

JULY 2025 – LARD – STERCKX NICOLAS

TIME-RESOLVED DOSE RATE MODELING WITH GEANT4-DNA :

A STEP-BY-STEP APPROACH FOR RADIATION CHEMISTRY

SOMMAIRE

01

GENERAL CONTEXT P.03

The growing challenge in radiotherapy	P.03
Why Chymistry matters in radiotherapy	P.04

02

TOOLS P.05

Monte Carlo track structure code (MCTS)	P.05
Geant4-DNA: Monte Carlo Track Structure Simulation Toolkit	P.06

03

GENERAL PROBLEM P.07

Physics is Instantaneous — Chemistry is Time-Dependent	P.07
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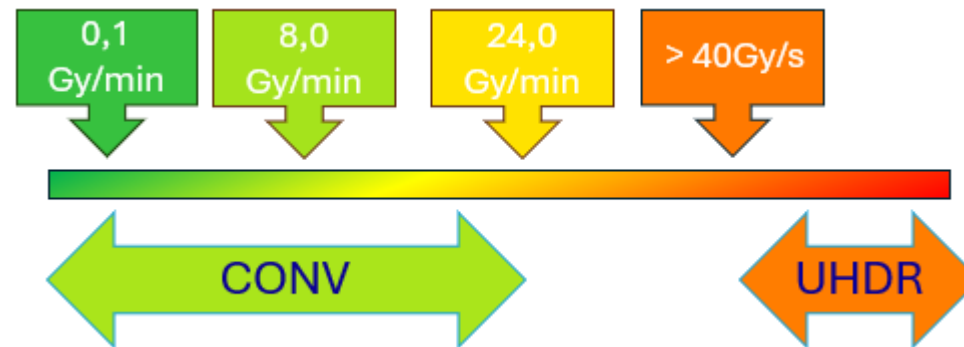
04

IMPLEMENTATION AND EARLY RESULT P.08

Geometry Overview	P.08
Breaking down the time-resolved model	P.09
Validation of this work	P.10
Comparison of This work with and without intertrack	P.12
Illustration of the dose rate effect	P.14
Comparison of Dose Rate Effects With and *Without Intertrack Interactions	P.15

THE GROWING CHALLENGE IN RADIOOTHERAPY

- CANCER INCIDENCE IS INCREASING WORLDWIDE
- RADIOTHERAPY : ESSENTIAL TREATMENT FOR ~50% OF ALL CANCER PATIENTS
- CONVENTIONAL DOSE RATES : ~0.1-2 GY/MIN (CONTINUOUS DELIVERY)
- EFFECT OF DOSE RATE ON DNA DAMAGE BUT NOT ACCOUNTED FOR IN MECHANISTICAL SIMULATIONS
- FLASH RADIOTHERAPY : ULTRA-HIGH DOSE RATES (UHDR) > 40GY/S (SHORT PULSES).
- FLASH EFFECT : BETTER NORMAL TISSUE SPARING – MECHANISM UNCLEAR.
- QUESTION : COULD RADIATION CHEMISTRY EXPLAIN DOSE RATE EFFECTS ?



WHY CHEMISTRY MATTERS IN RADIOTHERAPY ?

- RADIATIONS INTERACT WITH WATER – THE MAIN COMPONENT OF BIOLOGICAL TISSUE
- GENERATES IONIZATIONS AND EXCITATIONS IN FEMTOSECOND SCALE
- LEADS TO FORMATIONS OF REACTIVE CHEMICAL SPECIES (RADICALS) :
 - $\text{OH}\cdot$, $\text{H}\cdot$, e^-_{aq} , H_2O_2 , etc
- INDIRECT DNA DAMAGE :
 - Radicals diffuse, react. $\text{OH}\cdot$ radicals and attack DNA backbone leading to strand breaks
 - Majority of DNA damage radiation is indirect
- HETEROGENEOUS CHEMISTRY STAGE EVOLVES OVER ps TO μs TIMESCALE
- TIME-RESOLVED MODELING IS NEEDED TO CAPTURE RADICAL DYNAMICS UNDER VARYING DOSE RATES

Monte Carlo Track Structure Code (MCTS)

- WHAT IS MCTS :

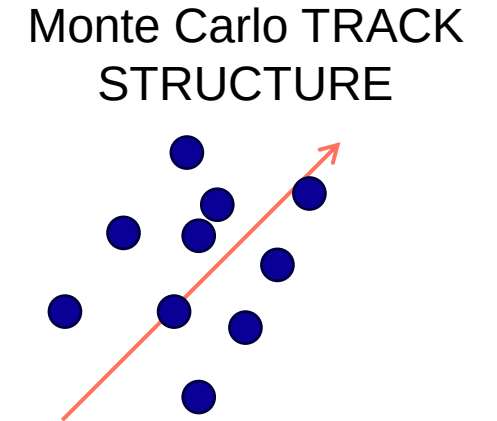
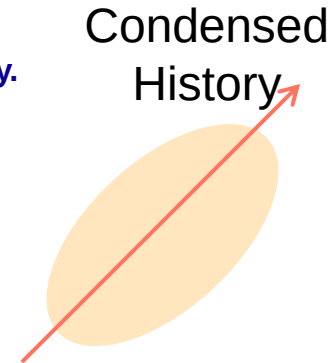
- Simulates each individual interaction of radiation with matter in a discrete way.
- Resolves energy deposition sites in space at nanometer scale
- Follows the particle down to very low energy (thermalization for e-)

- CONTRAST WITH CONDENSED HISTORY MODELS :

- Average over many interactions → lose special details
- Suitable for dose calculations, but insufficient for molecular-level damage modelling

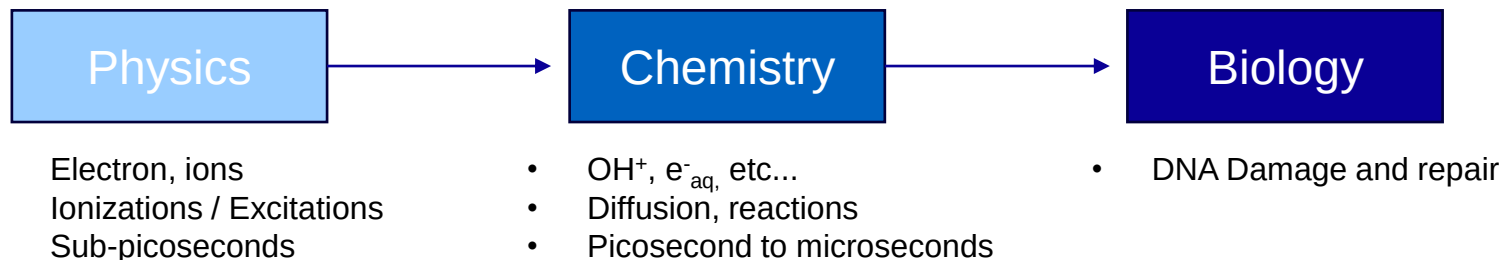
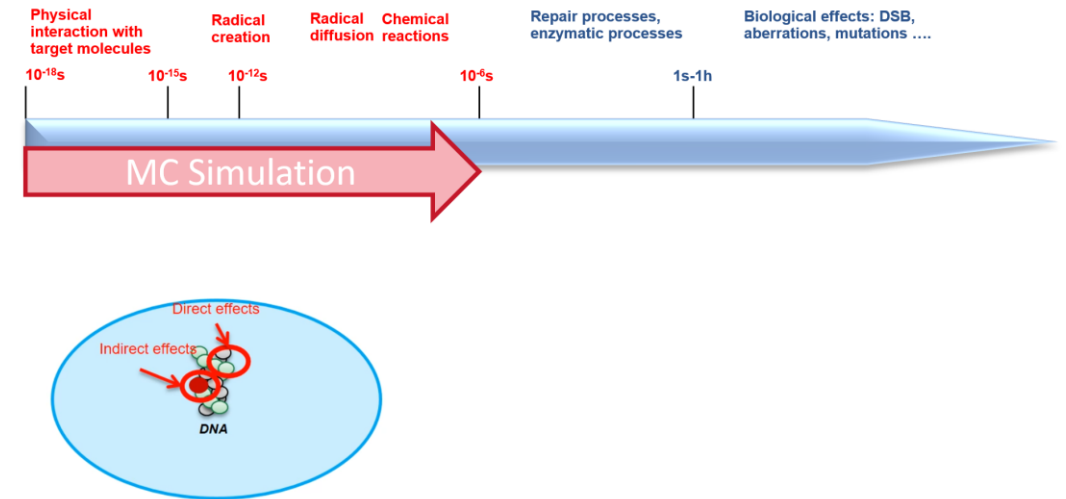
- WHY DO WE NEED MCTS ?

- Need to nanometric resolution due to target dimensions (DNA elements)
- DNA double-strand breaks (DSBs) often occur from clustered damage
- Spatial distribution of radicals affects the chemical reactions (recombination vs damage)



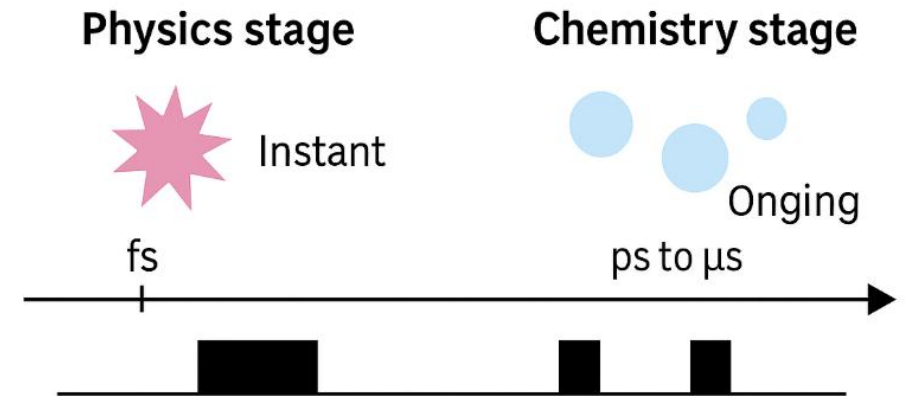
GEANT4-DNA: MONTE CARLO TRACK STRUCTURE SIMULATION TOOLKIT

- GEANT4-DNA = MCTS FRAMEWORK ADAPTED TO THE UNDERSTANDING OF THE ACTION OF RADIATIONS ON BIOLOGICAL MEDIA
- FULLY INTEGRATES :
 - Physics stage (fs) : ionizations, excitations, elastic scatterings
 - Chemistry stage (ps to μ s) : radical formation, diffusion, reactions
 - (Optional) Biology stage : Repair of DNA damage
- BASED ON ADAPTED CROSS-SECTIONS FOR ELECTRONS, PROTONS, ALPHA PARTICLES
- FULLY SPATIALLY RESOLVED DOWN TO nm SCALE
- OPEN-SOURCE, WIDELY USED IN RADIOBIOLOGY AND MEDICAL PHYSICS
-  LIMITATION : BY DEFAULT, ASSUMES ALL PARTICLES ARE INDEPENDENT



PHYSICS IS INSTANTANEOUS — CHEMISTRY IS TIME-DEPENDENT

- PHYSICS STAGE : INSTANTANEOUS IONIZATIONS & EXCITATIONS (fs SCALE)
- HETEROGENEOUS CHEMISTRY STAGE : RADICALS DIFFUSE AND REACT OVER ps TO μ s
- PROBLEM FOR DOSE RATE MODELLING
- DEFAULT GEANT4-DNA CONSIDERS ALL PARTICLES ARE INDEPENDENT
- NO CONSIDERATION OF INTER TRACK EFFECT
- AT HIGH DOSE RATES :
 - Overlapping radicals from different tracks
 - Radical recombination depends on the temporal overlap.
- NEED TIME-RESOLVED INJECTION TO CAPTURE DOSE RATE EFFECTS REALISTICALLY



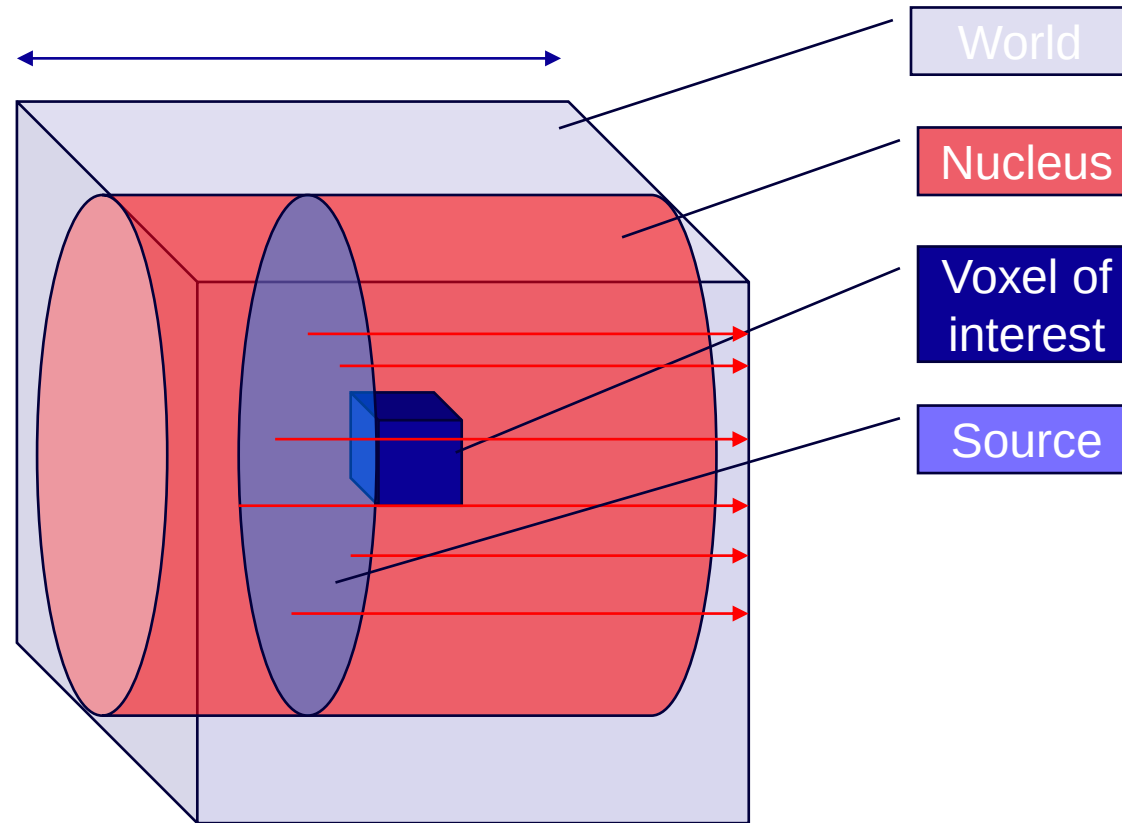
GEOMETRY OVERVIEW

- World 10 μ m side
- Voxel of interest 5 μ m size
- Physic list option 2
- Chemistry List option 2 et 3
- Number of particle dependent of the dose threshold
- 15 MeV Protons

→ Dose computed in the nucleus

→ Deposition of energy along the track of the particle

→ Physical track independent but chemical track dependant



BREAKING DOWN THE TIME-RESOLVED MODEL

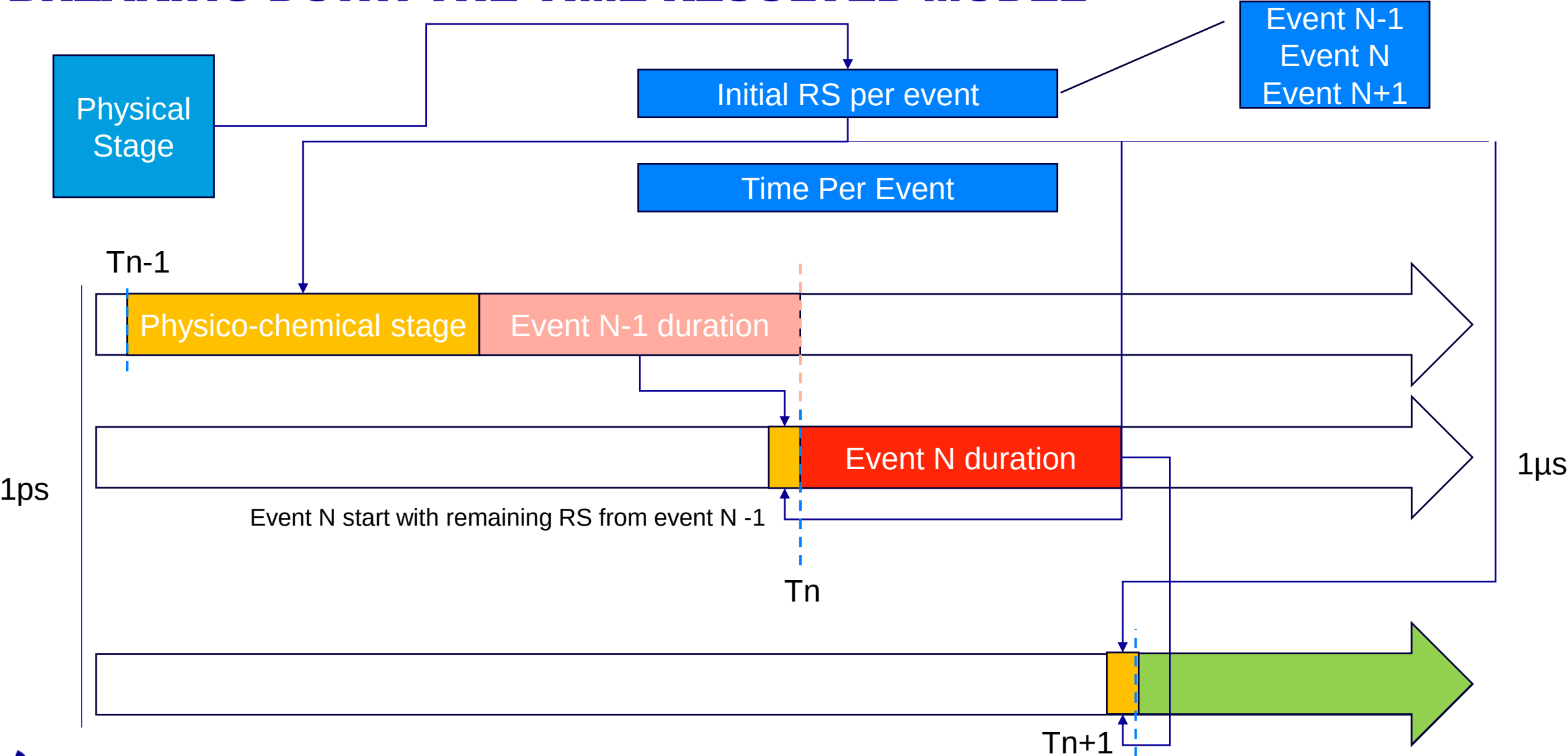
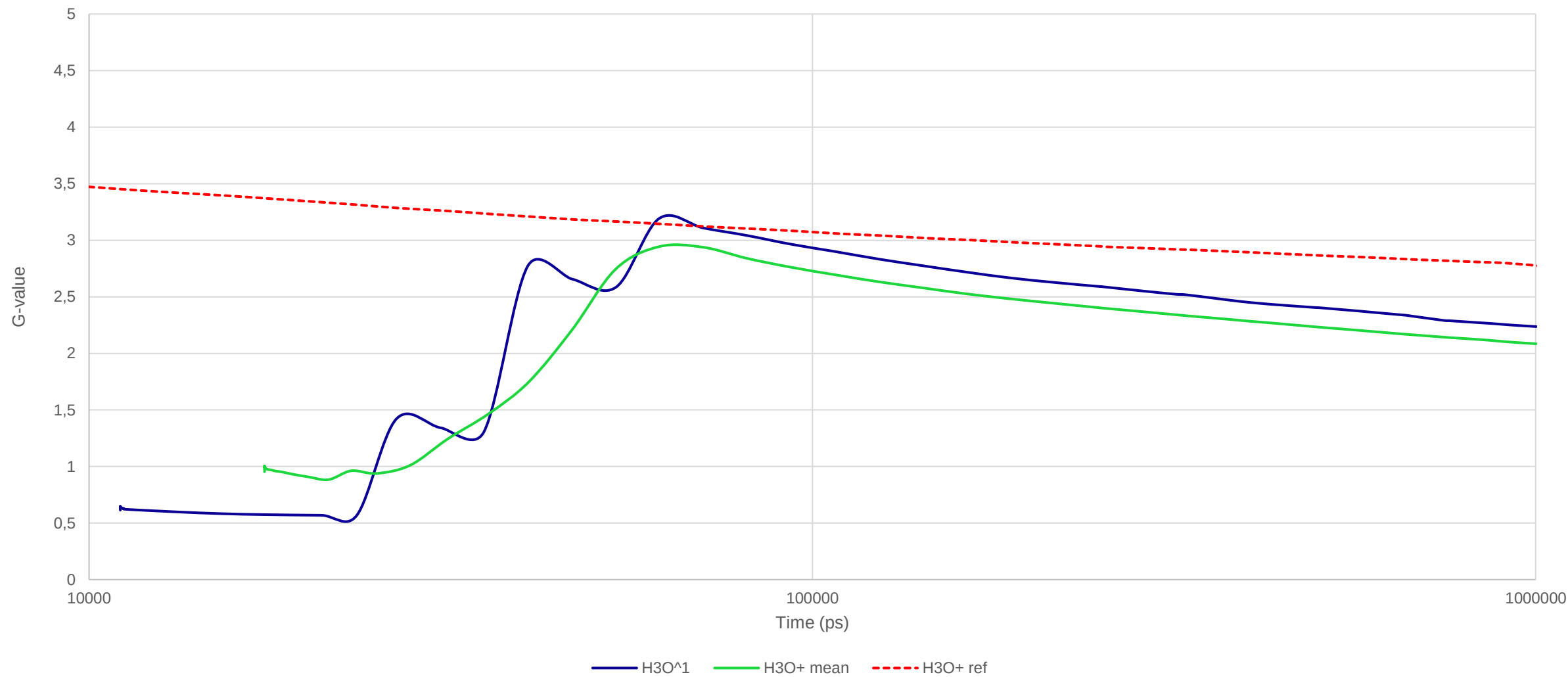
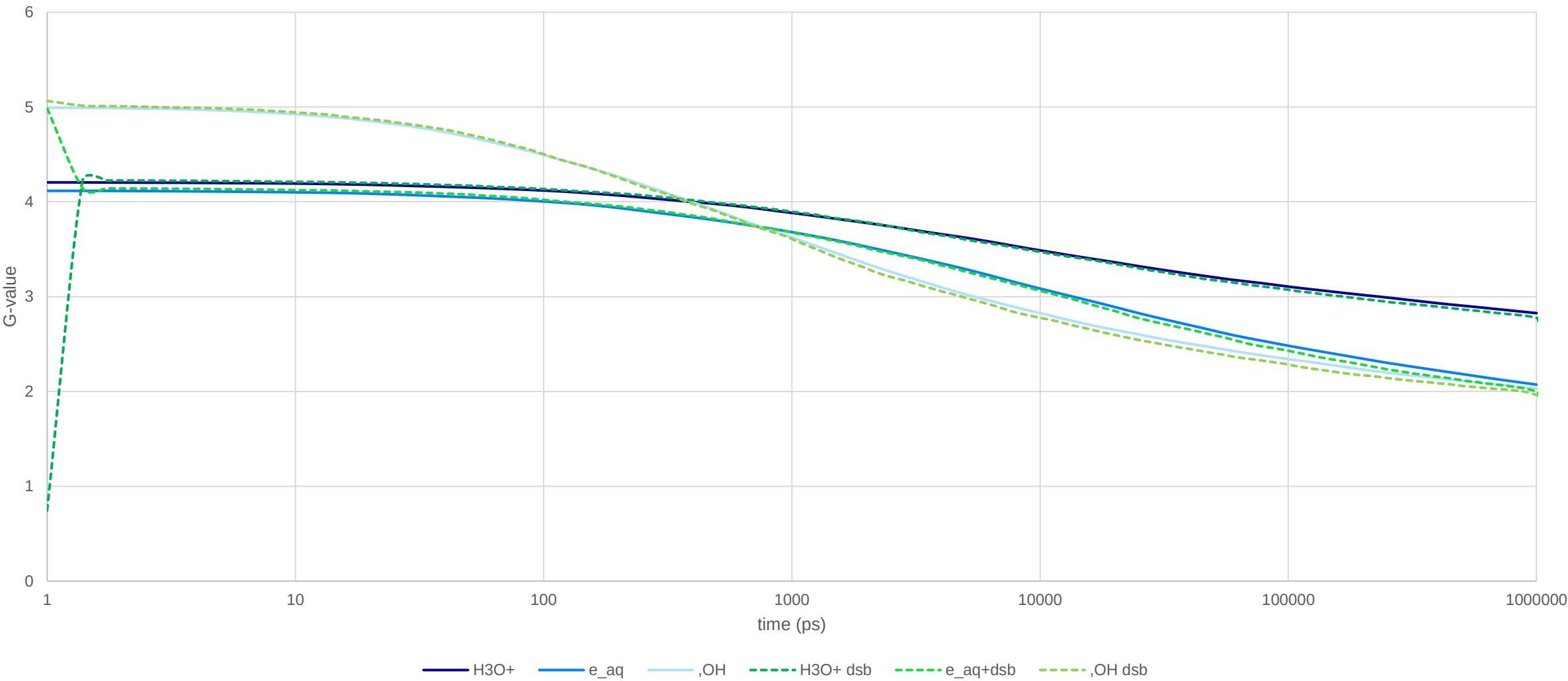


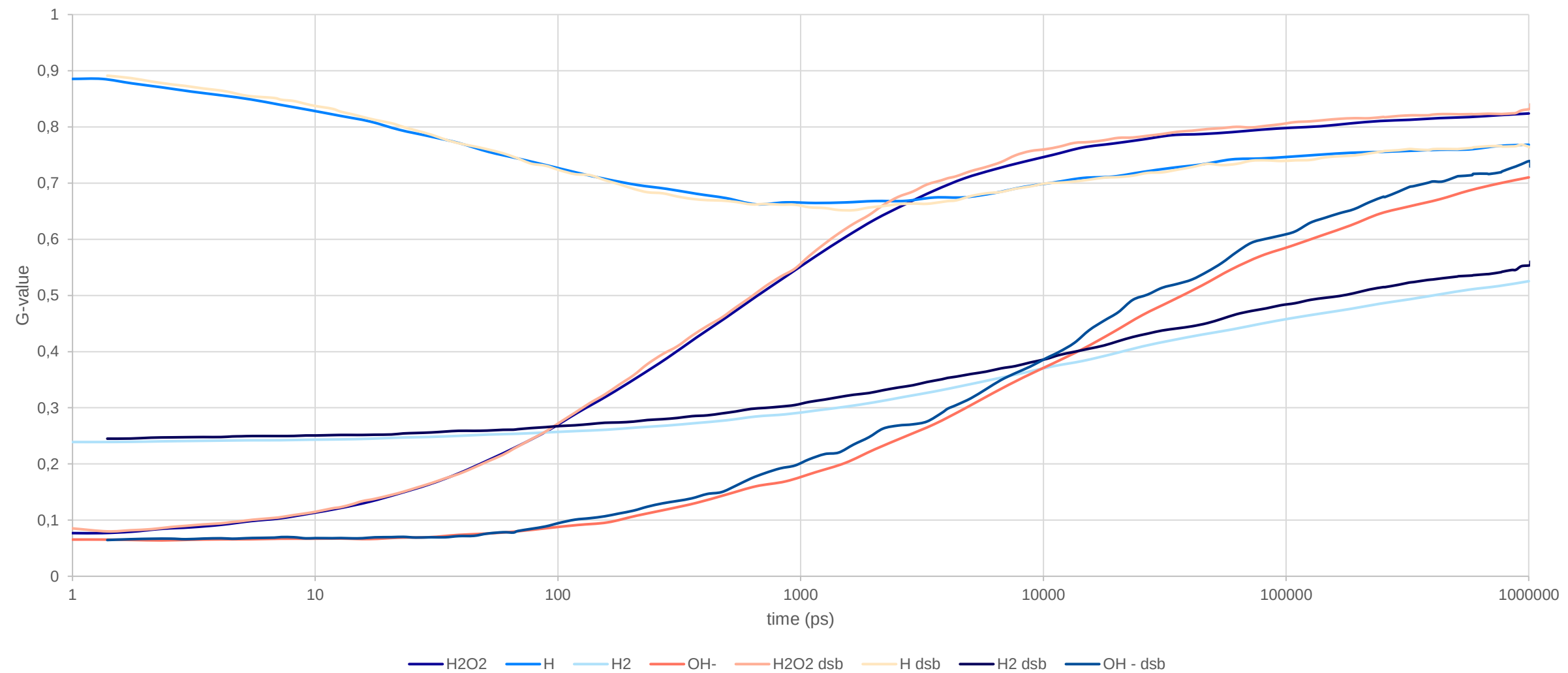
ILLUSTRATION OF THE DOSE RATE EFFECT



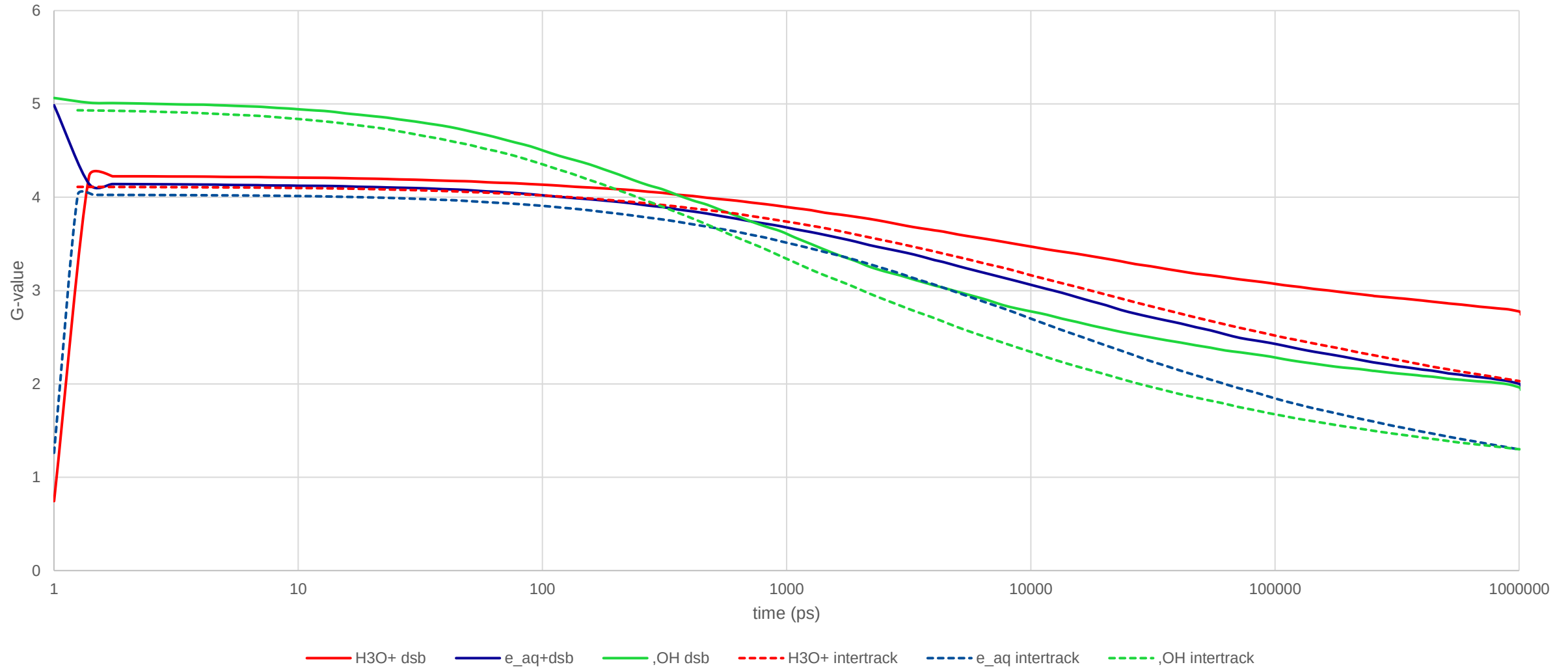
VALIDATION OF THIS WORK (1)



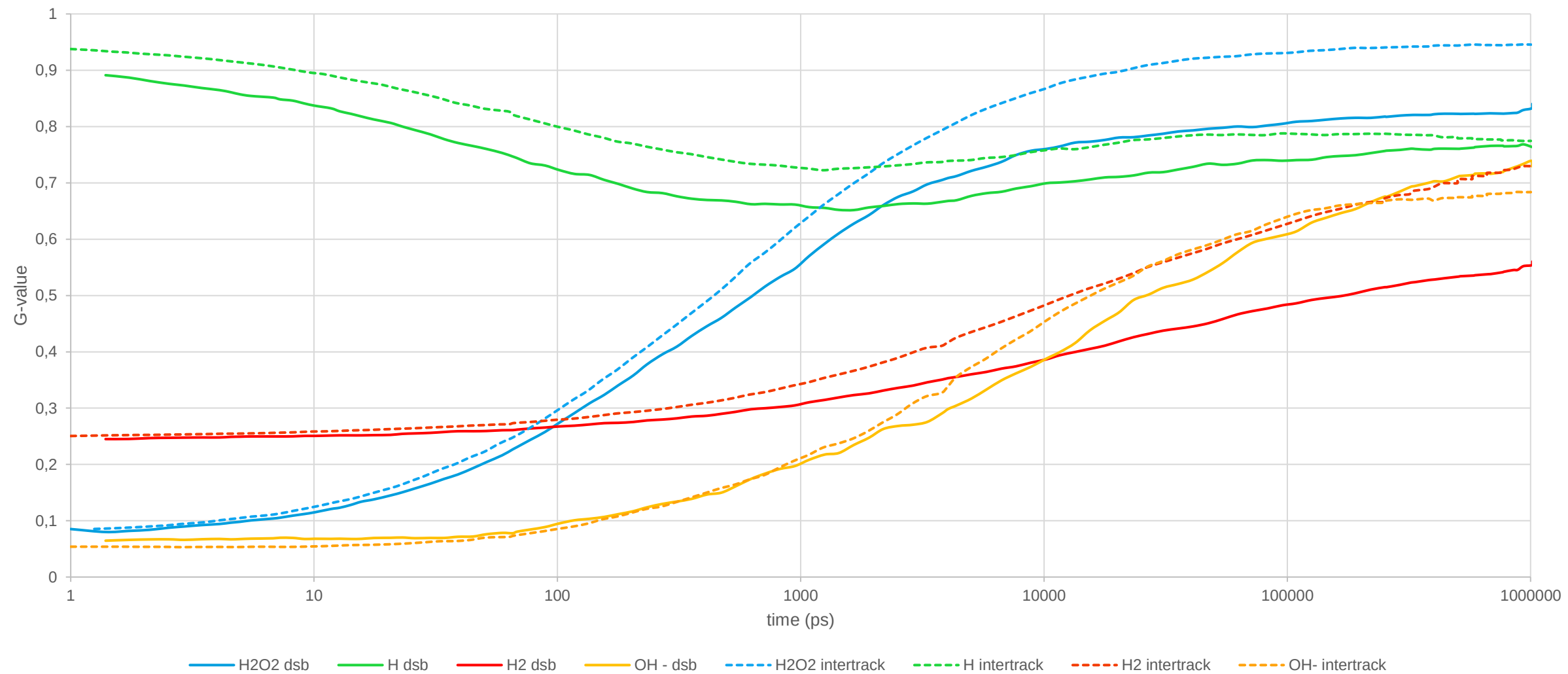
VALIDATION OF THIS WORK (2)



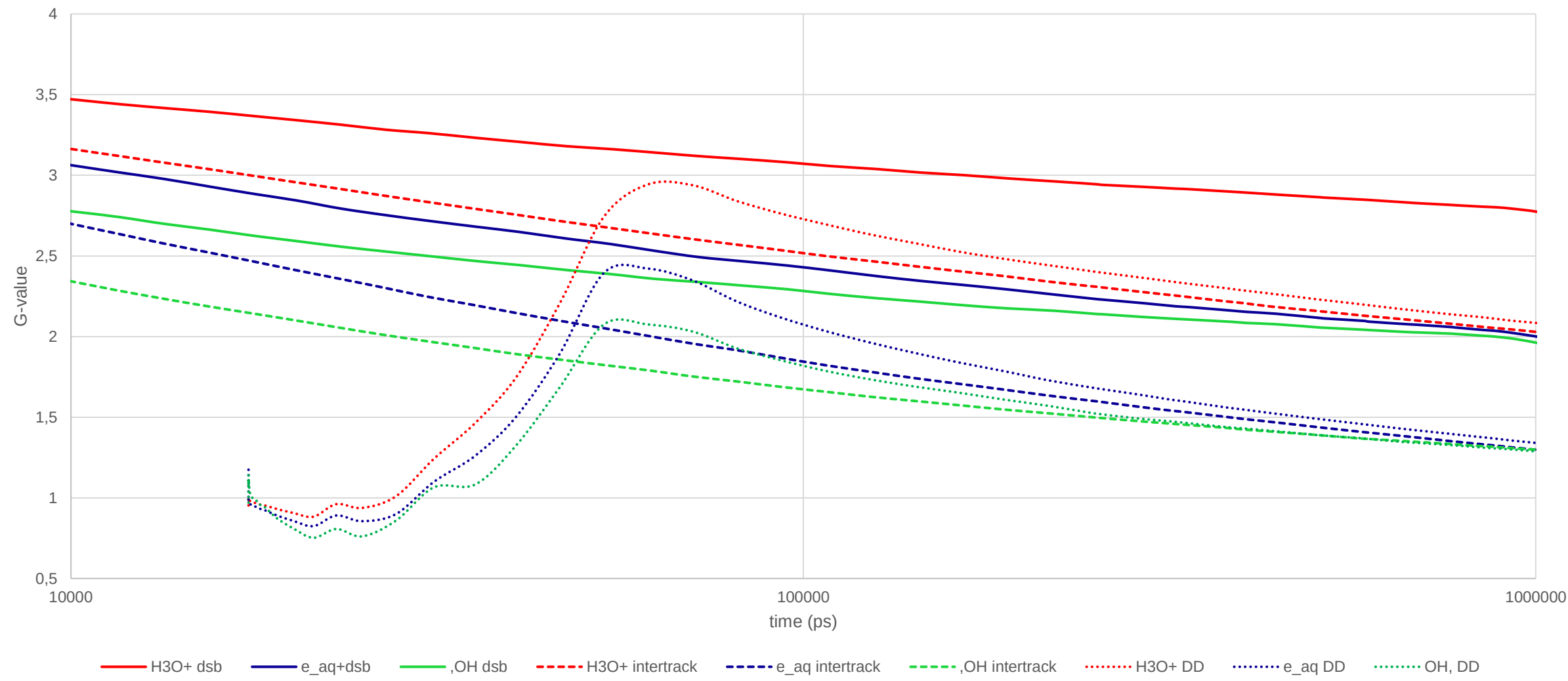
COMPARISON OF THIS WORK WITH AND WITHOUT INTERTRACK(1)



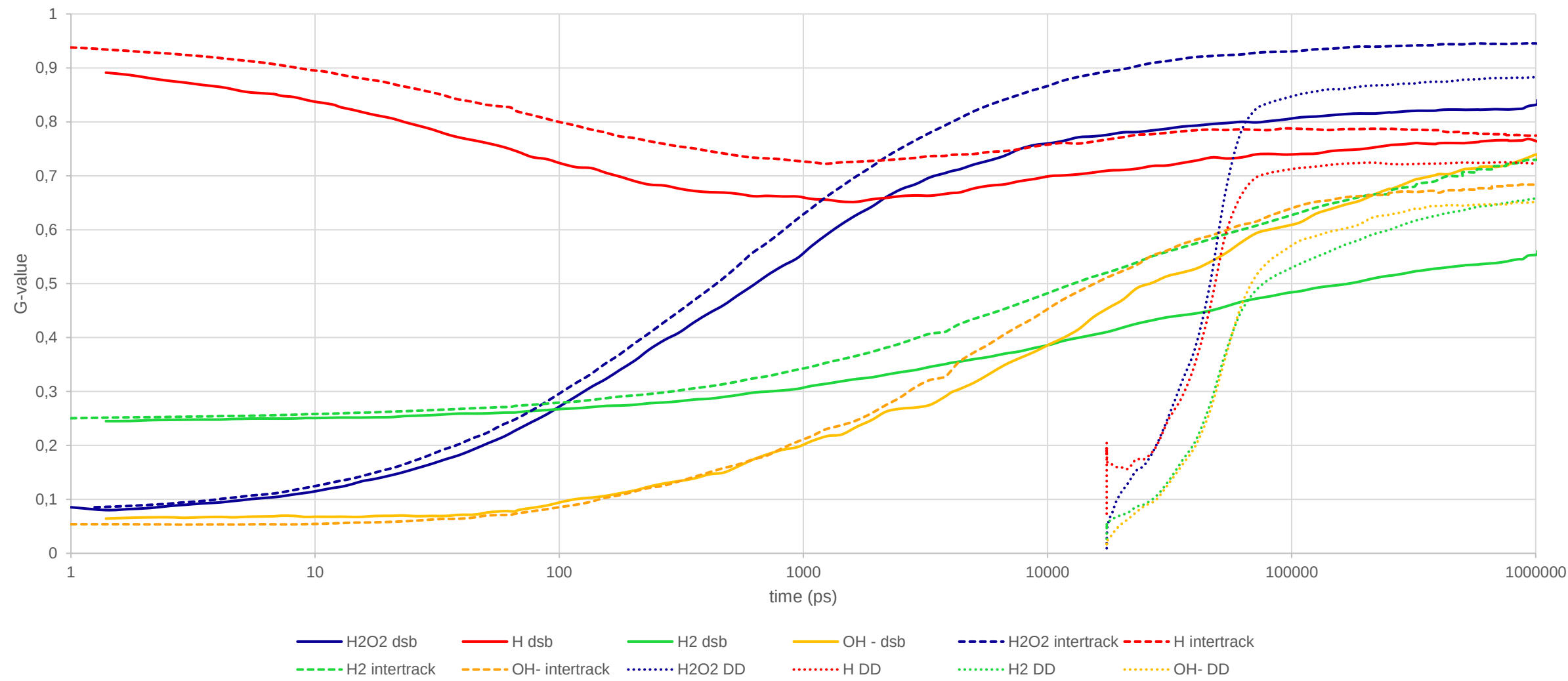
COMPARISON OF THIS WORK WITH AND WITHOUT INTERTRACK (2)



COMPARISON OF DOSE RATE EFFECTS WITH AND WITHOUT INTERTRACK INTERACTIONS(1)



COMPARISON OF DOSE RATE EFFECTS WITH AND WITHOUT INTERTRACK INTERACTIONS (2)



CONCLUSION & OUTLOOK

1. WHAT HAS BEEN DONE :

- Implementation of an initial framework to model various dose rate.
- illustrate the potential impact of intertrack on G-value

2. LIMITATIONS

- limited simulation time windows of 1 μ s
- No inclusion of scavenger or cellular environment yet

3. WHAT'S NEXT

- Implementation of scavenger
- Extend simulation so each molecule live at least 1 μ s (consideration of individual molecule life)
- Explore biological outcome (DSB, SSB, etc)
- Potential exploration of FLASH modelling