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A Target-Level Oxygen Fixation Extension of the LPL Model Explains Oxygen-Mediated FLASH Trends

A mechanistic framework linking dynamic nuclear $pO_2(t)$, oxygen-dependent lesion fixation, repair, and cell survival

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ABSTRACT

Purpose: Extend the LPL model to include oxygen-dependent fixation of precursor lesions.

Methods: Couple repair/fixation kinetics to dynamic nuclear $pO_2(t)$ during UHDR irradiation and recovery.

Result: Sparing appears when oxygen depletion moves nuclei through the steep region of the OER curve.

Conclusion: The model predicts a low-to-moderate "Goldilocks" oxygen range governed by pulse structure and reoxygenation.

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INTRODUCTION

- FLASH sparing is promising but inconsistent across systems, suggesting that dose rate alone is not a sufficient explanatory variable.
- We extend the classical lethal–potentially lethal (LPL) framework by coupling precursor-lesion repair/fixation to time-dependent target-level oxygen.
- The model predicts that sparing emerges only when radiolytic depletion shifts nuclear $pO_2(t)$ through the steep part of the OER curve before reoxygenation restores oxygen.

MODEL DESIGN:

Three coupled processes

Precursor lesions compete between first-order repair and oxygen-dependent fixation while nuclear $pO_2(t)$ evolves during irradiation and recovery.

Component	Description
Dynamic nuclear $pO_2(t)$	Radiolytic oxygen depletion during UHDR irradiation plus vascular reoxygenation with a characteristic recovery time.
Oxygen-Dependent Fixation	Potentially lethal lesions fix into lethal lesions at a rate governed by local $pO_2(t)$ and the OER response.
Repair & Survival	Unfixed precursor lesions are repaired by first-order kinetics; survival follows from accumulated lethal lesions.

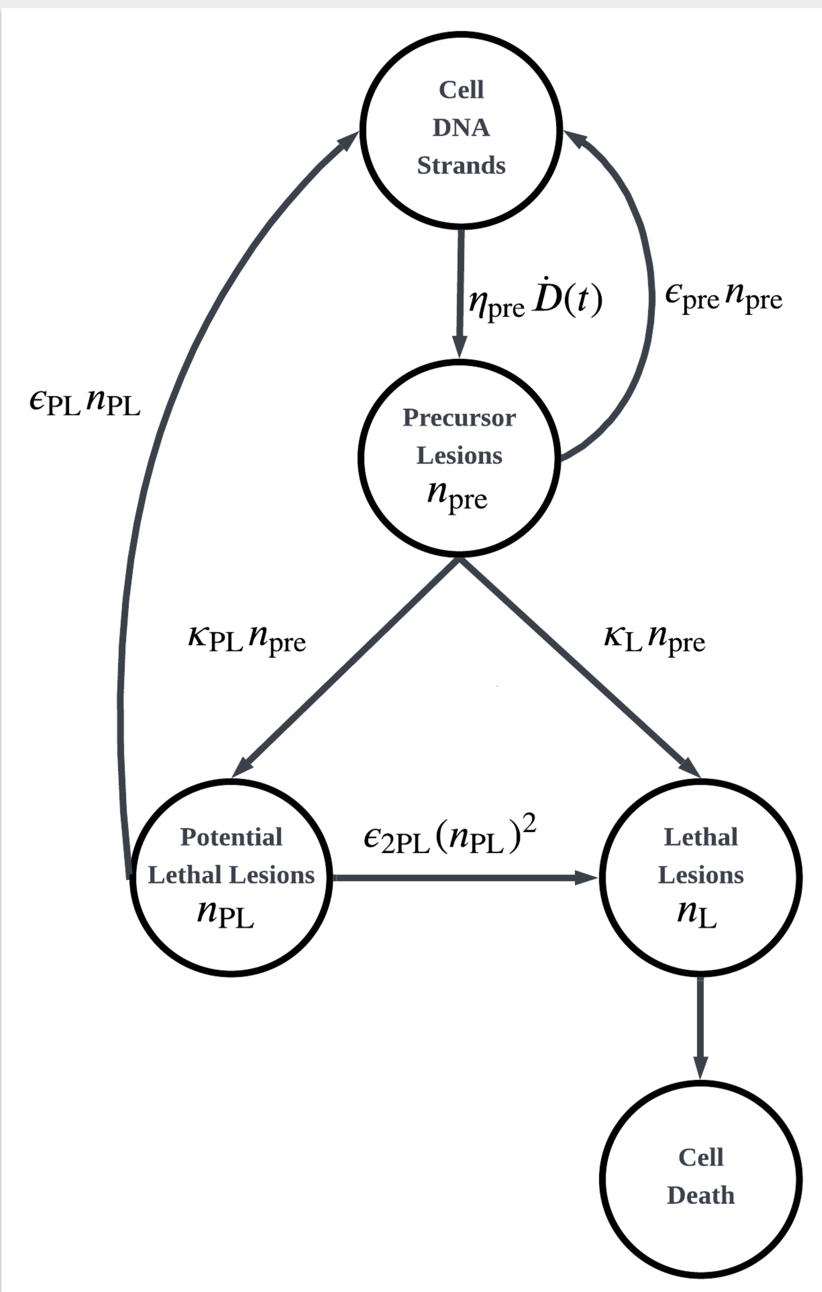


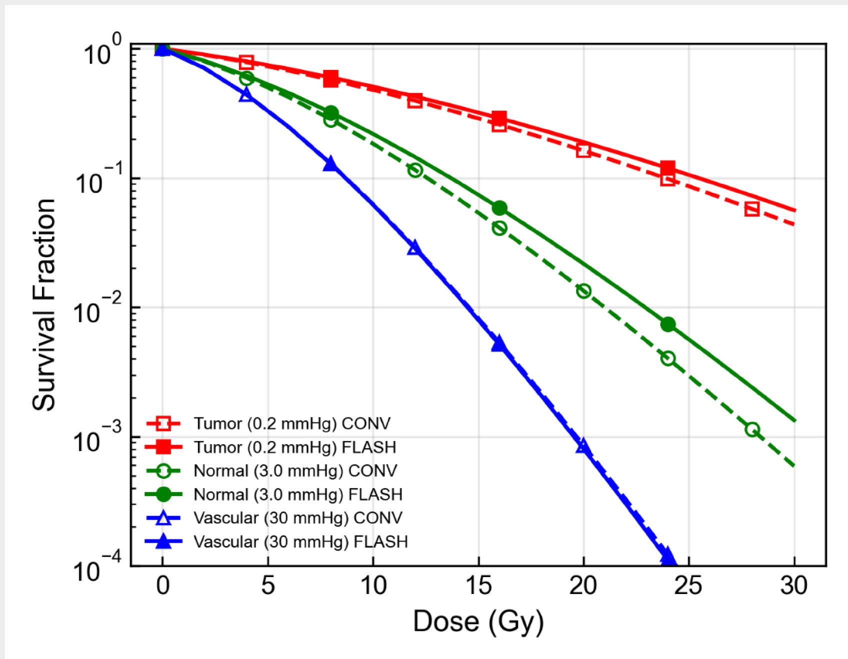
Fig 1: Coupled oxygen dynamics, repair, and fixation in the modified LPL model.

RESULTS

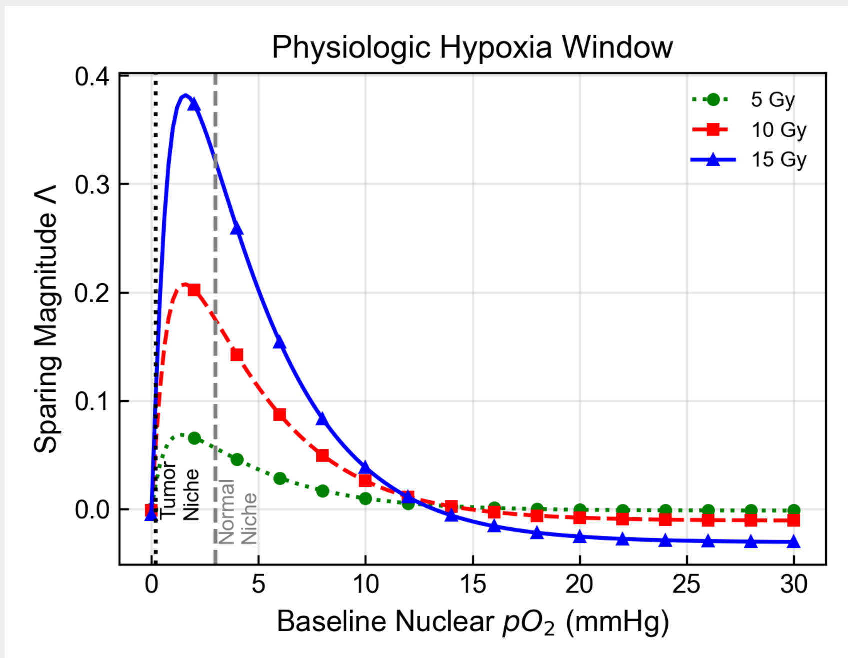
Take-home message

FLASH sparing requires the right baseline pO_2, oxygen depletion, and repair–fixation kinetics.

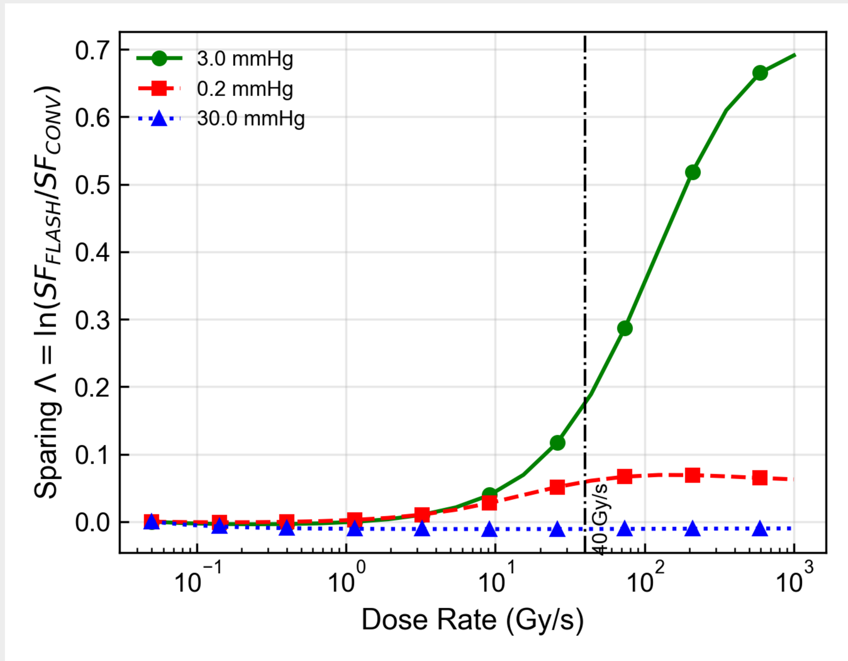
Factor	Finding
FLASH window	Sparing is maximized when radiolytic oxygen depletion, steep OER response, and delayed reoxygenation overlap.
Normoxic targets	OER is near saturation; modest oxygen depletion produces limited change in fixation probability.
Severely hypoxic targets	Limited oxygen remains to deplete; fixation is already reduced, so additional sparing is small.
Heterogeneous tissues	Only subregions in the oxygen-sensitive window show strong sparing; other oxygen states dilute the population-average effect.
Pulse structure	Dose per pulse, pulse duration, and inter-pulse interval shape the target-level $pO_2(t)$ trajectory.



A. Survival response depends on baseline oxygen.
FLASH = 40 Gy/s; CONV = 0.05 Gy/s.



B. FLASH sparing peaks in a low-to-moderate oxygen window.



C. Dose-rate response of FLASH sparing depends on baseline oxygen.
Simulations follow Zhou 2026.

CONCLUSIONS

- Oxygen-mediated FLASH sparing can arise from dynamic oxygen-dependent fixation without prescribing dose-rate-dependent radiosensitivity.
- Sparing is maximized in a low-to-moderate "Goldilocks" oxygen range.
- Pulse structure, reoxygenation, repair kinetics, and oxygen heterogeneity may explain both positive and negative FLASH findings.

Clinical implications

- Optimize UHDR beam structure for normal-tissue sparing.
- Interpret negative FLASH findings as potentially oxygen-/timing-limited rather than model failure.
- Use oxygen heterogeneity as a candidate biomarker for response stratification.

Symbol	Meaning
$pO_2(t)$	Dynamic nuclear oxygen
$pO_{2,0}$	Baseline nuclear oxygen
τ	Reoxygenation time constant
PLL	Potentially lethal lesion
LL	Lethal lesion
k_r	Repair rate
$k_f(pO_2)$	Oxygen-dependent fixation rate
$\Lambda = \ln\left(\frac{SF_{FLASH}}{SF_{CONV}}\right)$	FLASH sparing index— Positive Λ indicates predicted FLASH sparing.

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