2026 JULY 19–22 VANCOUVER, BC
JOINT AAPM | COMP MEETING

The “Goldilocks” Pulse: Mechanistic Constraints on Dose-per-Pulse and Repetition Rate for FLASH Sparing

Why mean dose rate alone does not predict FLASH sparing

Sumin Zhou, Kyle Gallagher, Andrew Fanning, Christopher Jenkins, Shuo Wang, and Ying Yan
Department of Radiation Oncology, University of Nebraska Medical Center, Omaha, NE

TAKE-HOME MESSAGE

Mean dose rate is a summary metric — not the control variable. FLASH sparing depends on whether oxygen depletion accumulates between pulses.

1. High dose-per-pulse drives transient hypoxia
2. Short inter-pulse gap limits reoxygenation
3. Intermediate pO_2 sits on steep OER slope

ABSTRACT

We modeled 10 Gy FLASH delivery as equal pulse trains with independently varied pulse number N and repetition rate f using an oxygen-dependent modified LPL framework. Differential sparing was quantified as $\Lambda = \ln(SF_{\mathrm{FLASH}}/SF_{\mathrm{CONV}})$ for baseline oxygenations of 0.2, 3, and 30 mmHg. The largest pulse-structure sensitivity occurred at 3 mmHg, where high dose-per-pulse and incomplete inter-pulse reoxygenation shift nuclear oxygen along the steep portion of the OER curve. In contrast, very hypoxic and well-oxygenated regimes were comparatively insensitive to pulse structure. These results suggest that mean dose rate is an incomplete descriptor of FLASH biology unless dose-per-pulse, pulse spacing, and oxygenation regime are also specified.

INTRODUCTION

FLASH delivery is often summarized by mean dose rate (MDR), but pulsed beams with identical MDR can differ in dose-per-pulse and inter-pulse recovery. In the modified LPL (m-LPL) framework, radiation creates precursor lesions. Each pulse depletes nuclear oxygen; each gap allows reoxygenation.
Question: For fixed total dose, which pulse number N and inter-pulse gap Δt maximize Λ?

METHODS AND MATERIALS

Simulation design

- Total dose fixed: $D = 10$ Gy
- Equal pulse trains: $d_p = D/N$
- Pulse number: $N = 1 - 320$
- Repetition rate: $f = 5$– 320 Hz
- Inter-pulse gap: $\Delta t = 1/f$
- Oxygen regimes: 0.2, 3, 30 mmHg

Visual timeline: pulse number changes dose-per-pulse

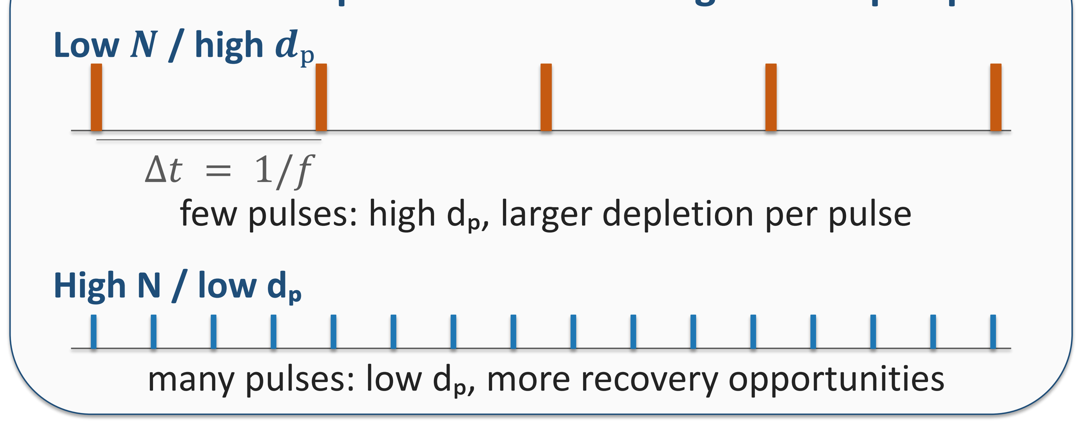

Fig. 1 Fixed D split into fewer pulses gives higher d_p; larger gaps allow pO_2 recovery.

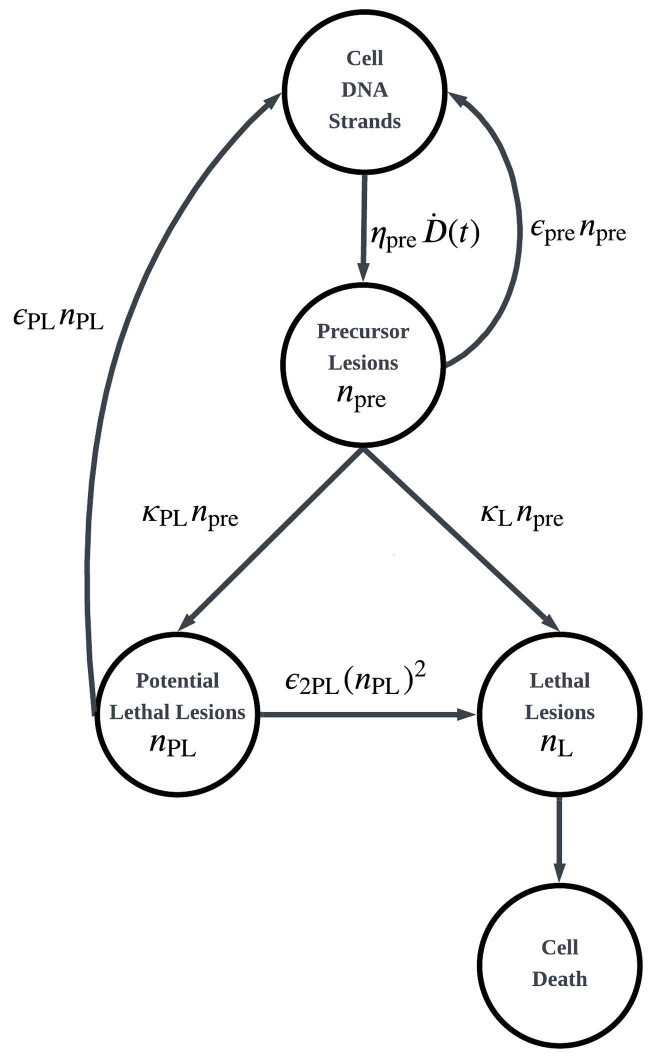

Fig. 3 Coupled oxygen dynamics, repair, and fixation in the modified LPL model.

Biological readout

- Oxygen-dependent modified LPL model
- Per-pulse oxygen depletion and inter-pulse reoxygenation
- Sparing metric: $\Lambda = \ln(SF_{\mathrm{FLASH}}/SF_{\mathrm{CONV}})$

Table 1. Key simulation parameters

Group	Parameter	Symbol	Value
Fix.	Precursor formation	η_{pre}	2000 Gy^{-1}
Fix.	Precursor decay	ε_{pre}	50 s^{-1}
Fix.	L / PL fixation	η_L η_{PL}	0.137/Gy 0.6/Gy
O_2	Radiolytic yield	G	0.42 mmHg/Gy
O_2	Reoxygenation	k_{reox}	20 s^{-1}
O_2	Michaelis const.	K_g	0.21 mmHg
OER	max/min	—	3.0 / 1.0
OER	Sensitivity	$\sim K_m$	~3.0 mmHg

Recommended beam reporting:
D, MDR, N, d_p, f, inter-pulse gap Δt, total delivery time, and target oxygenation regime. This avoids hiding biologically important pulse-structure differences inside MDR.

CONTACT

Sumin Zhou, PhD
Department of Radiation Oncology
University of Nebraska Medical Center
Email: szhou@unmc.edu

RESULTS: SIMULATION DATA

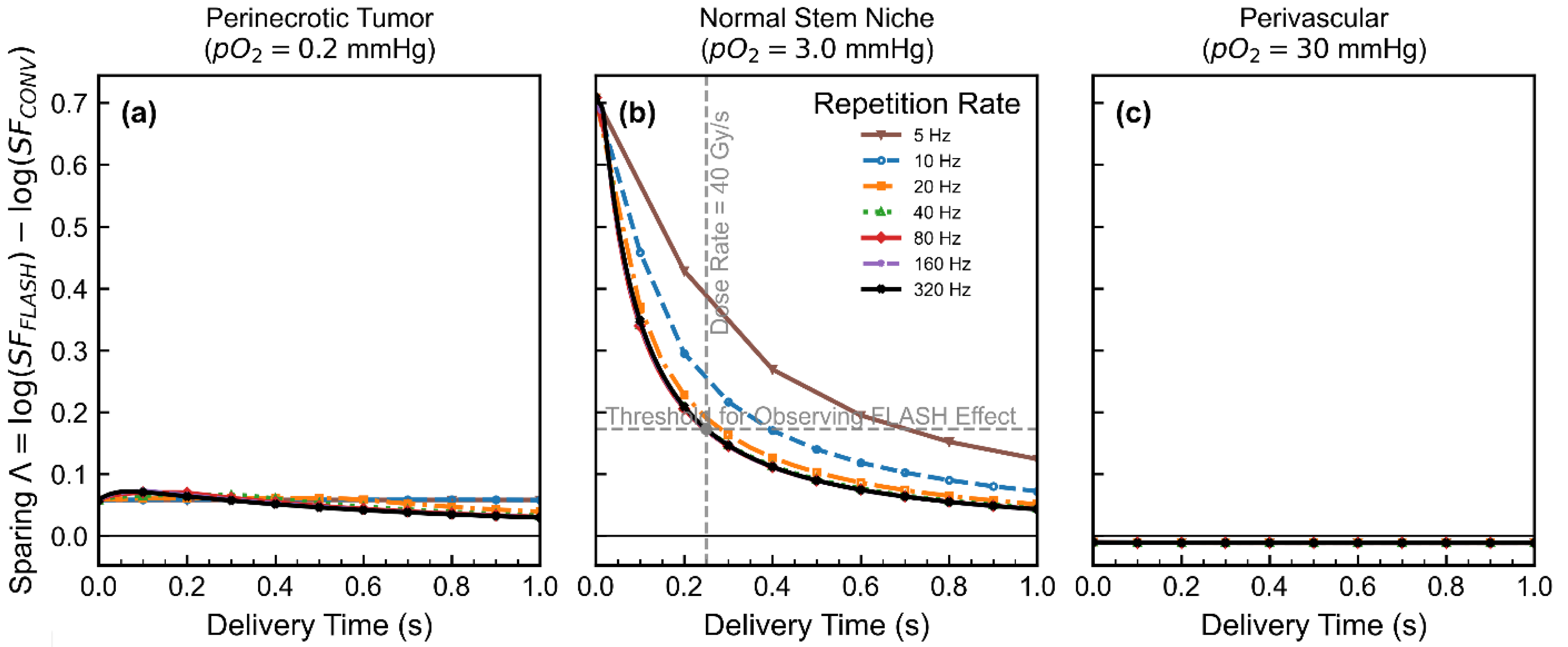

Fig. 2 Differential sparing Λ versus delivery time for 10 Gy. Only the 3-mmHg niche exhibits strong pulse-structure dependence; oxygen extremes are nearly invariant.

Identical MDR can hide different biology because dose-per-pulse and recovery time are independent variables.

Table 2. Pulse-structure comparison for fixed $D = 10$ Gy

Case	N	f (Hz)	d_p (Gy)	Time (s) $T = (N-1)/f$	MDR (Gy/s)	Mechanistic expectation
Few large pulses	5	5	2.00	0.80	12.5	High d_p; strong transient hypoxia despite modest MDR
MDR benchmark	11	40	0.91	0.25	40.0	Moderate d_p near FLASH threshold
Same MDR, many pulses	81	320	0.12	0.25	40.0	Same MDR but smaller d_p; less depletion per pulse
Many low-frequency pulses	100	20	0.10	4.95	2.0	Low d_p plus recovery; weak sparing expected

Why only intermediate oxygenation is pulse-sensitive

0.2 mmHg
Already near OER floor
→ little additional sparing from transient depletion

3 mmHg
On steep OER slope
→ **strongest Λ response** to pulse structure

30 mmHg
Near OER plateau
→ depletion insufficient to move biology much

DISCUSSION

The simulation supports a mechanistic distinction between average dose rate and biologically effective pulse structure. At fixed total dose, N controls dose-per-pulse and Δt controls inter-pulse recovery.

The normal niche shows the largest Λ because its baseline oxygenation lies near the steep portion of the OER curve. Large pulses can push nuclear oxygen into a transiently radioresistant state.

Table 2 highlights the translational issue: two beams may share the same MDR but differ strongly in d_p. Sparing is controlled by the balance between depletion amplitude per pulse and recovery between pulses.

CONCLUSIONS

Design rules from the model

1. Oxygen window matters: FLASH sparing is strongest near the steep OER region, not at oxygen extremes.
2. Dose-per-pulse matters: At fixed D, smaller N increases d_p and transient oxygen depletion.
3. Recovery time matters: Short Δt preserves depletion; long Δt allows reoxygenation.
4. MDR is conditional: Mean dose rate becomes predictive only when pulse spacing is short relative to local reoxygenation.
5. Report pulse structure: D, MDR, N, d_p, f, Δt, total delivery time, and oxygenation regime should be reported together.

REFERENCES

1. Zhou S. Med Phys. 2026;53:e70469.
2. Curtis SB. Radiat Res. 1986;106:252–270.
3. Pratx G, Kapp DS. Phys Med Biol. 2019;64:185005.
4. Grimes DR, Partridge M. Biomed Phys Eng Express. 2015;1:045209.
5. Favaudon V, et al. Sci Transl Med. 2014;6:245ra293.
6. Montay-Gruel P, et al. Radiother Oncol. 2017;124:365–369.