THE
Tuscany Health Ecosystem

A minimalistic phenomenological model of the FLASH effect.

I.Bodrenko, V.Tozzini

CNR-NANO, Pisa

CNR-NANO in Sub-project 2

Molecular mechanisms, in vitro validation and radiobiological effect modelling of ultra-high dose rate

- ✔ modeling & simulations
- ✔ cross-validation theory-experiment
- ✔ statistical data analysis

People @ NANO

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Collaborations

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Emanuele Scifoni	INFN-TIFPA Tn
Lorenzo Petrolli	UnitTn

CPFR: F Di Martino, Fabiola Paiar, S Capaccioli, E Da Pozzo,…

M1.2.1 Developed and implemented multi-scale procedure for the in silico simulation of the UHDR

M1.2.2 Radiobiological effects at UHDR vs. CONV and radiation parameters

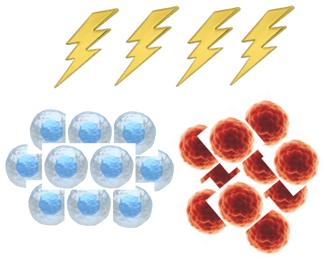
M1.2.3 Developed and implemented a database for sharing, elaborating and combining data from experiments and simulations

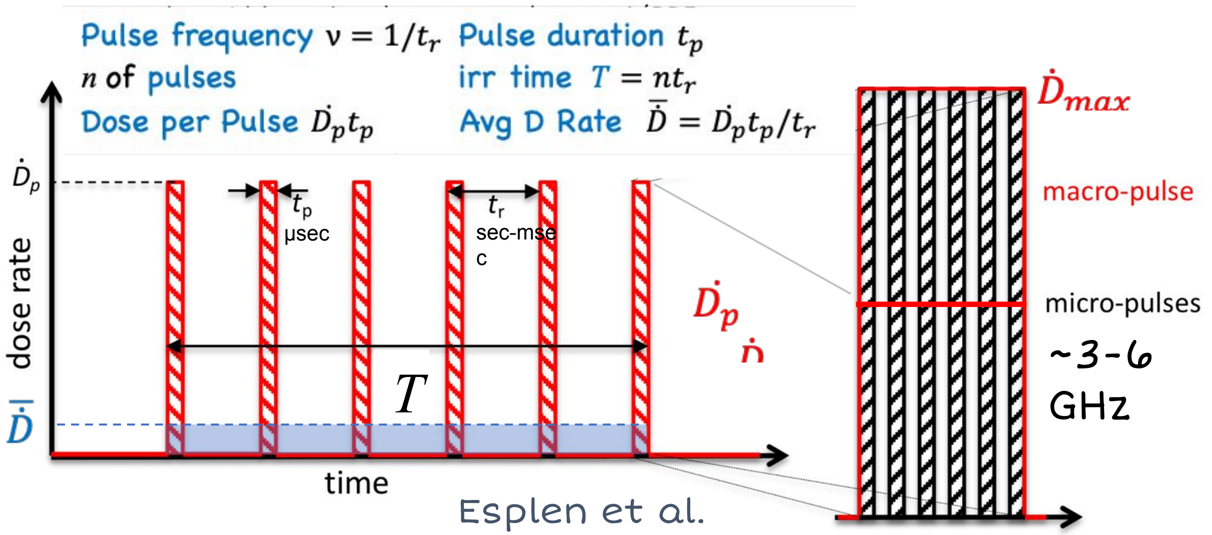
FLASH effect in a nutshell

- ✔ UHDR kills cancer cells and spare normal cells
- ✔ Pulsed radiation enhances this effect

Irradiation parameters

- ✓ Average dose rate and delivery time $\bar{\dot{D}}, T$
- ✓ Total delivered dose $D = \bar{\dot{D}} \times T$
- ✓ Width and separation of the pulses t_p, t_r
- ✓ Peak dose rate $\dot{D}_p = \bar{\dot{D}}\, t_r / t_p >$ 40Gy/s
- ✓ Intra-pulse structure: GHz modulation





Esplen et al. PMB 2020

Effect characterization: Define a function $\mathbf{F}(\bar{\dot{D}}, D, \dot{D}_p, \nu, \ldots)$ **"Flash modifying factor"** such that

- ✓ F describes the change of radiobiological effects in FLASH conditions → $\mathbf{F}(\bar{\dot{D}}, D, \dot{D}_p, \nu) < 1$ **= sparing**
- ✓ $\mathbf{F}(\bar{\dot{D}}, D, \dot{D}_p, \nu, \ldots) = 1$ in conventional irradiation conditions (**> 1 = overkilling)**
- ✓ F is expected to depend on: tissue type AND cell state (=cancer/normal) $\mathbf{F} = \mathbf{F}_{tiss,state}$

Selective FLASH effect: For given tissue $F_{tiss,normal} < F_{tiss,cancer}$ in some part of the $(\bar{\dot{D}}, D, \dot{D}_p, \nu)$ parameter space

FLASH effect in Normal Tissue Complication Probability

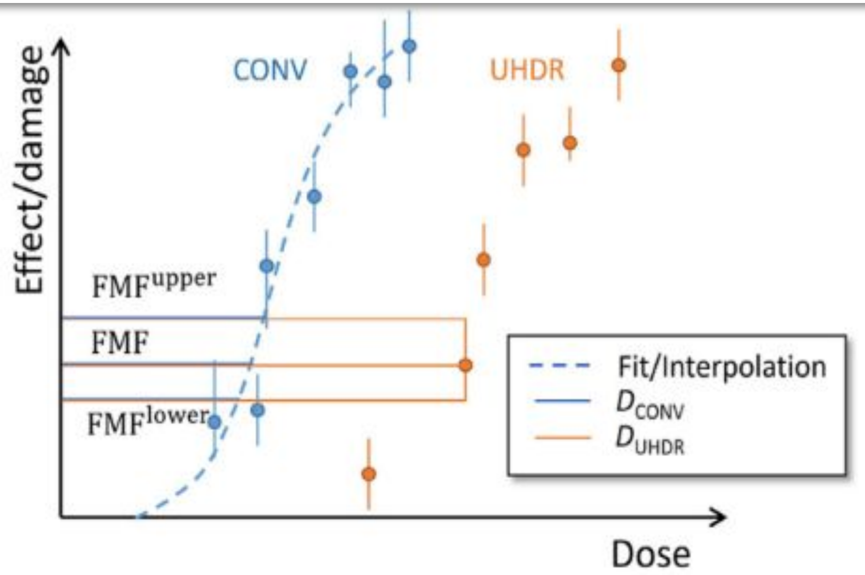


Fig. 1. Conversion of dose-effect data to FLASH-modifying factor (FMF) values for in vivo data. Datapoints were used for ultrahigh dose rates (D_{UHDR}), and interpolated values for conventional dose rates (D_{CONV}). Uncertainties for FMF values (FMF^{upper} and FMF^{lower}) were obtained according to the same procedure but using the upper and lower error bar for the UHDR data, if available.

Definition of FLASH-modifying factor

Analogous to the definition of relative biological effectiveness for different radiation qualities,[25] the FLASH-modifying factor (FMF) for UHDR irradiations is defined as the ratio of doses that need to be administered at conventional dose rates (D_{CONV}) and UHDR (D_{UHDR}) to achieve an isoeffect for a given biologic system and endpoint:

$$FMF = \frac{D_{CONV}}{D_{UHDR}}\bigg|_{isoeffect} \quad (1)$$

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PHYSICS CONTRIBUTION

Normal Tissue Sparing by FLASH as a Function of Single-Fraction Dose: A Quantitative Analysis

Till Tobias Böhlen, PhD,* Jean-François Germond, PhD,* Jean Bourhis, MD, PhD,† Marie-Catherine Vozenin, PhD,† Esat Mahmut Ozsahin, MD, PhD,† François Bochud, PhD,* Claude Bailat, PhD,* and Raphaël Moeckli, PhD*

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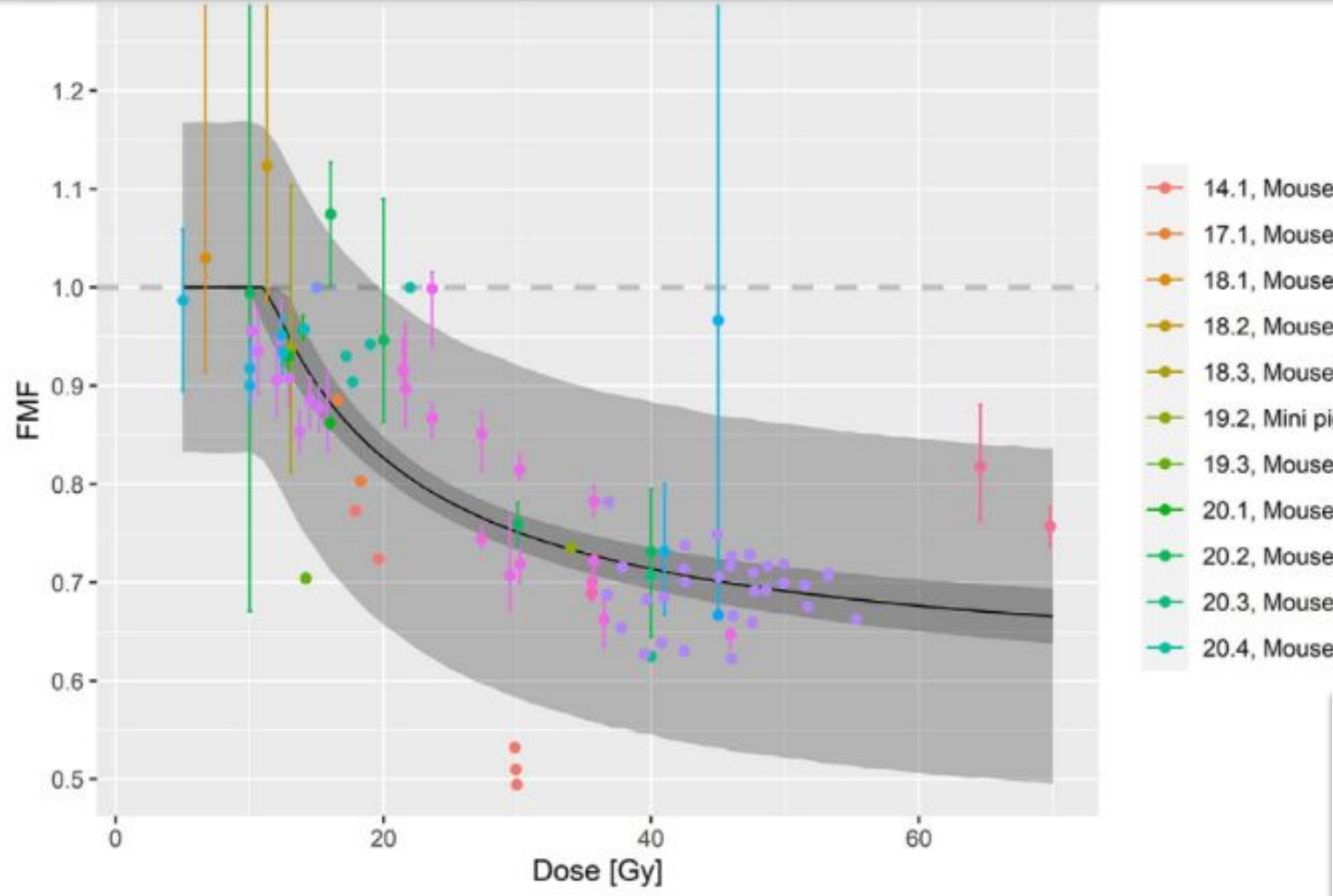

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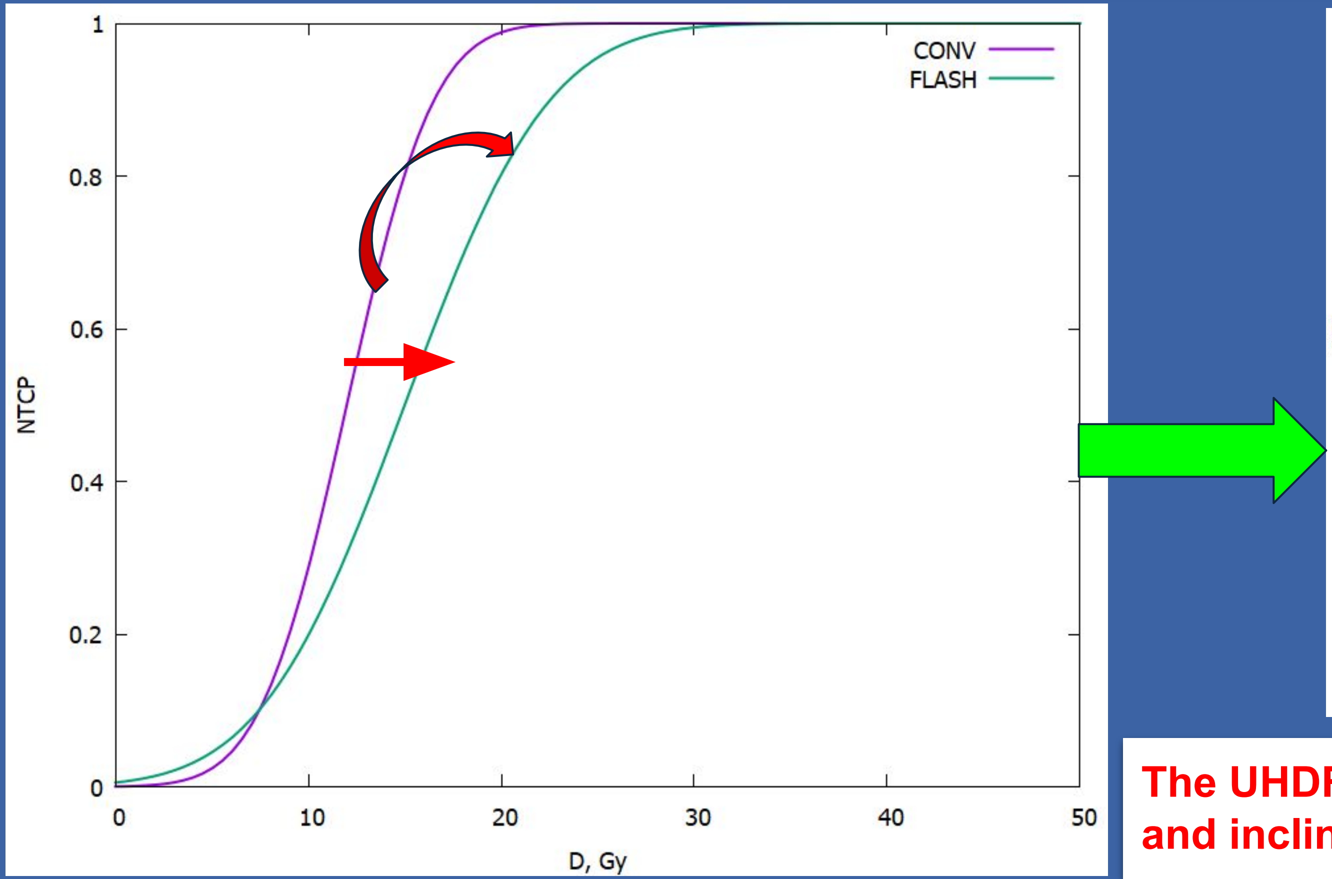

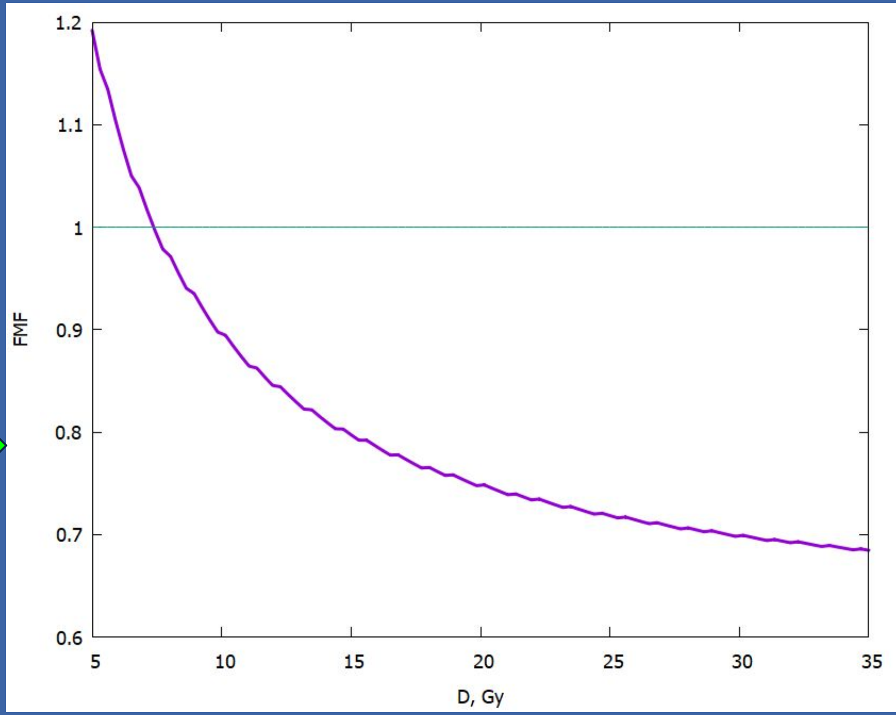

The UHDR response curve is shifted to higher doses and inclined with respect to the CONV one.

Radiation response processes and the temporal scales

< 100 fs	100 fs - 1 us	1 us - 10 ms	> 10 ms
- primary electron crosses the cell (40 fs) - secondary electrons slow down (10 fs) - track termalization (10 fs)	- generation of initial ions/radicals - diffusion of ions within the track	- chemical reactions of ions and radicals - **diffusion of ions/radicals within the cell**	- biochemical reactions within the cell - cellular response - intercellular interactions

UHDR effect, kGy/s

Phenomenological stochastic model

Local cellular damage:

- direct and indirect local damage to the biomolecules
- <10 ms, < 100 nm

Biological response to the local damage

- >10 ms
- generation of cellular ROS, oxygen depletion
- damage of organelles
- cell malfunction or death
- tissue damage, etc.

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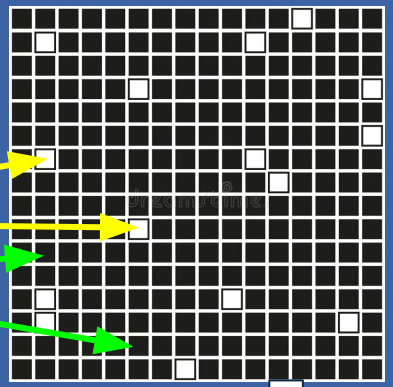
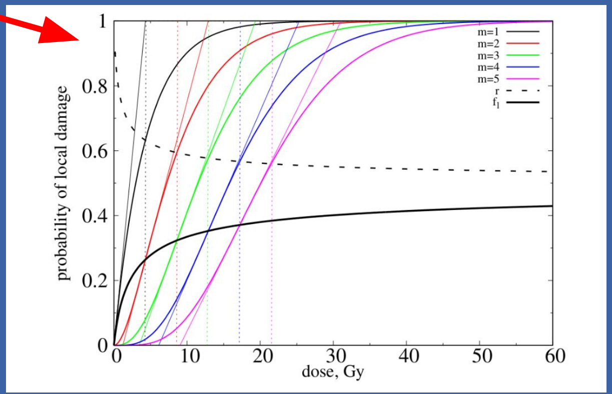
Threshold model (extended STMH)

- the damage certainly happens if **m** or more electrons hit the site, equivalent of the threshold concentration of ions/primary radicals, **$n_c = m * n_0$ (probability 1)**;
  - it does not happen otherwise **(probability 0)**;
- sigmoidal cumulative Poissonian distribution;
- strong mesoscopic spatial fluctuations of ions/radicals concentration;
- the fluctuations of ion concentration dissipate due to recombination and diffusion in competition with the new ions generation at a given dose rate **R** - UHDR effect !!!





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Minimalistic multiple sites model of the cell damage - (extended MTMH)

- there are $\mathbf{M_C}$ critical sites in the cell;
- If the radiation causes local damage to at least any $\mathbf{M_P}$ of them the cell gets damaged with (**probability 1);**
  - otherwise the cell can be fully repaired (eventual biological effect **probability equals 0**).
- sigmoidal cumulative binomial distribution;

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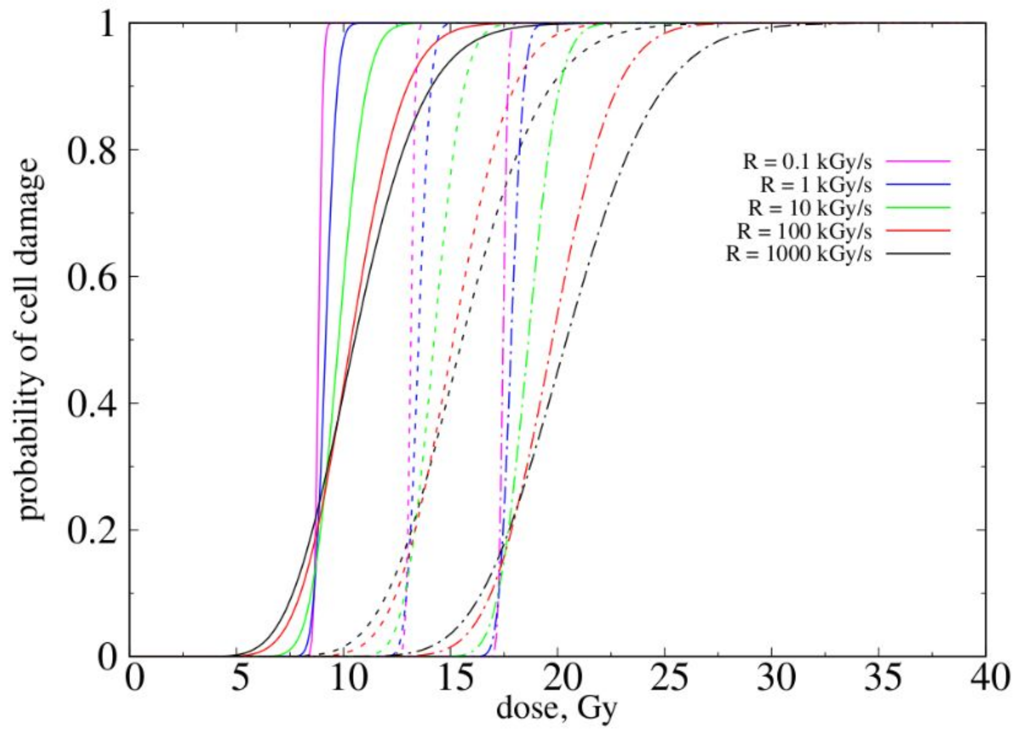

Figure.6.1.-1. The FLASH effect. The cell damage probability vs the absorbed dose and the dose rate (coded by different colors) for $\alpha_c = 2$ (solid lines), 3 (dashed lines) and 4 (dot-dashed lines). For all cases $\beta_{cd} = 0.8$, $M_c = 10$, $\lambda_r = 1/600\ s^{-1}$, $D_w = 0.01\ nm^2/ns$.

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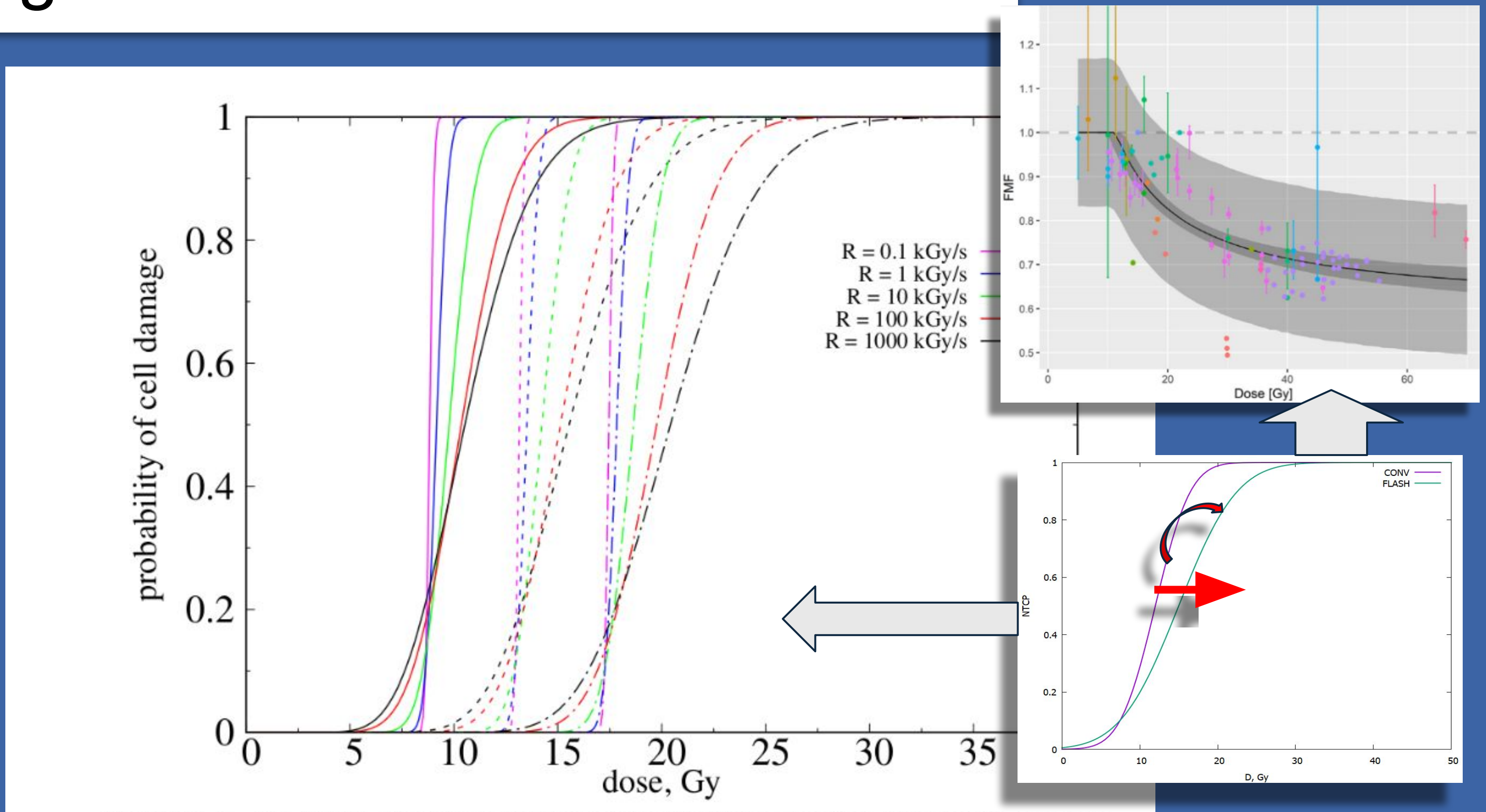

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Phenomenological stochastic model: conclusions and plans

- We have pointed out a new mechanism of the Ultra High Dose Rate dependance of the biological response to ionizing radiation - the homogenization of the radiation-generated ion/radical concentration due to the inter-track diffusion.
- We present a simple theory of the diffusive relaxation of mesoscopic, non-thermodynamic fluctuations of radical concentration and its application to the dose rate (FLASH) effect in radiotherapy.
- The conclusions of the model are in qualitative agreement with the recent review [Böhlen et.al.] of the available experimental results of the FLASH sparring effect for normal tissue complications probability.
- In particular, the model predicts the increase of the FLASH effect at higher doses and also the threshold (minimal dose) below which the FLASH sparring is not observed.

- The model will be extended to a pulsed dose deposition especially in application to the electron beam RT (EBRT).
- The model in combination with ML techniques will be used to analyze the experimental data of the local damage and cellular damage in EBRT and to optimize the UHDR protocols.
- The model will be confronted with the systematic microscopic approaches and microdosimetric kinetic models in order to validate approximations and incorporate further improvements.

M1.2.1 Developed and implemented multi-scale procedure for the in silico simulation of the UHDR

- ✔ Interfacing different tools for multi-scale simulations
- ✔ Optimizing Hamiltonian and models
- ✔ Performing simulations

M1.2.2 Radiobiological effects at UHDR vs. CONV and radiation parameters

- ✔ Analyzing data and understanding phenomenology
- ✔ Developing predictive macroscopic models for the effect– irradiation parameters relationship
- ✔ Cross-validation of simulations-vs-experiment