A NEW BIOLOGY-BASED MATHEMATICAL MODEL FOR RADIATION CELL SURVIVAL

INTRODUCTION

The cell death due to radiation is predominantly due to two pathways, apoptosis, and mitotic catastrophe, leading to cellular necrosis. This phenomena are due to lesions to the DNA and the production of free radicals

Linear-Quadratic model

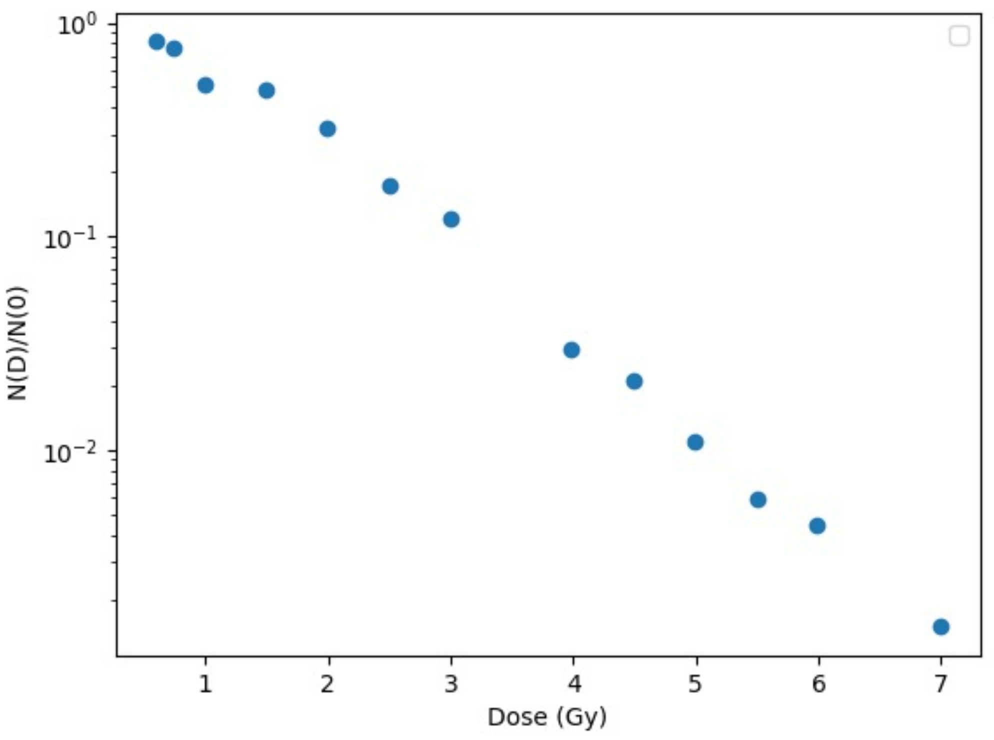
$$S(D) = e^{-\alpha \cdot D - \beta \cdot D^2}$$

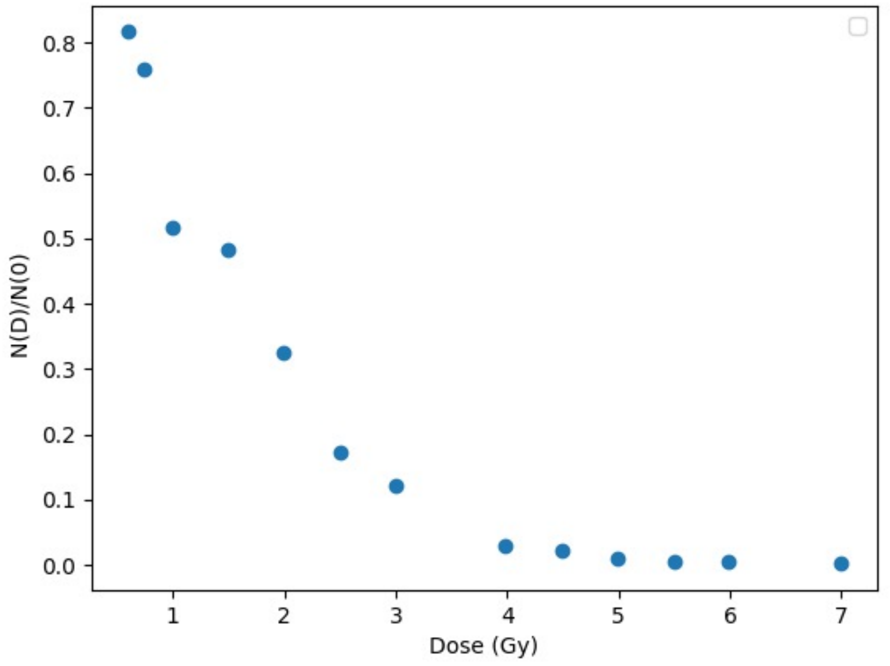
the cell survival level is determined by two exogenous radiation killing phenomena

Several Radiobiological experiments demonstrate that the main processes following the radiation absorption are direct killing (exogenous process) and counteracting internal recovery (endogenous process).

CELLS SURVIVAL CURVES S(D)

S(D) curves represent the fraction N(D)/N(0) of the cells surviving when exposed to a variable dose D of radiant energy



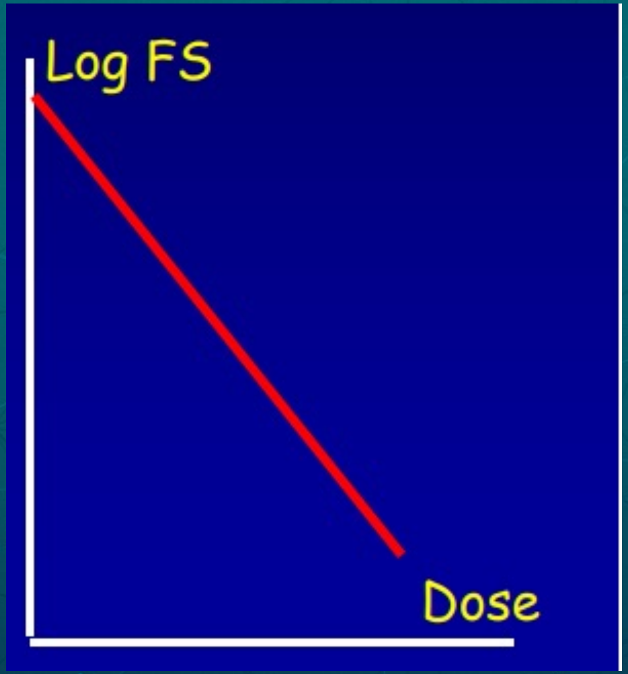


N(D) is the number of cell survived after a dose D

N(0) is the initial number of cell

SINGLE TARGET- SINGLE HIT MODEL

1902 The first S(D) curves observed was a straight line in a semi-logarithmic graph



The hypothesis was: in every cell there is a single sensitive volume and a single hit into this volume is sufficient to kill the cell

SINGLE TARGET- SINGLE HIT EQUATION

If we assume that the hits follow the Poisson statistics,
with a mean value m, the probability that a cell receives just k hits is:

$$P(k,m) = \frac{m^k}{k!}e^{-m}$$

m is proportional to dose D (m=a·D), the probability P(0, D), that a single cell survives is:

$$P(0,D) = S(D) = e^{-a \cdot D}$$

a [Gy^{-1}] is the slope of the line a = 1/D_o
D_o represents the dose required to reduce the initial cell number by $\frac{1}{e}$

this equation implies that the target cell is completely passive,
NO ability to repair the received damage

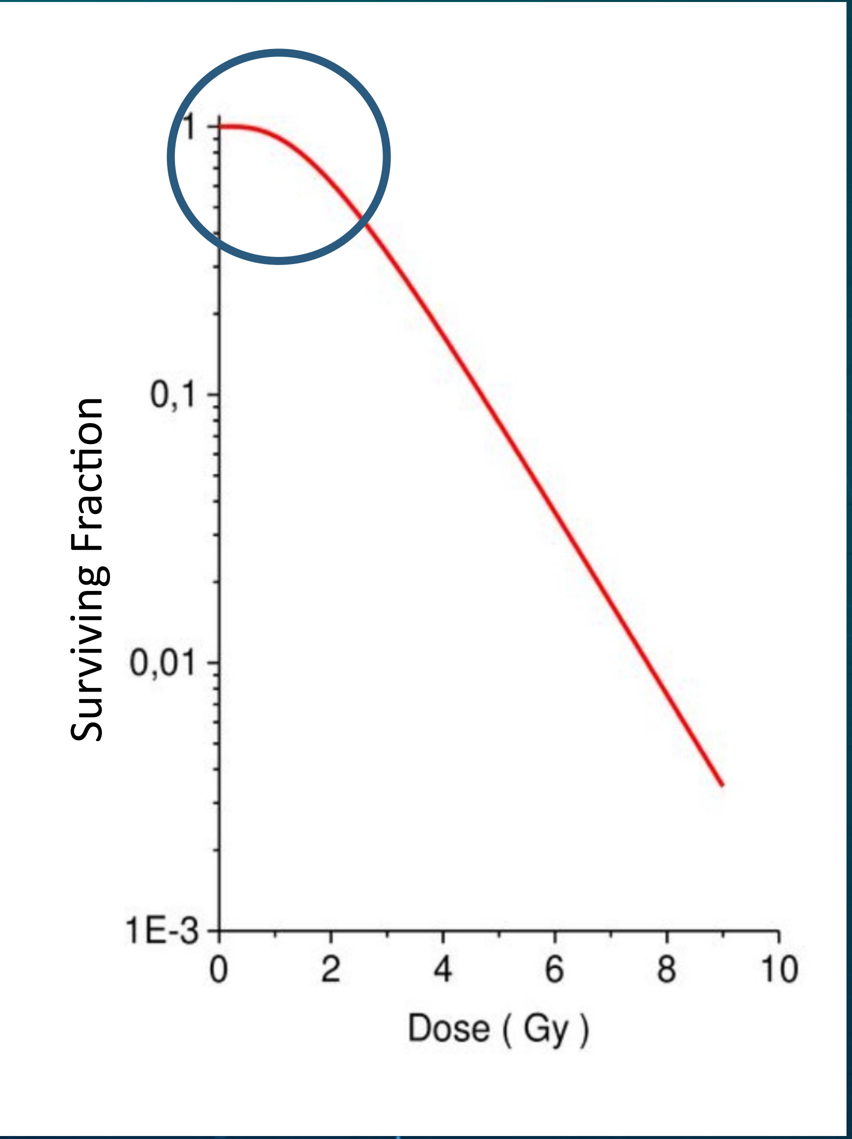
MULTI-TARGET-SINGLE HIT MODEL

the S(D) curves in no mono-exponential exhibited an evident “shoulder” at the lowest doses.

It is interpreted as the presence of more than one target inside the cell

$$S(D) = [1 - (1 - e^{-a \cdot D})^n]$$

n represents the number of targets present in the cell.
$e^{-a \cdot D}$ represent the probability for the single target to survive
$1 - e^{-a \cdot D}$ represent the probability that this target is inactivated
$(1 - e^{-a \cdot D})^n$ is the probability for n (identical) targets to be inactivated
$1 - (1 - e^{-a \cdot D})^n$ is the probability that n targets will survive

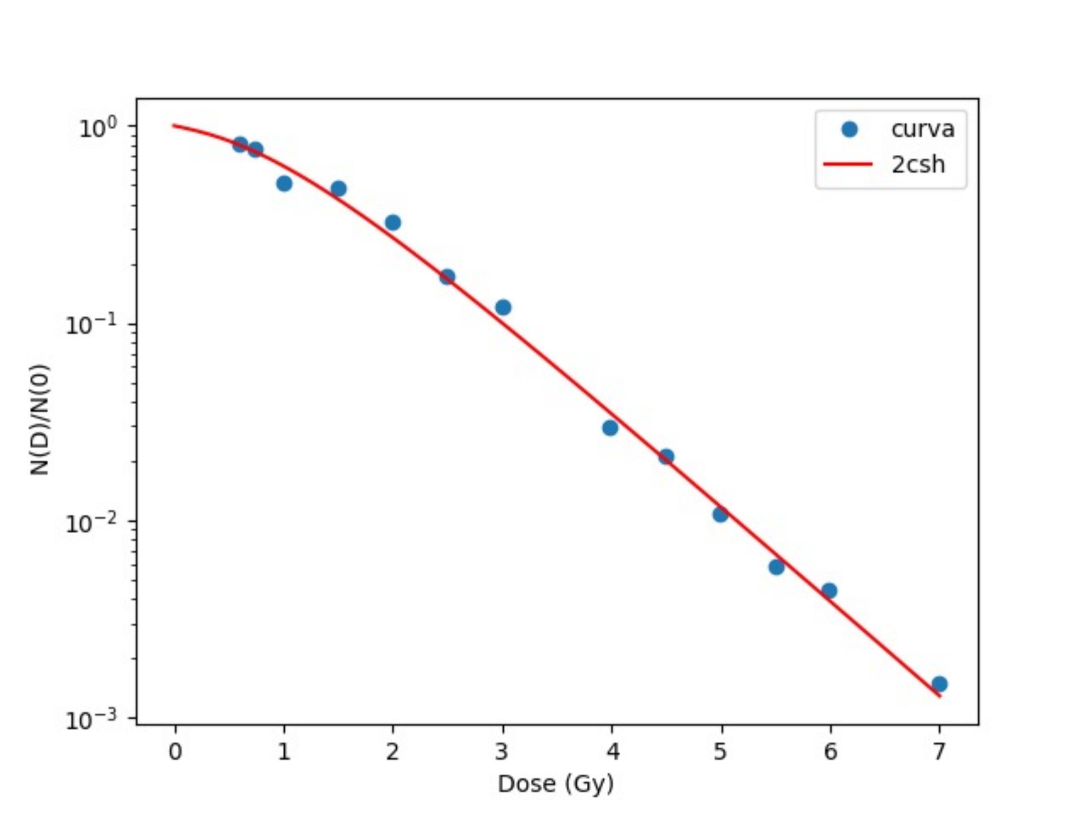


TWO COMPONENTS SINGLE HIT MODEL

S (D) curve can be the product of the survival of different killing processes:

single target-single hit model

several **multi target-single hit models**



The “first-order” approximation of this

two-components single hit model give the equation:

$$S(D) = e^{-\mathrm{k1}\cdot\, \mathrm{D}} \cdot \left[1 - \left(1 - e^{-k2\cdot D}\right)^{n}\right]$$

- k1 is the slope of the single target-single hit components
- k2 the slope of a compound multi-hit component
- n the average “hit number”

LINEAR QUADRATIC MODEL

Theory of Dual Radiation Action

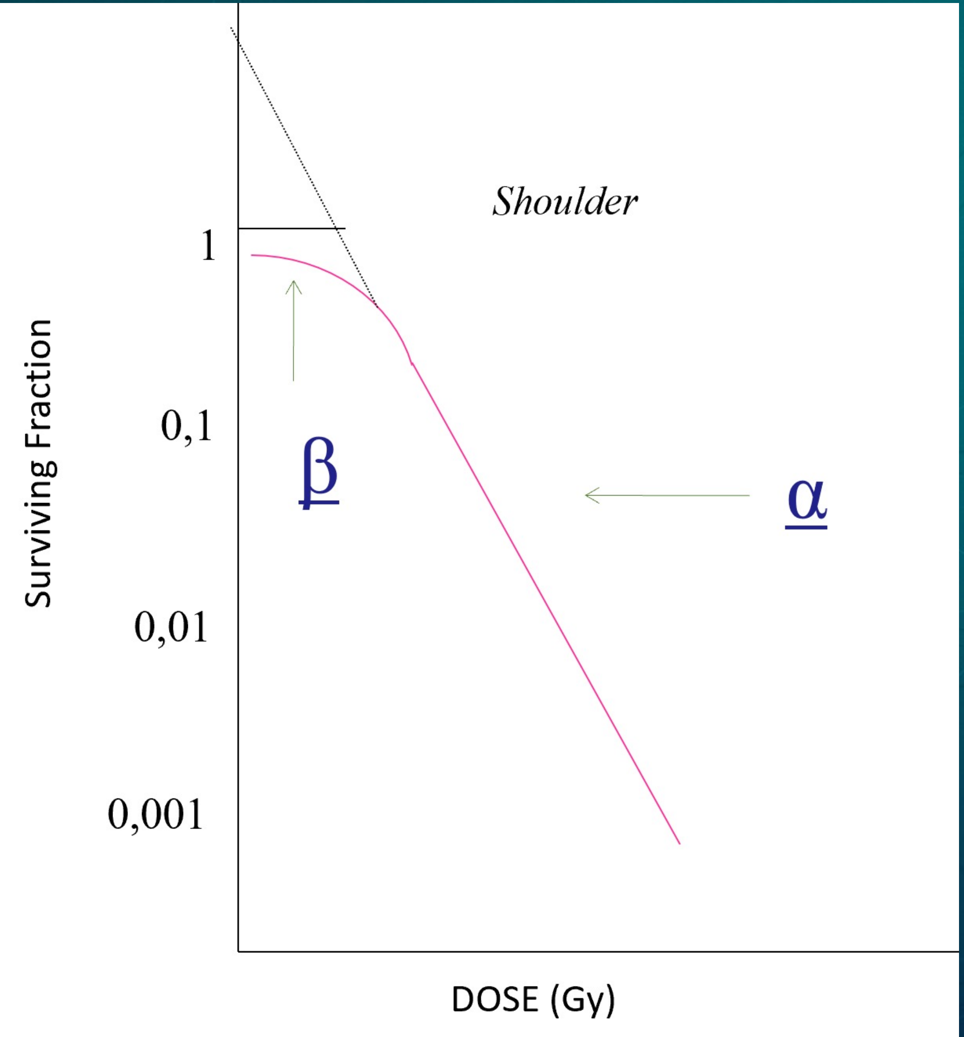
the lethal event, produced by a dose D, is caused by

a single hit due to one particle track

the superposition of 2 particle tracks

$$S(D) = e^{-\alpha \cdot D} \cdot e^{-\beta \cdot D^2}$$

LINEAR QUADRATIC MODEL



Chadwick and Lenouts

The theory assumptions are that critical damage is the double-strand break (DBS) of the helix of the DNA molecules:

- the first term ($\alpha \cdot D$) represents the directly lethal (unrepairable) damage
- the second term ($\beta \cdot D^2$) represents the damage produced by a couple of two sublethal SSB whose combination cannot be repaired

$$S(D) = e^{-\alpha \cdot D - \beta \cdot D^2}$$

ADVANTAGES

It is easily evaluated the parameters parameters α and β that best fit the experimental

the development of the concept of isoeffective treatments

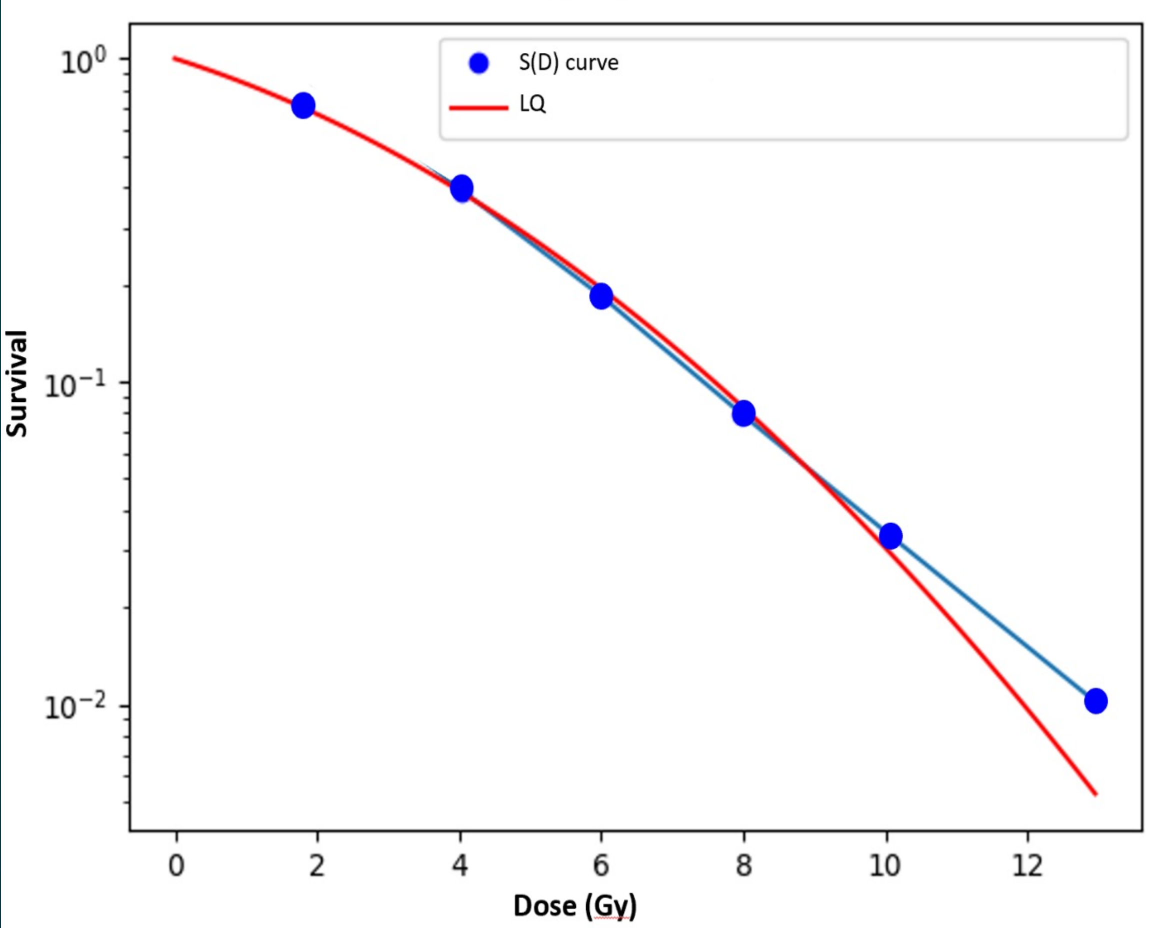
the development of the ipofraction tratment

The ratio α/β [Gy^{-1}] allow to classify tissues

early responding
(when α component dominates)

late responding
(when the β component dominates)

PROBLEMS



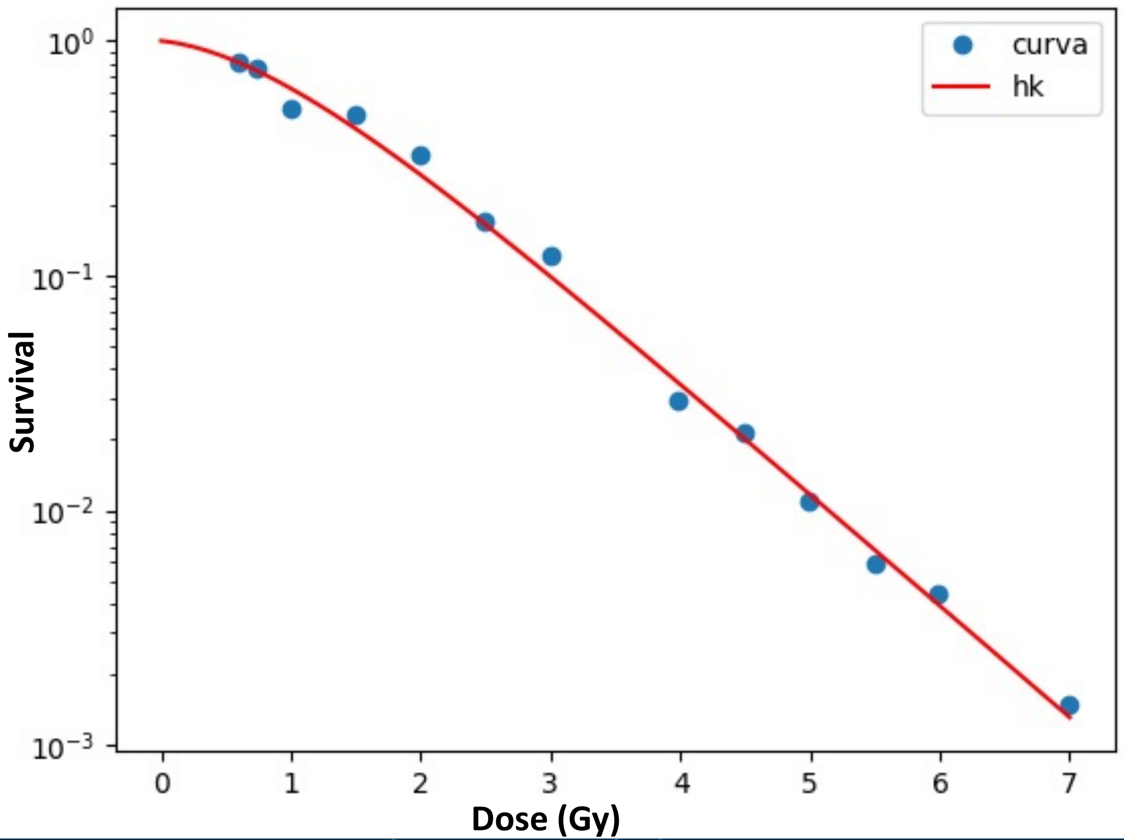
In LQ the cell survival level is determined only by two exogenous radiation killing phenomena.

The main processes following the radiation absorption are direct killing (exogenous process) and a counteracting internal recovery (endogenous process).

Goodhead [1982] with the use of ultrasoft X-Rays and correlated ions, demonstrated that the probability that two-particle tracks overlap to produce a DBS from two overlapping SSB in RT is negligible up to hundreds of Gy.

HUG KELLER EQUATION

$$S(D) = e^{-a \cdot D} \cdot e^{b \cdot \left(1 - e^{-c \cdot D}\right)}$$



two different cell-damaging mechanisms must be considered as the basis of the S(D) curves:

1. irreversible leading to exponential cell death
2. expressing the recovery of the cells.

a [Gy^{-1}] represents the direct killing
c [Gy^{-1}] the "rate" of the disappearing of the recovery process
b [unitless] the amplitude of the same process.

a, b, c all positive and the constrain $b \cdot c \leq a$

THE TAYLOR EXPANSION FOR $D \to 0$

$$S(D) = e^{-(a-b\cdot c)\cdot D-\frac{b\cdot c^2}{2}\cdot D^2+\cdots}$$

$$S(D) = e^{-\alpha\cdot D-\beta\cdot D^2}$$

$\alpha =$ **(a-b·c)** multiplying the linear term doesn't represent only the killing term, but includes a counteracting contribution (b·c), belonging to the recovery process.
This product reduces the original steepness of the curve

$\beta =$ **(b·c²/2)** is a mixing of amplitude and rate of the disappearing of the recovery

the quantity β/α is a mixing of the different basic mechanisms of the survival curves

THE NEWLY PROPOSED MODEL

Considering c·D as the linear term of the series-defining the exponential function $1 + c \cdot D + \frac{c \cdot D^2}{2} + \ldots$

$$S(D) = e^{-a \cdot D} \cdot e^{b \cdot \left(1 - e^{\left(1 - e^{c \cdot D}\right)}\right)}$$

a [Gy^{-1}] parameter is the direct cell killing — is dominant when the doses is high (asymptotic term)

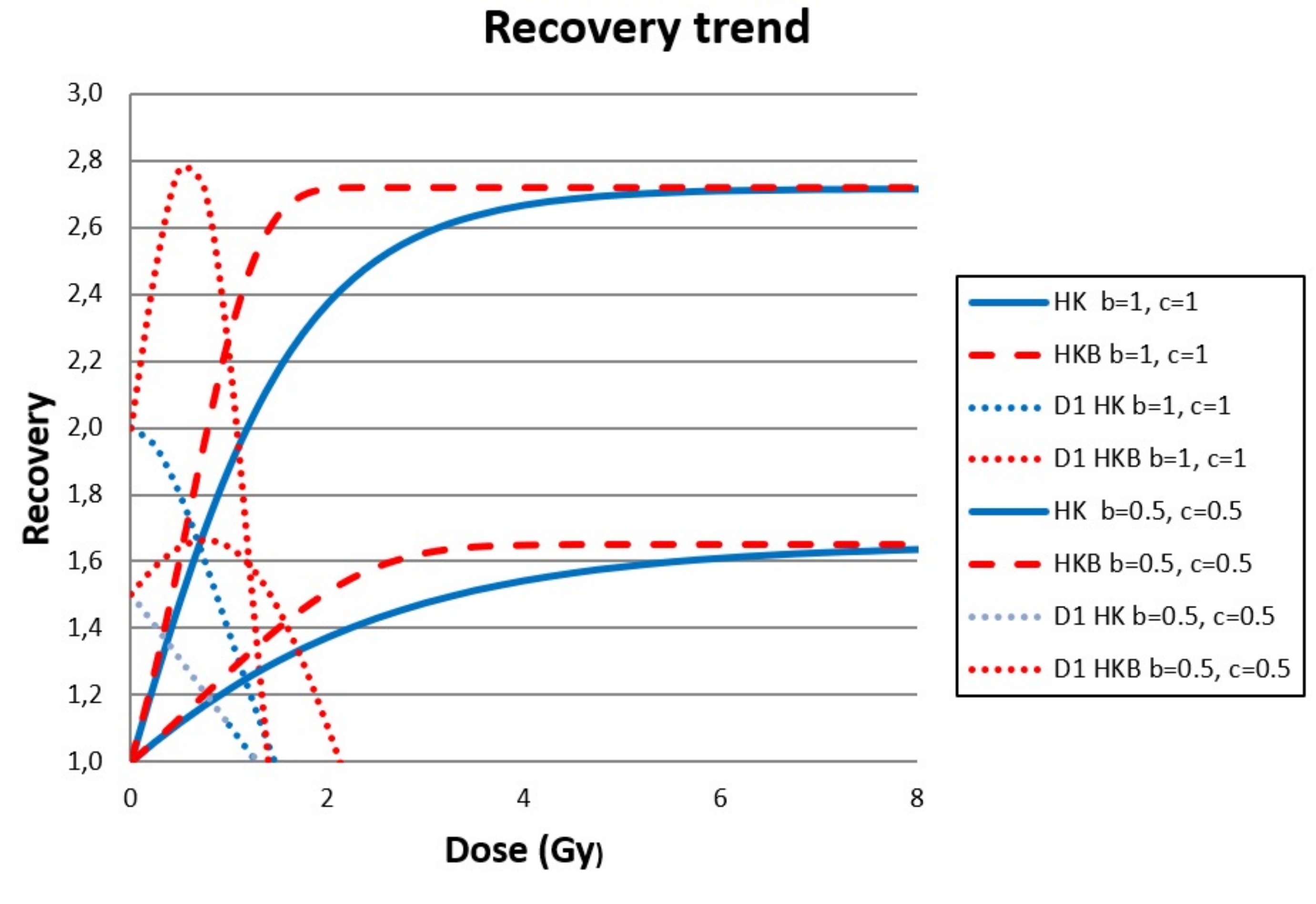
b [unitless] represents the maximum amplitude of the recovery process

c [Gy^{-1}] represents the rate at which the maximum is reached

The second term represent the counteracting effect of the internal recovery (parameters b and c) and reaches the saturation at high doses (recovery term).

a, b, c all positive and the constrain $b \cdot c \leq a$

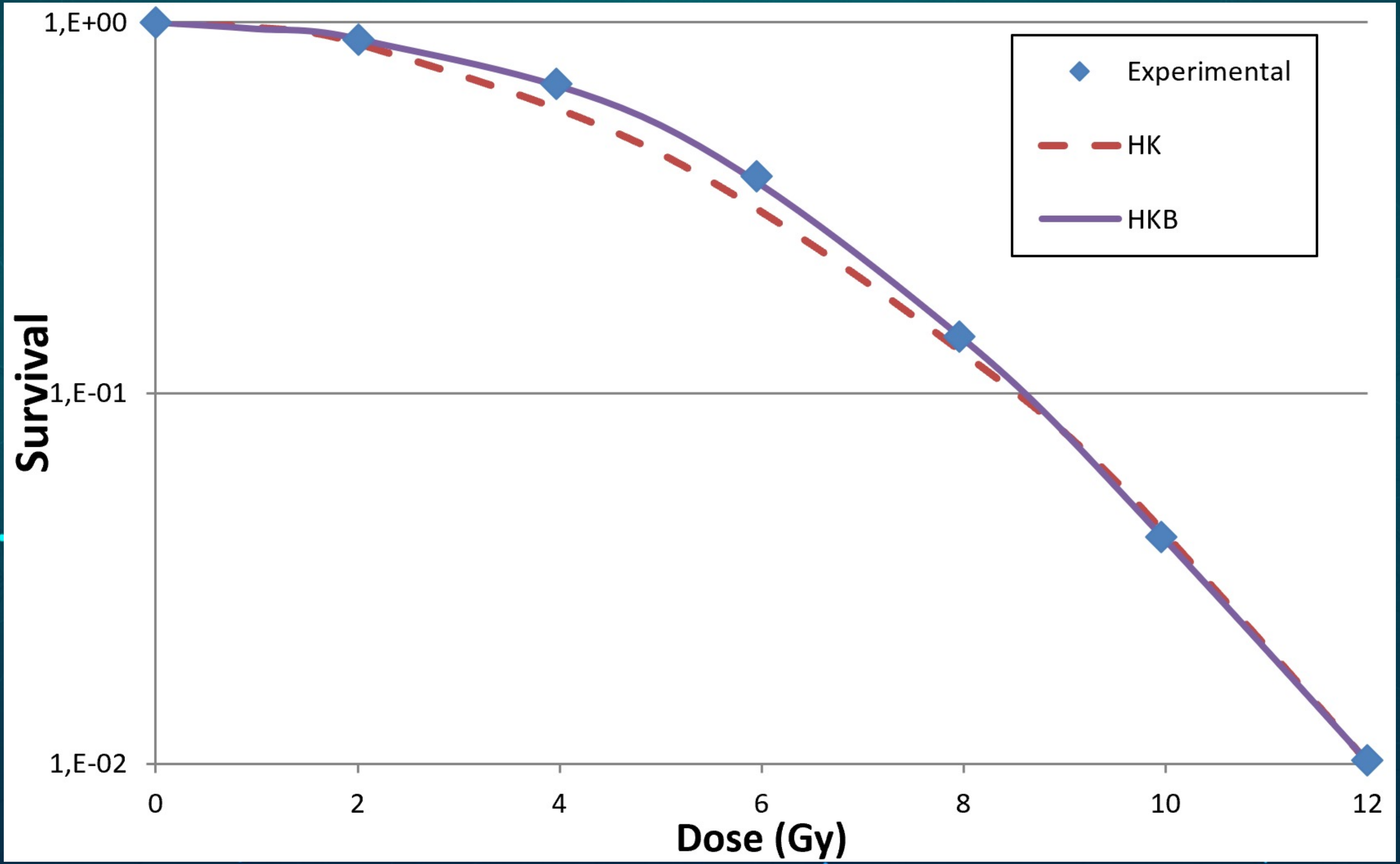
RECOVERY TREND COMPARISON



It is compared the shape of the cell recovery trend from HK and HKB obtained by assuming b=1 and c=1 and b=0.5 and c=0.5.

Also the first derivatives of the functions are reported.

HK-HKB COMPARISON



RADIBIOLOGICAL MODELS

Author and date	Short name	Equation S = f(D,p) (p parameters ≥ 0)	p (p_1, p_2, p_3)	lnS - Initial slope (Gy[-1])	lnS - Final slope (Gy[-1])	lnS - D=0 extrap. or suggestion
1-Bender and Gooch, 1962, ref	2CSH	$e^{-k1\cdot D}\cdot[1-(1-e^{-k2\cdot D})^{n}]$	$k1, k2, n$ $n \geq 1$	$-k1$	$-(k1+k2)$	$\ln(n)$
2-Hug and Kellerer, 1962, ref	HK	$e^{-a\cdot D+b\cdot(1-e^{-c\cdot D})}$	a, b, c $a \geq b\cdot c$	$b\cdot c-a$	$-a$	b
3-Kellerer and Rossi, 1971, ref	LQ	$e^{-\alpha\cdot D-\beta\cdot D^2}$	α, β	$-\alpha$	$-2\cdot\beta\cdot D$	∞
4-Tobias, 1985, ref	RMR	$e^{-\delta\cdot D}\cdot\left(1+\frac{\delta\cdot D}{\epsilon}\right)^{\phi\cdot\epsilon}$	$\delta, \varepsilon, \phi$ $\phi \leq 1$ $\varepsilon \leq 1$	$-\delta\cdot(1-\phi)$	$-\delta$	$-\phi\cdot\epsilon\cdot\ln(\varepsilon)$
5-Curtis, 1986, ref	LPL $\dot{D}\to\infty$	$e^{-(\eta_L+\eta_{PL})\cdot D}\cdot\left(1+\frac{\eta_{PL}\cdot D}{\epsilon}\right)^{\epsilon}$	$\eta_L, \eta_{PL}, \varepsilon$ $\varepsilon \leq 1$	$-\eta_L$	$-(\eta_L+\eta_{PL})$	$-\varepsilon\cdot ln(\varepsilon)$
6-Sutherland, 2006, ref	RDR	$e^{-(1-\phi)\cdot\frac{D}{D1}}\cdot Q\left(n,\phi\cdot\frac{D}{D1}\right)$	$\phi, n, D1$ $n \geq 1$ $\phi \leq 1$	$-\frac{(1-\phi)}{D1}$	$-\frac{1}{D1}$	$n = 4$
7-McKenna and Ahmad, 2009, ref	MA	$e^{-\alpha\cdot D-\frac{\gamma\cdot\beta\cdot D^2}{\gamma+\beta\cdot D}}$	α, β, γ	$-\alpha$	$-(\alpha+\gamma)$	$\frac{\gamma^2}{\beta}$
8-Besserer and Schneider, 2015, ref	BS	$e^{-(p+q)\cdot q\cdot D}\cdot[1+D\cdot(q+R\cdot p)+D^2\cdot\left(\frac{R\cdot q^2}{2}+R\cdot p\cdot q\right)+D^3\cdot\left(\frac{R^2\cdot q^2\cdot p}{2}\right)]$	p, q, R $R \leq 1$	$p\cdot(R-1)$	$-(p+q)$	$R = 0.8$
9-Zhao et al, 2020, ref	GMH	$[1-(1-Q(n,V\cdot D))^{a}]^{1/a}$	a, V, n	$n = 4$	$-\frac{V}{a}$	$\frac{ln(a)}{a}$
10-Shuriak and Cornforth, 2020, ref	NB	$\left(\frac{1}{1+\mu\cdot r}\right)^{\frac{1}{r}}, \quad \mu=\alpha\cdot D+\beta\cdot D^2$	α, β, r	$-\alpha$	0	α, β $from$ LQ $r = 0.14$
11-Shuriak and Cornforth, 2020, ref	MNB	$\left(\frac{1}{1+\mu\cdot X}\right)^{\frac{1}{X}}, \quad X=r\cdot(1-e^{-\mu})$	α, β, r	$-\alpha$	0	α, β $from$ LQ $r = 0.14$
13-HKB, Authors, 2021	HKB	$e^{-a\cdot D+b\cdot(1-e^{-(e^{C\cdot D}-1)})}$	a, b, c $a \geq b\cdot c$	$b\cdot c-a$	$-a$	b

PYTHON CODE

The code allows to analyze any set of experimental survival cell curves through the different radiobiological mathematical models, without any distinction and for every radiobiological mathematical models.

The code through the scipy.optimize library and the minimize routine defines the parameters (pfit) that best fit the considered radiobiological model. It also permits to determine the statistical values such as Chi2 and Chi2 reduced, R2, Akaike and Akaike reduced.

Thanks this code you can compare all the statistic results obtained by the models and you can also graph the different models curve in order to get an objective evaluation of the most faithful radiobiological model

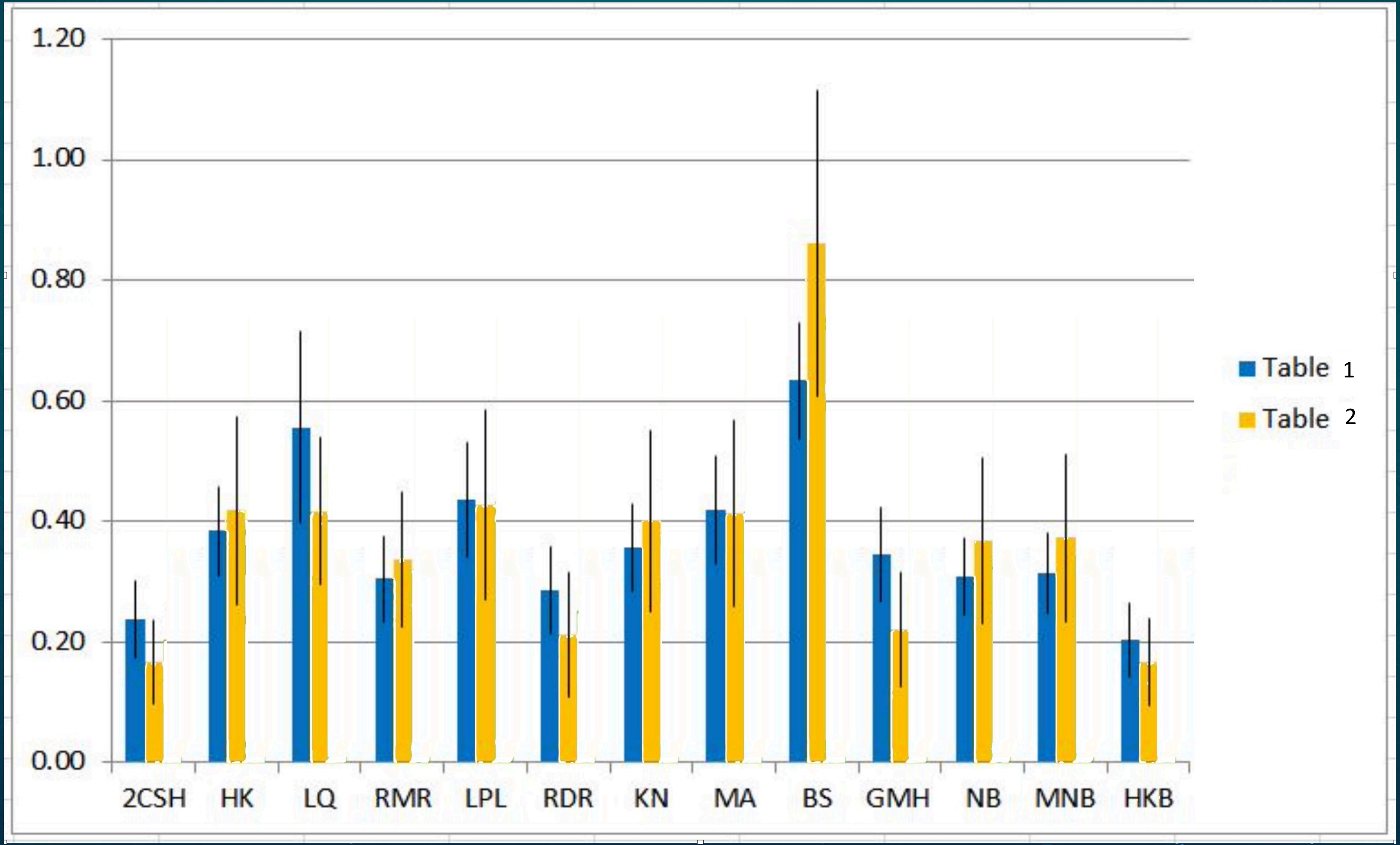
STATISTICAL COMPARISONS: TABLE 1

n.	CHIred	2CSH	HK	LQ	RMR	LPL	RDR	KN	MA	BS	GMH	NB	MNB	HKB
1	Barendsen 1960 T1	0.309	0.131	0.117	0.118	0.135	0.214	0.129	0.129	0.391	0.328	0.130	0.129	0.199
2	Barendsen 1964 T1-N2	0.022	0.143	0.109	0.107	0.135	0.077	0.131	0.134	0.255	0.183	0.120	0.126	0.037
3	Thomson 1975 1 39-4 Hum Mela	0.142	0.044	0.032	0.035	0.038	0.059	0.037	0.037	0.464	0.295	0.037	0.037	0.064
4	Lovhaug 1977 5 NHIK 3025	0.339	0.464	0.179	0.124	0.534	0.471	0.438	1.189	0.485	0.431	0.369	0.375	0.252
5	Han 1980 2 CH3/10 T1/2	0.331	0.784	0.734	0.735	0.783	0.529	0.783	0.783	1.456	0.998	0.778	0.781	0.506
6	Shibamoto 1986 2 EMT6/Ku-Air	0.187	0.205	0.418	0.165	0.220	0.104	0.200	0.215	0.563	0.104	0.156	0.157	0.247
7	Shibamoto 1986 2 Hypoxic	0.114	0.500	0.921	0.441	0.551	0.297	0.484	0.534	0.492	0.229	0.346	0.367	0.083
8	Furusawa 1990 1 V79	0.230	0.076	0.120	0.058	0.072	0.127	0.078	0.074	0.127	0.091	0.087	0.081	0.240
9	Furusawa 1990 1 T1	0.247	0.207	0.169	0.156	0.156	0.179	0.207	0.207	1.407	0.692	0.197	0.199	0.097
10	Raaphorst 1994 1 U87MG D	0.422	0.598	1.620	0.588	0.784	0.699	0.525	0.718	0.810	0.127	0.405	0.343	0.098
11	Raaphorst 1994 1 U87MG I	0.252	0.928	1.548	0.731	1.097	0.726	0.862	1.043	0.990	0.445	0.558	0.639	0.176
12	Suzuchi 2000 1G U251 MG	0.056	0.327	0.198	0.313	0.344	0.043	0.297	0.304	0.922	0.043	0.297	0.297	0.033
13	Bartowiak 2001 3 CHO	0.039	0.017	0.015	0.016	0.016	0.029	0.016	0.016	0.100	0.192	0.016	0.016	0.038
14	Garcia 2006 4 U373MG	0.343	0.351	0.781	0.347	0.366	0.363	0.346	0.360	0.369	0.366	0.340	0.340	0.359
15	Garcia 2006 5 CP3	0.601	0.417	0.697	0.412	0.429	0.439	0.414	0.425	1.258	0.405	0.407	0.405	0.507
16	Garcia 2006 5 DU 145	1.374	1.432	3.140	1.432	1.489	1.462	1.404	1.486	1.487	1.604	1.322	1.378	1.290
17	Miyakawa 2014 EMT6	0.008	0.149	0.118	0.110	0.110	0.057	0.145	0.146	0.721	0.190	0.136	0.139	0.041
18	Bathia 2017 DAOY NS	0.028	0.766	0.761	0.406	1.487	0.157	0.752	0.797	0.799	0.082	0.523	0.518	6.96E-06
19	Bathia 2017 UW228 NS	0.102	0.471	0.276	0.105	0.437	0.173	0.193	0.206	0.234	0.234	0.166	0.189	0.055
20	Song 2018 1-B1 SKOV3	0.007	0.125	0.074	0.101	0.126	0.015	0.112	0.115	0.115	0.128	0.112	0.112	0.026
21	Song 2018 1-C1 OVCAR3	0.043	0.276	0.180	0.183	0.271	0.036	0.270	0.270	0.383	0.365	0.270	0.270	0.095
22	Zhou 2019 4-A MDA-MDB-231	0.031	0.026	0.016	0.017	0.025	0.019	0.025	0.025	0.112	0.063	0.025	0.025	0.014
	Mean CHIred	0.238	0.384	0.556	0.305	0.437	0.285	0.357	0.419	0.634	0.345	0.309	0.315	0.203
	St.Dev. CHIred	0.300	0.350	0.743	0.334	0.442	0.342	0.341	0.413	0.454	0.359	0.298	0.310	0.285
	St.Err. CHIred	0.064	0.075	0.158	0.071	0.094	0.073	0.073	0.088	0.097	0.077	0.064	0.066	0.061

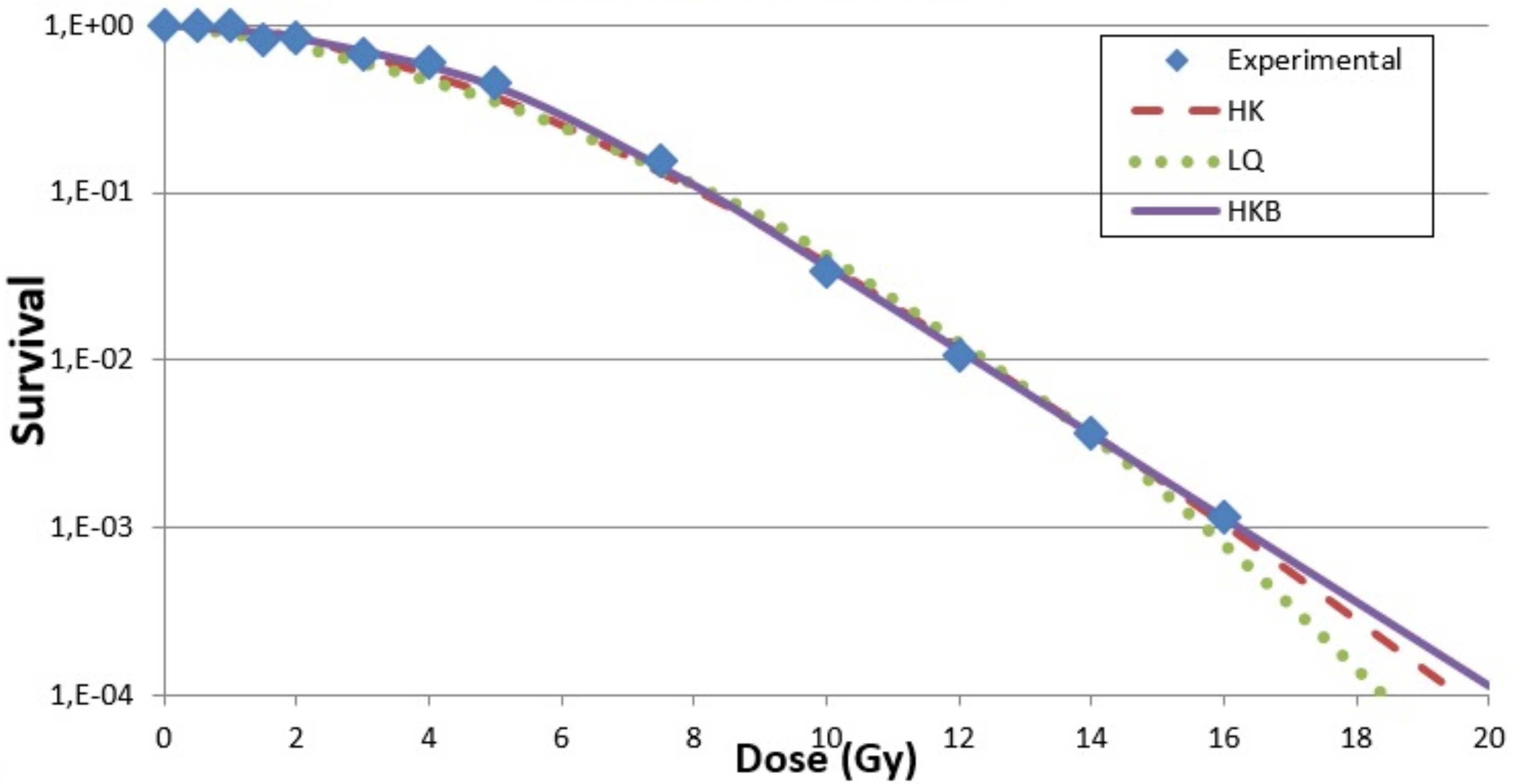
STATISTICAL COMPARISONS: TABLE 2

N	CHIred	2CSH	HK	LQ	RMR	LPL	RDR	KN	MA	BS	GMH	NB	MNB	HKB
1	Puck-Markus 1959 HeLa	0.197	0.197	0.411	0.200	0.220	0.221	0.178	0.212	0.222	0.214	0.153	0.164	0.165
2	Elkind-Sutton 1959 CHO Ovary	0.107	0.124	0.482	0.138	0.166	0.157	0.107	0.149	0.173	0.144	0.093	0.101	0.081
3	Phillips-Tolmach 1964 HeLaS3	0.161	0.528	0.780	0.482	0.563	0.347	0.517	0.552	0.614	0.231	0.422	0.443	0.138
4	Bedford-Mitchell 1973 CHL-F	1.100	2.639	2.299	1.827	2.741	1.950	2.597	2.709	3.464	1.582	2.235	2.282	1.229
5	Chapman 1978 CH-V79	0.071	0.031	0.024	0.091	0.028	0.031	0.031	0.028	0.338	0.102	0.028	0.028	0.025
6	Szechter 1978 Morris	0.032	0.037	0.186	0.042	0.047	0.039	0.034	0.044	0.041	0.041	0.028	0.029	0.036
7	Pohlit-Heider 1981 Ehrich Ascites I	0.057	0.018	0.016	0.014	0.017	0.032	0.018	0.017	0.057	0.056	0.018	0.018	0.046
8	Pohlit-Heider 1981 Ehric Ascites D	0.007	0.008	0.010	0.007	0.009	0.008	0.008	0.009	0.009	0.016	0.008	0.008	0.019
9	Cornforth-Bedford 1987 AG1522	0.066	0.046	0.064	0.038	0.046	0.049	0.047	0.046	0.073	0.068	0.048	0.047	0.074
10	Carmichael 1989 HCI H841 V	0.091	0.085	0.322	0.088	0.099	0.047	0.081	0.094	0.333	0.054	0.059	0.060	0.087
11	Stackhouse-Bedfortd 1993 10B2	0.098	0.037	0.268	0.035	0.046	0.042	0.034	0.043	0.086	0.049	0.028	0.027	0.077
12	Hall 2000 EMT6	0.006	0.342	0.211	0.276	0.345	0.064	0.329	0.323	1.280	0.041	0.317	0.317	0.031
13	Hall 2000 MO16	0.018	0.164	0.098	0.141	0.151	0.006	0.143	0.144	1.073	0.025	0.130	0.130	0.001
14	Hall 2000 AHT29	0.010	0.004	0.006	0.003	0.004	0.005	0.004	0.004	0.015	0.004	0.004	0.004	0.014
15	Park 2008 H460	0.042	0.131	0.326	0.134	0.149	0.103	0.125	0.143	0.160	0.118	0.090	0.099	0.037
16	Liao 2010 BGC-823	0.026	1.678	1.027	1.240	1.649	0.024	1.571	1.568	3.281	0.142	1.541	1.541	0.075
17	Liao 2010 SGC 7901	0.022	1.102	0.665	0.899	1.094	0.046	1.022	1.016	2.950	0.185	0.997	0.997	0.086
18	Liao 2010 BGC 823+PROPRANOLOL	0.054	0.098	0.120	0.068	0.100	0.023	0.097	0.099	1.101	0.037	0.079	0.081	0.042
19	Liao 2010 SGC 7901+PROPRANOLOL	0.174	0.018	0.044	0.011	0.017	0.045	0.018	0.017	0.267	0.023	0.020	0.019	0.080
20	Andisheh 2013 U1690	1.010	1.076	0.986	0.993	1.066	1.004	1.063	1.062	1.681	1.294	1.062	1.062	0.962
	CHIred mean	0.168	0.418	0.417	0.336	0.428	0.212	0.401	0.414	0.861	0.221	0.368	0.373	0.165
	CHIred St.Err.	0.069	0.155	0.122	0.113	0.158	0.104	0.151	0.155	0.253	0.095	0.137	0.139	0.072

STATISTICAL COMPARISONS



GRAPHIC COMPARISON



RINGRAZIAMENTI

- Giovanni Borasi
- Giorgio Russo
- Silvia Strolin
- Lidia Strigari

UNIVERSITÀ degli STUDI di CATANIA

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