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*“Does radiochemistry play a role in FLASH effect?”*

# Investigation of hydrogen peroxide production under ultra-high dose rate (UHDR) X-ray irradiation in presence of solvated electron scavengers

In the framework of PhD thesis
*“Optimization of ion beam parameters for very high dose rate ( FLASH ) radiotherapy”*

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# Outline

- Introduction to *FLASH* effect and the potential it holds for radiotherapy
- Mechanism of *FLASH* effect: past and present biophysical theories

- Role of hydrogen peroxide production in water radiolysis chain
- Aims of the study
- Methods used
  - Sample preparation
  - Irradiation and dosimetry
  - Hydrogen peroxide concentration measurement, G-value calculation and statistical analysis
- Uncertainty source analysis

- Results
- Conclusions. Future outlooks

# Acknowledgements

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**E041 Biomedical Physics in Radiation Oncology research team from German Cancer Research Center:**

**Tengda Zhang** (*Heidelberg University*)
**Elpida Theodoridou** (*Aristotle University of Thessaloniki*)
**Konstantinos Koristeidis** (*Aristotle University of Thessaloniki*)
**Konstantinos Kostakis** (*Aristotle University of Thessaloniki*)

# Introduction

## *FLASH* effect: potential and possible mechanisms

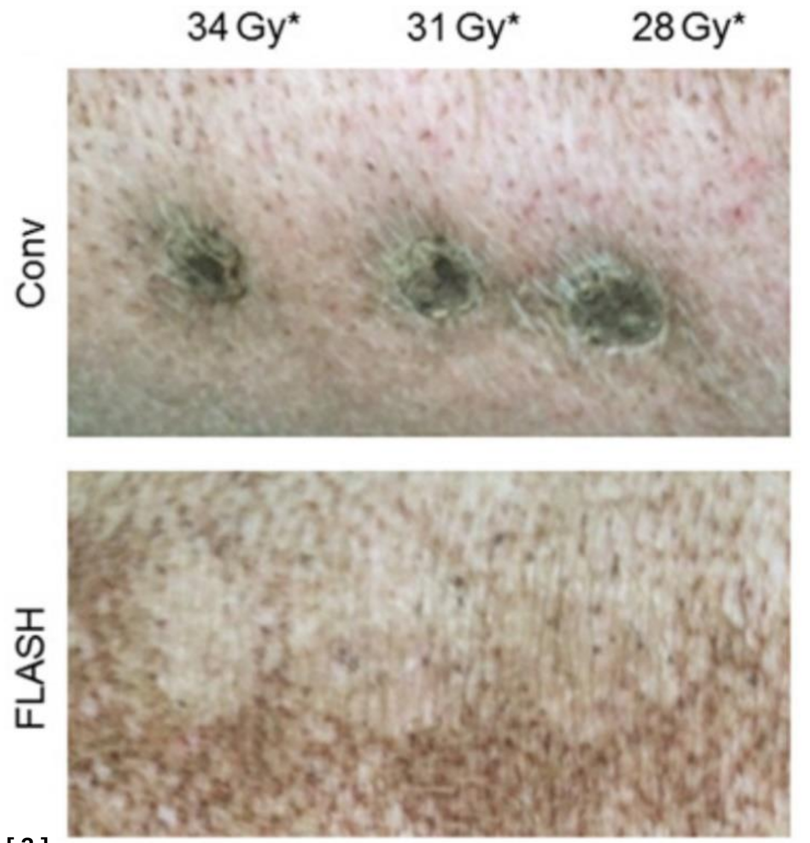
# Introduction to *FLASH* effect

## Historically . . .

- Ξ First observed radiosensitivity changes in biological systems: **1959 for** *Serratia marcescens* **bacteria** [1]
- Ξ *FLASH* effect in terminology **from 2014: the differential effect** in mice model lung tumors [2]

## The *FLASH* effect

Biologically observed **differential effect** – when irradiation with ionizing radiation is performed at ultra-high dose rates (*delivery timescale of miliseconds*) **adverse effects in healthy tissue are greatly reduced while DNA damage in cancerous tissue remains the same**




[ 3 ]

## To achieve dosimetrically . . .

In order to achieve *FLASH* effect:

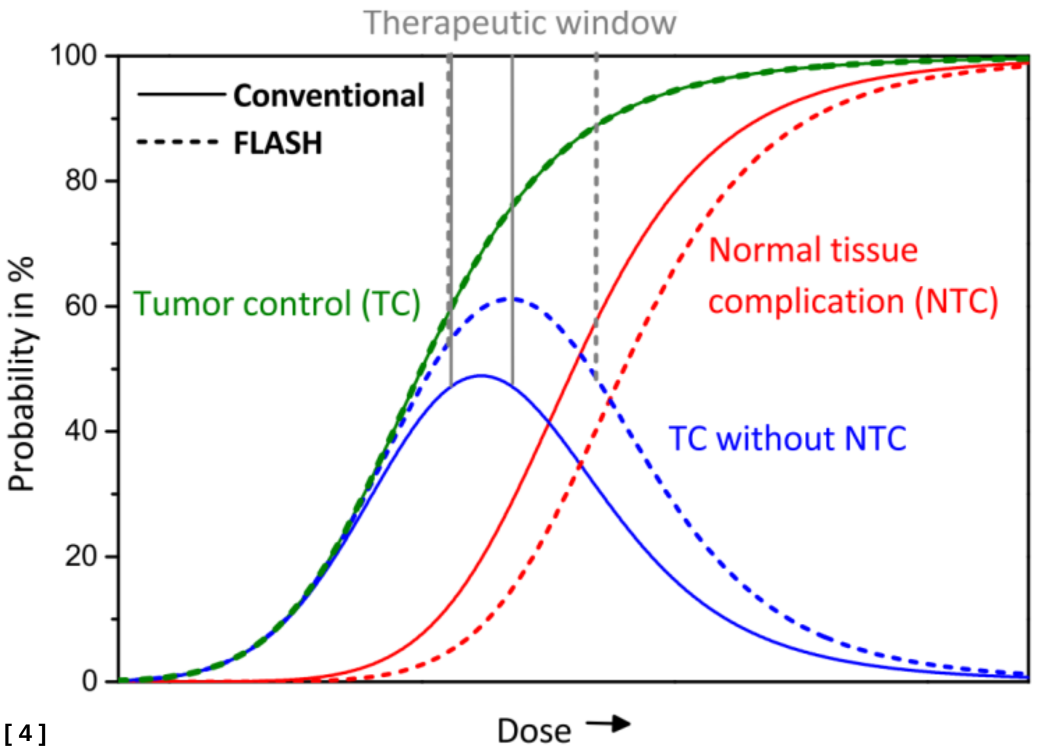
- Ξ **High dose rate of more than 40 Gy/s**
- Ξ **High delivered dose above 8 – 10 Gy** *(hypofractionation)*

**[ 1 ]** DEWEY DL, BOAG JW. *Modification of the Oxygen Effect when Bacteria are given Large Pulses of Radiation.* Nature 1959
**[ 2 ]** Favaudon V, Caplier L, Monceau V, et al. *Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice.* Sci. Transl. Med. 2014
**[ 3 ]** Vozenin M-C, De Fornel P, Petersson K, et al. *The Advantage of FLASH Radiotherapy Confirmed in Mini-pig and Cat-cancer Patients.* Clinical Cancer Research 2019

# The clinical potential of *FLASH* effect

## PRIMARILY

Tumor control probability is sustained, while decreasing normal tissue complication probability – **it is possible to reduce adverse effects of therapy or increase delivered dose due to increased therapeutic window**

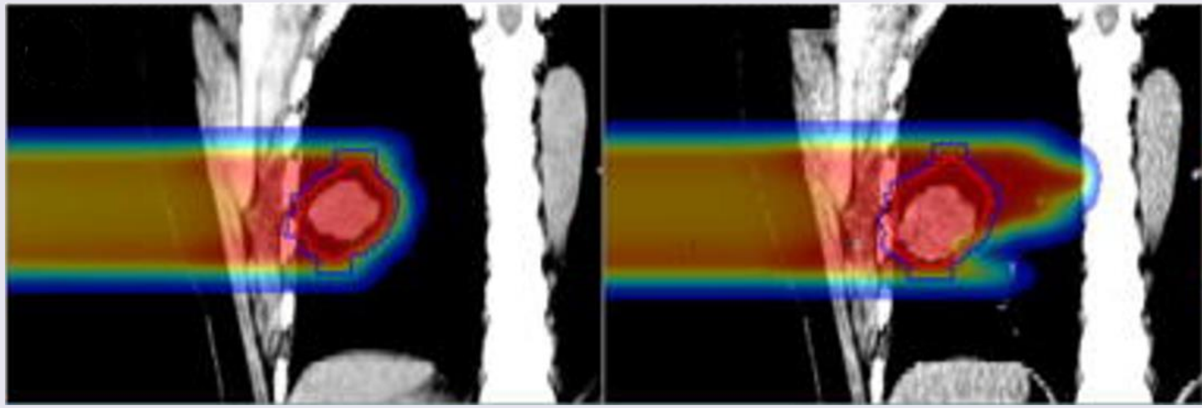



[ 4 ]

## Secondarily . . .

Ξ Possibly **reduced treatment course**, as *FLASH* effect has been found for **hypofractionation** (1-5 fractions)

Ξ **Impact of physiological motions** (*breathing, heartbeat, peristalsis etc.*) **is reduced** due to shorted beam delivery time




**[ 4 ]** Schüller A, Heinrich S, Fouillade C, et al. *The European Joint Research Project UHDpulse – Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates.* Physica Medica 2020

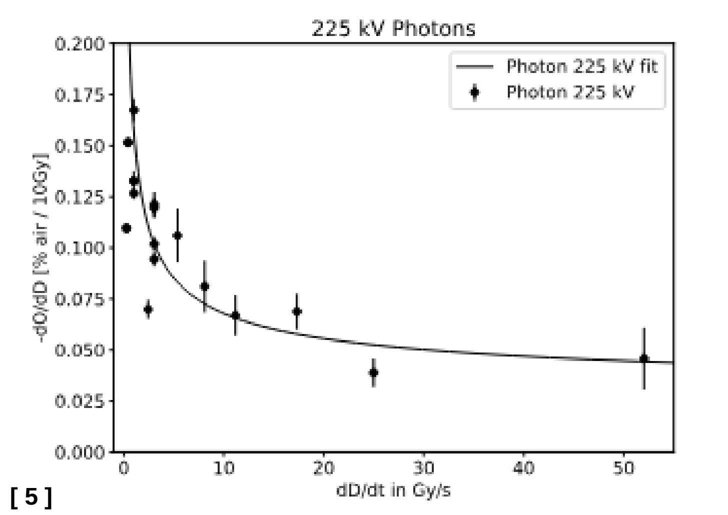
# Proposed mechanisms contributing to *FLASH* effect

- Radical-radical recombination reactions
- Metabolism of peroxidized compounds
- Transient oxygen depletion
- Fenton chemistry
- Protection of circulating immune system cells
- Vasculature related damage
- Stem cell resistance
- . . . . .

[ 5 ] Lin B, Huang D, Gao F, et al. *Mechanisms of FLASH effect.* Front. Oncol. 2022

## Transient oxygen depletion

- One of the early theories of *FLASH* effect
- High dose rate in healthy tissue consumes more oxygen than regenerated through diffusion – **transient hypoxic conditions are induced while irradiating**
- **Theory "debunked"** [5], [6] – could contribute, but not sole cause:
  - doses in range of 100s of Gy are necessary for depletion – in contrast to experimental studies
  - oxygen depletion rate is reduced for UHDR



[ 5 ]

## Radical-radical recombination

- At UHDR, instantaneous radical concentrations are higher, possibly *skewing* the balance of chemical interactions
- Higher probability of self-annihilation reactions - **reducing stable concentration post-irradiation** – reduced DNA damage
- Modelling studies have shown that peroxyl radicals could be the main contributor to *FLASH* effect, though experimental validation impossible due to short lifetime of these radicals

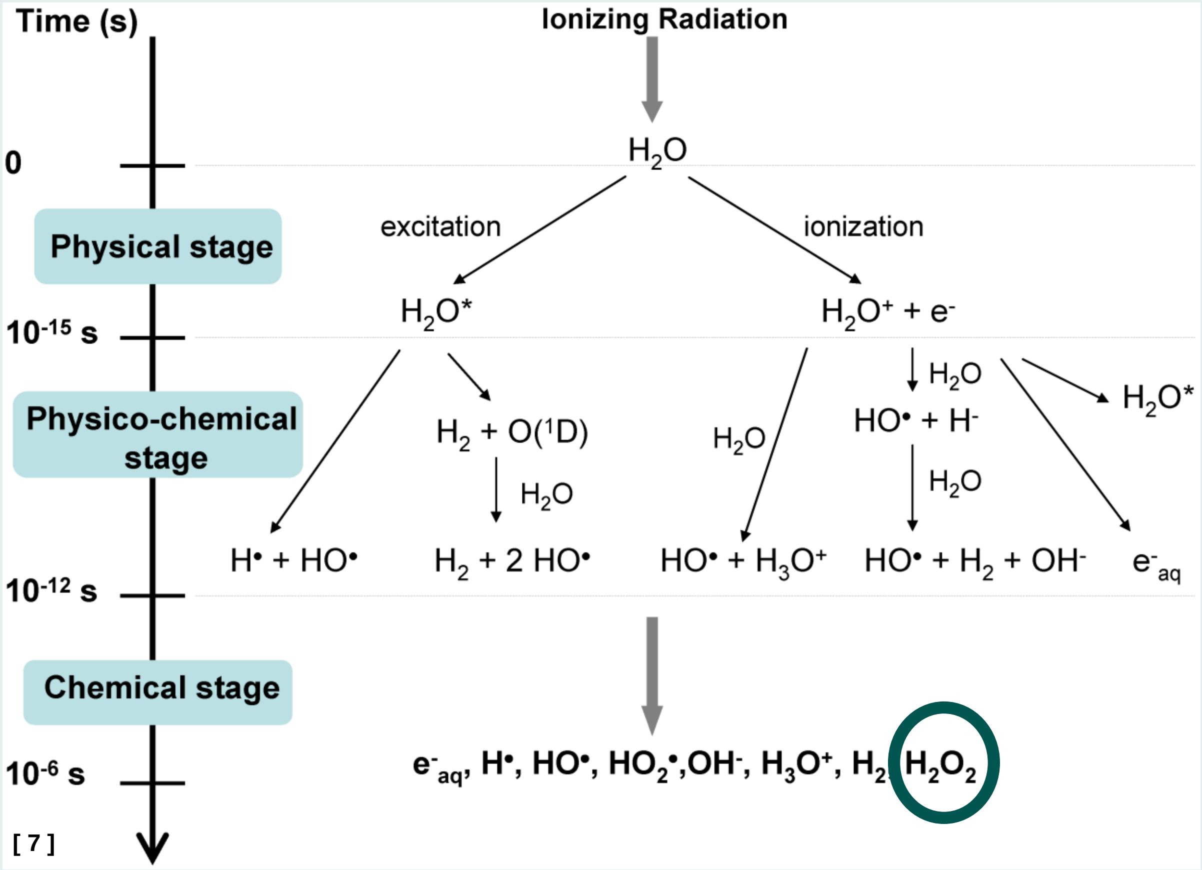
**Could there be an alternative radical or chemical species for assessment ?**

[ 5 ] Jansen J, Knoll J, Beyreuther E, et al. *Does FLASH deplete oxygen? Experimental evaluation for photons, protons, and carbon ions.* Medical Physics 2021
[ 6 ] Jansen J, Beyreuther E, García-Calderón D, et al. *Changes in Radical Levels as a Cause for the FLASH effect: Impact of beam structure parameters at ultra-high dose rates on oxygen depletion in water.* Radiotherapy and Oncology 2022

# Motivation for the study

# Methods. Results. Conclusions

# Hydrogen peroxide in water radiolysis chain




## Water radiolysis

- Describes how ionizing radiation excites and ionizes molecules of water, which in turn undergo chemical and physical interactions **creating reactive species at the end of chemical stage - indirect interactions with cellular DNA**
- Under UHDR – higher concentrations of chemical species are induced (**closer both in temporal and spatial domains**) – the balance of chemical interactions can be shifted

## Hydrogen peroxide

- Most of water radiolysis products are highly chemically reactive and short lived – almost impossible to measure
- **Hydrogen peroxide is stable enough to perform measurements after irradiation – could be used as an indicator for radiochemical changes under UHDR irradiation**

Main question:

**Could UHDR induced radiochemical changes be correlated with biologically relevant changes of *FLASH* effect?**

[ 7 ] Le Caër S. *Water Radiolysis: Influence of Oxide Surfaces on H2 Production under Ionizing Radiation.* Water 2011

# Furthermore . . .

**MC simulations** predict **INCREASED hydrogen peroxide** production under UHDR

**Experimental measurements** [8]-[12] have shown **DECREASED hydrogen peroxide** production under UHDR

Research gap:

**It is necessary to investigate mechanistically hydrogen peroxide production changes under UHDR to understand mechanisms causing the discrepancies for simple systems, before exploring biologically complex media**

**[ 8 ]** Sunnerberg JP, Zhang R, Gladstone DJ, Swartz HM, Gui J, Pogue BW. *Mean dose rate in ultra-high dose rate electron irradiation is a significant predictor for O2 consumption and H2O2 yield*. Phys. Med. Biol. 2023
**[ 9 ]** Blain G, Vandenborre J, Villoing D, et al. *Proton Irradiations at Ultra-High Dose Rate vs. Conventional Dose Rate: Strong Impact on Hydrogen Peroxide Yield.* Radiation Research 2022
**[ 10 ]** Montay-Gruel P, Acharya MM, Petersson K, et al. *Long-term neurocognitive benefits of FLASH radiotherapy driven by reduced reactive oxygen species.* Proc. Natl. Acad. Sci. U.S.A. 2019
**[ 11 ]** Thomas W, Sunnerberg J, Reed M, et al. *Proton and Electron Ultrahigh-Dose-Rate Isodose Irradiations Produce Differences in Reactive Oxygen Species Yields*. International Journal of Radiation Oncology*Biology*Physics 2024
**[ 12 ]** Kacem H, Psoroulas S, Boivin G, et al. *Comparing radiolytic production of H2O2 and development of Zebrafish embryos after ultra high dose rate exposure with electron and transmission proton beams.* Radiotherapy and Oncology 2022;

# AIMS OF THE STUDY

- **To study $H_2O_2$ production changes with X-ray irradiation at UHDR and conventional dose rates in water medium**
- **To assess the impact of self-annihilation** *(radical-radical)* **interactions, study the medium with added solvated electron ($e_{aq}^-$) scavengers**

# Starting point

- Previous measurement work by DKFZ E041 team, specifically **Tengda Zhang**, with electron and carbon ion beams [13]
- **Measurement approach adapted and further expanded**

**[ 13 ]** Zhang T, Stengl C, Derksen L, et al. *Analysis of hydrogen peroxide production in pure water: Ultrahigh versus conventional dose-rate irradiation and mechanistic insights*. Medical Physics 2024

# Materials and methods: **Sample preparation**

## Preparation of samples

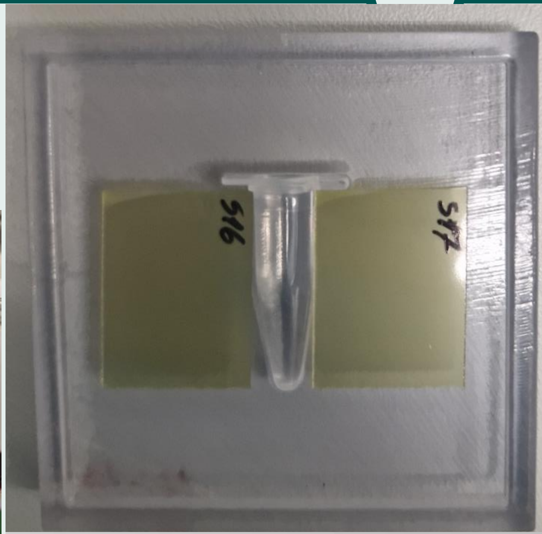
- Liquid samples are prepared in **200 μL PCR eppendorf tubes**
- Filled fully to **avoid any dose distribution perturbations due to air gaps**
- Afterwards, inspected for air bubbles and new sample is prepared

## Solutions studied

- Reference: **pure MilliQ water** prepared by *TKA GenPure* system
- To assess impact of solvated electron scavengers (*more in next slide*):
    - **nitrous oxide ($N_2O$) saturated solutions**
        - $N_2O$ gas by *Guttroff, Germany*
        - solutions were bubbled with gas for 1 hour
    - **sodium nitrate ($NaNO_3$) water solutions**
        - ACS reagent grade $NaNO_3$ (*Sigma-Aldrich, Germany*) was used
        - dissolved, vortexed and serial dilution for different concentrations

## Oxygen levels studied

- *Most of the study*: **aerated samples** ( $p_{O_2} = 21\ \%$ ), leaving water for ~1 hour
- **Physoxic samples** ( $p_{O_2} = 4\ \%,\ p_{CO_2} = 0.1\ \%$ ) were also studied:
    - conditioning samples for 24 hours in hypoxia chamber *SciTive (Baker)*
    - flushing by nitrogen gas



## Role of scavengers

- Compounds reacting with certain water radiolysis species – **disrupts the radiolysis chain**
- By introducing $e_{aq}^{-}$ scavenger – multiple pathways changed, changing end products. Impact of certain species can be assessed

## Nitrous oxide

- Method as studied previously by DKFZ E041 Group [13]
- **Method has multiple drawbacks**:
  - no direct concentration measurement possible – no scavenging capacity
  - “concentration” not reproducible day-to-day – room temperature, gas flow etc.
  - time consuming process of bubbling

| | |
|---|---|
| $N_2O + e_{aq}^{-} \rightarrow {}^{*}N_2O^{-}$ | 9.1 x $10^{9}$ $M^{-1}s^{-1}$ |
| $N_2O + e_{pre}^{-} \rightarrow {}^{*}N_2O^{-}$ | < $10^{12}$ $M^{-1}s^{-1}$ |

## Alternatives

**Acrylamide** | **Bromine ion** | **Nitrate ion**

## Sodium nitrate

- Nitrate ion effective scavenger of solvated electron, as well as precursor of solvated electron and molecular cation of water
- Sodium nitrate (NaNO3) extensively studies in water radiolysis process
- Solid and dissolvable – **possibility to accurately control the concentratio**
- **Additional measurements taken to characterize the approach**:
  - pH of the solution
  - hydrogen peroxide measurement assay independence
  - impact of the sodium nitrate concentration

| | |
|---|---|
| $NO_3^{-} + e_{aq}^{-} \rightarrow {}^{*}NO_3^{2-}$ | 9.7 x $10^{9}$ $M^{-1}s^{-1}$ |
| $NO_3^{-} + H_2O^{+} \rightarrow {}^{*}NO_3 + H_2O$ | ~ 1 x $10^{12}$ $M^{-1}s^{-1}$ |
| $NO_3^{-} + e_{pre}^{-} \rightarrow {}^{*}NO_3^{2-}$ | 1 x $10^{13}$ $M^{-1}s^{-1}$ |

**[ 13 ]** Zhang T, Stengl C, Derksen L, et al. *Analysis of hydrogen peroxide production in pure water: Ultrahigh versus conventional dose-rate irradiation and mechanistic insights*. Medical Physics 2024

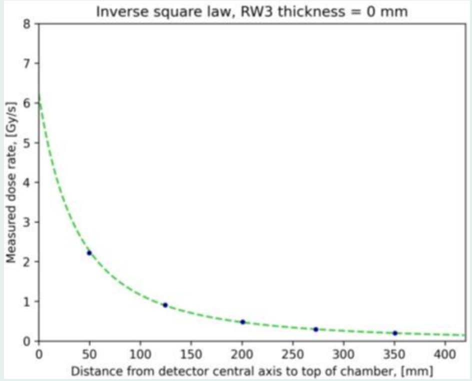
# Materials and methods: **Sample irradiation**

## X-ray system used

- **MultiRad225 X-ray irradiation system** was used
- Operated at nominal **voltage of 200 kV** and **beam current of 17.8 mA**
- *Explored: 118 kV and 30 mA, but surface dose rate increase diminished with PDD*
- Provides continuous beam, with irradiation time resolution of 1 s


## Dose rate characterization

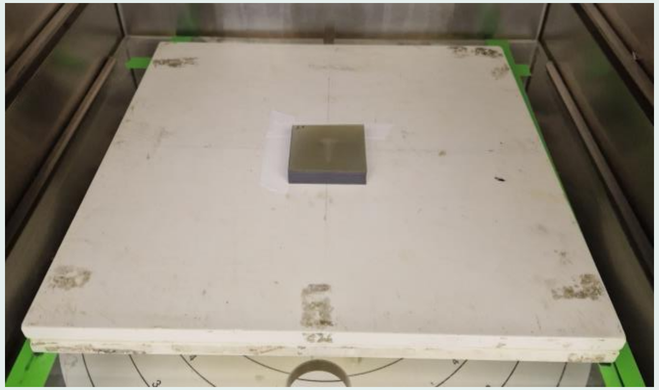
- **Dose rate (DR) variation achieved by changing SDD**
- Using the phantom setup, dose rate was measured at the “pre-set” SDDs
- By ISL, SDD values for higher DR calculated and validated with measurements

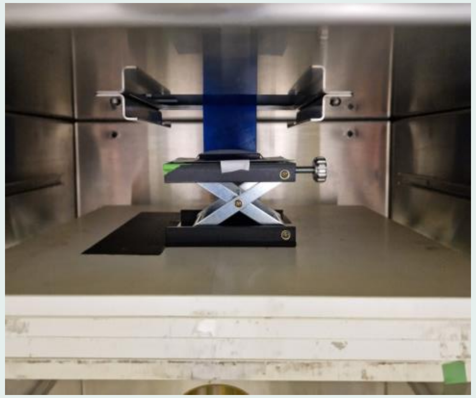



| SDD | Dose Rate |
|---|---|
| 498 mm | 0.1 Gy/s |
| 123 mm | 2 Gy/s |
| 79 mm | 5 Gy/s |
| 59 mm | 10 Gy/s |

## Phantom setup

- *Phantom developed for previous studies used*
- **Material:** 3D printed with water equivalent plastic ( *VeroClear* )
- **In beam direction:** 20 mm, 2 mm in front of sample ( *limits dose gradient )*
- **Transversal to beam:** 50 x 50 mm, ensuring lateral scattering equilibrium
- **For back-scatter:** phantom placed on 20 mm of RW3 plates (*large SDD)*
- **Position:** center of the beam, small SDDs with lab jack ( *Elpida Theodoridou* )

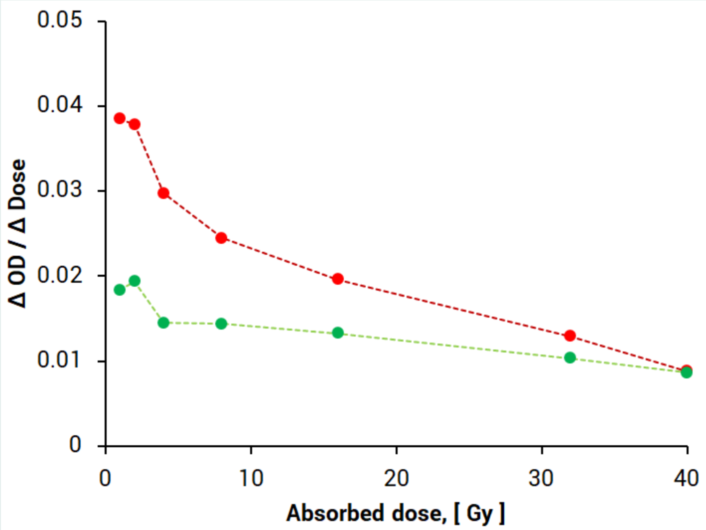




# Materials and methods: **Dosimetry for the samples**

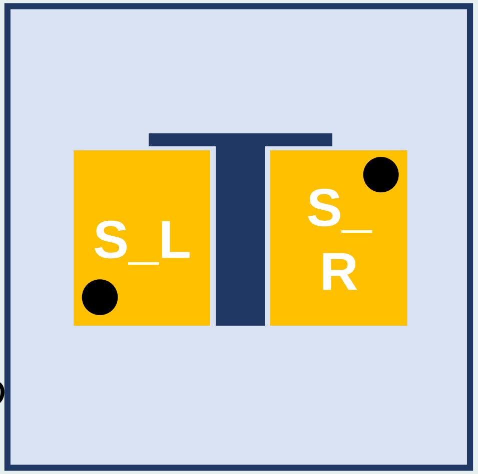
## Radiochromic film dosimetry

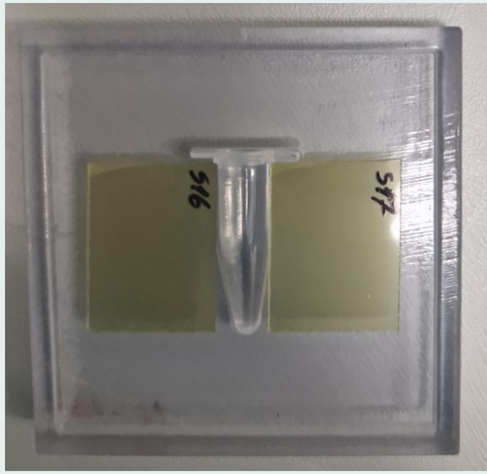
- **Radiochromic films dosimetry chosen**: phantom setup + spatial information
- ***Gafchromic EBT-XD* films were used**
- Protocol for use:
  - cut 24 hours before irradiation (*mechanical stress*)
  - pre-scanning before irradiation
  - post-scanning 24 hours after irradiation (*OD growth stabilization*)
- Optical density (OD) readout with **flatbed scanner *Epson 10000XL***
  - scan settings: transmission mode, 150 dpi, no corrections, 3-channel TIFF
  - sensitivity measurements performed – **red color channel used for analysis**
  - ***ImageJ macro created*: 2D OD transformation into dose map**




## Dosimetry setup

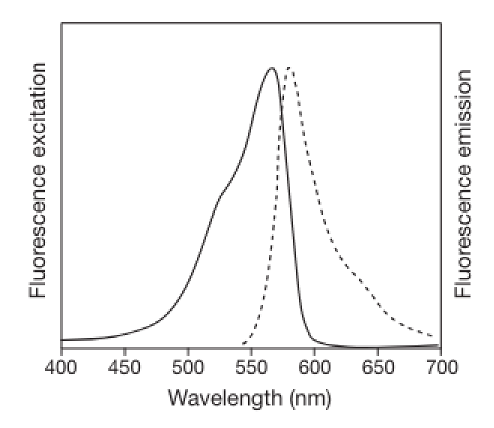
- **Dosimetry performed for each sample:** positioning setup and output variations
- *Initially: additional measurements of dose distribution (PDD and transversal profiles)*
- **Film size used:** 10 x 20 mm
- **Region of interest (ROI) for analysis:** ~ 2 x 15 mm near sample
- Mean and standard deviation extracted
- **Films on both sides of the sample to account for "heel-effect"** (*especially low SD*

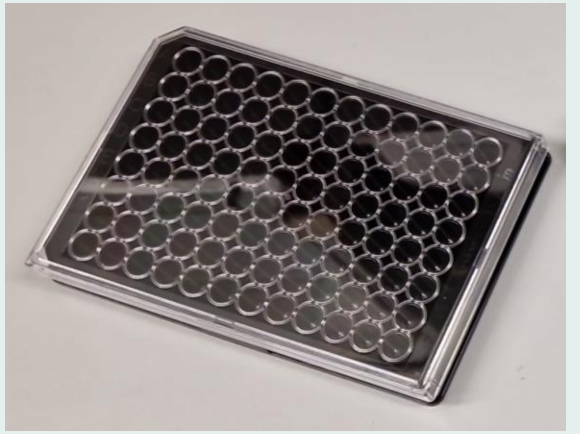


## Concentration measurement

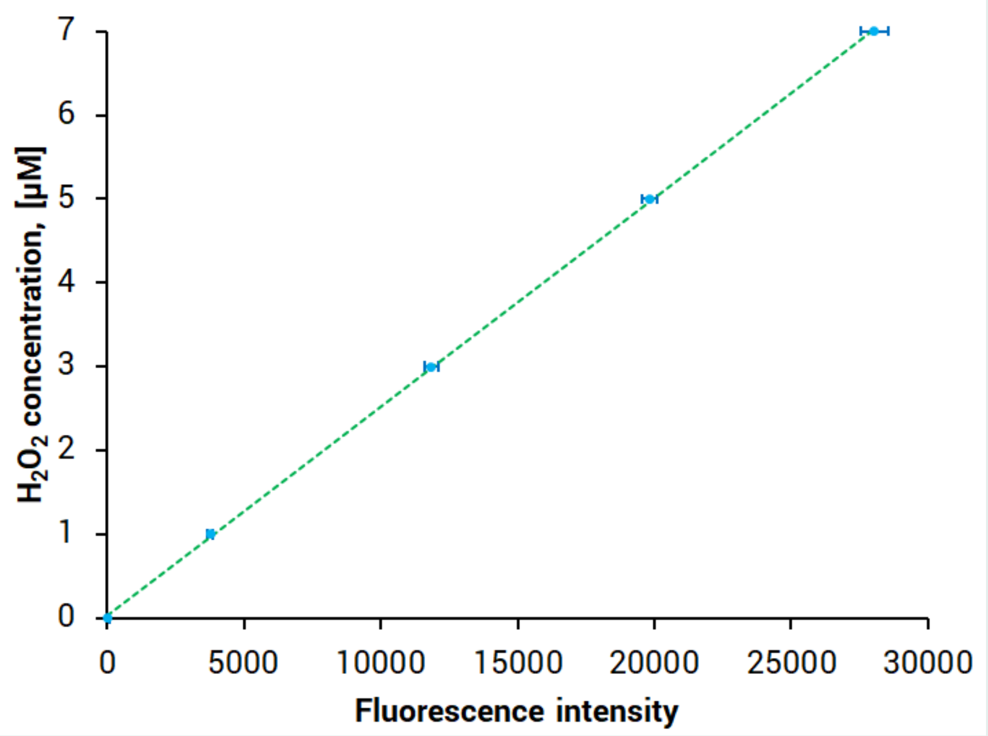
- *Note: hydrogen peroxide light-sensitive, samples kept in dark after irradiation*
- **Amplex UltraRed assay used**:
  - reagent is mixed with enzyme – horseradish peroxidase (HPR)
  - under exposure of hydrogen peroxide – fluorescent compound formed
- After irradiation, **50 μL of sample mixed with 50 μL of assay** in 96-well plate
- After **incubation period of 30 minutes**, fluorescence readings are done
- Calibration curve is established:
  - re-done for every session
  - **hydrogen peroxide water solutions of 0, 1, 3, 5 and 7 μM** mixed with assa



## Fluorescence readings

- ***BMG Labtech Clariostar*** **well plate reader used**
- Readout settings:
  - **top-read** measurement mode
  - flashes per well: 4
  - excitation wavelength (*filter*): **530 ± 15 nm**
  - emission wavelength (*filter*): **590 ± 20nm**
- Readings corrected by background measurement
- **For calibration: linear fit, extracting also fit error**

## Measurement statistics

- **3 samples for each condition** ( *solution* + *dose rate* )
- **3 $H_2O_2$ concentration measurements for each sample**

## G-value. Error propagation

- Of interest – **$H_2O_2$ production yield ( G-value )**
- Produced concentration / Absorbed dose
- Error propagation based on dose, concentration errors and variability of measurements

## Statistical analysis

- Based on approach outlined by Sunnerberg et al. [8]
- **linear regression between logarithm of dose rate and G-value**
- To assess the statistical significance of the findings, **t-test for linear regression was performed, with confidence of 95 %**

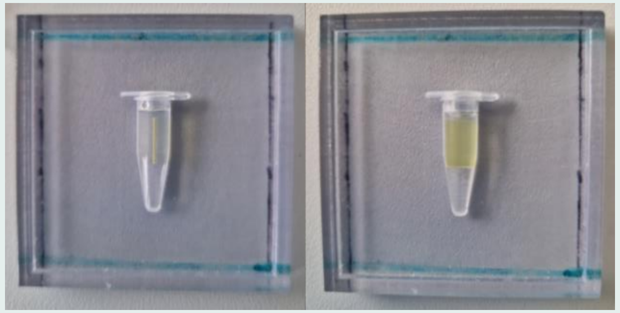
## Sources of uncertainty

### Radiochromic film calibration function

- uncertainty of radiochromic film measurement arises also from choice of calibration function
- **3 different calibration functions were assessed** (*full error propagation and fitting errors)*

### Dose distribution within the sample

- although samples are irradiated radially, there is still a significant dose gradient due to nature of X-rays
  - ***miniature* radiochromic films were prepared and placed within eppendorf tubes –** axially and transversally
    - **average dose calculated, compared with sample dose measurements**

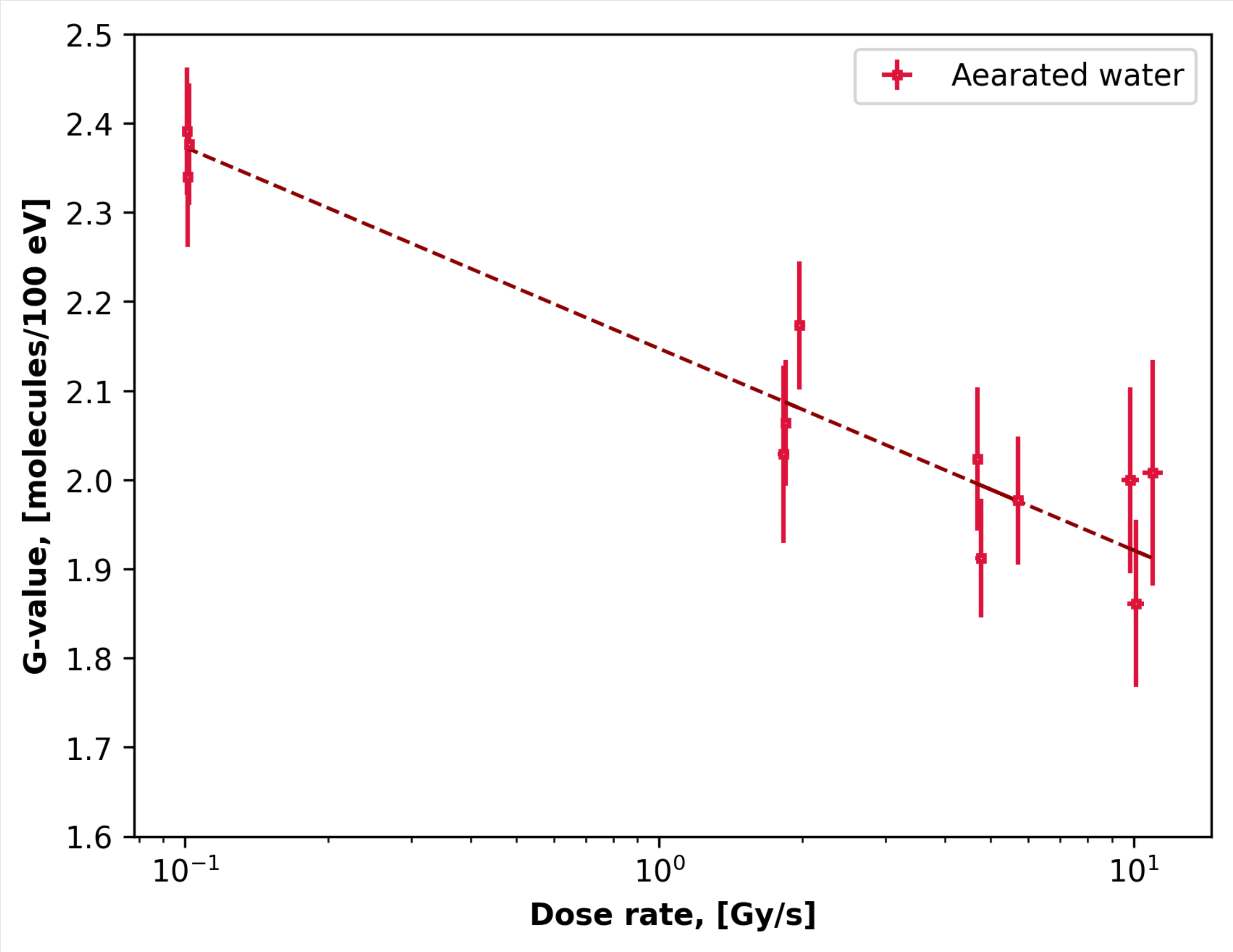


### Finite rise-time of X-ray tube

- X-ray tubes have finite rise time for stable output, important for dose rate at short irradiation times
- **output temporal distribution measured with microDiamond detector and PTW UNIDOS electrometer in «Current» mode (500 ms resolution)**
  - **dose-averaged dose rate calculated**

**[ 8 ]** Sunnerberg JP, Zhang R, Gladstone DJ, Swartz HM, Gui J, Pogue BW. *Mean dose rate in ultra-high dose rate electron irradiation is a significant predictor for O2 consumption and H2O2 yield*. Phys. Med.

# Results: **Pure aerated water**




In agreement with previous experiments**, decreased hydrogen peroxide production yield is observed at higher dose rates**, even for the relatively low range studied (0.1 – 10 Gy/s)

## Statistical analysis

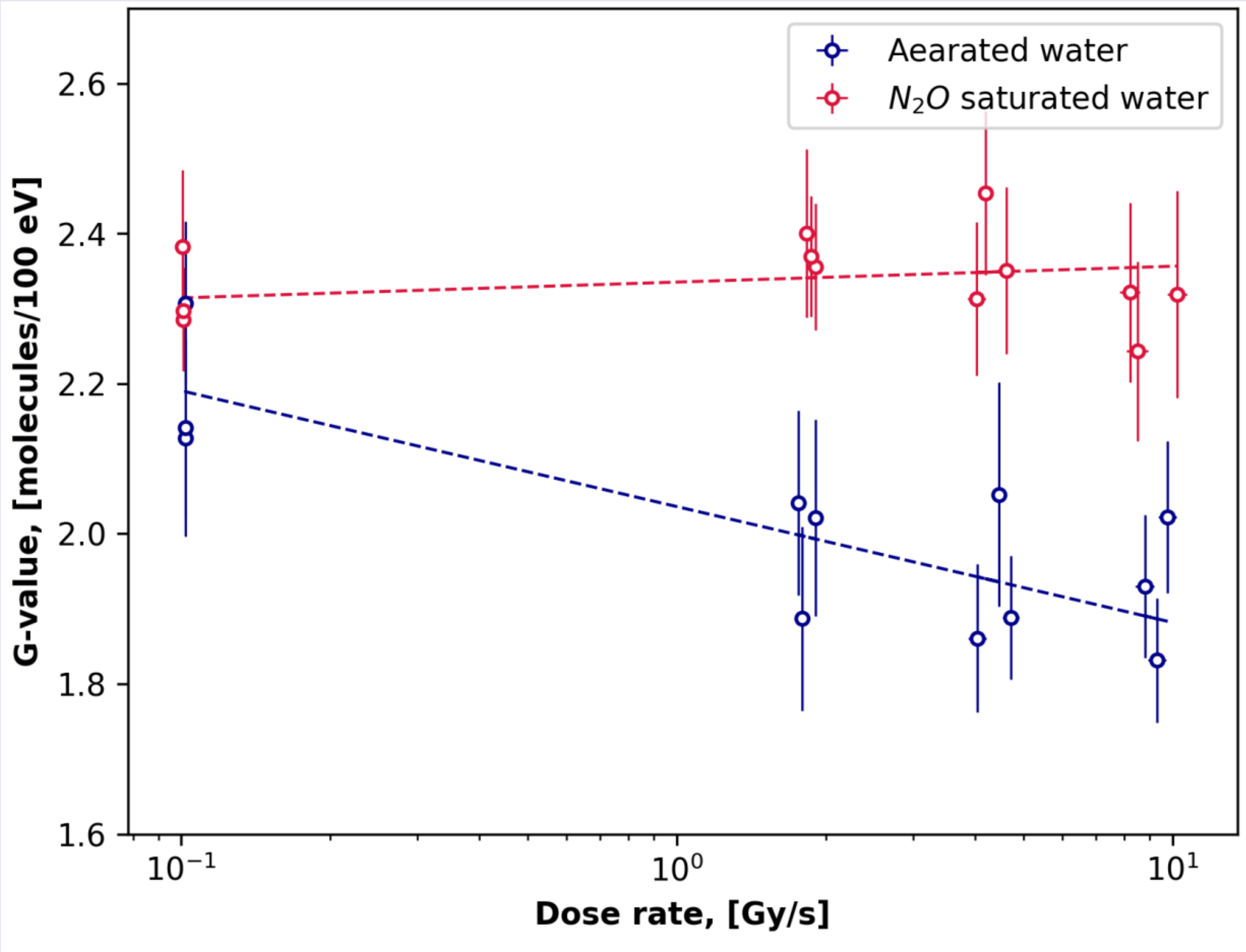
Slope for linear regression of G-value with respect to logarithm of dose rate

**-0.2260 ± 0.0297**

p-value for t-test of linear regression – 0.00002

**Statistically significant ($p < 0.05$)**

# Results: **Nitrous oxide as $e_{aq}^-$ scavenger**




**Addition of nitrous oxide – a solvated electron scavenger – diminishes the dose rate dependence of hydrogen peroxide production**

## Statistical analysis

Slope for linear regression of G-value with respect to logarithm of dose rate

**0.0211 ± 0.0334**

p-value for t-test of linear regression – 0.5422

**Statistically insignificant ($p > 0.05$)**

**Addition of solvated electron scavenger – nitrous oxide – has a statistically significant impact on dose rate dependence DIMINISHING IT**

# Results: **Characterization of sodium nitrate system**

## pH of the solution

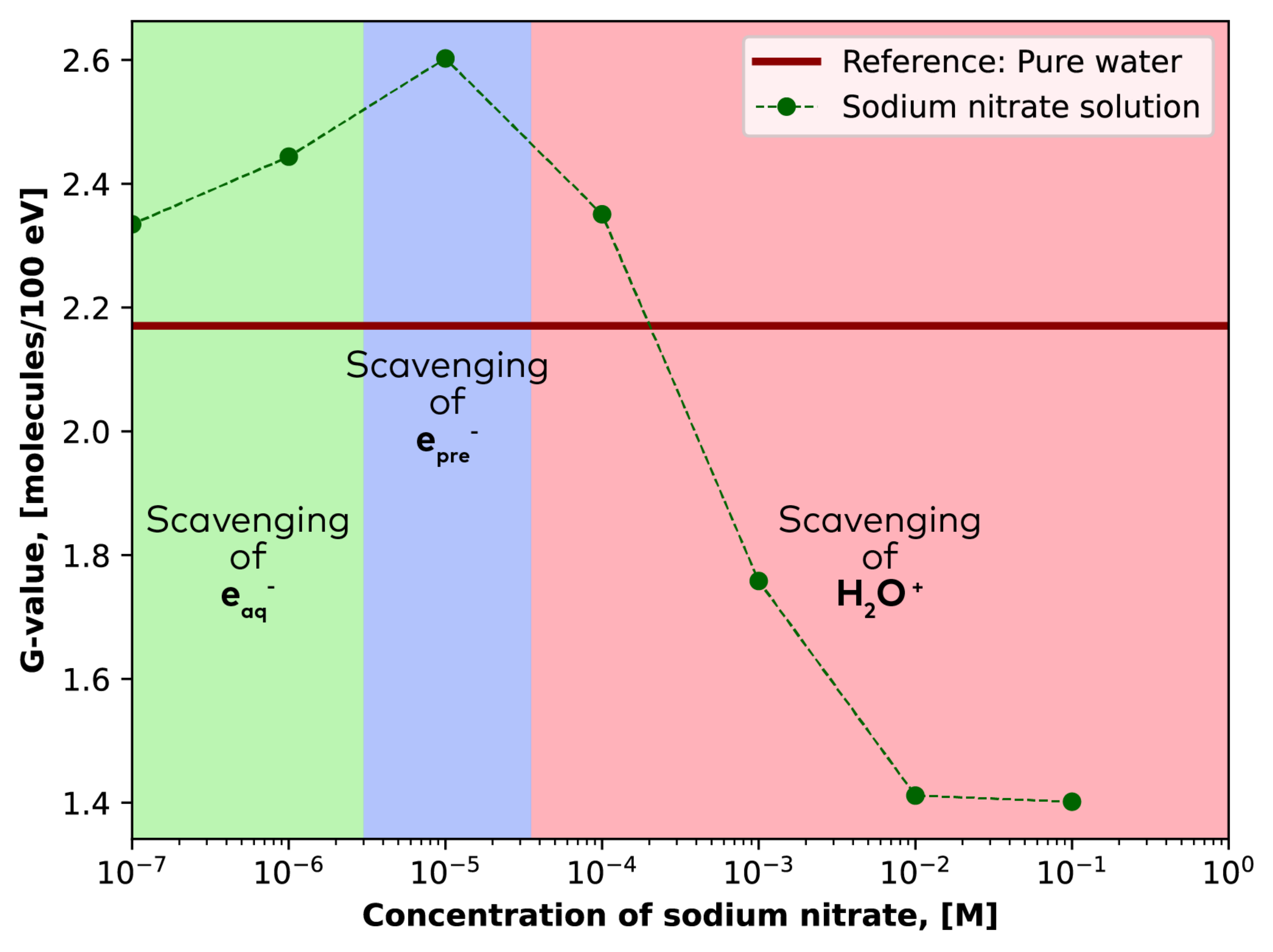
- Sodium nitrate: **neutral salt** (*strong base: sodium hydroxide, strong acid: nitric acid*)
- Measurements with *Mettler Toledo pH Probe:* **6.5 to 7**

## Interaction with assay

- 0, 1 and 3 μM of hydrogen peroxide mixed with 1 M, 100 mM, 10 mM, 1 mM, 100 μM and 10 μM sodium nitrate
- **Solutions were not irradiated, fluorescence measured**
- **No significant differences observed in fluorescence readings: assay is not interacting with sodium nitrate**

## Impact of concentration

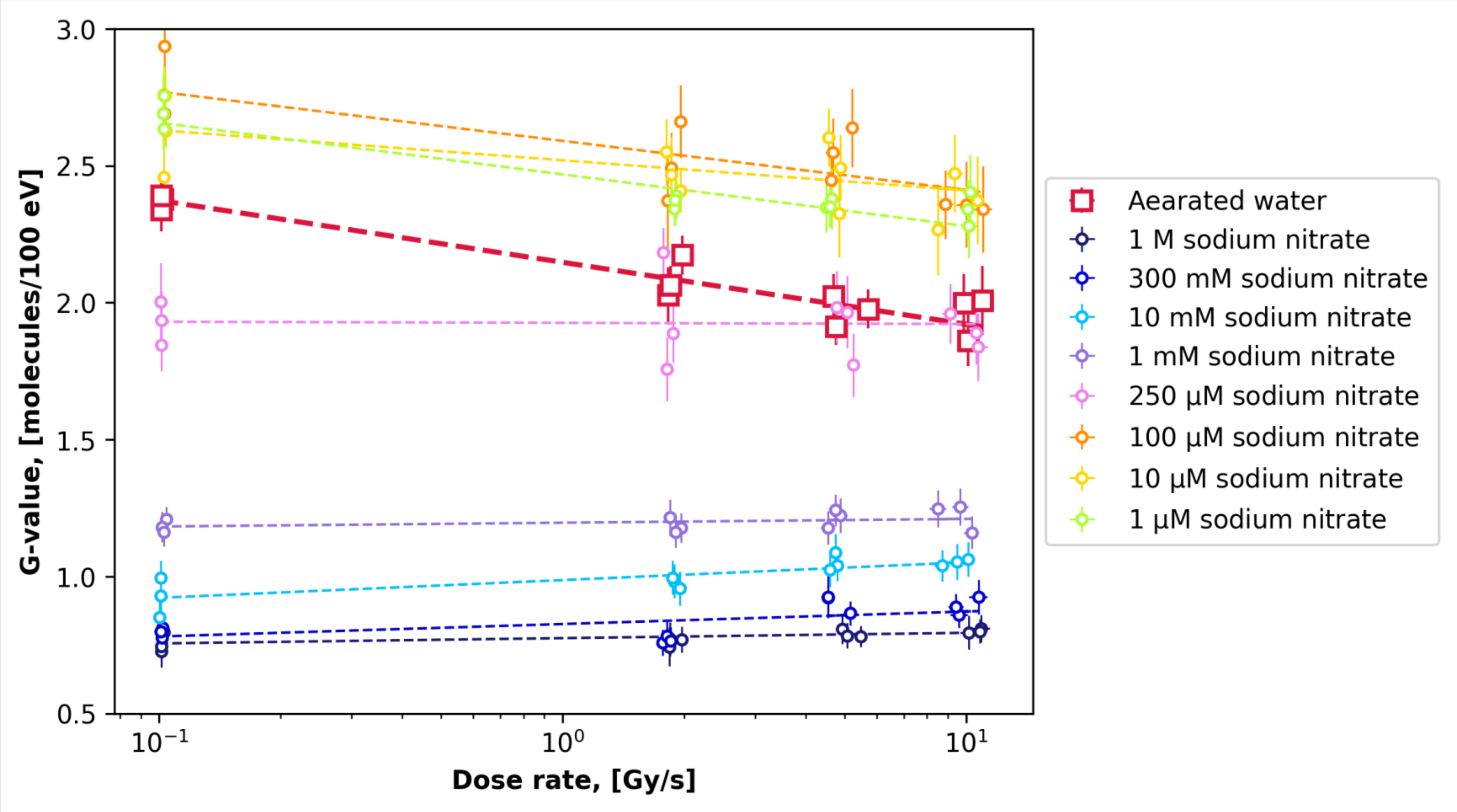
- Samples with sodium nitrate concentration from 0.1 μM to 1 M (*steps in magnitude*) irradiated at 2 Gy/s for dose of 11 Gy
- **Low concentrations of sodium nitrate INCREASE production of $H_2O_2$ relative to water**
- **Concentrations above 100 μM – DECREASE it**
- **By changing the concentration of sodium nitrate, the main scavenged chemical product is changed** [14]





[ 14 ] Hiroki A, Pimblott SM, LaVerne JA. *Hydrogen Peroxide Production in the Radiolysis of Water with High Radical Scavenger Concentrations*. J. Phys. Chem. A 2002; 106(40): 9352–9358.

# Results: **Sodium nitrate as $e_{aq}^-$ scavenger**




**Dose rate dependency of hydrogen peroxide was still observed at low concentration of sodium nitrate (*reduced impact*) , while completely diminished at sodium nitrate concentration above 250 μM**

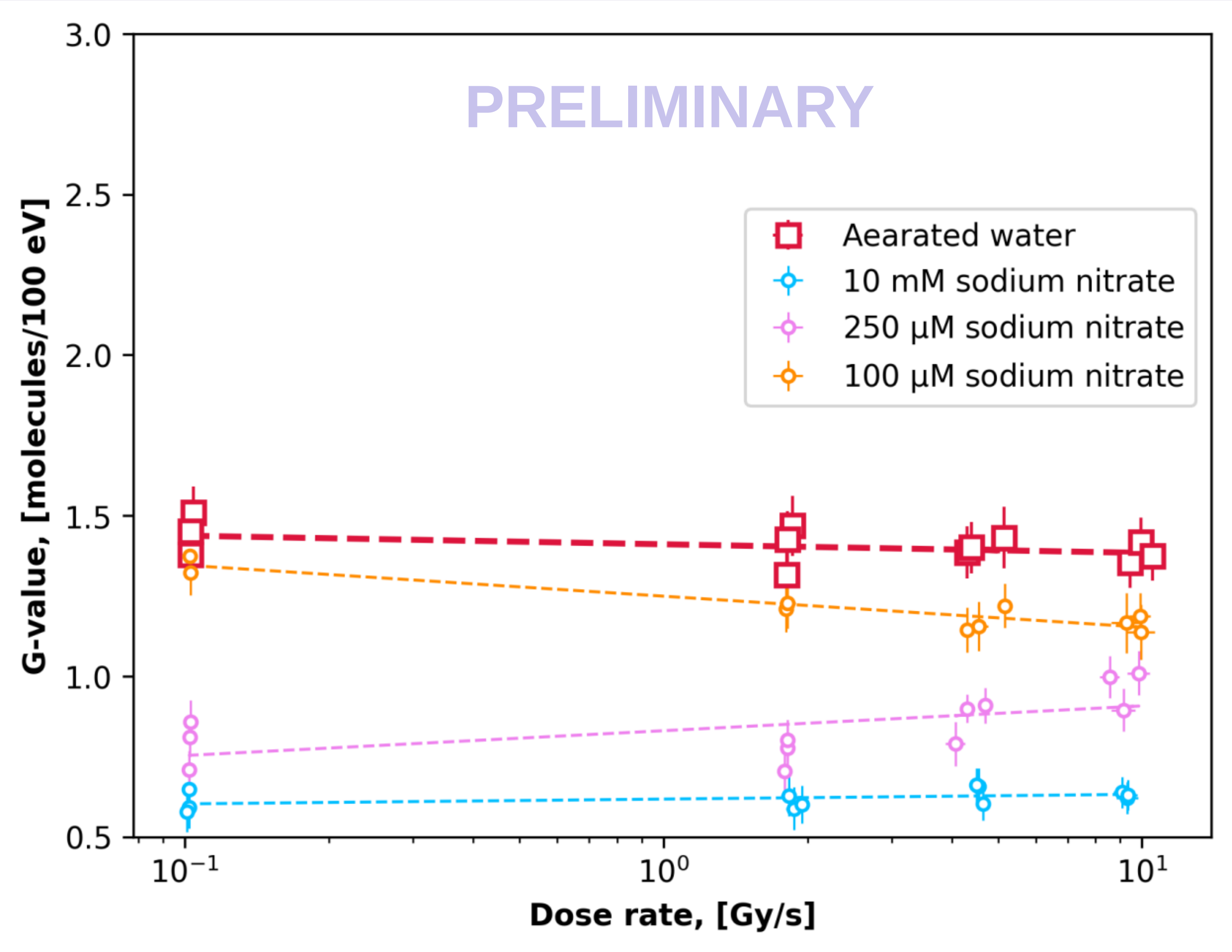
## Statistical analysis

| | | |
|---|---|---|
| **1 M** | **0.0194 ± 0.0193** | **p = 0.3395** |
| 300 mM | 0.0457 ± 0.0182 | p = 0.0313 |
| 10 mM | 0.0694 ± 0.0193 | p = 0.0245 |
| **1 mM** | **0.0139 ± 0.0210** | **p = 0.5241** |
| **250 μM** | **-0.0042 ± 0.0427** | **p = 0.9243** |
| 100 μM | -0.1793 ± 0.0403 | p = 0.0012 |
| 10 μM | -0.1099 ± 0.0391 | p = 0.0186 |
| 1 μM | -0.1889 ± 0.0419 | p = 0.0011 |

**Sodium nitrate concentrations above 250 μM have statistically significant impact, diminishing DR dependency**

(*increasing production at 10 and 300 mM – not further investigated currently*)

# Results: **Impact of oxygen level**




Preliminary: **lower oxygen concentration of 4%, no DR dependency was observed both for pure water and sodium nitrated solutions**

## Statistical analysis

| | | |
|---|---|---|
| **Pure water** | **-0.0268 ± 0.0298** | **p = 0.3903** |
| Sodium nitrate: **10 mM** | **0.0149 ± 0.0226** | **p = 0.5232** |
| Sodium nitrate: **250 µM** | **0.0772 ± 0.0245** | **p = 0.0103** |
| Sodium nitrate: **10 µM** | **-0.0965 ± 0.0313** | **p = 0.0150** |

**Additional measurements necessary to investigate the impact of oxygen concentration further**

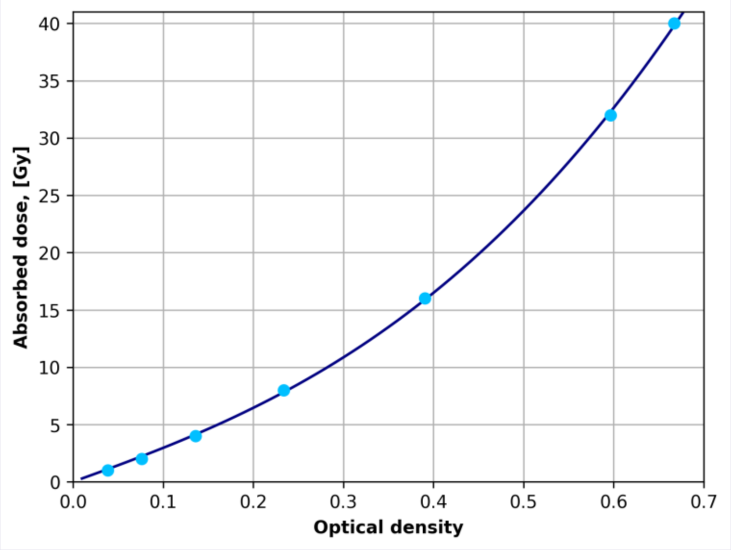
# Results: **Measurement errors. Sources of uncertainty**

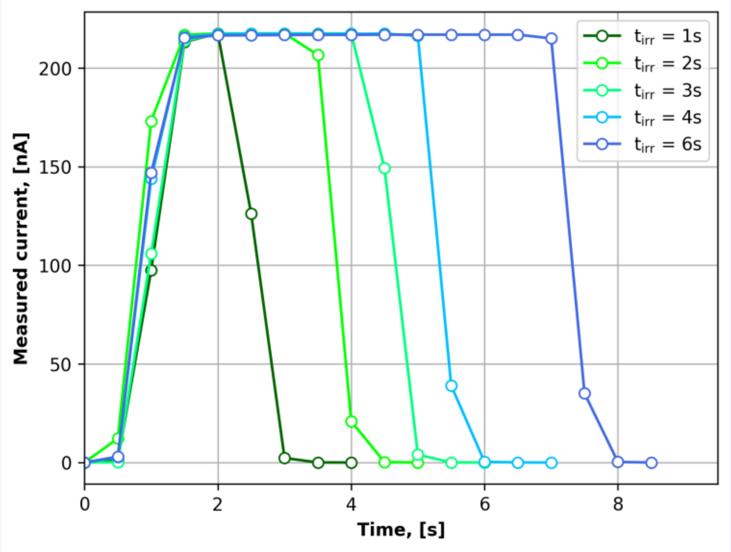
## Overall measurement errors

- **Dose and dose rate relative error:** 1.5 – 2 %
- **$H_2O_2$ concentration relative error:** 3 – 6 % (*meas. variability*)
- **Total G-value relative error: 5 – 10 %**

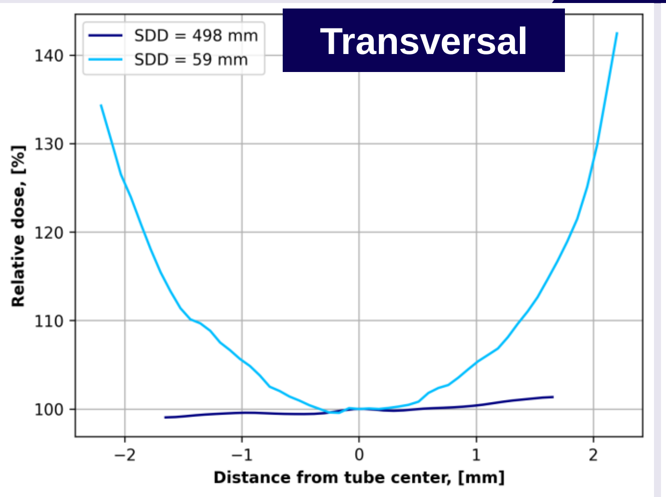
## RCF calibration function

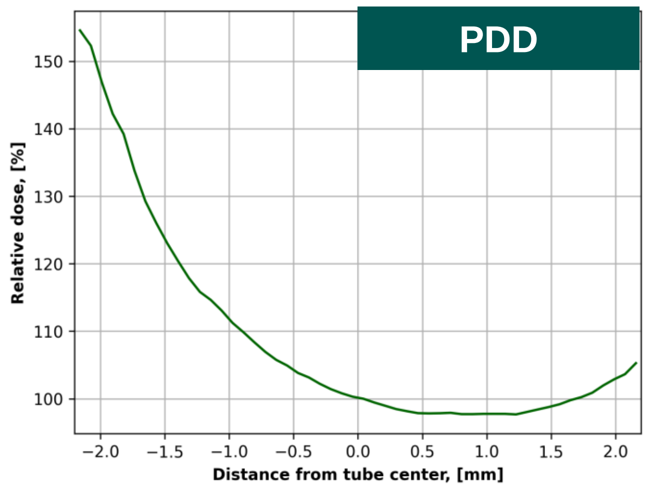
- **3 different radiochromic film calibration functions assessed**
- $Dose = \frac{b}{OD-a} + c$ : uncertainty of 8 – 40 % *(manufacturer recommended)*
- $Dose = a * OD + b * OD^n$: uncertainty below 5 %
- $Dose = c * \left(\frac{a-d}{OD-d} - 1\right)^{\frac{1}{b}}$ : uncertainty of ~ 15 %
- Chosen based on lowest uncertainty and high accuracy




## Dose distribution in sample




*Transversally:* "heel-effect" for small SDD, *PDD:* exponential depth dose, *both:* **air gaps**

**By volumetric averaging calculation : delivered dose in PCR is about 6 % higher**

## Temporal variability of DR

- System indicated time – stable DR
- Finite rise time ~ 1 s
- Finite "fall-off" time ~ 1s
- **Effect low for irradiation time > 6 s: DADR 2% lower than average**
- **For 3 s irr. ( 5 Gy/s): DADR 14% lower**
- **For 2 s irr. ( 10 Gy/s): DADR 22% lower**

# Conclusions

- Study explored hydrogen peroxide production under UHDR with low energy X-ray beam, compared to most studies performed with electron or proton beams.
- In the dose rate range investigated (0.1 – 10 Gy/s), **statistically significant ( $p < 0.05$ ) decrease of hydrogen peroxide in aerated samples was observed at higher dose rates**. This finding is in agreement with previously reported experiments.
- Disrupting water radiolysis chain, **addition of solvated electron scavengers diminishes the dose rate dependency of aerated samples ( $p > 0.05$ ). Phenomenon was observed with two different systems: nitrous oxide and sufficiently high concentrations of sodium nitrate.**
- Further investigations are necessary, though initial measurements show no dose rate dependency at 4% oxygen concentration in the 0.1 - 10 Gy/s range studied.
- Radiochemical measurements with X-rays pose a significant challenge due to dose distribution inhomogeneity, thus G-value errors of 5-10 % were observed. Additional systematic errors need to be taken into account due to dose distribution and dose-rate “ramp-up” time.
- **Study clearly indicates the role of solvated electrons (*and/or other products)* in radiochemical changes under UHDR irradiation of *FLASH* therapy. These results justify usage of solvated electrons as possible surrogate parameter in studying various UHDR effects.**

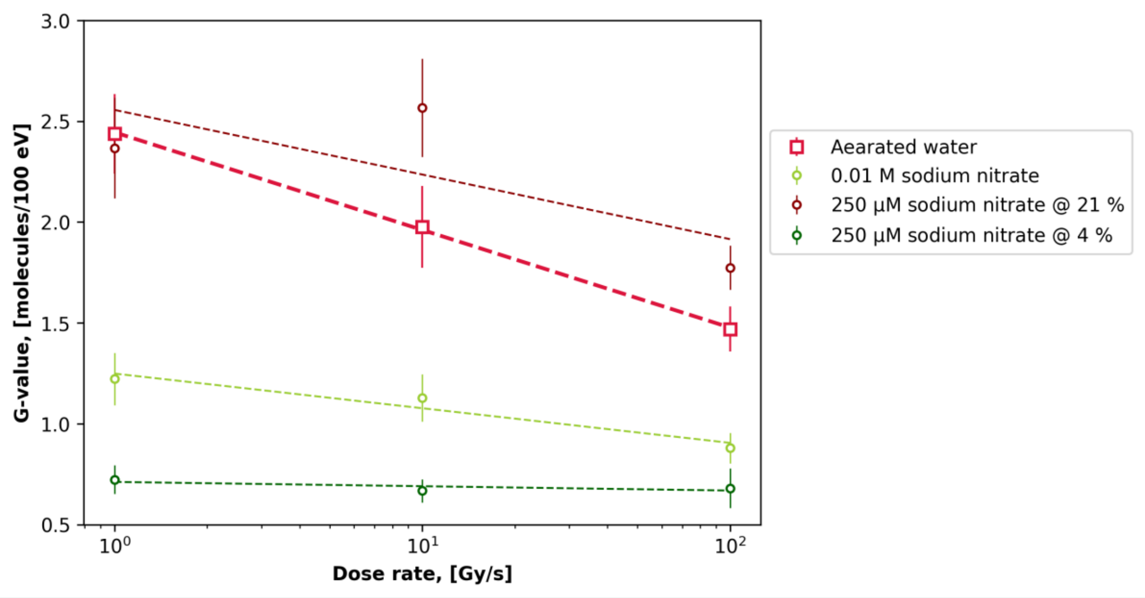
# Future outlooks

## Modelling studies

- Continuation of previous modelling studies regarding scaling of dose threshold aspect of *FLASH* effect for heavy ions
- Experimental measurements with X-rays need to relatated to modelling results with heavy ions. **On-going radiochemical interaction simulations under UHDR irradiation, to be expanded towards LET dependency**
- *In context of PhD project – usage of radiochemical findings for technological delivery of UHDR beams*

## Additional experiments

- Following the developed methodology, additional experiments were performed at **DESY PITZ *FlashLab* with electrons**
- 18 MeV beam with 10x10 FWHM beam – **challenging and inhomogeneous distribution**
- Average dose rates of 1, 10 and 100 Gy/s studied
- Average dose rate of 100 Gy/s studied with two different pulse dose rates
- Measurement analysis undergoing, **though initial findings suggest same phenomena as observed**



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# Thank you for your attention!