The „UNIfied and VERSetile bio response Engine“ - UNIVERSE

Dr. H. Liew, Prof. Dr. A. Mairani

- UNIVERSE: multipurpose mechanistic modelling framework of radiation action
- **Goal:** **Translating** the action of **“effect-modifiers”** (e.g., DNA damage inhibition) from readily available **photon data to charged particle scenarios**

The „UNIfied and VERSetile bio response Engine“ - UNIVERSE

Open Access Article

Modeling the Effect of Hypoxia and DNA Repair Inhibition on Cell Survival after Photon Irradiation

by Hans Liew [1,2,3,4,5,6], Carmen Klein [2,3,4,5], Frank T. Zenke [7], Amir Abdollahi [2,3,4,5], Jürgen Debus [1,2,3,4,5,6], Ivana Dokic [2,3,4,5,*,†] and Andrea Mairani [2,3,4,5,*,†]

International Journal of Radiation Oncology • Biology • Physics ASTRO

Physics Contribution

Deciphering Time-Dependent DNA Damage Complexity, Repair, and Oxygen Tension: A Mechanistic Model for FLASH-Dose-Rate Radiation Therapy

Hans Liew, MSc,[*,†,‡,§,‖] Stewart Mein, PhD,[*,†,‡,§] Ivana Dokic, PhD,[*,†,‡,§] Thomas Haberer, PhD,[¶] Jürgen Debus, MD, PhD,[†,§,‖,¶,#] Amir Abdollahi, MD, PhD,[*,†,‡,§] and Andrea Mairani, PhD[#,**]

Open Access Article

Modeling Direct and Indirect Action on Cell Survival After Photon Irradiation under Normoxia and Hypoxia

by Hans Liew [1,2,3,4,5,6], Stewart Mein [2,3,4,5], Jürgen Debus [1,2,3,4,5,6], Ivana Dokic [2,3,4,5] and Andrea Mairani [2,3,4,5,*]

Combined DNA Damage Repair Interference and Ion Beam Therapy: Development, Benchmark and Clinical Implications of a Mechanistic Biological Model

Hans Liew, MSc ** • Sarah Meister, MSc • Stewart Mein, PhD • ... Jürgen Debus, MD, PhD • Ivana Dokic, PhD • Andrea Mairani, PhD • Show all authors • Show footnotes

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Impact of DNA Repair Kinetics and Dose Rate on RBE Predictions in the UNIVERSE

by Hans Liew [1,2,3,4,5,6], Stewart Mein [2,3,4,5], Thomas Tessonnier [5], Christian P. Karger [3,7], Amir Abdollahi [2,3,4,5], Jürgen Debus [1,2,3,4,5,6], Ivana Dokic [2,3,4,5] and Andrea Mairani [2,3,4,5,*]

International Journal of Molecular Sciences MDPI

Article

The Impact of Sub-Millisecond Damage Fixation Kinetics on the In Vitro Sparing Effect at Ultra-High Dose Rate in UNIVERSE

Hans Liew [1,2,3,4,5,6], Stewart Mein [2,3,4,5], Thomas Tessonnier [5], Amir Abdollahi [2,3,4,5], Jürgen Debus [1,2,3,4,5,6], Ivana Dokic [2,3,4,5] and Andrea Mairani [2,3,4,5,*]

Open Access Article

Do We Preserve Tumor Control Probability (TCP) in FLASH Radiotherapy? A Model-Based Analysis

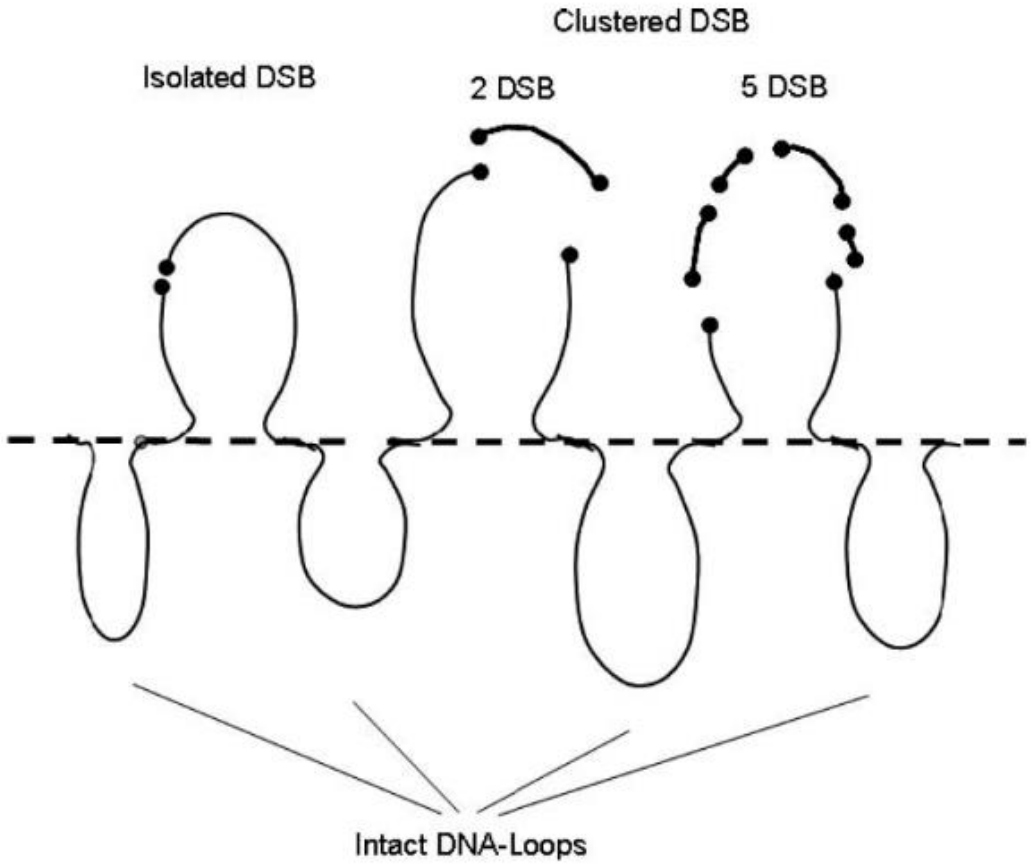
by Hans Liew [1,2,3], Stewart Mein [1,2,3,4], Thomas Tessonnier [5], Amir Abdollahi [1,2,3], Jürgen Debus [2,3,6,7], Ivana Dokic [1,2,3] and Andrea Mairani [5,8,*]

Building blocks of the UNIVERSE – Giant Loops

Giant Loops:
Chromatin substructure containing ≈ 2 Mbp, with either side attached to a backbone

Isolated DSB (iDSB):
- **one DSB** inside loop
- associated with **fast repair kinetics**

Clustered/Complex DSB (cDSB):
- **two or more DSB** inside loop
- associated with **slow repair kinetics**
- associated with **high risk of chromatin loss**



Adapted from Friedrich et al. 2012 and Yokota et al. 1995

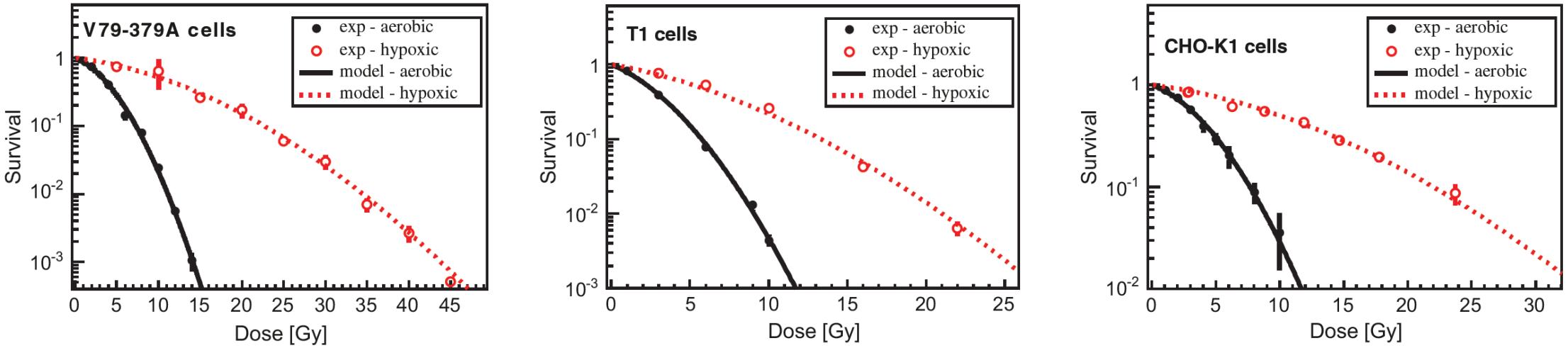
Survival in the UNIVERSE

1. Subdivide nucleus into **domains of ≈ 2 Mbp** (Giant Loops)
2. Simulate number of **isolated and complex DSB** (N_{iDSB} and N_{cDSB})
3. Associate DSBs with **inactivation probabilities** (K_{iDSB} and K_{cDSB})
4. Calculate the **Survival Fraction** following:

$$S = (1 - K_{iDSB})^{N_{iDSB}} \cdot (1 - K_{cDSB})^{N_{cDSB}}$$

Oxygen Status and Reference Radiation Quality in the UNIVERSE

Adapted from Mairani et al. 2013



Survival after irradiation with **photons under hypoxia** can be described by **reducing the total number of induced DSB** by a **hypoxia reduction factor** (**HRF**) while ***keeping*** K_{iDSB} ***and*** K_{cDSB} ***constant***!

The HRF resembles the **Oxygen Enhancement Ratio (OER)**

Radiation Quality:

Low Energy Photons (e.g. X-rays) and **High Energy Photons** (e.g. LINAC)/**Electrons** induce **different amounts of DSB per unit dose** (yield)

Effect **directly considered** using RBE_{DSB} from the literature as yield modifying factor.

A FLASH in the UNIVERSE?

- A search for „**FLASH radiotherapy**“ using *Google Scholar* finds ~**14.000 results** published **since 2014**

- Wide range of **biological endpoints, radiation qualities, doses, dose-rates** and **environmental oxygen levels** employed complicate clear characterization

- **UNIVERSE** can model their impact and **aid development, experimentation** and **assessment** of **FLASH** and other dose-rate effects

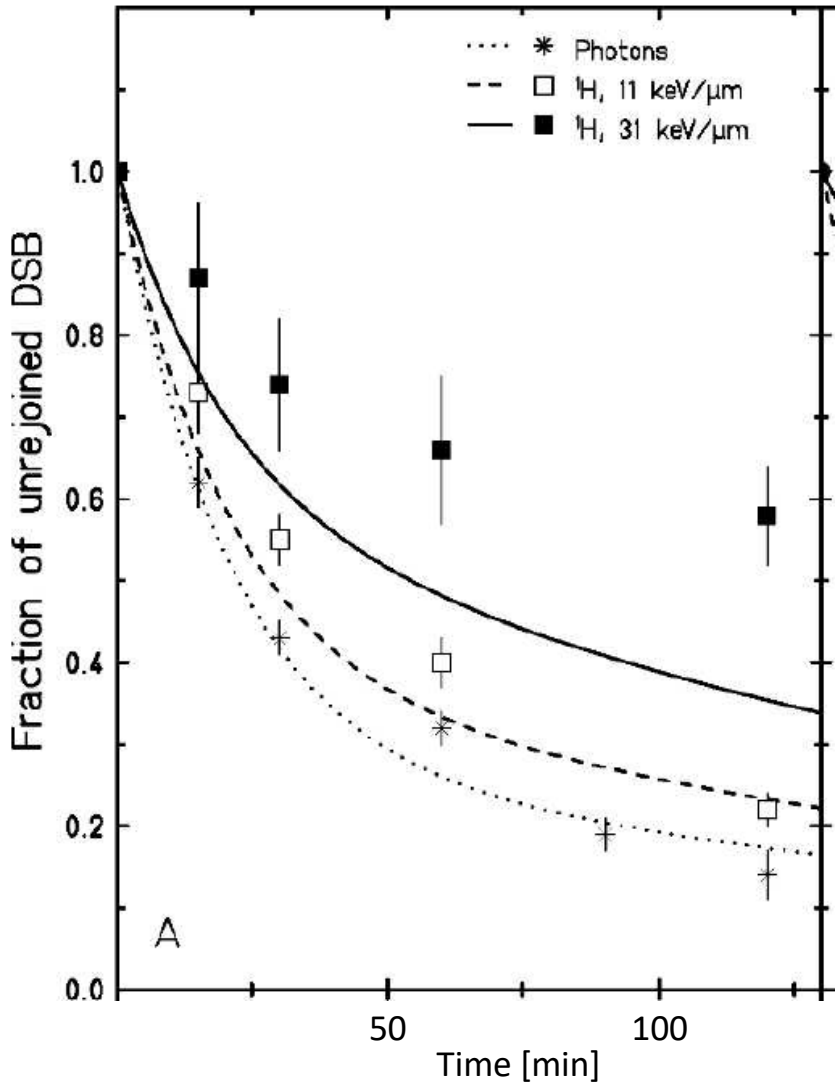
- Development of a time-dependent **dynamic UNIVERSE**

Dose-Rate: Repair

- Rejoining-Kinetics of DSB can be described by **double-exponential decay** (fast and slow component)

- Tommasino et al. succesfully predicted ratio of fast and slow component by associating N_{iDSB} **with fast and** N_{cDSB} **with slow** repair

- $\tau_{iDSB} \sim minutes$
- $\tau_{cDSB} \sim hours$



Taken from Tommasino 2013

Dose-Rate: Radiolytic Oxygen Depletion

Time-dependent oxygen level O(t) *as suggested by Petersson et al. 2020*

- $\frac{dO}{dt} = -g\,\dot{D}\,O(t)$ **oxygen depletion** *g: depletion rate constant (0.053 Gy^{-1})*
- $\frac{dO}{dt} = \lambda\,(O_{env} - O(t))$ **re-oxygenation** *λ : oxygen recovery rate (1 s^{-1})*

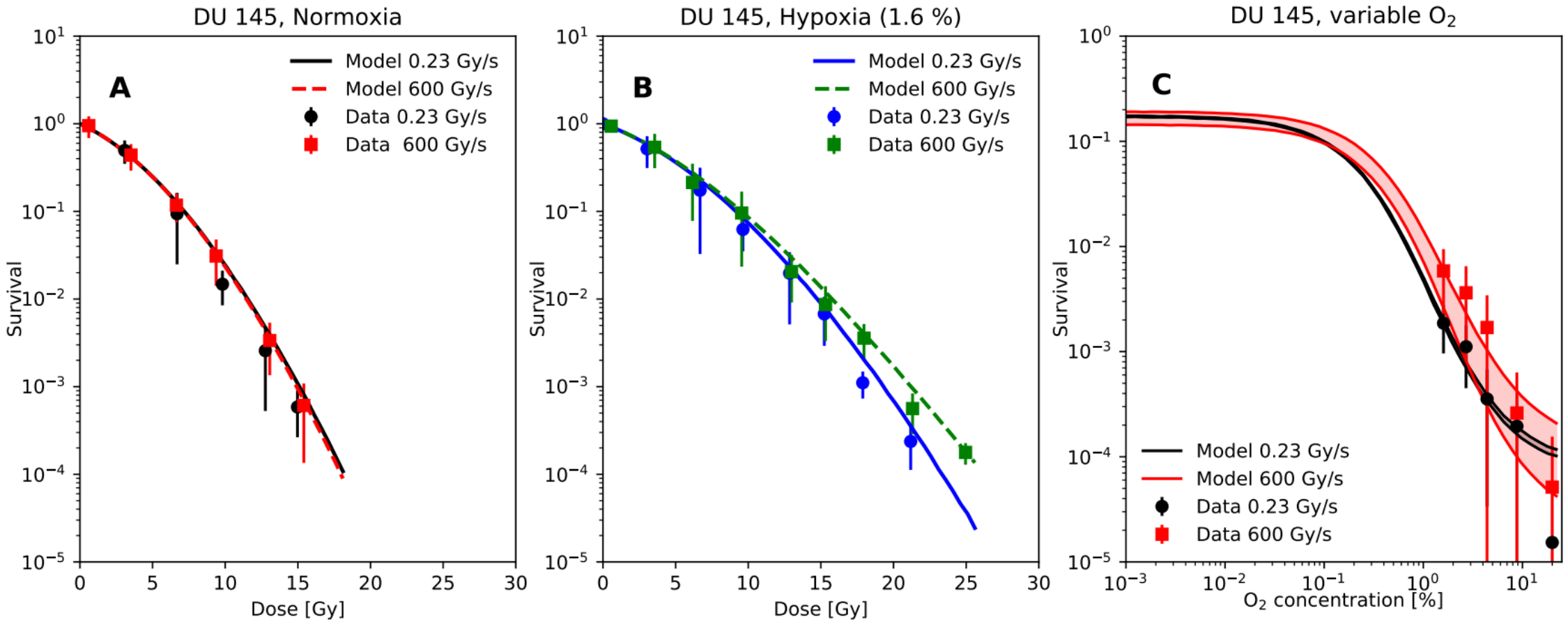
O_{env} : environmental oxygen level

→ $\frac{dO}{dt} = -g\,\dot{D}\,O(t) + \lambda\,(O_{env} - O(t))$

→ $O(t) = O_{env}\left(\frac{\lambda}{\gamma} + \left(1 - \frac{\lambda}{\gamma}\right)e^{-\gamma t}\right)$ *with: $\gamma = g\dot{D} + \lambda$*

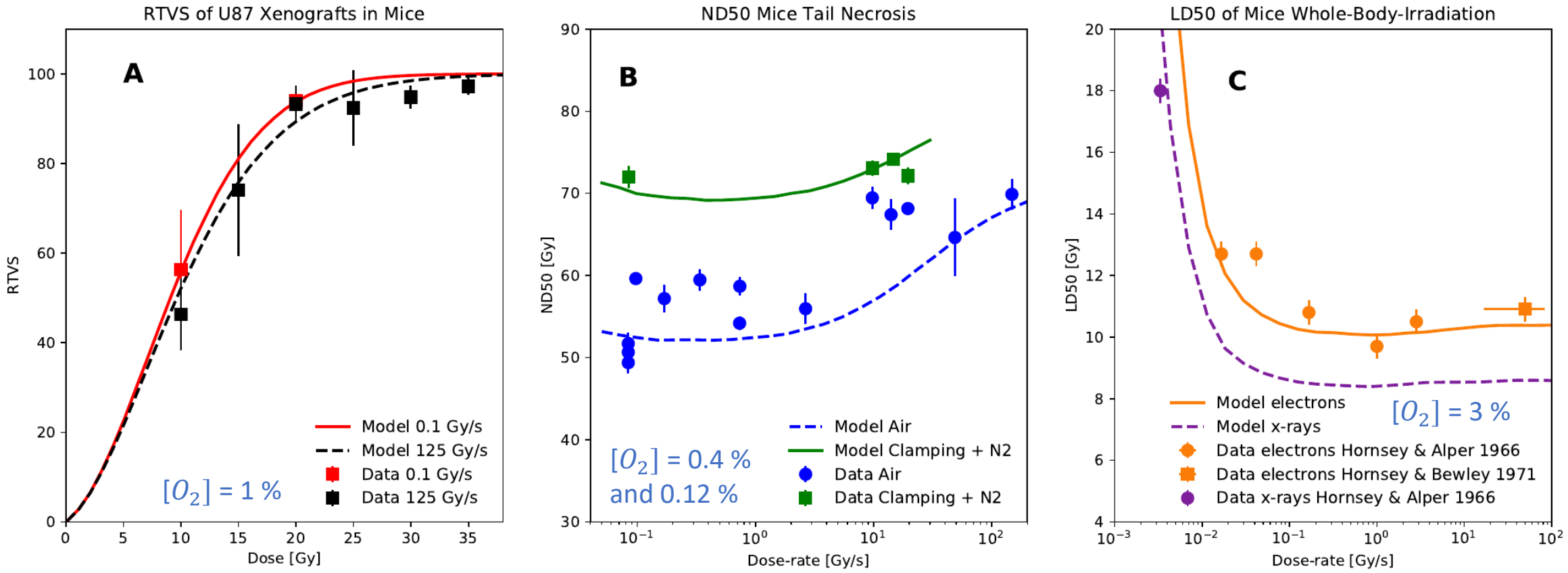
→ $HRF(t) = \frac{K + mO(t)}{K + O(t)}$ *m = 3.1 K = 0.27*

UNIVERSE predicts in vitro data (Adrian et al. 2019)



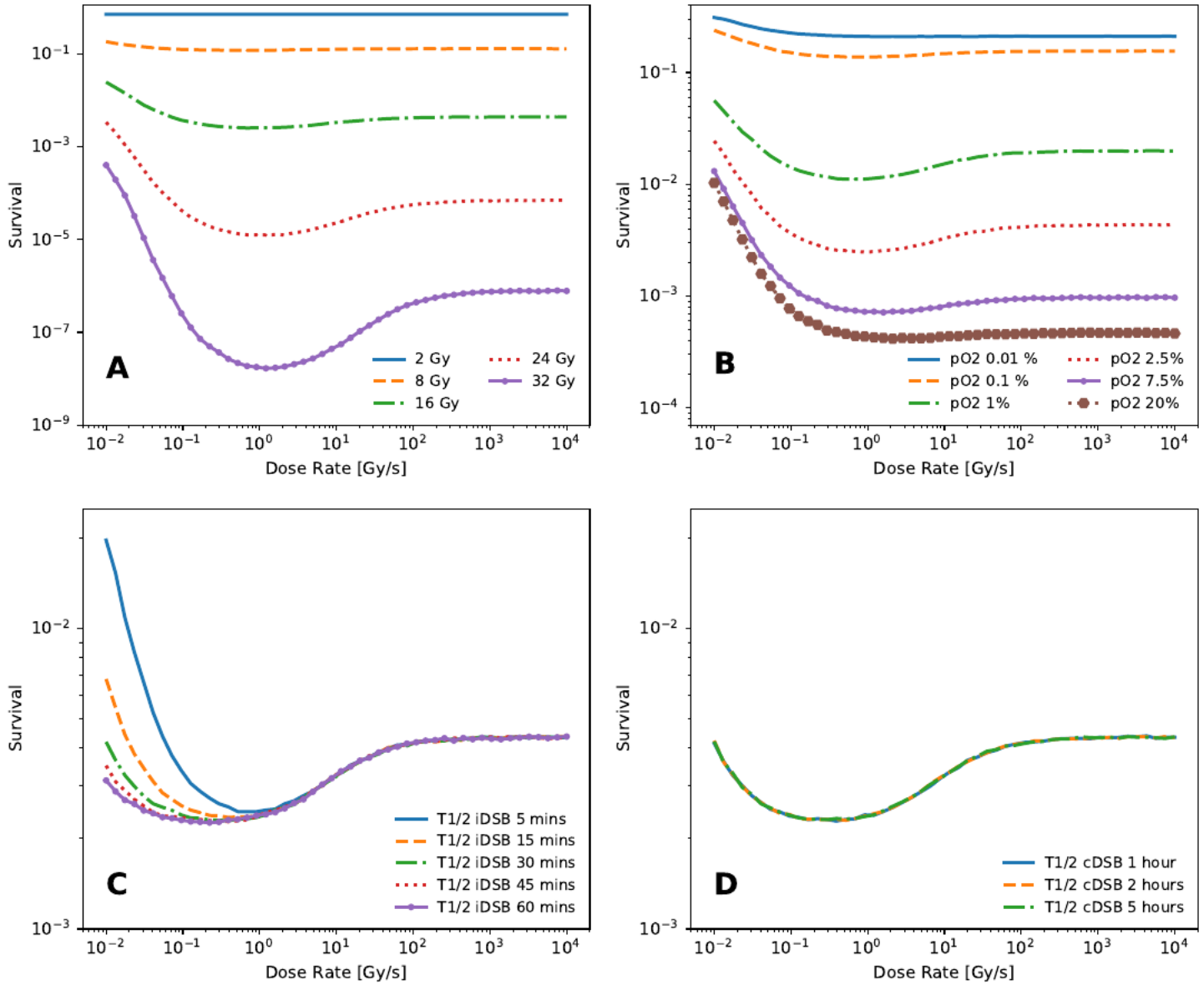
DU145 survival after irradiation with conventional (0.23 Gy/s) and high dose-rate (600 Gy/s) of 10 MeV electron radiation under normoxia (20% O2) (A), hypoxia (1.6% O2) (B) and different oxygen levels at 18 Gy (C) taken from Adrian 2019. Lethality parameters fitted to high dose-rate data under normoxia. Repair half-life times taken from literature [El-Awady 2003].

UNIVERSE predicts in vivo data



(A) **Relative Tumor Volume Suppression** of U87 xenografts in mice, after irradiation with 5-6 MeV electrons at 0.1 Gy/s (red) and 125 Gy/s (black) [Bourhis 2019]
(B) **ND50** of mice tail necrosis over dose-rates of 10 MeV electrons in oxygenated (blue) and anoxic environment (green: N2 + clamping of tail) [Hendry 1982]
(C) **LD50** after whole-body-irradiation of mice with either 250kV x-rays (purple) or ~8 MeV electrons (orange) over a range of dose-rates [Hornsey 1966+1971]

FLASH dependencies in UNIVERSE



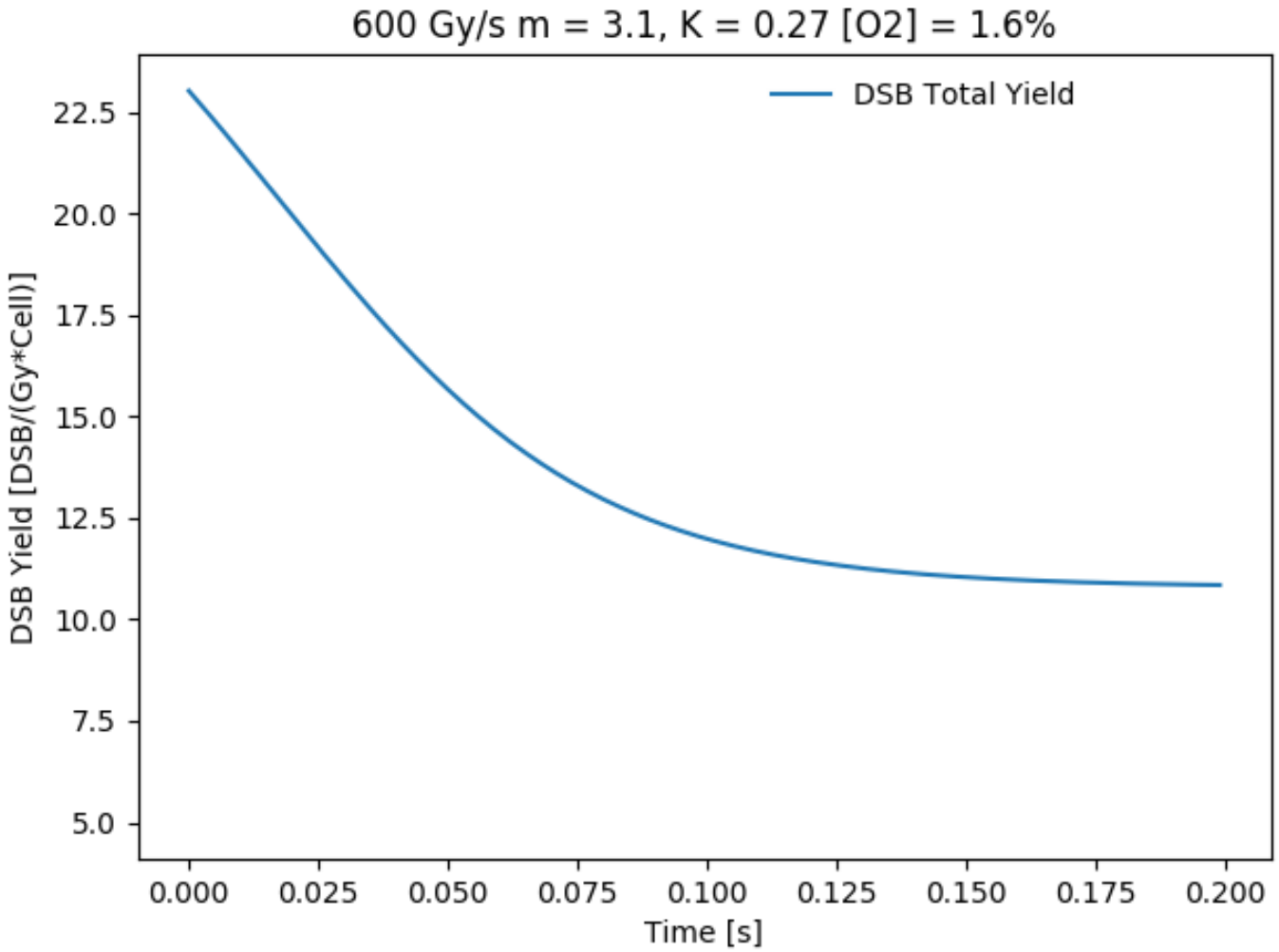
Impact of

A: Dose
B: Environmental Oxygen Level
C: Repair Half Life of iDSB
D: Repair Half Life of cDSB

Fixed Values

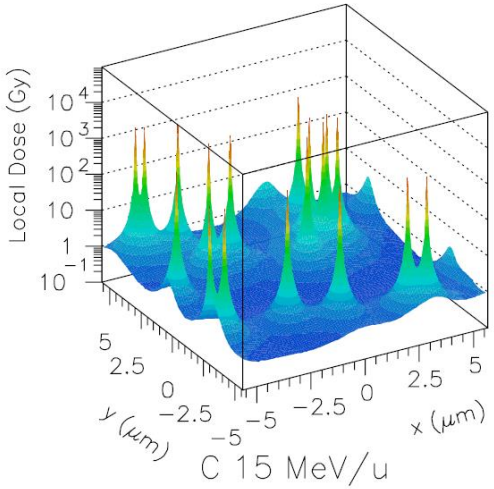
Dose: 16 Gy
$[O_2]$: 2.5 %
$T_{iDSB}^{1/2}$ = 30 minutes
$T_{cDSB}^{1/2}$ = 5 hours

Oxygen Depletion or Nothing?

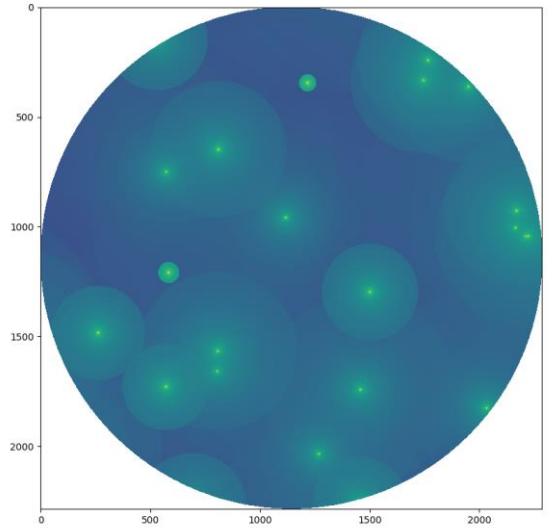


- **Any mechanism** that reproduces the **same DSB yield kinetics** would produce **identical results**
- Possibly a connection to **indirect damage** that is susceptible to **radio-chemical** mechanisms?
- Also **subpopulations** would be possible to implement using **sampling**

Core of the UNIVERSE

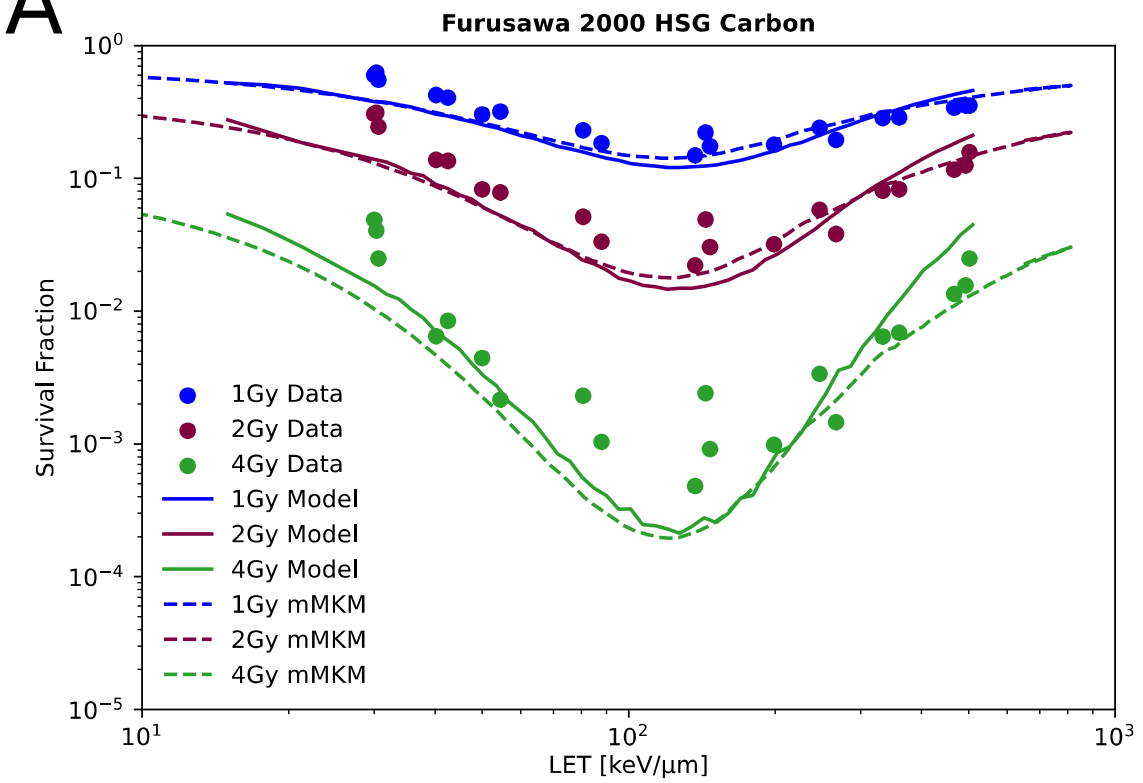


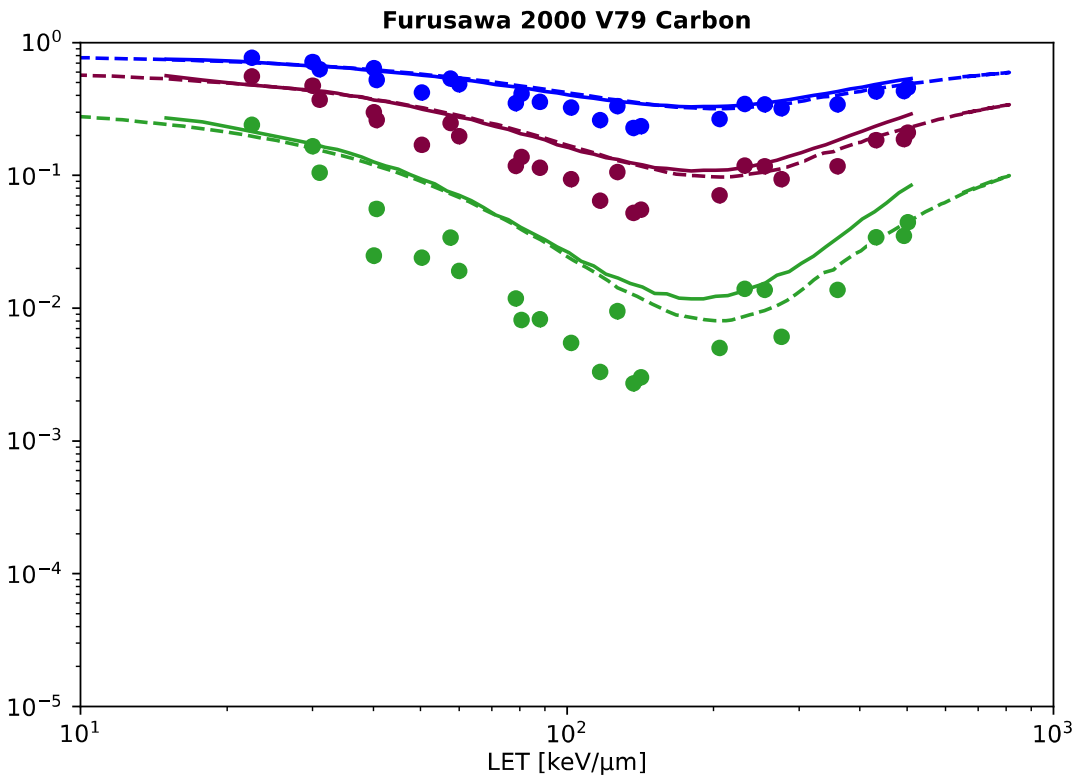
Simulation of Dose on GPU



Cell Survival as function of LET for clinical relevant dose levels : HSG and V79

A





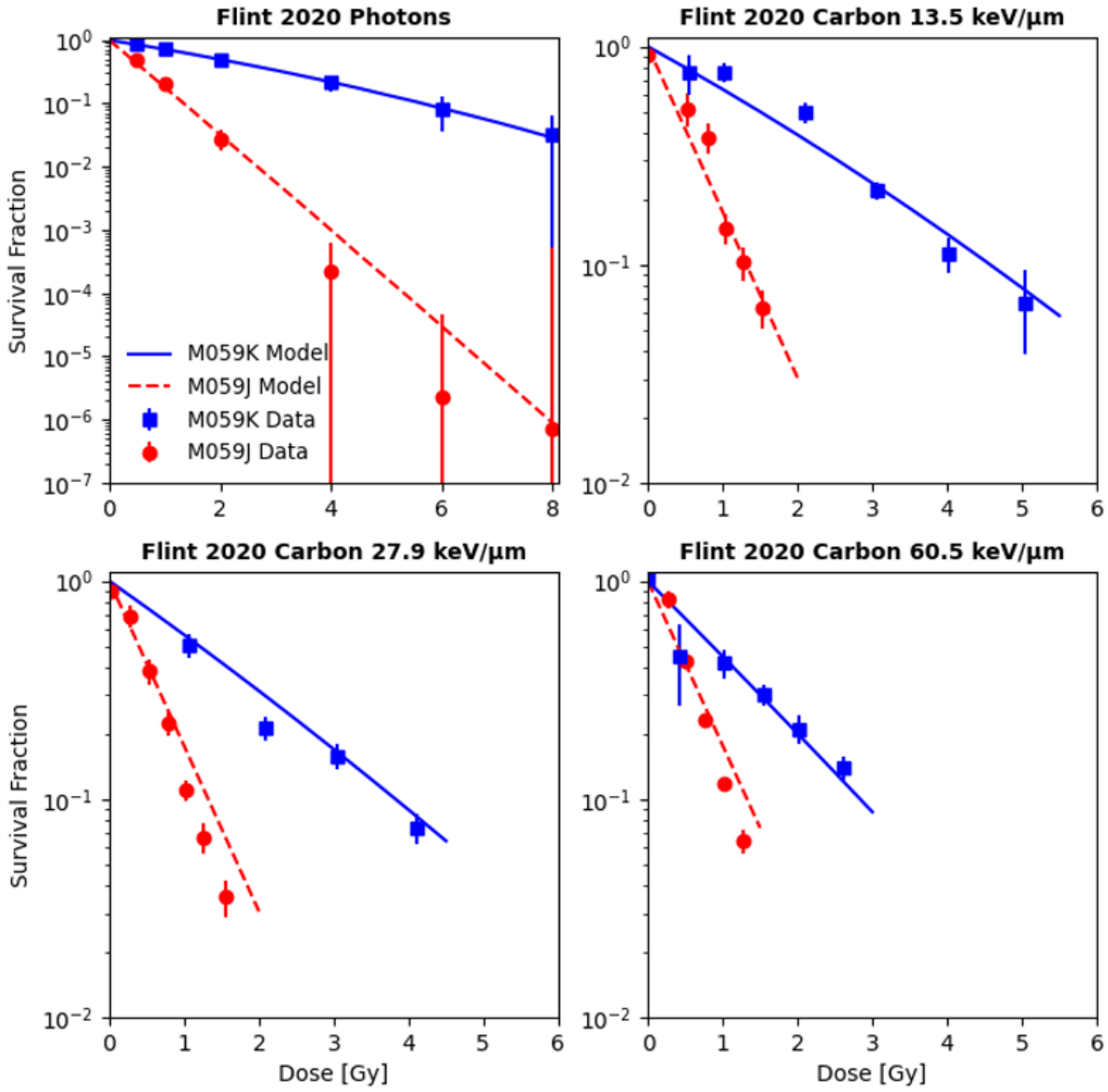
Radiosensitization

- *Hypothesis:* Supression of **DNA-Damage-Repair** by **drugs and mutations** only influences the lethality of **isolated DSB (K_{iDSB})**

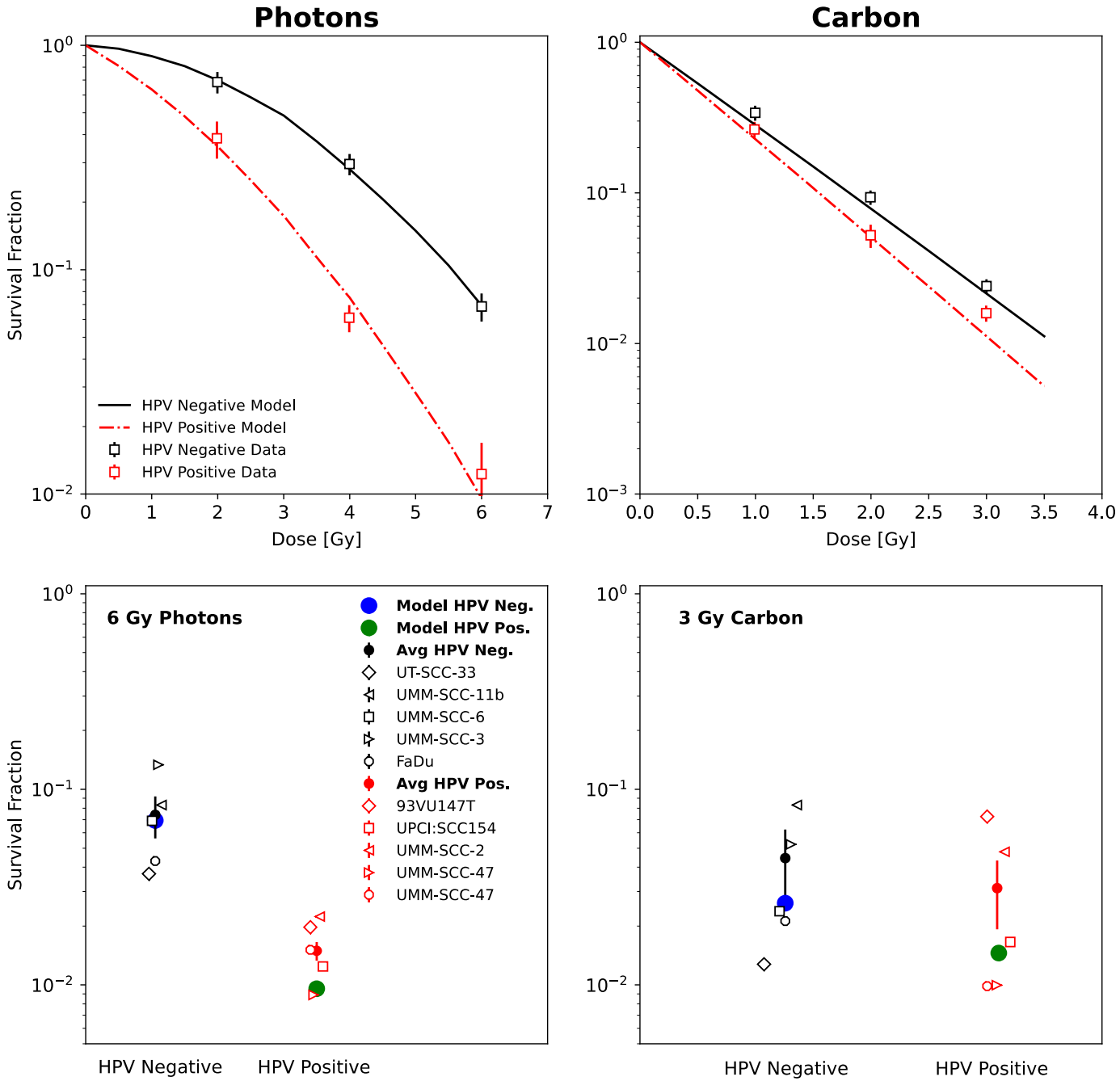
- Introduction of „**Radiosensitization Factor**“ = **RSF**

$$S = (1 - RSF \cdot K_{iDSB})^{N_{iDSB}} \cdot (1 - K_{cDSB})^{N_{cDSB}}$$

Survival of DNA Repair Deficient Cell Lines



Survival of HPV Positive/Negative Cell Lines



Ions hypoxic model and ion FLASH ?

- *Hypothesis: Oxygen in track and Oxygen depletion hypothesis*

-> Development of MonteRay-DNA: a flexible MC for biological investigations

Thank you for your attention!

BioPT