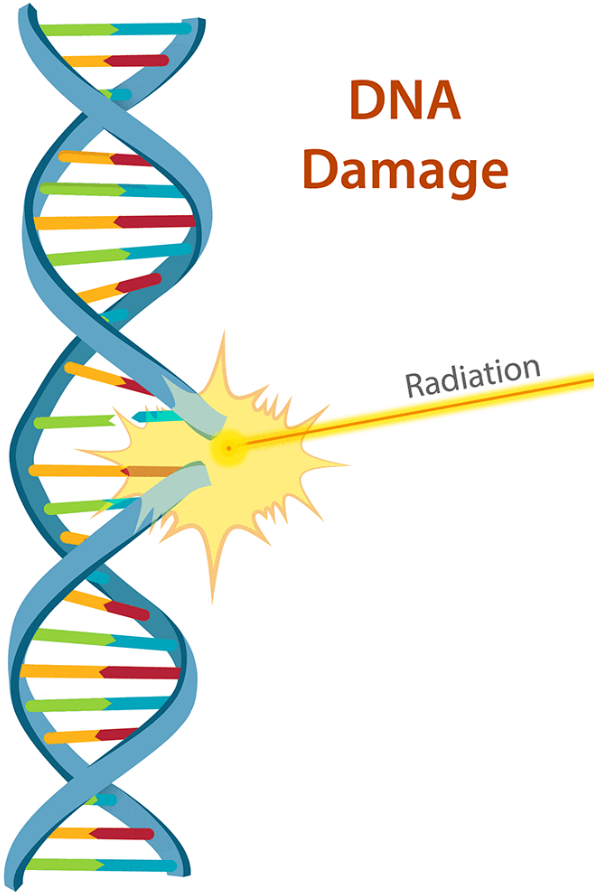
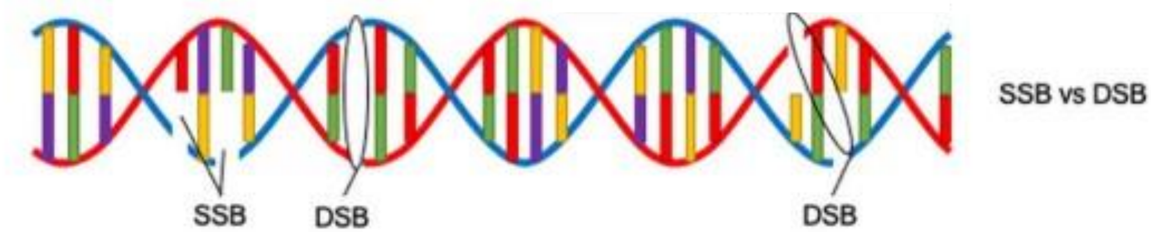
Unraveling the complexities of radiation damage through Microdosimetric Kinetic Model: The role of clonogenic data in clinical RBE

IGFAE workshop on technologies and applied research at the future Galician proton-therapy facility

Santiago de Compostela
May 9, 2023
Daniel Suárez García

DNA damage





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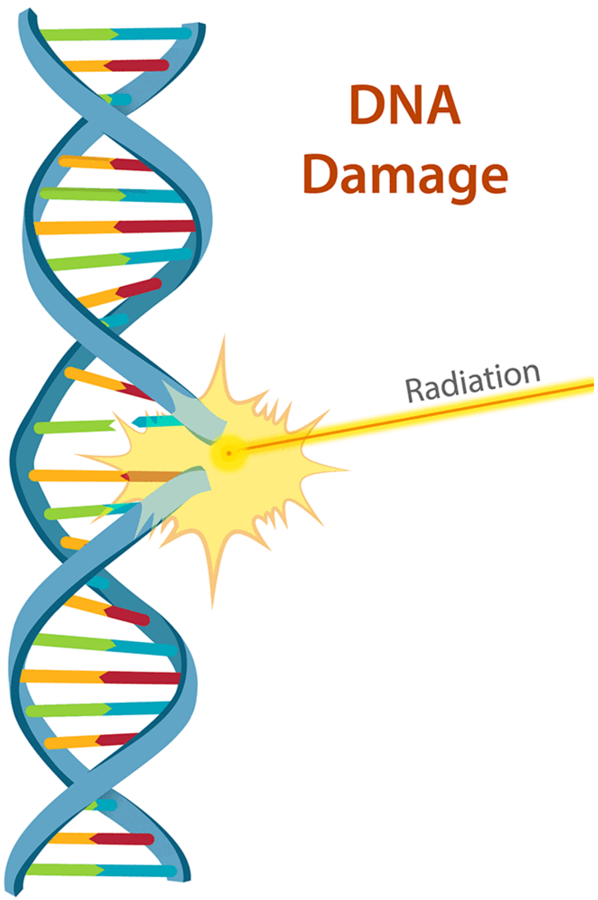
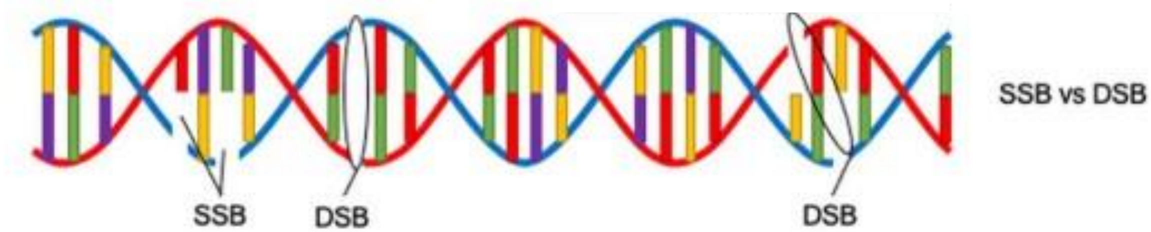
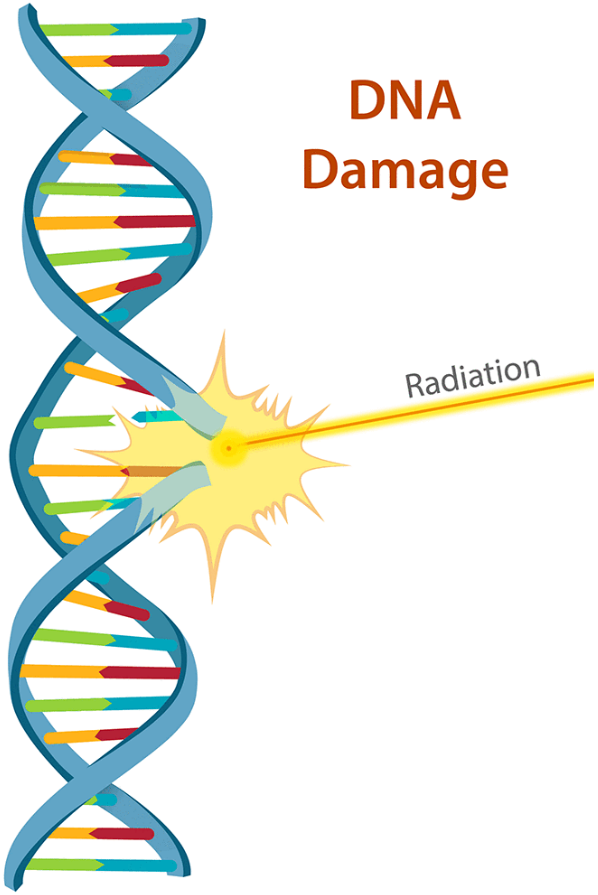


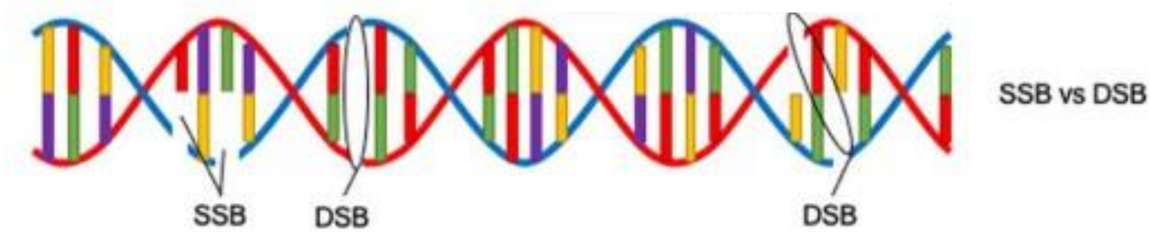


- SSB → Single-strand breaks
- DSB → Double-strand breaks

⇨ **Cell death**

DNA damage





- SSB → Single-strand breaks
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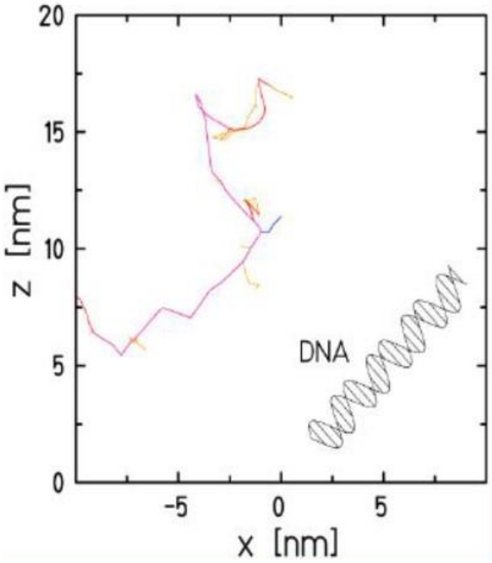
⇨ **Cell death**

- It is more relevant for **high LET** radiation

High LET vs Low LET

Low LET
Homogeneous dose deposition

High LET vs Low LET



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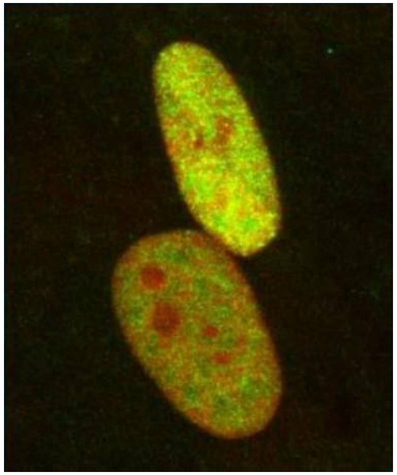

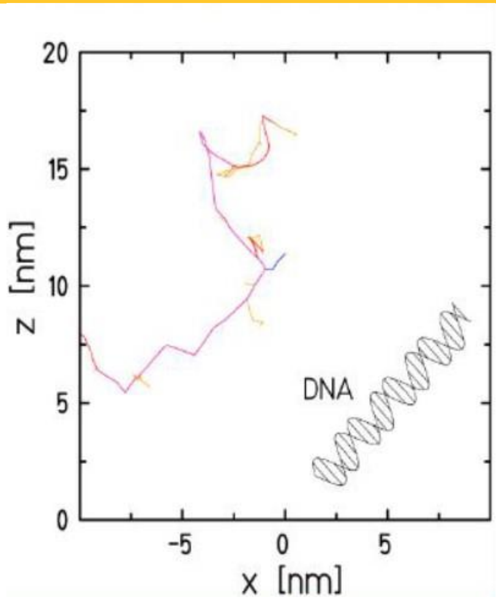

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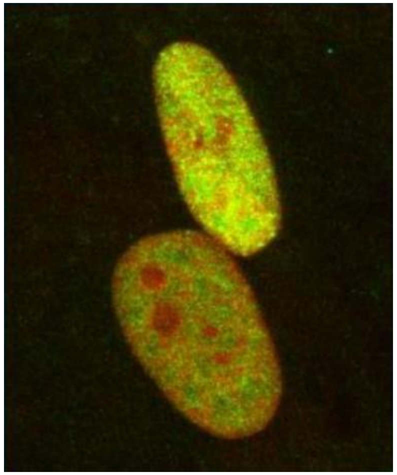
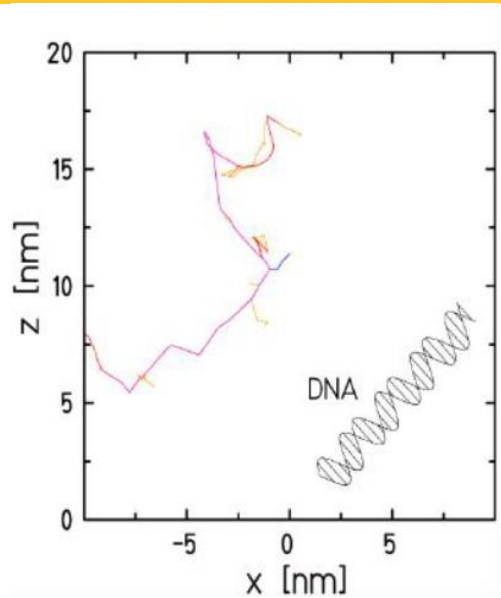


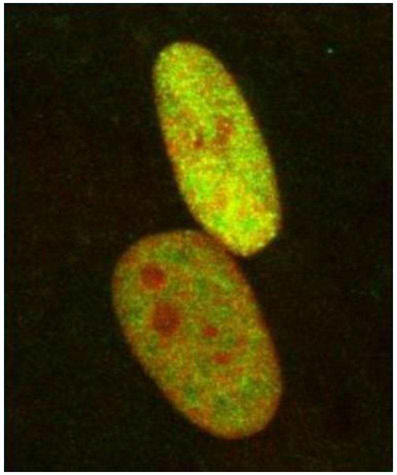


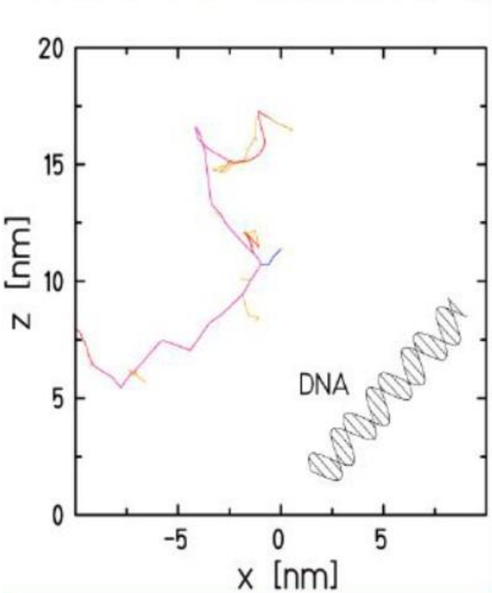
Low LET
Homogeneous dose deposition

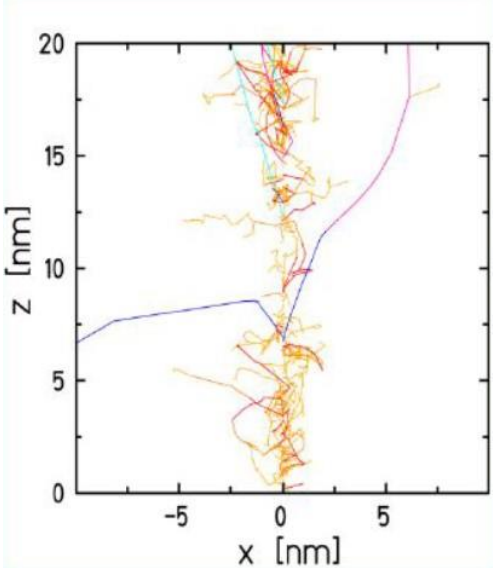
Same dose

High LET
Localized dose depositions

High LET vs Low LET







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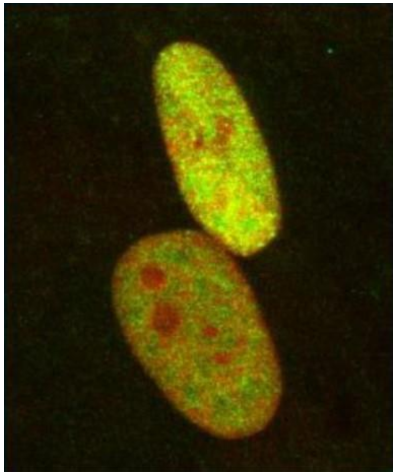

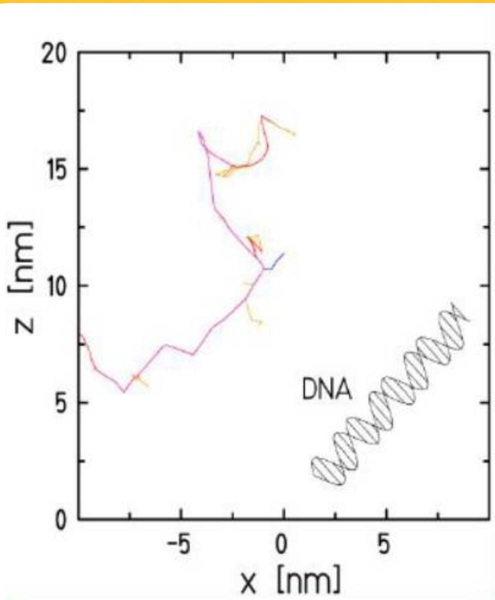

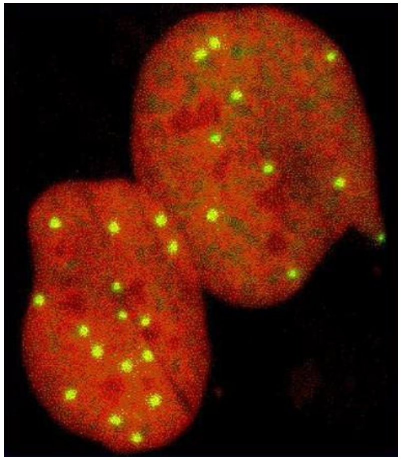

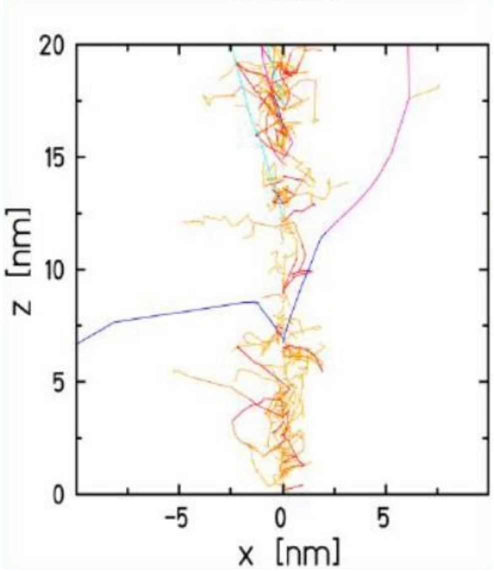

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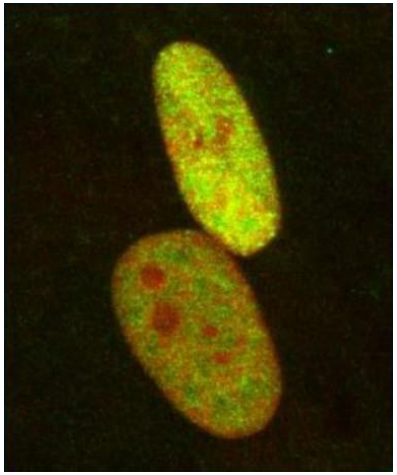
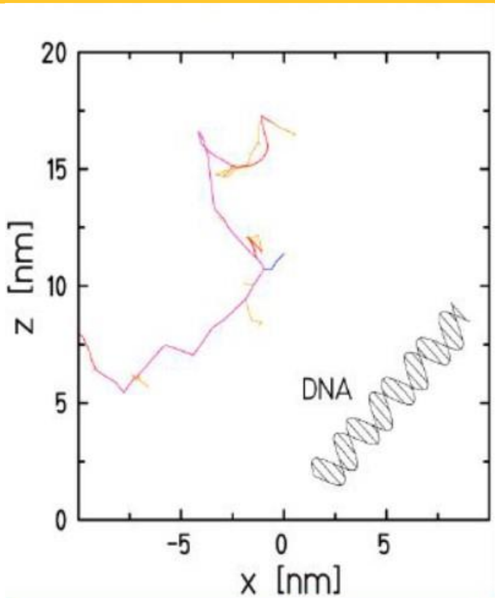
High LET vs Low LET

Spatial distribution of energy deposition





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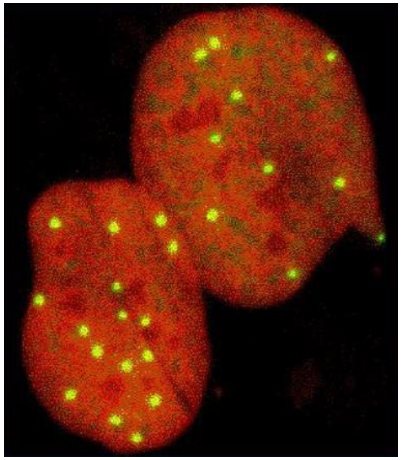
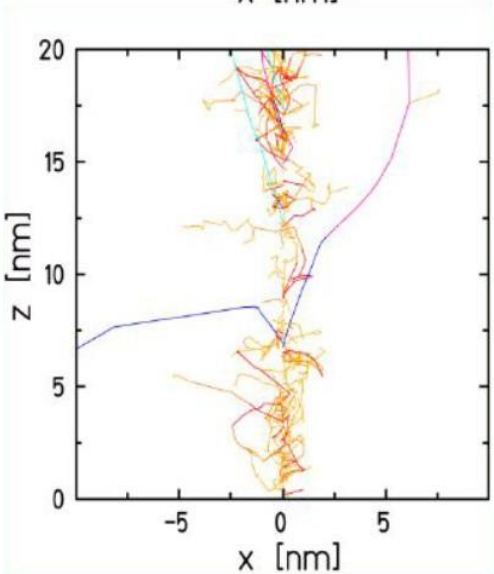
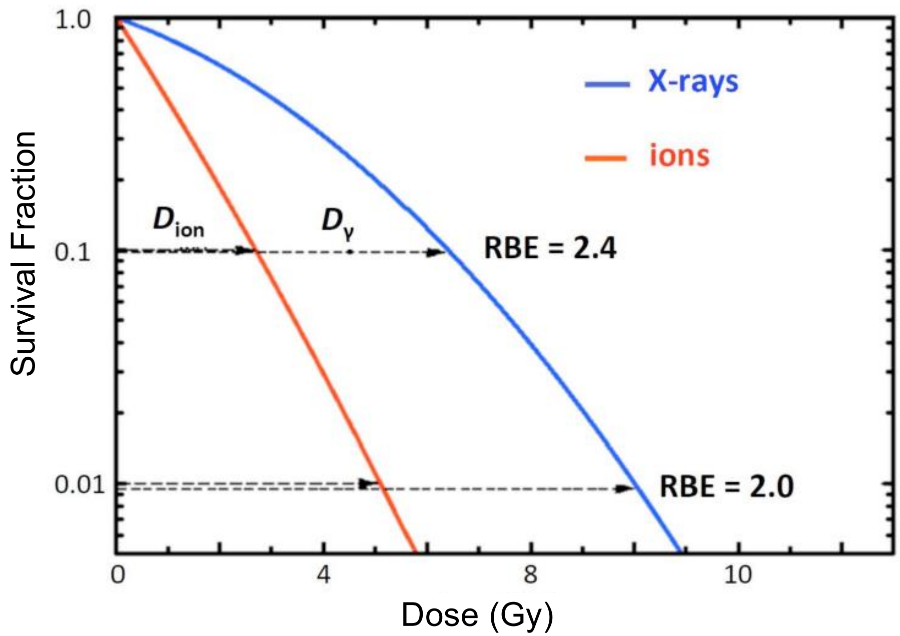




High LET
Localized dose depositions

Linear-Quadratic model

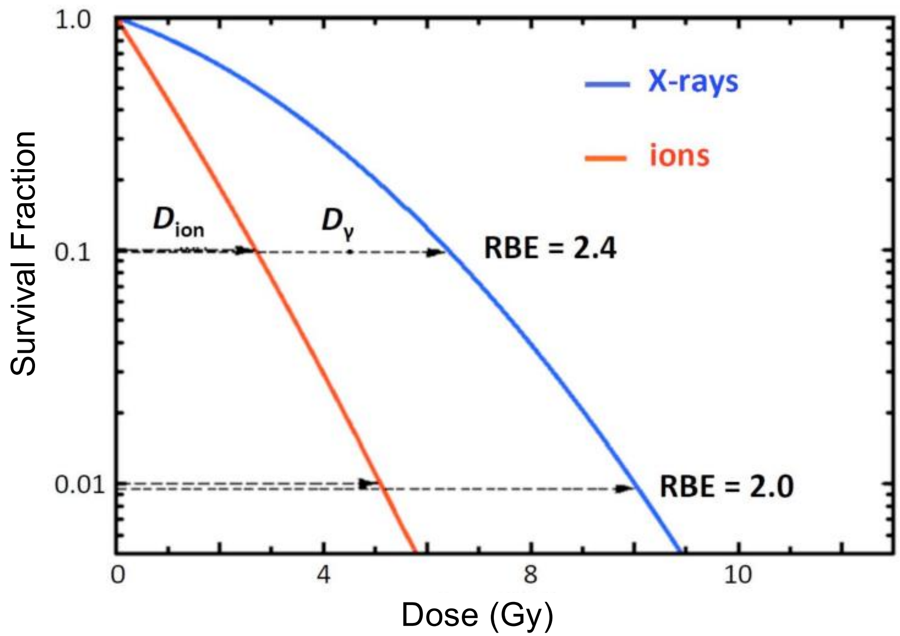


LQ model

- Phenomenological model

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

Linear-Quadratic model



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

- S → Cell survival fraction
- D → Dose delivered
- α and β → Model parameters

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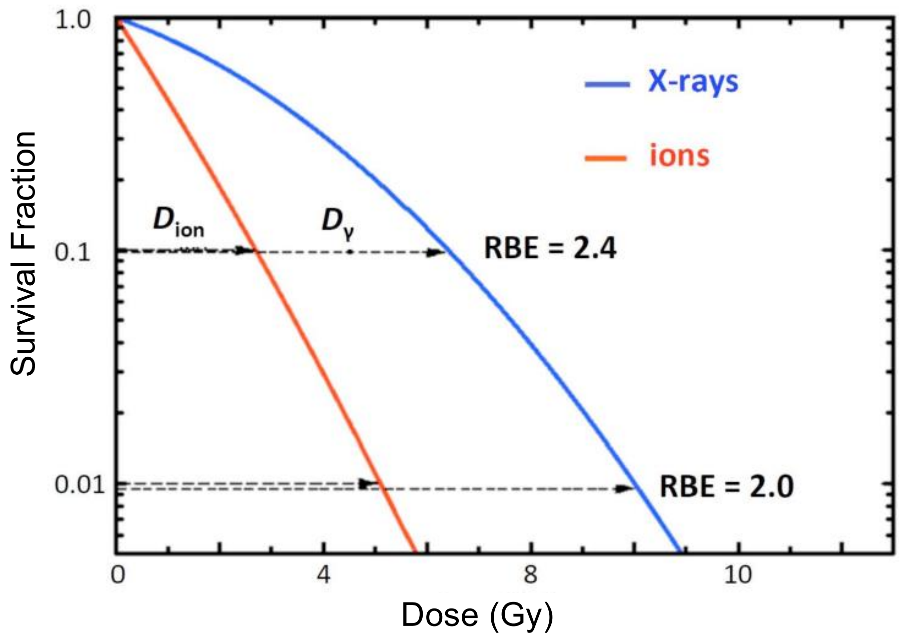

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- Experiments to determine the corresponding α and β

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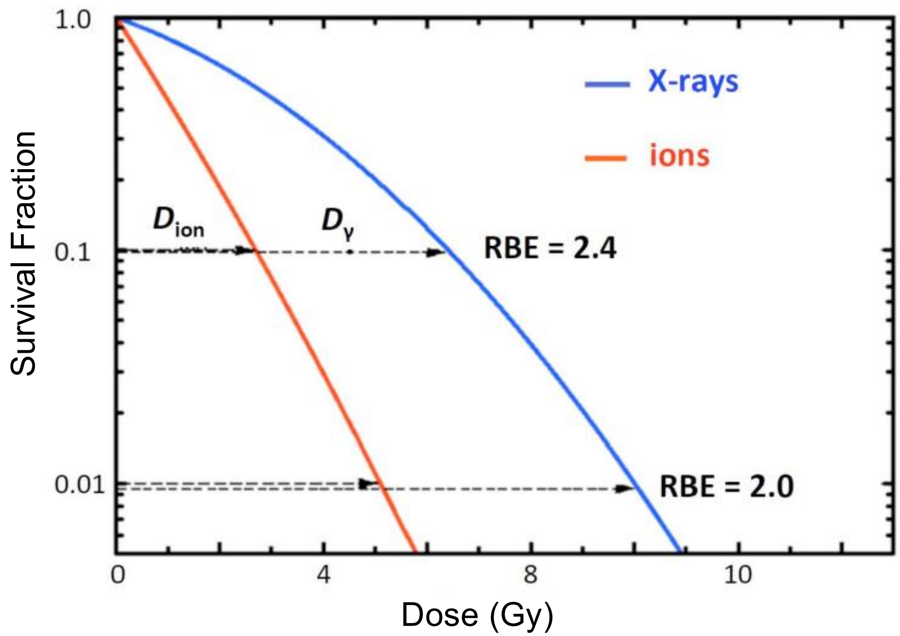

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→ PIDE database

PIDE database

Particle Irradiation Data Ensemble → PIDE

- Publication
- Cell line
- Ion
- Energy
- Irradiation
- α and β

PublicationN	#IonExp	Cells	CellClass	CellOrigin	CellCycle	DNAcontent	PhotonRadia	#PhotonExp	Ion	Charge	IrradiationCc	LET	Energy	ax_paper	bx_paper	ai_paper	bi_paper	ax_fit	bx_fit	ai_fit	bi_fit
hill04	7	xrs5	n	r	a	5.6	250kVp	6	4He	2	m	121	0.815	1.86	0	2.91	0	2.11291568	-0.1457195	3.34740698	-0.7641789
antonelli15	1	AG01522	n	h	G0/G1	6	137Cs	1	12C	6	m	39.4	58	0.816	0	1.025	0	0.68139469	0.02029279	1.02294282	0
antonelli15	2	AG01522	n	h	G0/G1	6	137Cs	1	4He	2	m	125	0.75	0.816	0	2.432	0	0.68139469	0.02029279	2.85020613	-0.3081904
bettega09	1	CGL1	n	h	a	6	15MV	1	12C	6	m	13.8	270	0.22	0.033	0.29	0.023	0.33372574	0.00867069	0.20278827	0.04753559
bettega09	2	CGL1	n	h	a	6	15MV	1	12C	6	m	29.5	100	0.22	0.033	0.35	0.061	0.33372574	0.00867069	0.35104474	0.06137146
bettega09	3	CGL1	n	h	a	6	15MV	1	12C	6	m	172	11.4	0.22	0.033	1.5	0	0.33372574	0.00867069	1.61331024	0
beuve08	1	SCC61	t	h	a	6	250kVp	1	12C	6	m	33.6	72	0.39	0.024	1.08	0	0.35539728	0.03169642	1.0796088	0
beuve08	2	SCC61	t	h	a	6	250kVp	1	12C	6	m	184	9.8	0.39	0.024	2.1	0	0.35539728	0.03169642	2.10269862	0
beuve08	3	SCC61	t	h	a	6	250kVp	1	40Ar	18	m	302	85	0.39	0.024	1.2	0	0.35539728	0.03169642	1.50126785	-0.0887935
beuve08	4	SQ20B	t	h	a	6	250kVp	2	12C	6	m	33.6	72	0.11	0.037	0.76	0	0.06194521	0.0464557	0.56108277	0.04792892
beuve08	5	SQ20B	t	h	a	6	250kVp	2	12C	6	m	184	9.8	0.11	0.037	1	0	0.06194521	0.0464557	1.24833612	-0.0692007
beuve08	6	SQ20B	t	h	a	6	250kVp	2	40Ar	18	m	302	85	0.11	0.037	0.85	0	0.06194521	0.0464557	0.84593707	0
britten13	1	HEP2	t	h	a	6	120kVp	1	1H	1	s	5.3	8.6	0.143	0.038	0.166	0.058	0.25433987	0.02479154	0.23085135	0.04610895
britten13	2	HEP2	t	h	a	6	120kVp	1	1H	1	s	9	4.4	0.143	0.038	0.286	0.044	0.25433987	0.02479154	0.40500346	0.02117841
britten13	3	HEP2	t	h	a	6	120kVp	1	1H	1	s	20.5	1.4	0.143	0.038	0.598	0.017	0.25433987	0.02479154	0.40757012	0.04683074
britten13	4	HEP2	t	h	a	6	120kVp	1	1H	1	s	28.8	0.9	0.143	0.038	0.555	0.053	0.25433987	0.02479154	0.69364389	0.02336518
britten13	5	HEP2	t	h	a	6	120kVp	1	1H	1	s	7.8	5.3	0.143	0.038	0.344	0.044	0.25433987	0.02479154	0.34525502	0.04304484
britten13	6	HEP2	t	h	a	6	120kVp	1	1H	1	s	11	3.4	0.143	0.038	0.385	0.051	0.25433987	0.02479154	0.40231782	0.04466961
britten13	7	HEP2	t	h	a	6	120kVp	1	1H	1	s	13.6	2.55	0.143	0.038	0.372	0.063	0.25433987	0.02479154	0.27895059	0.07984758
britten13	8	V79	n	r	a	5.6	120kVp	2	1H	1	s	5.3	8.6	0.016	0.032	0.024	0.033	0.13740027	0.02122937	0.12622784	0.02148078
britten13	9	V79	n	r	a	5.6	120kVp	2	1H	1	s	20.5	1.4	0.016	0.032	0.018	0.048	0.13740027	0.02122937	0.05749853	0.04265964
britten13	10	V79	n	r	a	5.6	120kVp	2	1H	1	s	28.8	0.9	0.016	0.032	0.016	0.033	0.13740027	0.02122937	0.07972964	0.06301455
chaudhary14	1	AG01522	n	h	a	6	225kVp	1	1H	1	m	1.11	59	0.54	0.062	0.75	0.119	0.6630973	0.08042955	0.74970579	0.11668335
chaudhary14	2	AG01522	n	h	a	6	225kVp	1	1H	1	m	4.02	10.8	0.54	0.062	1.02	0.061	0.6630973	0.08042955	1.00824637	0.08213811
chaudhary14	3	AG01522	n	h	a	6	225kVp	1	1H	1	m	7	6	0.54	0.062	1.29	0.041	0.6630973	0.08042955	1.36087072	0
chaudhary14	4	AG01522	n	h	a	6	225kVp	1	1H	1	m	11.9	3.05	0.54	0.062	1.7	0.079	0.6630973	0.08042955	1.82658577	-0.083903
chaudhary14	5	AG01522	n	h	a	6	225kVp	1	1H	1	m	18	1.7	0.54	0.062	1.87	0.074	0.6630973	0.08042955	1.87616655	0
chaudhary14	6	AG01522	n	h	a	6	225kVp	1	1H	1	m	22.6	1.25	0.54	0.062	2.43	0.057	0.6630973	0.08042955	2.48285957	-0.0795186
chaudhary14	7	AG01522	n	h	a	6	225kVp	1	1H	1	s	1.2	53	0.54	0.062	0.66	0.117	0.6630973	0.08042955	0.64552124	0.11736545
chaudhary14	8	AG01522	n	h	a	6	225kVp	1	1H	1	s	2.6	20.3	0.54	0.062	0.89	0.075	0.6630973	0.08042955	0.89376021	0.06918997
chaudhary14	9	AG01522	n	h	a	6	225kVp	1	1H	1	s	4.5	10.6	0.54	0.062	1.15	0.047	0.6630973	0.08042955	1.17843442	0.03928049
chaudhary14	10	AG01522	n	h	a	6	225kVp	1	1H	1	s	13.4	2.6	0.54	0.062	1.36	0.037	0.6630973	0.08042955	1.31730854	0.05362292
chaudhary14	11	AG01522	n	h	a	6	225kVp	1	1H	1	s	21.7	1.32	0.54	0.062	1.61	0.023	0.6630973	0.08042955	1.65626054	0
chaudhary14	12	AG01522	n	h	a	6	225kVp	1	1H	1	s	25.9	1.02	0.54	0.062	2.01	0.011	0.6630973	0.08042955	2.28155706	-0.1290816
chaudhary14	13	U-87	t	h	a	6	225kVp	2	1H	1	m	1.11	59	0.11	0.06	0.14	0.064	0.10635298	0.05565753	0.17299533	0.0559509

Microdosimetry - MKM

- Biological effect can be determined by the energy deposited into critical cell structures: **domains**

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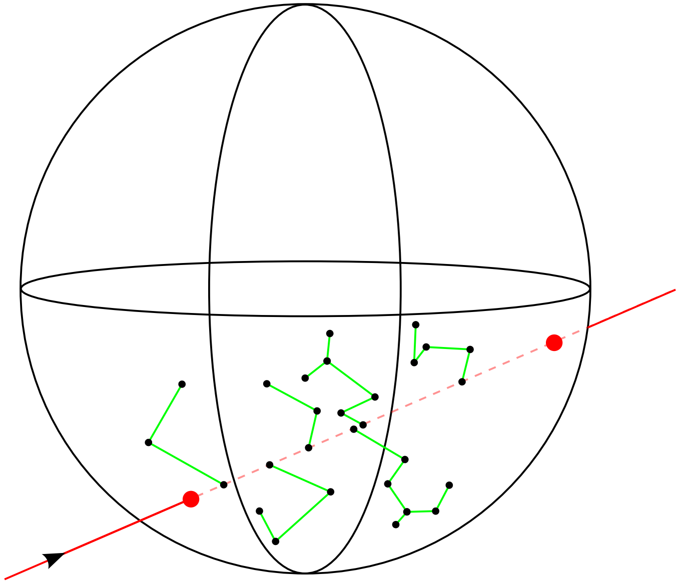

Domain volume

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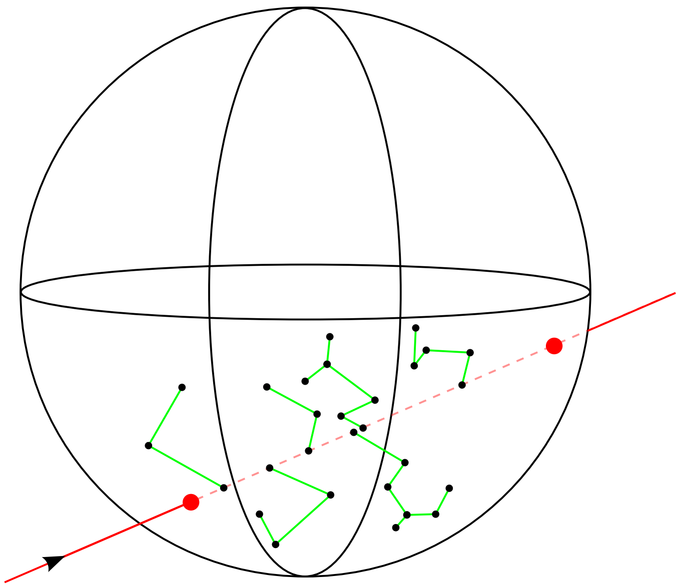

Domain volume

- The domain size is associated with the maximum distance two SSB may become DSB

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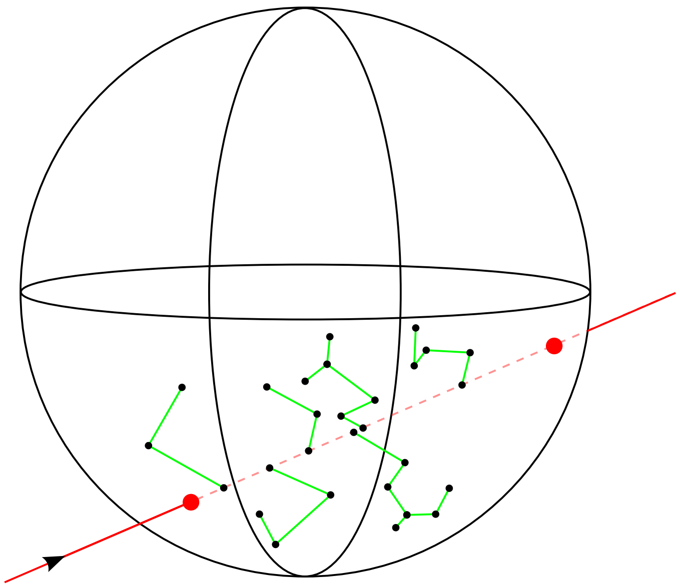
- **Lineal energy** $y_D = \frac{\epsilon}{\bar{l}}$ → Energy absorbed → Mean chord length



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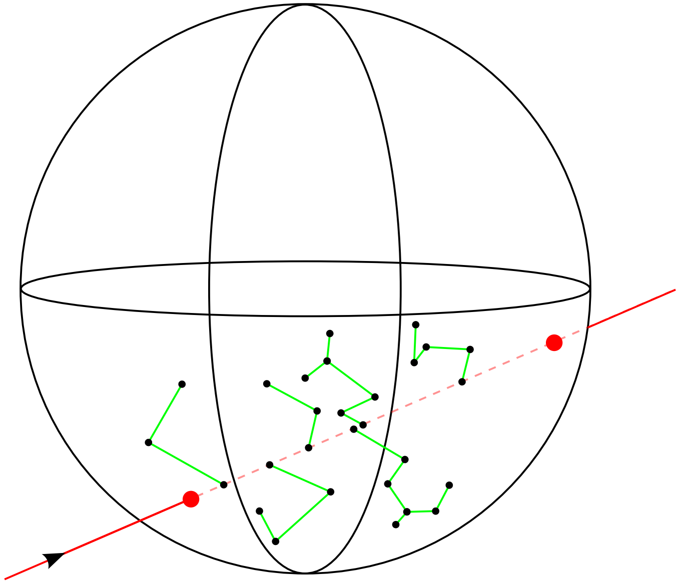
Microdosimetric kinetic model



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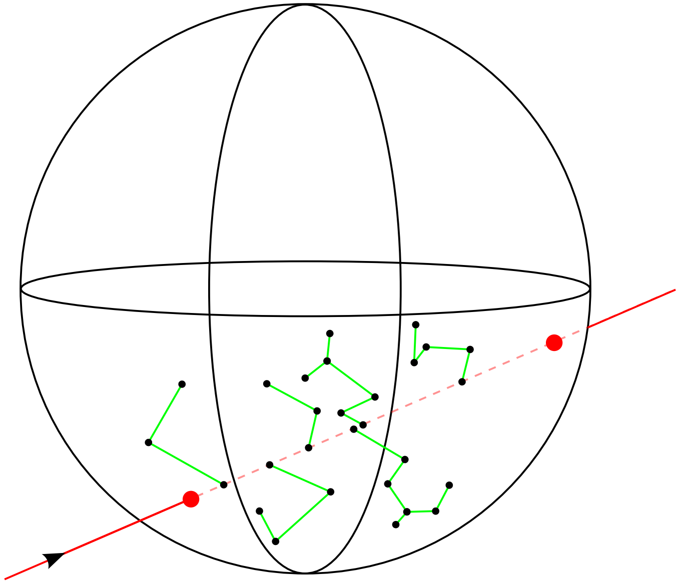
Microdosimetric kinetic model

$$\alpha_{\text{ion}} = \frac{1 - \exp\left[-\left(\alpha_0 + \beta \frac{y_D}{\rho \pi r_d^2}\right) \frac{y_D}{\rho \pi r_n^2}\right]}{\frac{y_D}{\rho \pi r_n^2}}$$



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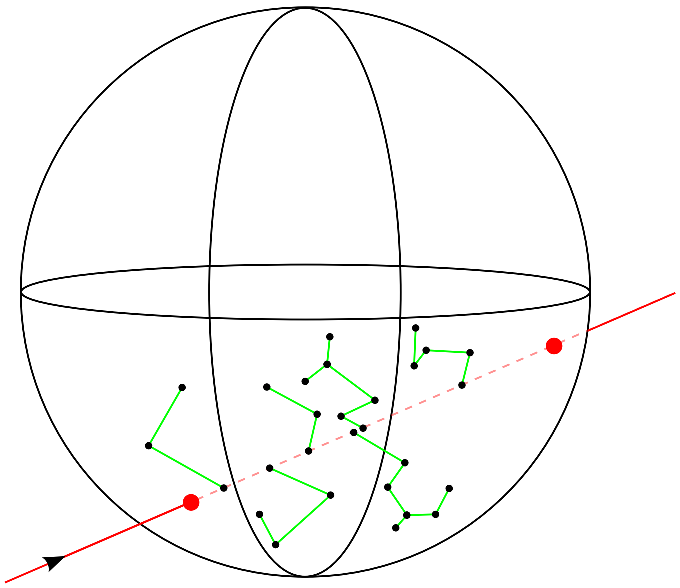

Microdosimetric kinetic model

$$\alpha_{\text{ion}} = \frac{1 - \exp\left[-(\alpha_0 + \beta\frac{y_D}{\rho\pi r_d^2})\frac{y_D}{\rho\pi r_n^2}\right]}{\frac{y_D}{\rho\pi r_n^2}}$$

- Photons parameters α_0 β
- Nucleus radius r_n
- Domain radius r_d

Domain volume

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Domain radius

- Assumption of fixed domain radius based on human salivary glands (HSG)

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$$\alpha_{\mathrm{ion}} = \frac{1 - \exp\left[-(\alpha_0 + \beta \frac{y_D}{\rho\pi r_d^2}) \frac{y_D}{\rho\pi r_n^2}\right]}{\frac{y_D}{\rho\pi r_n^2}} \Rightarrow r_d = \frac{\beta\left(\frac{y_D}{\rho\pi r_n}\right)^2}{-\log\left(1 - \alpha_{\mathrm{ion}}\frac{y_D}{\rho\pi r_n^2}\right) - \alpha_0 \frac{y_D}{\rho\pi r_n^2}}$$

Domain radius

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$$\alpha_{\text{ion}} = \frac{1 - \exp\left[-(\alpha_0 + \beta \frac{y_D}{\rho \pi r_d^2}) \frac{y_D}{\rho \pi r_n^2}\right]}{\frac{y_D}{\rho \pi r_n^2}} \Rightarrow r_d = \frac{\beta \left(\frac{y_D}{\rho \pi r_n}\right)^2}{-\log\left(1 - \alpha_{\text{ion}} \frac{y_D}{\rho \pi r_n^2}\right) - \alpha_0 \frac{y_D}{\rho \pi r_n^2}}$$

PIDE database

Domain radius

- Assumption of fixed domain radius based on human salivary glands (HSG) ⇨ $r_d = 320\ \mathrm{nm}$

$$\alpha_{\text{ion}} = \frac{1 - \exp\left[-\left(\alpha_0 + \beta \frac{y_D}{\rho\pi r_d^2}\right)\frac{y_D}{\rho\pi r_n^2}\right]}{\frac{y_D}{\rho\pi r_n^2}} \Rightarrow r_d = \frac{\beta\left(\frac{y_D}{\rho\pi r_n}\right)^2}{-\log\left(1 - \alpha_{\text{ion}}\frac{y_D}{\rho\pi r_n^2}\right) - \alpha_0\frac{y_D}{\rho\pi r_n^2}}$$

PIDE database → p, α and carbon ions experiments

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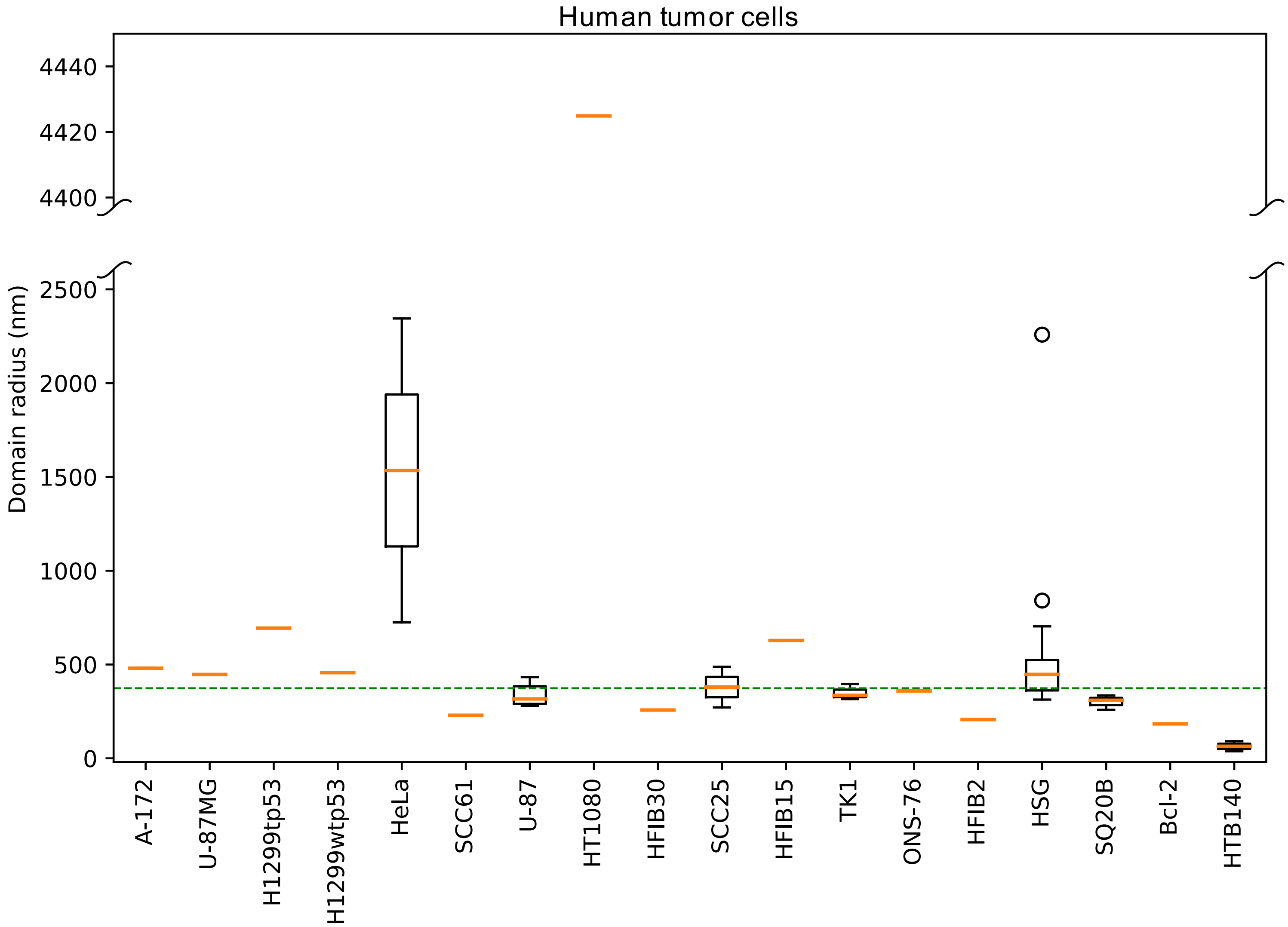
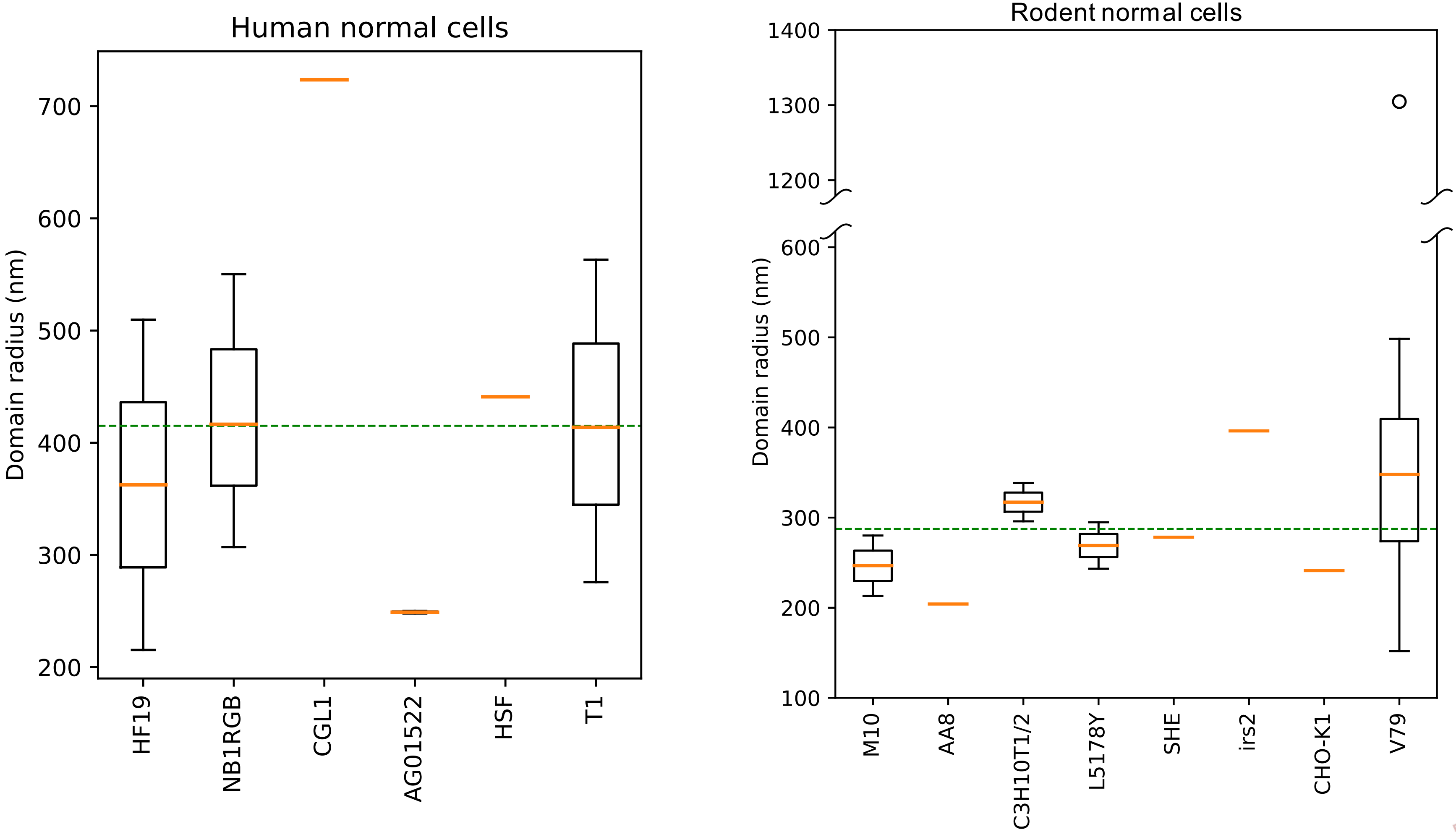
PIDE database → p, α and carbon ions experiments → Calculating domain radius

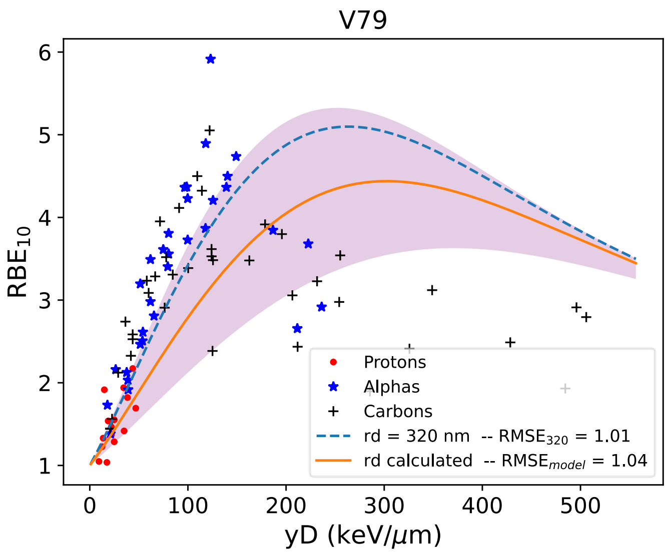
Domain size distributions

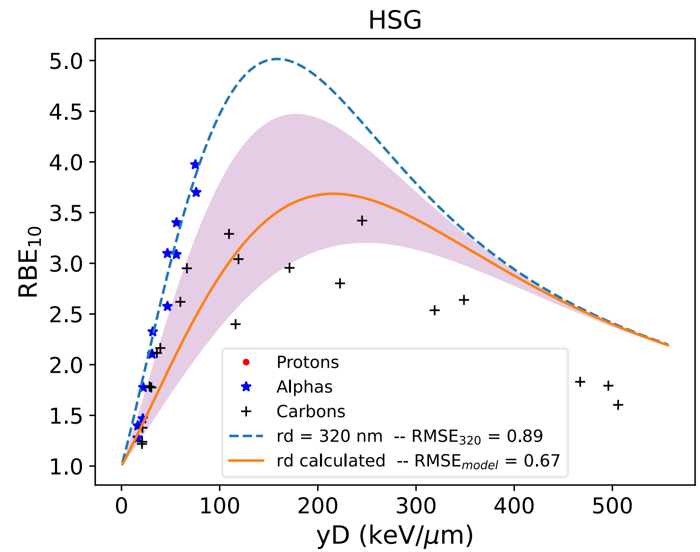


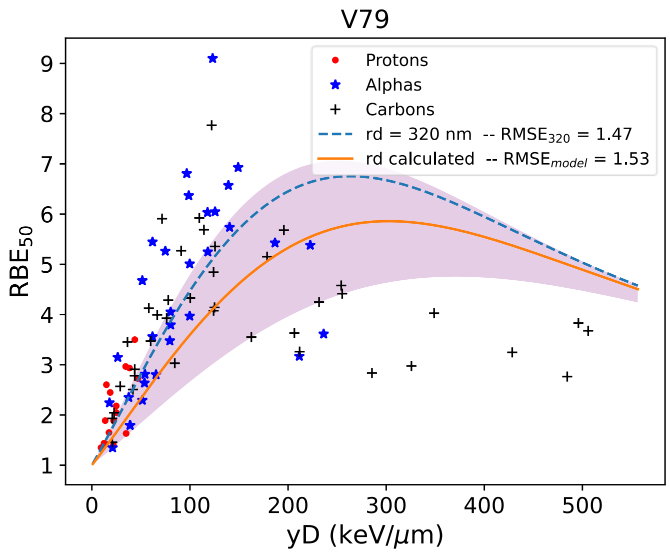
Domain size distributions

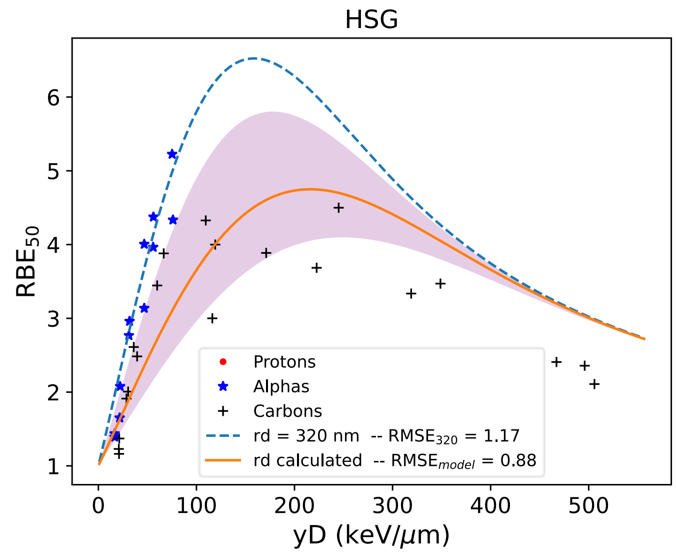


Impact of domain size on RBE









Conclusions

- This determination represents an approach to include further information on the cell line-specific radiosensitivity.
- Our results showed large variability among different cell lines, illustrating the importance of intrinsic response to radiation of different biological systems when determining RBE.

Future…

- Robust clonogenic assays for cell lines would be required to improve and expand a domain radius database.

Acknowledgments

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