60	Leukemic cells	Ldr + Fx	0.65	6.48×10^{-2}	10.0	5
AG-1522	Skin Fibroblast	Ldr	0.19	4.80×10^{-2}	4.0	23
CRL-1477	Skin Fibroblast	Ldr	0.28	8.93×10^{-2}	3.1	4
GM-498A	Skin Fibroblast	Ldr + Fx	1.11	5.61×10^{-2}	19.8	4
E.E.	Melanoma	Ldr + Fx	0.21	10.0×10^{-2}	2.1	7
M.F.	Melanoma	Ldr + Fx	0.28	8.79×10^{-2}	3.2	9
E.F.	Melanoma	Ldr + Fx	0.35	7.01×10^{-2}	5.0	17
V.N.	Melanoma	Ldr + Fx	0.53	7.83×10^{-2}	6.8	25
G.E.	Melanoma	Ldr + Fx	0.61	10.1×10^{-2}	6.0	8
G7	Grade 1 astrocytoma	Ldr	0.37	10.9×10^{-2}	3.4	3
G18	Grade 3 astrocytoma	Ldr	0.26	3.35×10^{-2}	7.8	24
G37	Grade 4 astrocytoma	Ldr	0.31	6.04×10^{-2}	5.1	17

REQUIRED EXPERIMENTAL DATA

Radiation sources → **Clonogenic assay** → **Relative Biological Effectiveness**



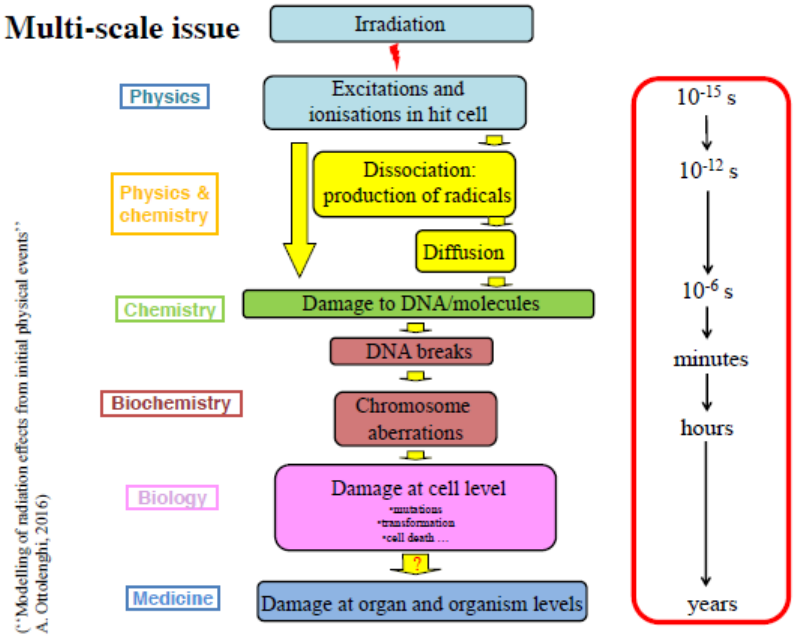


$$RBE = \frac{D(Reference\ source)}{D(Test\ source)}$$

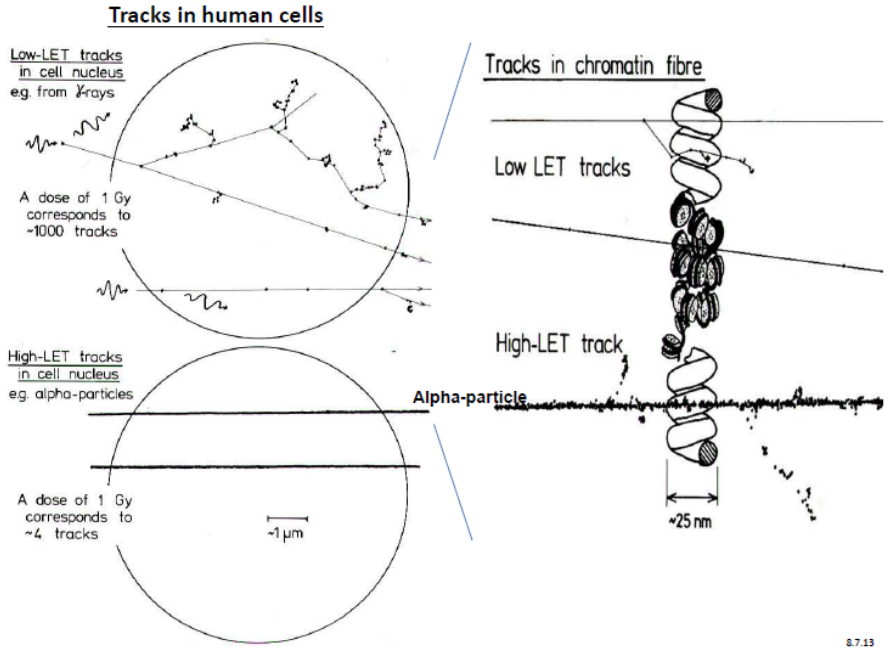
Defined as the ratio of doses which yield the same effect if one compares the test radiation (usually with 250 kV X rays or ^{60}CO radiation):

Simulation scenario

Multidisciplinary and **multiscale** problem



Problem related also to the incident **radiation quality**



MONTE CARLO SIMULATIONS

MCDS

UNIVERSITY of WASHINGTON

Monte Carlo Damage Simulation (MCDS) Software

It quickly generates nucleotide-level maps of the clusters of DNA lesions formed by electrons and light ions up to ^{56}Fe. Clusters of DNA lesions generated by ionizing radiation are typically composed of one or a few individual DNA lesions formed within one or two turns of the DNA. MCDS simulates damage induction in a segment of DNA uniformly irradiated by monoenergetic particles. Damage within that segment is then scaled in direct proportion to the total amount of DNA in a cell or reported as the number of clusters per unit absorbed dose per unit length of DNA.

+

MCNP

MCNP6

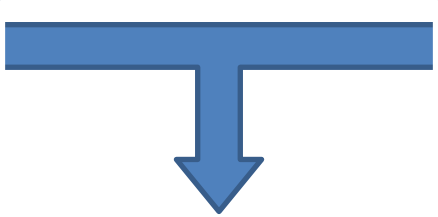
To estimate the overall level of DNA damage at the multi-cellular and tissue levels, Monte Carlo simulations need to correct for the effects of spatial variations as well as spatial variations in the nature of the radiation field. MCNP has built-in tallies to record the dose from specific types of particles. The standard dose tallies provided by MCNP can also be modified by a user-supplied dose–response function in the form of a data table consisting of an energy-specific data entry (DE) card with the corresponding dose–response (DF) function specified on a second data entry card.

OUTPUT and LIMITS

MCDS estimates RBE_{dsb} in ***CPE*** *(charged particle equilibrium) condition*:

$$RBE_{dsb} = \frac{(DSBs \cdot Gy^{-1}Gbp^{-1})_{test}}{(DSBs \cdot Gy^{-1}Gbp^{-1})_{rif.}}$$

MCDS requires the input particle spectra



Usually the target is thin respect to the mean free path and the CPE is not fullfilled

MCDS need to be coupled with **MCNP**

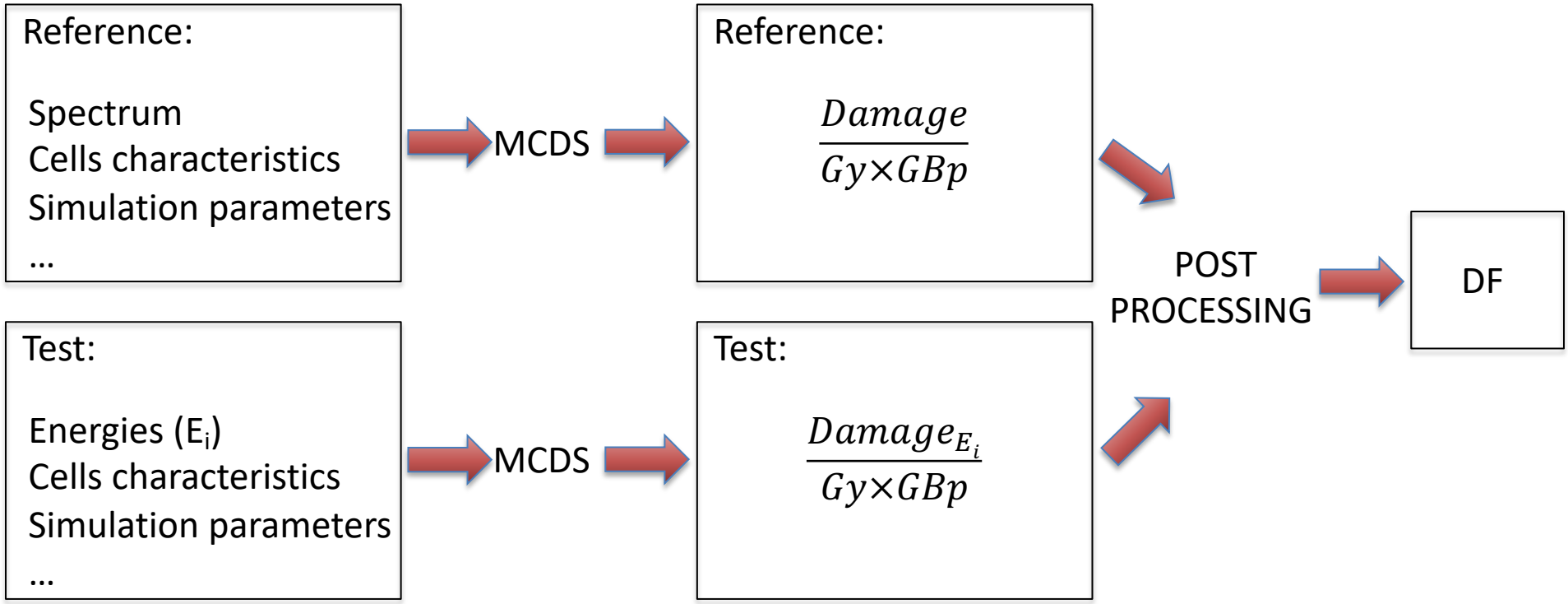
RBE_{dsb} can be translated in RBE_{sf} with the **RMF theory** support.

MONTE CARLO SIMULATIONS

MCDS

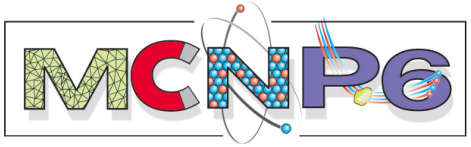
UNIVERSITY of WASHINGTON

Monte Carlo Damage Simulation (MCDS) Software



MONTE CARLO SIMULATIONS

MCNP



DF

FC936 RBE-weighted Electron (e-) dose; DSB induction (aerobic)
F936:E 68
SD936 1
FM936 0.1602
DE936 1.107E-03 1.225E-03 1.356E-03 1.501E-03 1.661E-03 1.839E-03
2.035E-03 2.252E-03 2.493E-03 2.759E-03 3.054E-03 3.381E-03
3.742E-03 4.141E-03 4.584E-03 5.074E-03 5.616E-03 6.216E-03
6.880E-03 7.615E-03 8.428E-03 9.329E-03 1.033E-02 1.143E-02
1.265E-02 1.400E-02 1.550E-02 1.715E-02 1.898E-02 2.101E-02
2.326E-02 2.574E-02 2.849E-02 3.154E-02 3.490E-02 3.863E-02
4.276E-02 4.733E-02 5.239E-02 5.798E-02 6.418E-02 7.103E-02
7.862E-02 8.702E-02 9.632E-02 1.066E-01 1.180E-01 1.306E-01
1.446E-01 1.600E-01
DF936 1.463E+00 1.424E+00 1.387E+00 1.352E+00 1.316E+00 1.284E+00
1.256E+00 1.228E+00 1.208E+00 1.185E+00 1.160E+00 1.139E+00
1.125E+00 1.110E+00 1.097E+00 1.082E+00 1.071E+00 1.057E+00
1.050E+00 1.040E+00 1.036E+00 1.023E+00 1.016E+00 1.011E+00
1.008E+00 9.987E-01 9.968E-01 9.931E-01 9.883E-01 9.838E-01
9.811E-01 9.773E-01 9.750E-01 9.743E-01 9.720E-01 9.698E-01
9.684E-01 9.645E-01 9.668E-01 9.677E-01 9.639E-01 9.616E-01
9.629E-01 9.616E-01 9.568E-01 9.563E-01 9.583E-01 9.568E-01
9.581E-01 9.599E-01
…
…
…

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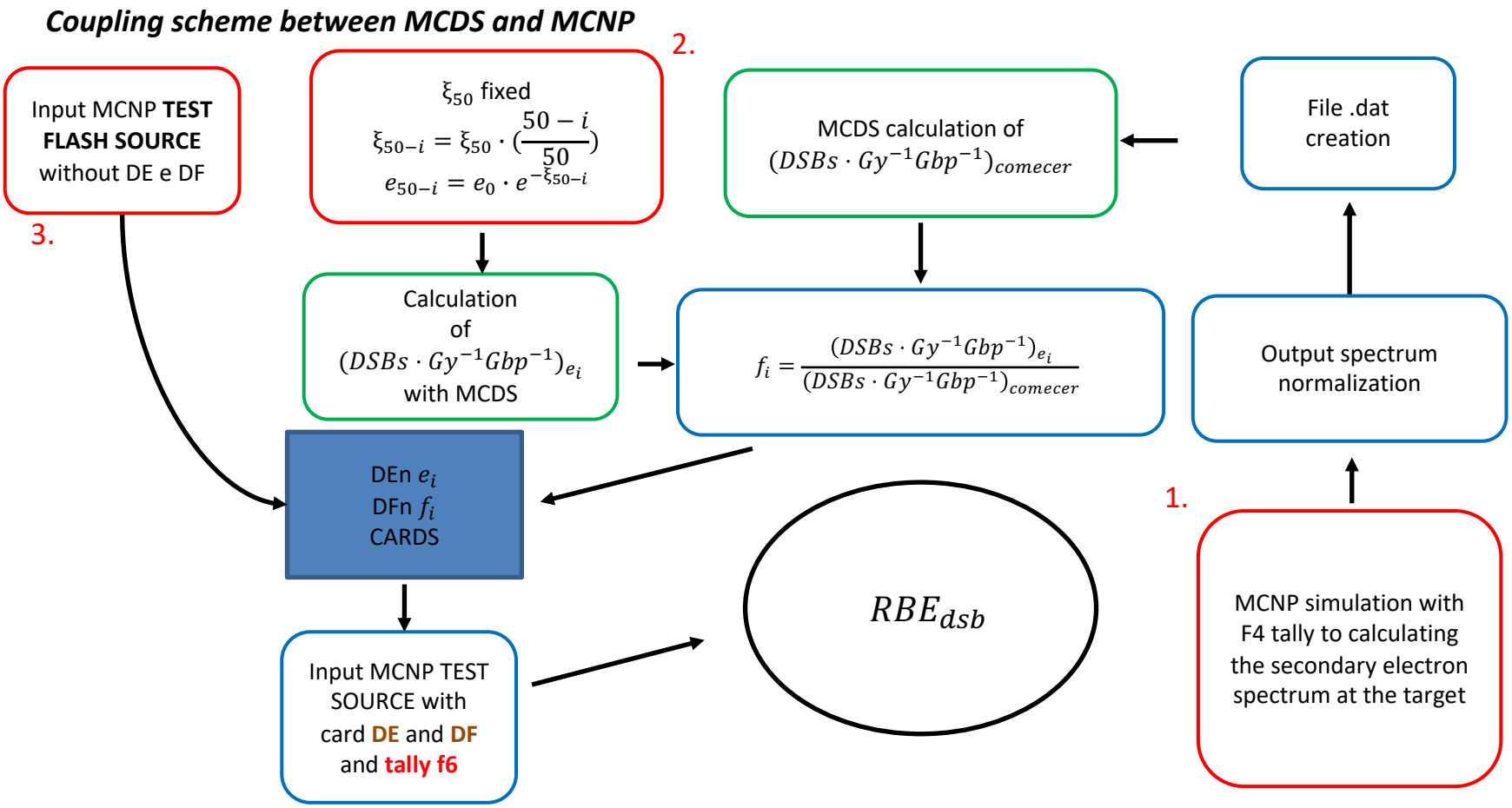
Test:

Source details
Geometry
Simulation parameters
…
…

→ RBE_{DBS}


Coupling scheme between MCDS and MCNP
2.
Input MCNP TEST FLASH SOURCE without DE e DF
3.
ξ_{50} fixed
$\xi_{50-i} = \xi_{50} \cdot (\frac{50-i}{50})$
$e_{50-i} = e_0 \cdot e^{-\xi_{50-i}}$
MCDS calculation of $(DSBs \cdot Gy^{-1}Gbp^{-1})_{comecer}$
File .dat creation
Calculation of $(DSBs \cdot Gy^{-1}Gbp^{-1})_{e_i}$ with MCDS
$f_i = \frac{(DSBs \cdot Gy^{-1}Gbp^{-1})_{e_i}}{(DSBs \cdot Gy^{-1}Gbp^{-1})_{comecer}}$
Output spectrum normalization
DEn e_i
DFn f_i
CARDS
1.
MCNP simulation with F4 tally to calculating the secondary electron spectrum at the target
Input MCNP TEST SOURCE with card DE and DF and tally f6
RBE_{dsb}

RADIOBIOLOGICAL PARAMETERS EVALUATION

ESTIMATED

RBE_{DBS}

$$\alpha_{Test} = \alpha_{Reference} RBE_{DBS}$$

$$\sqrt{\beta_{Test}} = \sqrt{\beta_{Reference}} RBE_{DBS}$$

COMPARISON

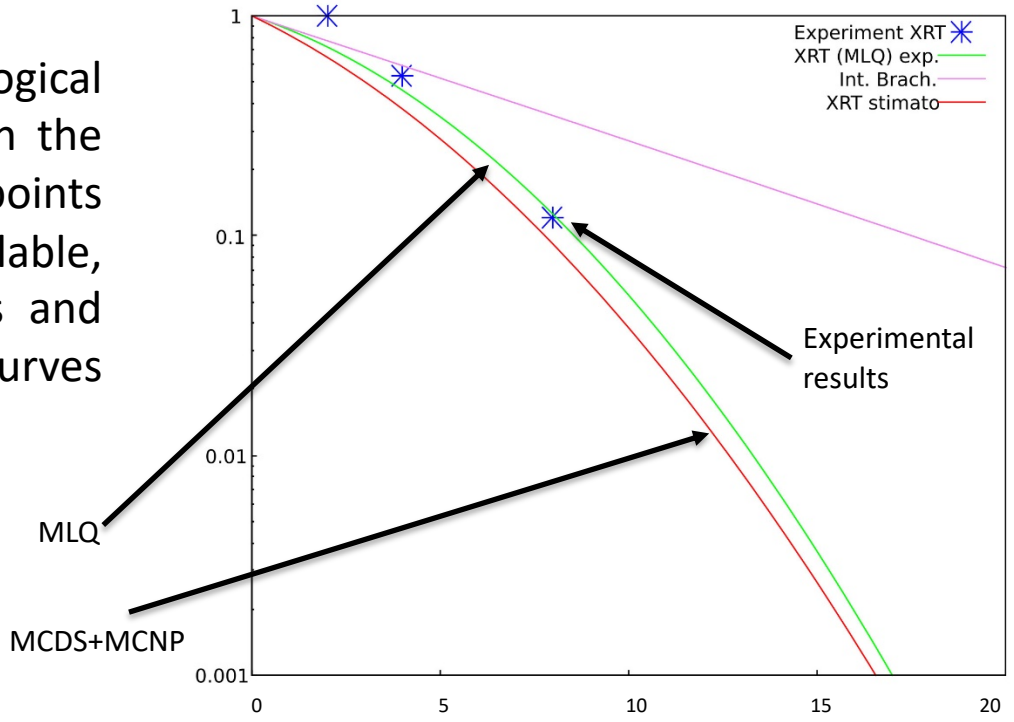
ESPERIMENTAL

$\mathrm{RBE}_{SF}, \alpha_{Reference}, \beta_{Reference}$

Note: If $D \gg \alpha/\beta \rightarrow \mathrm{RBE}_{DBS} \cong \mathrm{RBE}_{SF}$; under this condition, the type of quantity estimated from MCDS is approximatively the same of the ones from the Clonogenic Assay experiments.

The numerically estimated Relative Biological Effectiveness should be compared with the experimental one (the experimental points or even literature data), if available, providing a benchmark of the results and used for plotting the Survival Fraction curves through the α and β parameters.

$$S = e^{-\alpha D - G\beta D^2}$$

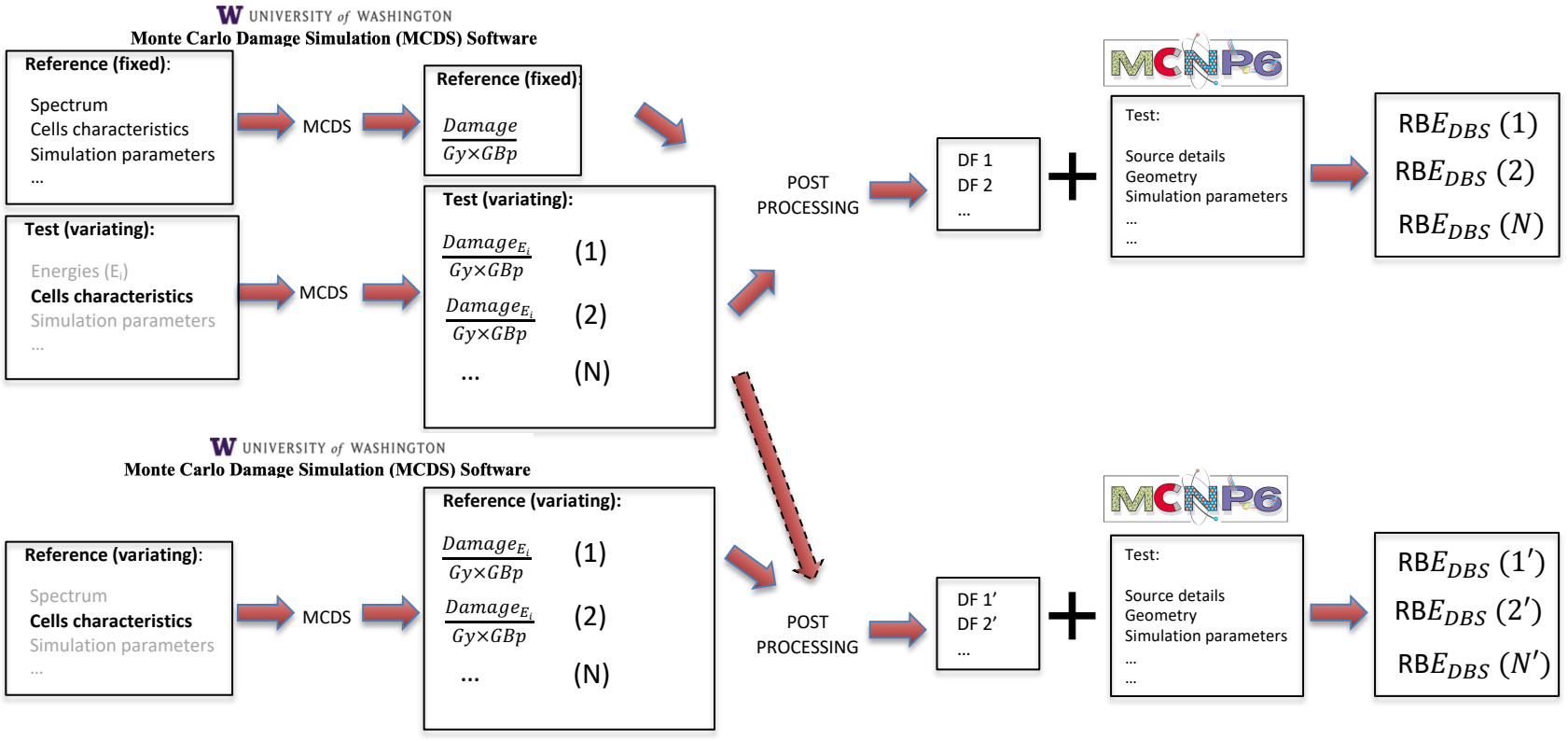


RADIOBIOLOGICAL PARAMETERS EVALUATION

Despite MCDS could not take into account the Dose Rate effects and the MLQ model resulted to be not suitable for reproducing the surviving curves in flash applications, the whole simulation process should be adapted and automatized by varying:

- the cell conditions for the test source,
- the test conditions for the reference source,

in such a way to find a "phase space" of possible RBE.



The final idea is to extract one RBE (or more) which fits the laboratory data and correlates its value with simulation and experimental parameters (e.g. repair capacity, etc.).

RADIOBIOLOGICAL PARAMETERS PHASE SPACE

TABLE III. MCDS and RMF model parameters.

Parameter	Symbol	Type	Value	Explanation/comments
MCDS[a]				
Kinetic energy	E	**Input** (ion specific)	~10 eV to 1 keV	Allow range of kinetic energies varies with atomic number
Partial oxygen concentration	pO_2	**Input**	0–100%	Normoxic cells ~ 5–8%; hypoxic cells <~5%. Small or negligible effect on damage induction for pO_2 values > 10%
Square of the effective ion charge to the speed of relative to speed of light	$(Z_{eff}/\beta)^2$	Computed based on ion type and E	~1 to 10^5	Metric of radiation quality (track structure)
Total number of strand breaks Gy^{-1} Gbp^{-1}	σ_{Sb}	Default[b]	216.7 Gy^{-1} Gbp^{-1}	Same for all particles and kinetic energies. SSB Gy^{-1} Gbp^{-1} < σ_{Sb}
Ratio of base damage to individual strand breaks	f	Default[b]	3	Same for all particles and kinetic energies. Small or negligible impact on yield of SSB and DSB
Distance between adjacent clusters of DNA lesions	N_{min}	Default[b]	9 bp	Used to group individual lesions into DSB and non-DSB clusters
Length of chromosome segment	$n_{seg}(u,v,w)$	Default[b]	u = 149200 bp v = 123600 bp w = 267 bp	Decreases from 149.2 kbp to ~25.9 kbp with increasing $(Z_{eff}/\beta)^2$. Controls density of lesions along DNA segment
Simulation of chemical repair and O_2 fixation	M_0,K, q, and r	Default[b]	M_0 = 1.740, K = 0.3372, q = 946.10, r = 2.15	See Stewart et al.[66] for details
RMF Model				
Diameter of cell nucleus	d	Default[c]	~4 μm	Used to compute $\overline{z_F}$. Determines in part the rate of intra-track binary misrepair
Number of DSB per cell or per Gbp of DNA relative to ^{60}Co γ rays	RBE_{DSB}	Computed[d]	~1 to <4	Varies with pO_2 level and $(Z_{eff}/\beta)^2$
Ratio of LQ parameters for reference radiation	$(\alpha/\beta)_R$	**Input**[e]	~1 to 10 Gy or more	Reflects repair capacity of cell; determines change in cell sensitivity as function of dose

[a]Additional details of the algorithm and mechanisms of action implemented in the MCDS are discussed in detail elsewhere (Semenenko and Stewart[64,65], Stewart et al.[16,66]).

[b]In general, this parameter may be cell and tissue specific. But as a first approximation, default value suffices among all eukaryotes.

[c]For most human and mammalian cells, a default value of 4 μm often suffices for analysis of cell survival data, but may be treated as an adjustable, cell-specific parameter. When treated as an adjustable parameter, values in the range from about 2 to 5 μm appear optimal for a range of mammalian cells.

[d]Within the RMF model, RBE_{DSB} is a computed parameter determined from independently tested (first principle) Monte Carlo simulations (track structure or MCDS) or measurements. As a first approximation, RBE_{DSB} is the same among all eukaryotes for a given value of $(Z_{eff}/\beta)^2$.

[e]Cell- and tissue-specific input determined from fits to measured data.

EXPECTED RESULTS

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LPA-2 SOURCES RBE PREDICTION

Python scripts for automatize the calculations on different cases and by variating 12 parameters per case in a large range of values.

EXAMPLE OF A SET:

N.	Note	nucleus diameter	cell diameter	% O2 reference source	DBS/Gy GBp reference source	% O2 test source	code note
1	Mixed/Fixed	20	20	100	8.26772E+00	100	maximum melanoma cell diameter, all nucleus
2	Mixed	20	20	24	8.14580E+00	24	maximum melanoma cell diameter, all nucleus
3	Mixed	20	20	12	7.98829E+00	12	maximum melanoma cell diameter, all nucleus
5	Mixed	20	20	4	7.45417E+00	4	maximum melanoma cell diameter, all nucleus
9	Mixed/Fixed	20	20	100	8.26772E+00	100	maximum melanoma cell diameter, all nucleus
10	Fixed	20	20	24	8.14580E+00	100	maximum melanoma cell diameter, all nucleus
11	Fixed	20	20	12	7.98829E+00	100	maximum melanoma cell diameter, all nucleus
15	Fixed	20	20	1	5.97789E+00	100	maximum melanoma cell diameter, all nucleus
16	Fixed	20	20	0	2.83656E+00	100	maximum melanoma cell diameter, all nucleus
17	Mixed/Fixed	12	12	100	8.26772E+00	100	average epitelial cell diameter, all nucleus
18	Mixed	12	12	24	8.14580E+00	24	average epitelial cell diameter, all nucleus
19	Mixed	12	12	12	7.98829E+00	12	average epitelial cell diameter, all nucleus
21	Mixed	12	12	4	7.45417E+00	4	average epitelial cell diameter, all nucleus
25	Mixed/Fixed	12	12	100	8.26772E+00	100	average epitelial cell diameter, all nucleus
26	Fixed	12	12	24	8.14580E+00	100	average epitelial cell diameter, all nucleus
27	Fixed	12	12	12	7.98829E+00	100	average epitelial cell diameter, all nucleus
31	Fixed	12	12	1	5.97789E+00	100	average epitelial cell diameter, all nucleus
32	Fixed	12	12	0	2.83656E+00	100	average epitelial cell diameter, all nucleus
33	Mixed/Fixed	6	12	100	8.26772E+00	100	average epitelial cell
34	Mixed	6	12	24	8.14580E+00	24	average epitelial cell
35	Mixed	6	12	12	7.98829E+00	12	average epitelial cell
37	Mixed	6	12	4	7.45417E+00	4	average epitelial cell
41	Mixed/Fixed	6	12	100	8.26772E+00	100	average epitelial cell
42	Fixed	6	12	24	8.14580E+00	100	average epitelial cell
43	Fixed	6	12	12	7.98829E+00	100	average epitelial cell
47	Fixed	6	12	1	5.97789E+00	100	average epitelial cell
48	Fixed	6	12	0	2.83656E+00	100	average epitelial cell
49	Mixed/Fixed	5	5	100	8.26772E+00	100	fibroblast, all nucleus
50	Mixed	5	5	24	8.14580E+00	24	fibroblast, all nucleus
51	Mixed	5	5	12	7.98829E+00	12	fibroblast, all nucleus
53	Mixed	5	5	4	7.45417E+00	4	fibroblast, all nucleus
57	Mixed/Fixed	5	5	100	8.26772E+00	100	fibroblast, all nucleus
58	Fixed	5	5	24	8.14580E+00	100	fibroblast, all nucleus
59	Fixed	5	5	12	7.98829E+00	100	fibroblast, all nucleus
63	Fixed	5	5	1	5.97789E+00	100	fibroblast, all nucleus
64	Fixed	5	5	0	2.83656E+00	100	fibroblast, all nucleus

PARAMETER	MIN	MAX	STEPS
DNA			
NDIA	1	12	5
CDIA	6	20	8
WEM	0	1	99
pO2	0	100	100
m0	0	1000	100
k	0	100	30
q	0	1000	2
r	0	100	4
fbl	0	0.9	2
CONC	0	5000	2
FNSD	0	1	2
CHMX	0	10000	10
AD			

EXPECTED RESULTS

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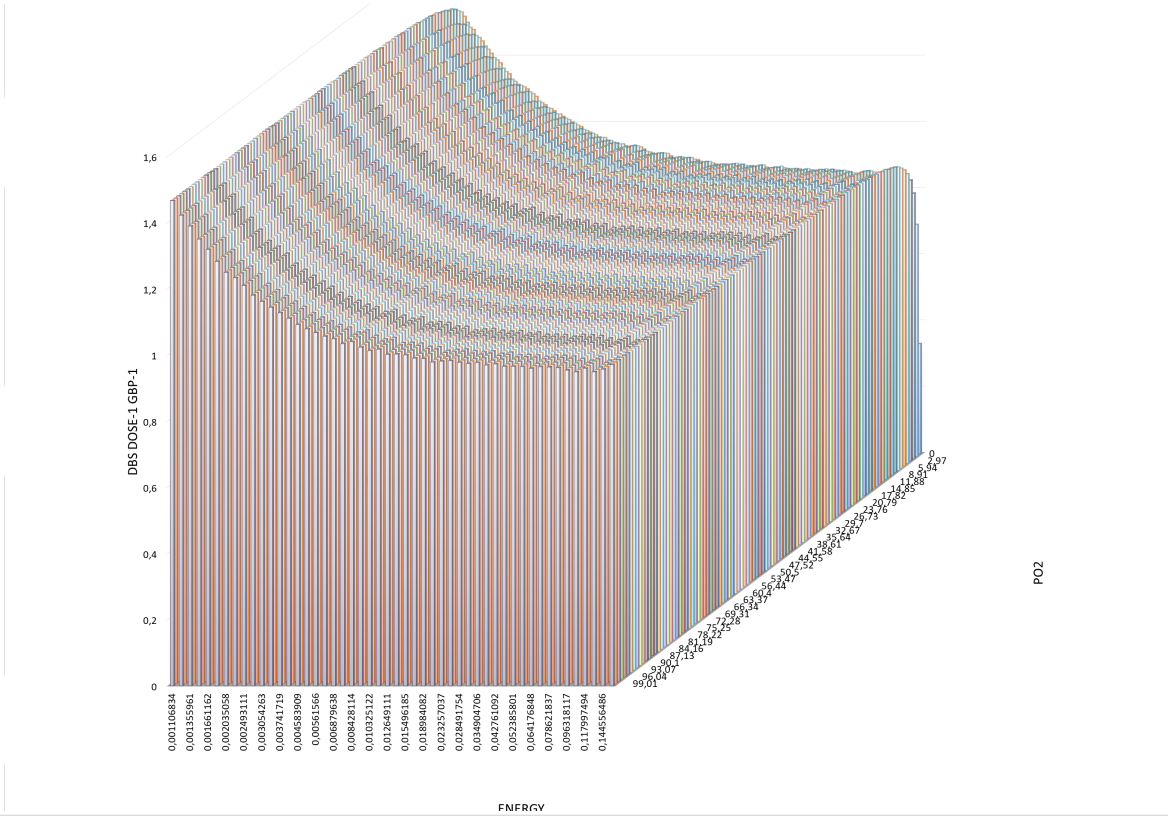
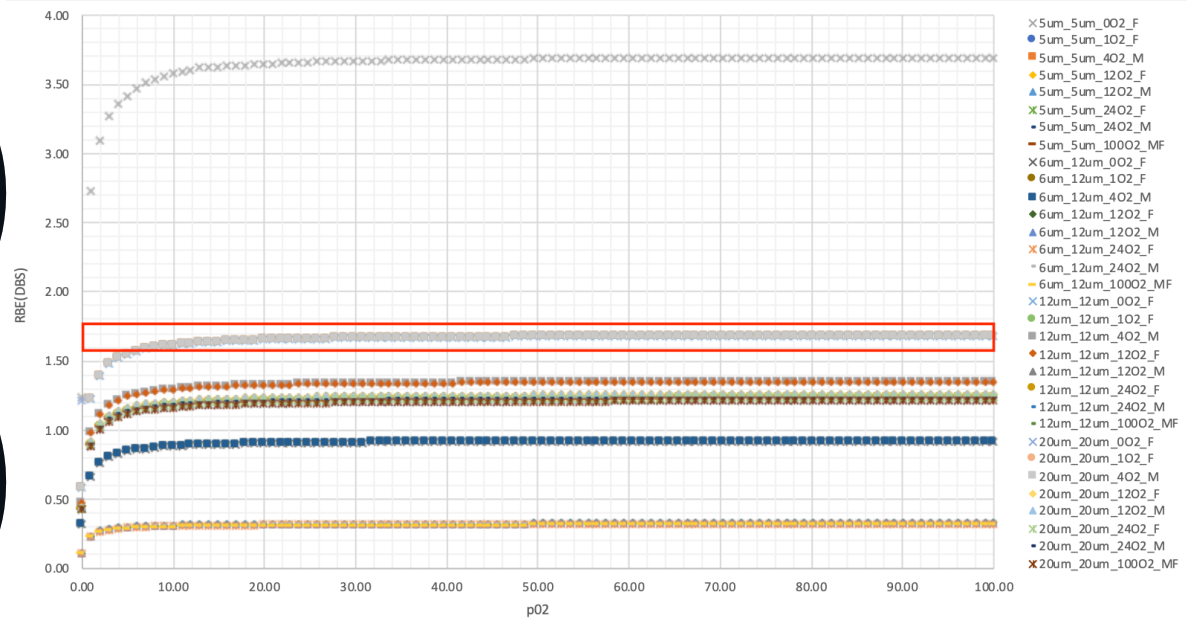
VERY HIGH DOSE RATE SOURCES RBE PREDICTION

- Example of a parameter variation output of one of the different cases and the associated RBE.





EXPECTED RESULTS

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LPA-2 SOURCES RBE PREDICTION AND EXPERIMENTAL VALIDATION

WICH ONE OF THE DIFFERENT ESTIMATED RBE THAT SATISFY THE GOAL COULD BE ASSOCIATED TO AN INCREASED REACTION RATE?

BY KNOWING THE PROTON SPECTRUM IT WILL BE POSSIBLE TO ESTIMATE THE EXPECTED RBE OF THE BEAM.

BY VARYING THE SIMULATION PARAMETERS, A CONDITION EQUIVALENT TO THE ULTRA-HIGH DOSE-RATE EFFECT ON A BIOLOGICAL TARGET WILL BE REPRODUCED.

FOR CELL CULTURE IRRADIATIONS THE BIOLOGICAL MATERIAL SHOULD BE INTRODUCED IN A CELL-HOLDER ABLE TO PROPERLY ‘’DRIVE’’ THE BEAM.

EXPECTED RESULTS

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LPA-2 SOURCES RBE PREDICTION AND EXPERIMENTAL VALIDATION

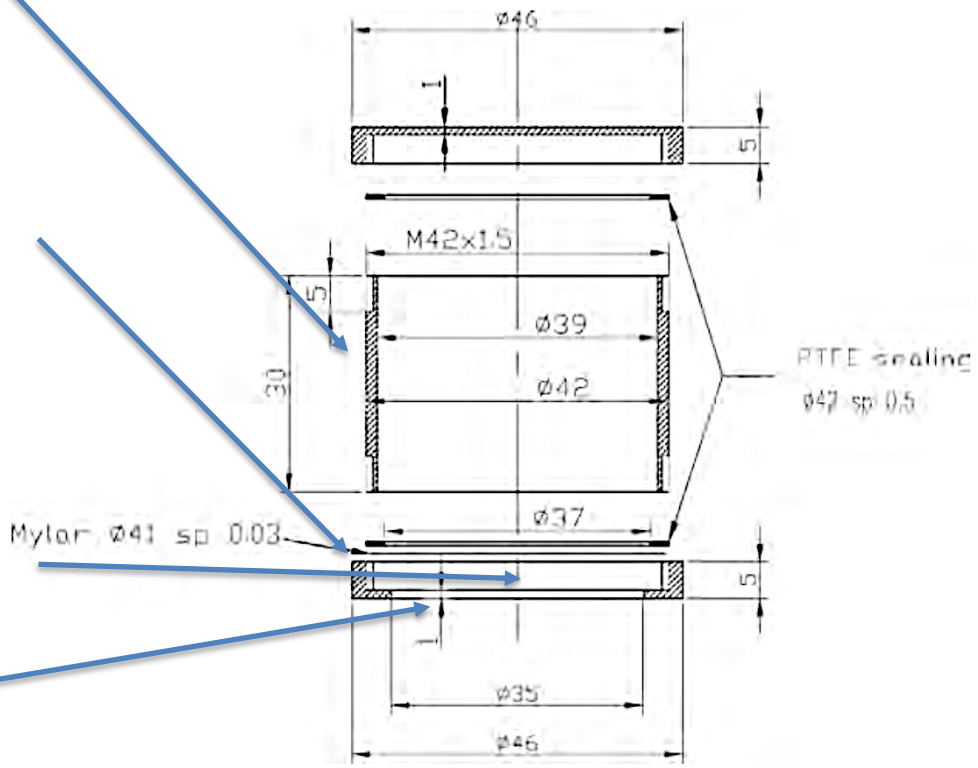
CELL-HOLDER PROPOSAL
(ALSO TO BE MODELED IN MCDS-MCNP):

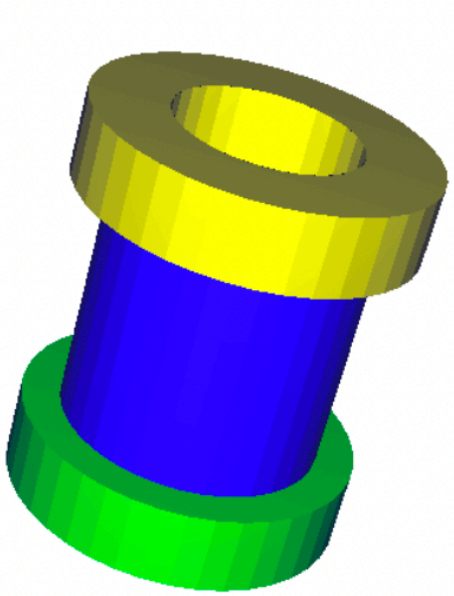
External case

Threadable support

Cell culture

4 micron mylar layer





EXPECTED RESULTS

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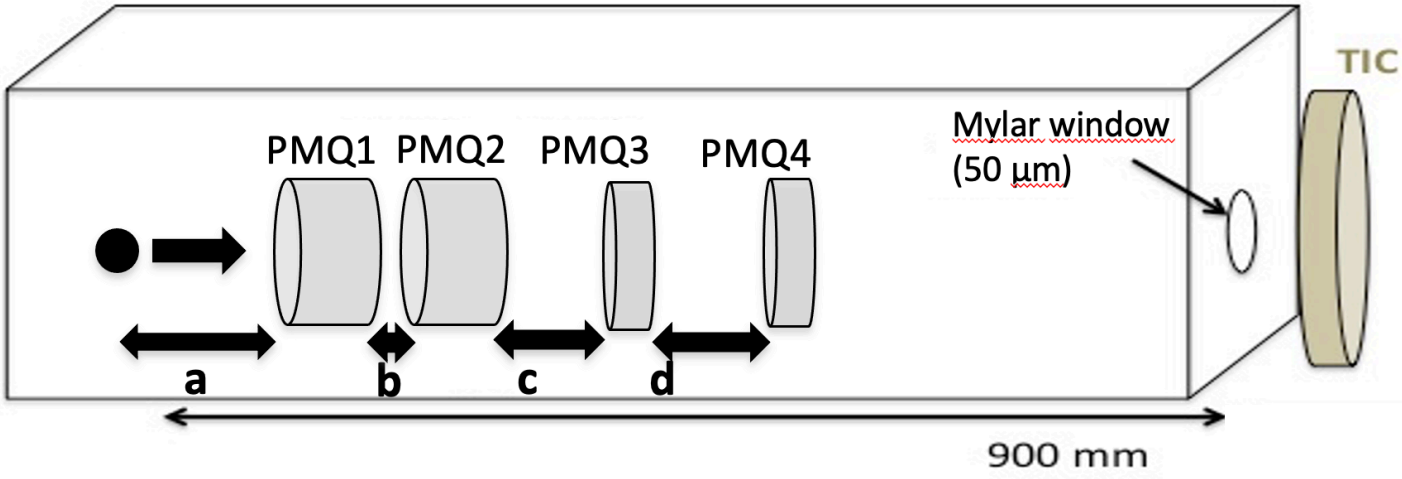
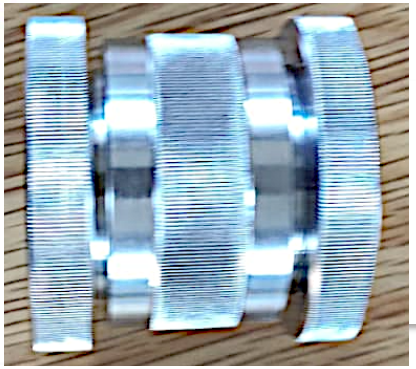
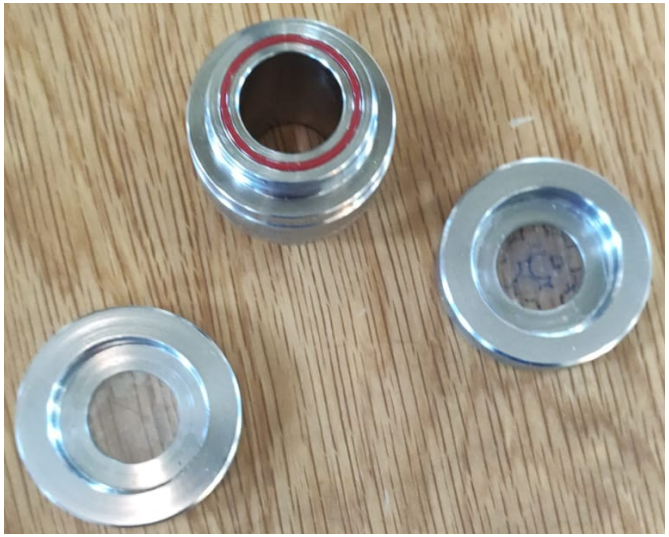
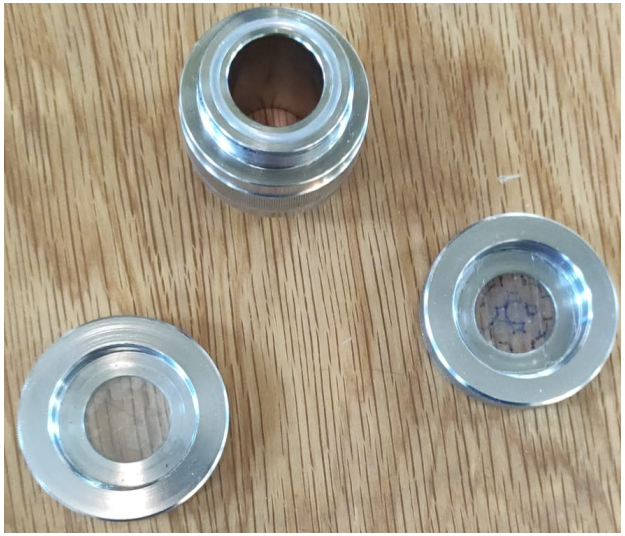
LPA-2 SOURCES RBE PREDICTION AND EXPERIMENTAL VALIDATION









THANK YOU

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