UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

The impact of spatial and temporal dose distributions on achieving the FLASH effect for scanning proton beams

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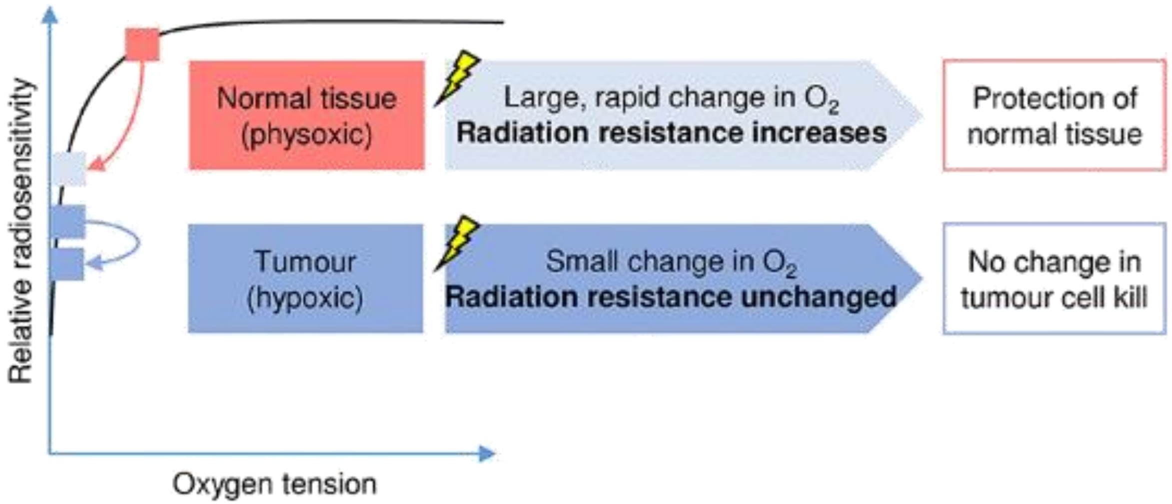
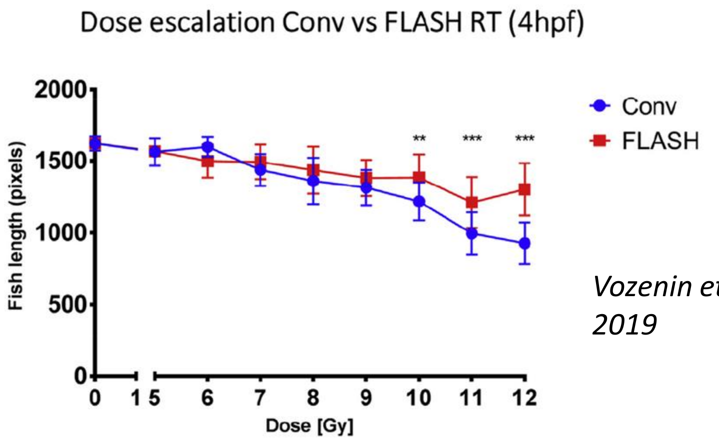
Council of Ionizing Radiation Measurement Standards

FLASH in a Nutshell

- The promise of FLASH: **All** the benefits of RT, **without** the drawbacks
  - Maintain tumoricidal effect, spare normal tissue
  - Oxygenation depletion and induced immune response



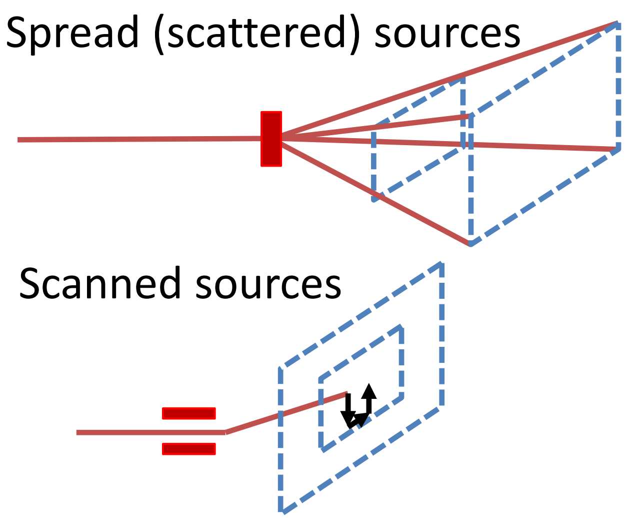


Vozenin et al, Clinc Onc 31 2019

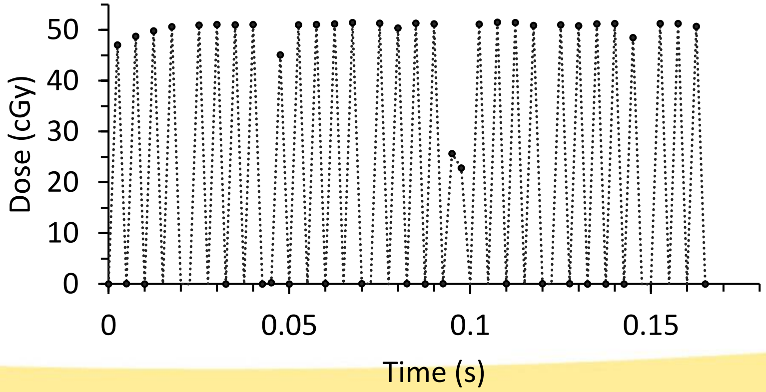
- The two ingredients of FLASH: **Dose** and **Ultra-High Dose rate** (UHDR)
  - Flash effect observed at ≥**10–15 Gy doses** and ≥**40Gy/s average dose rate**
  - ~5% effect <10 Gy, >30% effect >25 Gy (Bohlen et al 2022,
  - Conventional treatment: 1.8–2Gy, 0.1Gy/s (photons) to 1 Gy/s (protons)

Challenges in defining average dose rate

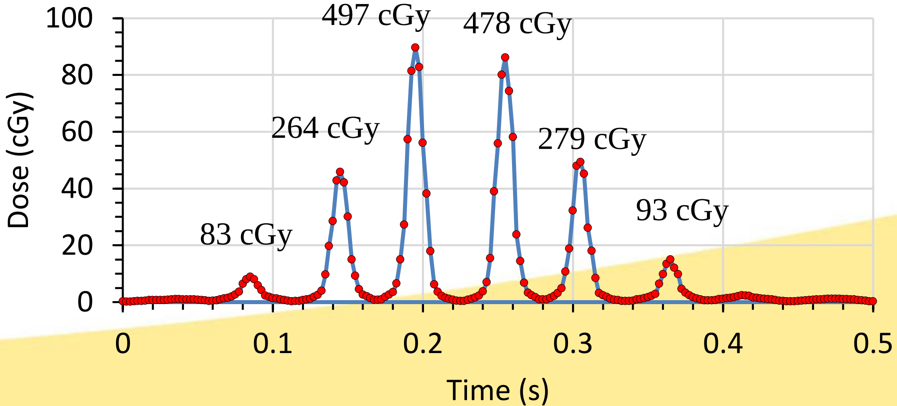
- FLASH sources come in two forms – **scattered** and **scanned**
  - Scattered sources include electron, photon FLASH, & passively scattered protons
  - Can be either pulsed or continuous
- Dose rate for scattered sources simple to define: Total dose/total time
  - Scanned sources may be more complex



Electron FLASH delivery –
30 × 0.5 Gy pulses in 0.16s = ~100 Gy/s



Proton FLASH delivery –
17 Gy total delivered in ~0.8s, concentrated in central 0.3s. What is the dose rate?

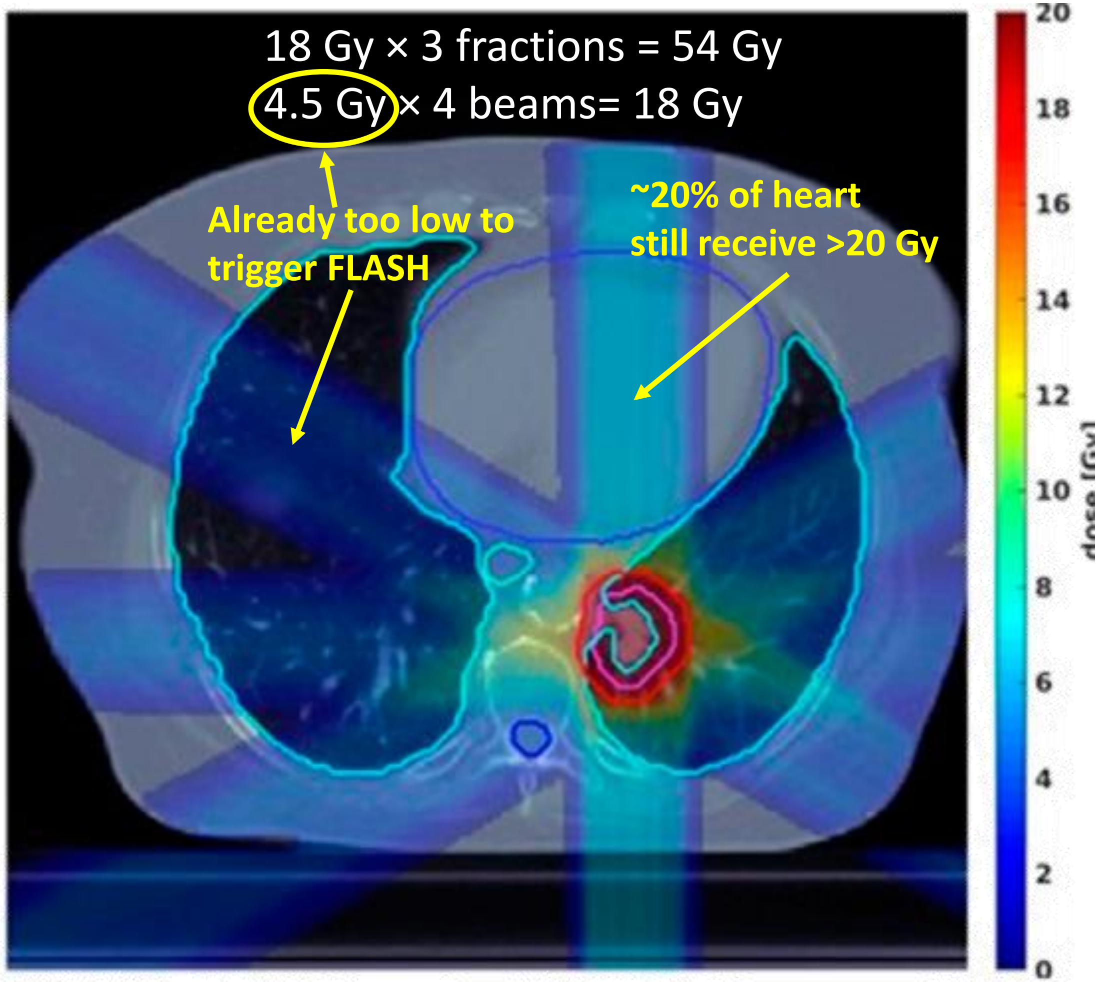


Conceptual difficulties in FLASH Radiotherapy

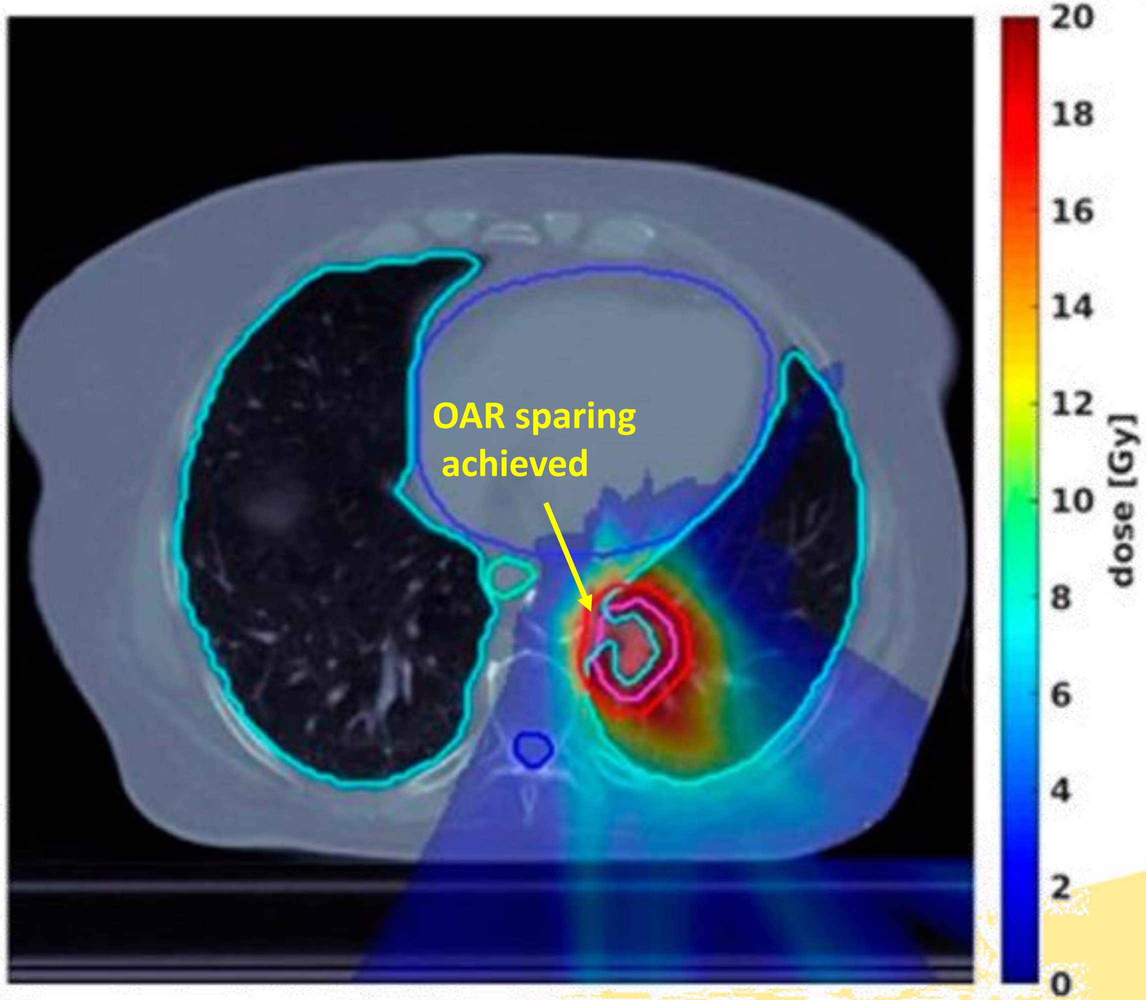
- Current technology – Proton or Electron – has following traits:
  - Mono-energetic, single field treatment
  - Large, single dose
    - Both due to technical limitations, and preclinical evidence
  - No modulation/tissue sparing/inverse planning etc…
  - Step back into the past
- Protons offer better penumbra, but no range sparing
  - Depth limited <20 cm to avoid Bragg Peak in patient
  - FAST-01 treating extremity mets, FAST-02 expands to chest, 8Gy × 1
- **Severely limits** clinical sites that can currently be treated

Translating FLASH to the clinic – Which plan would you treat?

Proposed FLASH Transmission Plan



Proposed Bragg Peak Plan

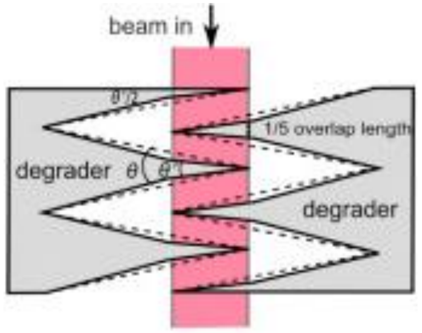


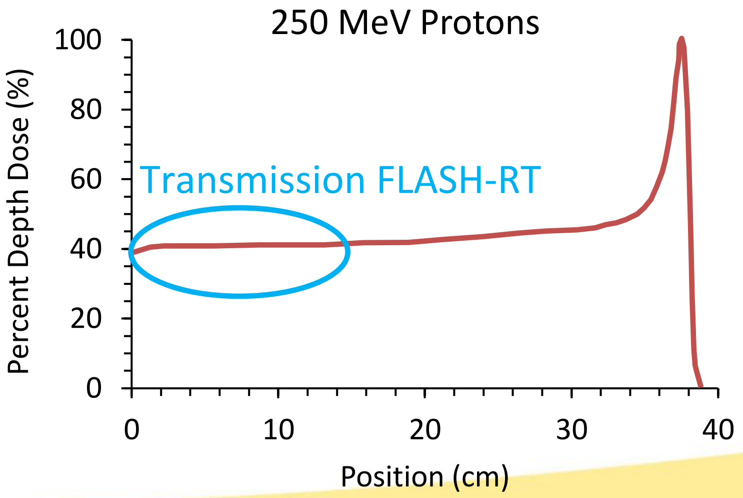
Wei et al., Cancers 2021, 13, 5790

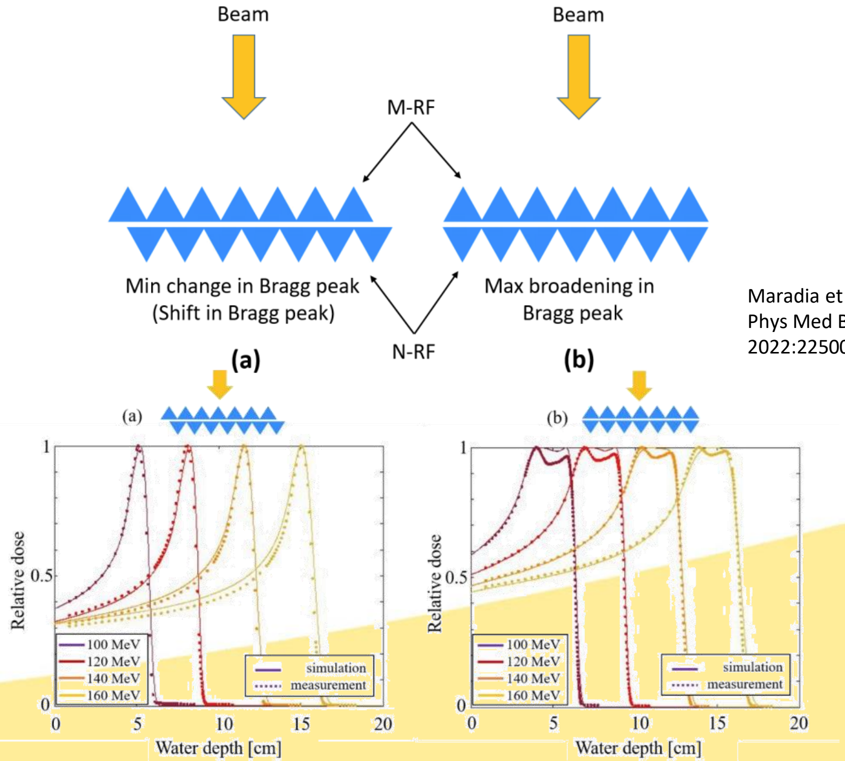
Proton FLASH system

- Varian ProBeam system with isochronous (near continuous) scanning beam used in FAST-01 & FAST-02 trials
- **High** beam current (100-215 nA, vs 2 nA used clinically)
- **High energy** (250 MeV) -> lower energies achieved with beam degraders that reduce dose rate
- **Small scanning area** – reduced time between “passes” of the proton beam, faster delivery
- **Single energy** – scanning multiple energies introduces unacceptable delay in dose delivery
  - Can either use **Transmission FLASH** or **ridge filters**
  - FAST-01 & FAST-02 clinical trials & most pre-clinical studies use transmission plateau

Beam degrader used in energy selection in protons





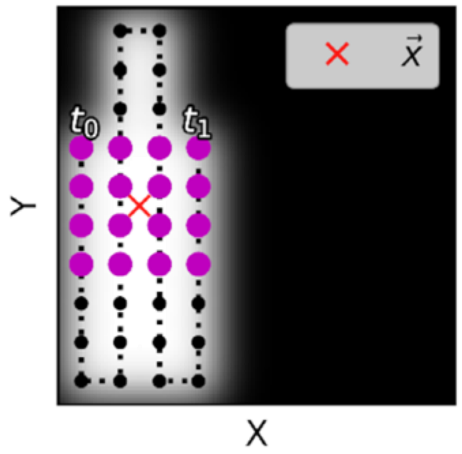


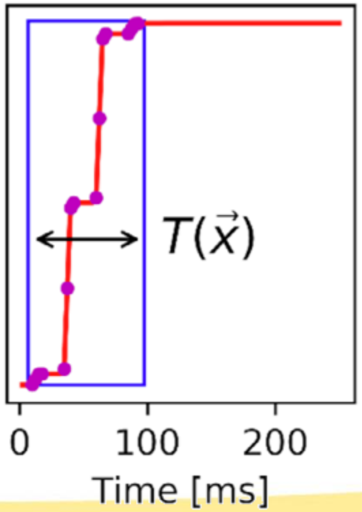
Maradia et al., Phys Med Biol 67, 2022:225005

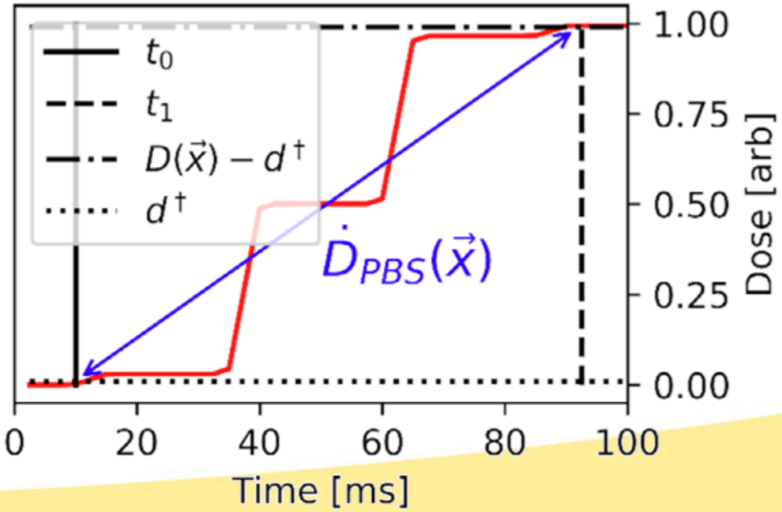
Defining Average Dose rate in Proton FLASH

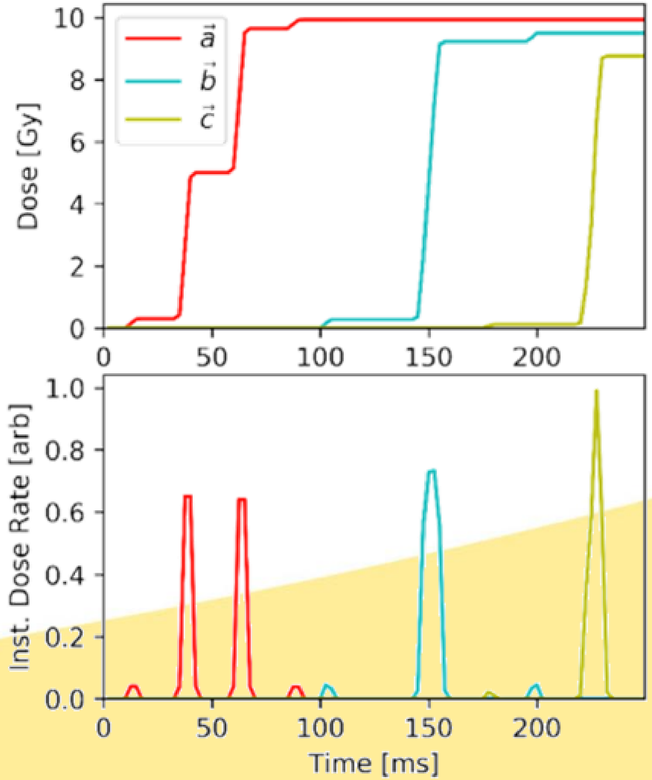
- Defining **average dose rate** in proton FLASH challenging – **nonsimultaneous** irradiation
  - Proton spot has Gaussian shape with σ=~4 mm, negligible dose > ~10 mm
- Average dose rate depends on **how fast** spot can travel across a point of interest
- Following the **Folkerts formalism** (developped by Varian for FAST-01), use time to deliver the **majority of the dose** (excluding first/last 10 cGy)

$$\dot{D}_{\mathrm{PBS}}\left(\vec{x}\right) = \frac{D\left(\vec{x}\right) - 2d^{\dagger}}{T\left(\vec{x}\right)}$$



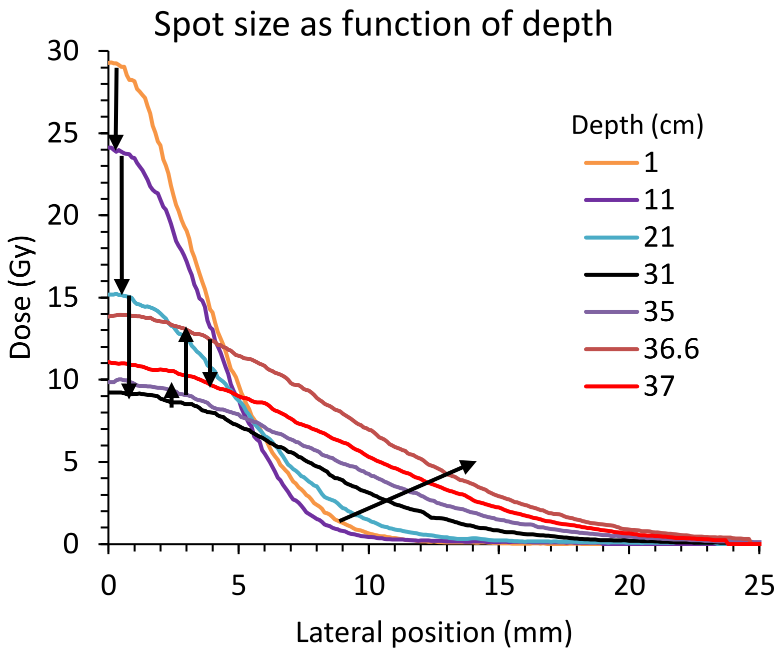




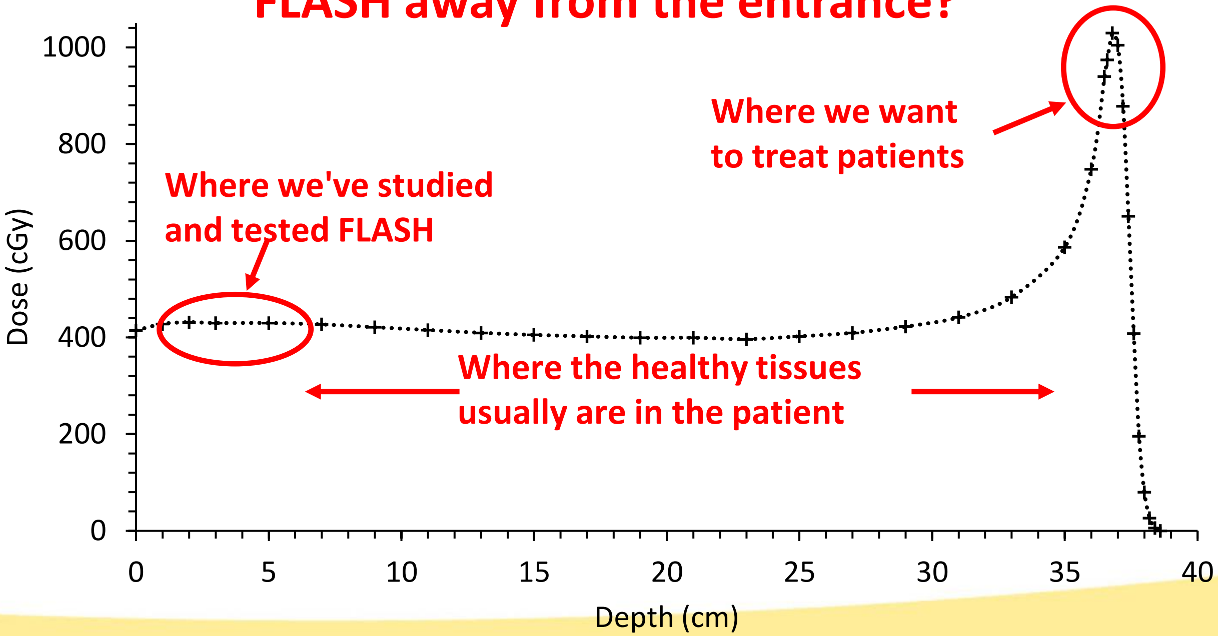


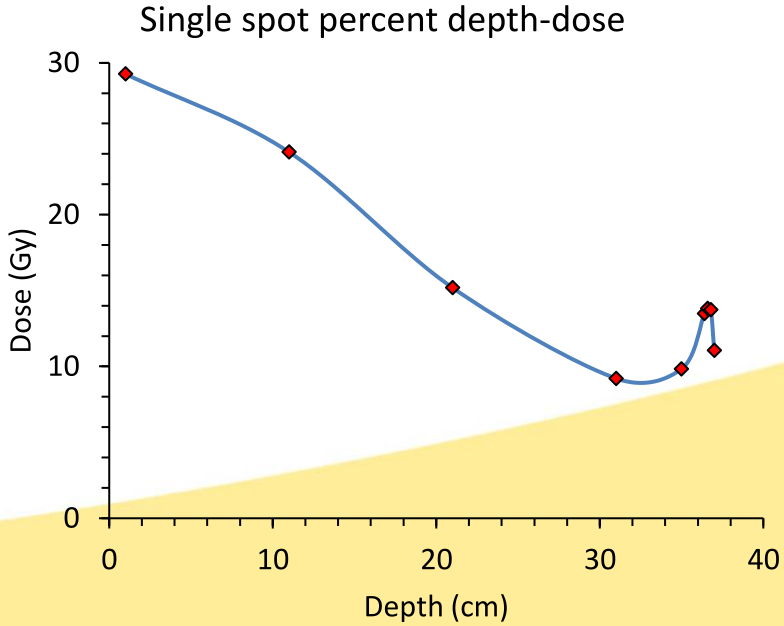
Open questions

- Dose rate geometry-dependent
- Proton spot **widens** and **flattens** as it enters the patient
  - Instantaneous dose rate must decrease – what of the average dose rate?
  - Is there more to the time structure of the dose delivery?



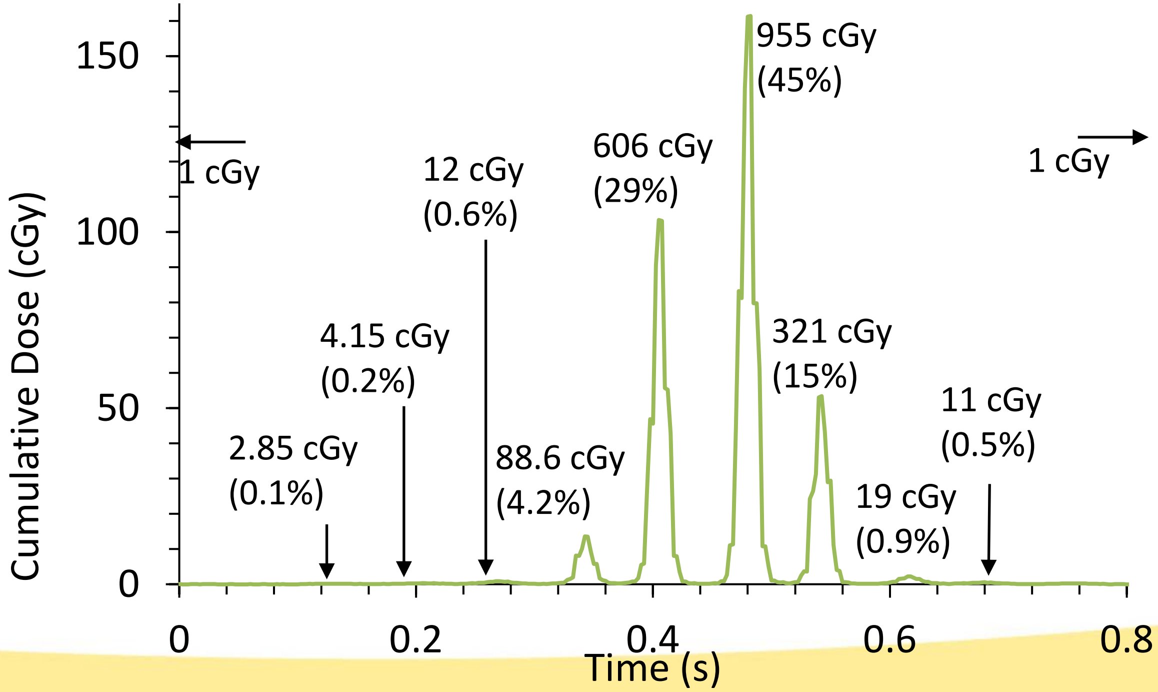
Do we maintain the benefits of FLASH away from the entrance?

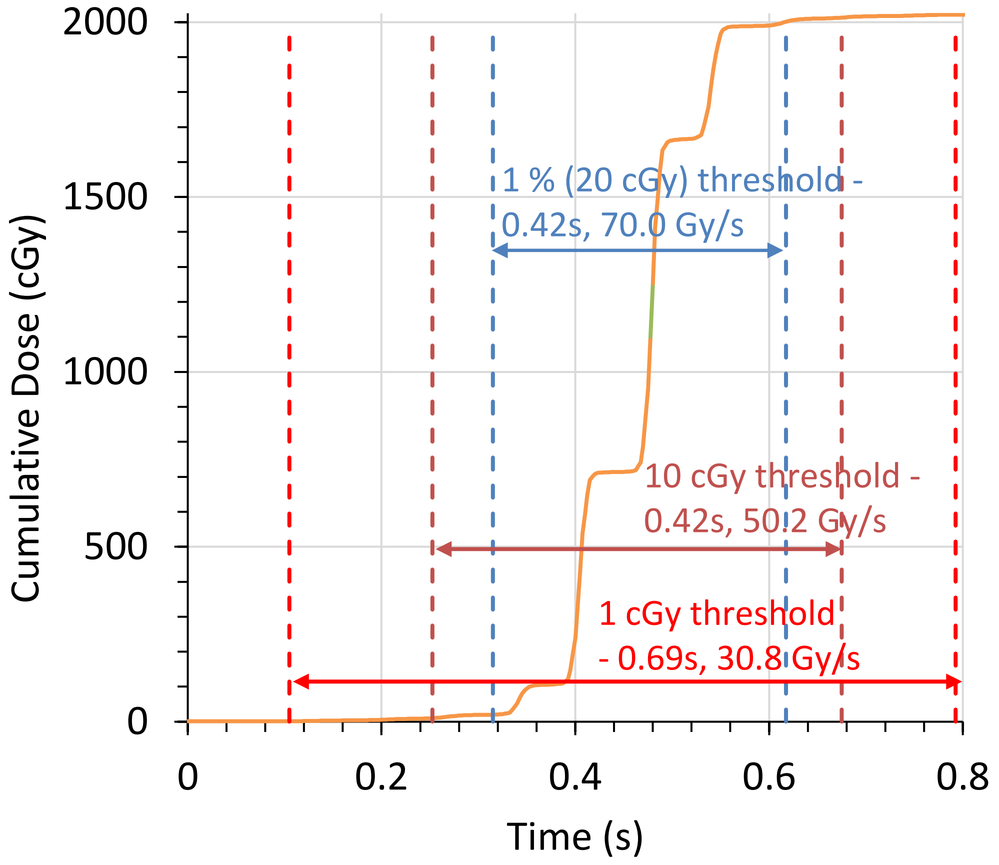


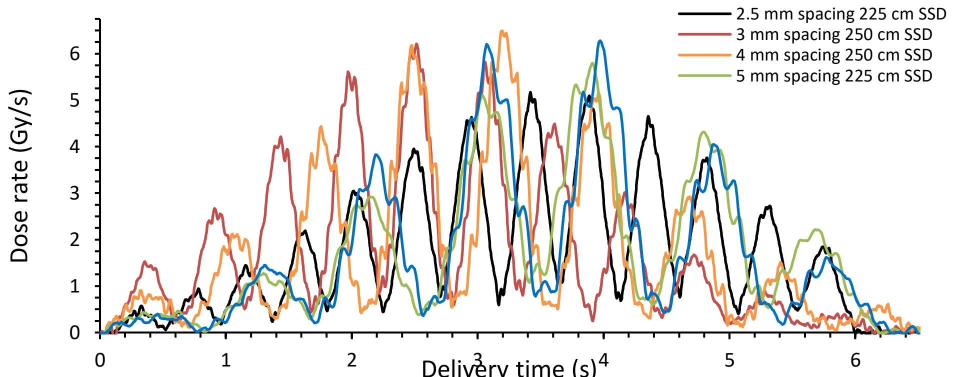


Anatomy of a proton FLASH delivery

- Average dose rate largely independent of dose or spot spacing
- Dose rate is highly dependent on threshold used when “clock” starts
  - We use 1% due to noise in the scintillator

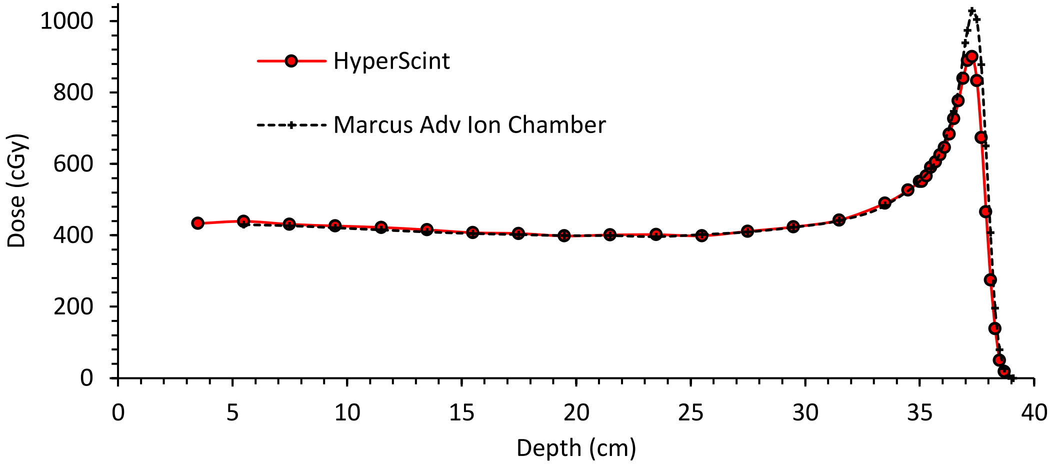


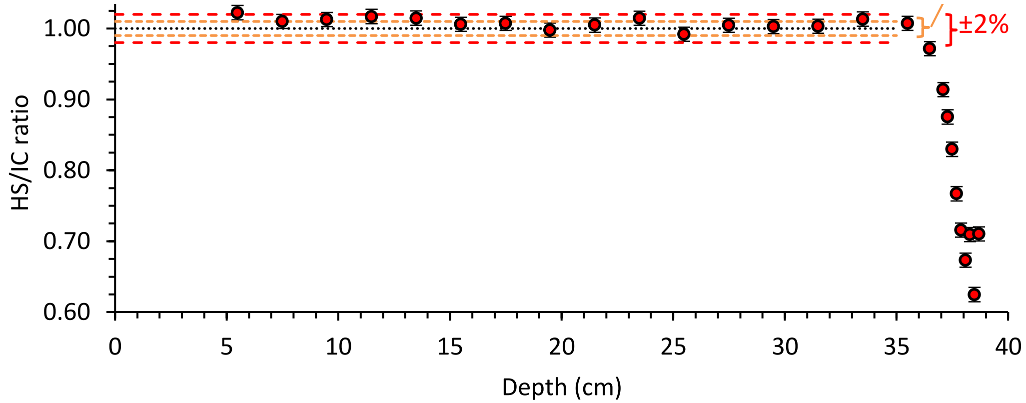


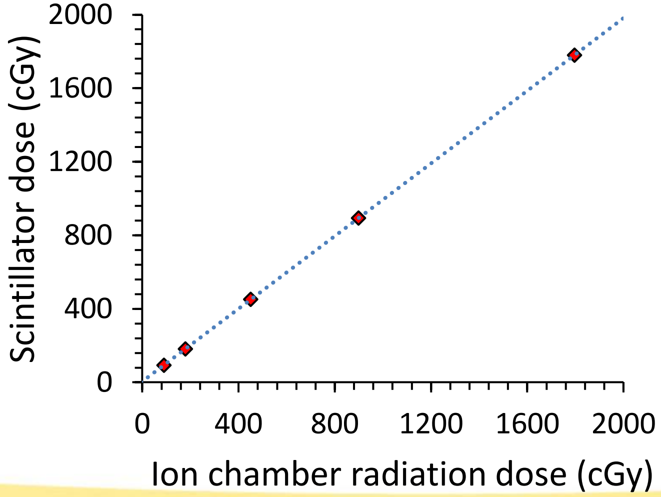


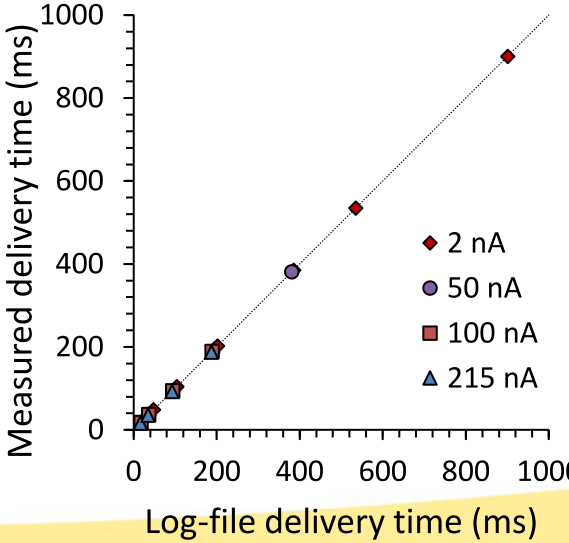
Measuring spaciotemporal proton dose using plastic scintillators

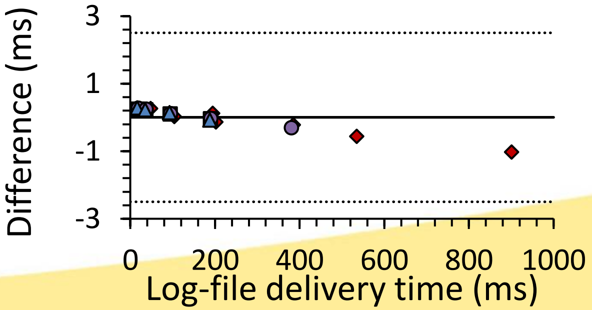
- Medscint Hyperscint RP-100 with 400 Hz acquisition
- Allows direct measurement of time distribution vs machine logfiles
- Well-characterized in electron FLASH
- Real-time signal, water equivalence, small (1×1 mm^3) volume, able to resolve individual spots.
- Linear with time, dose, quenching beyond >34 cm





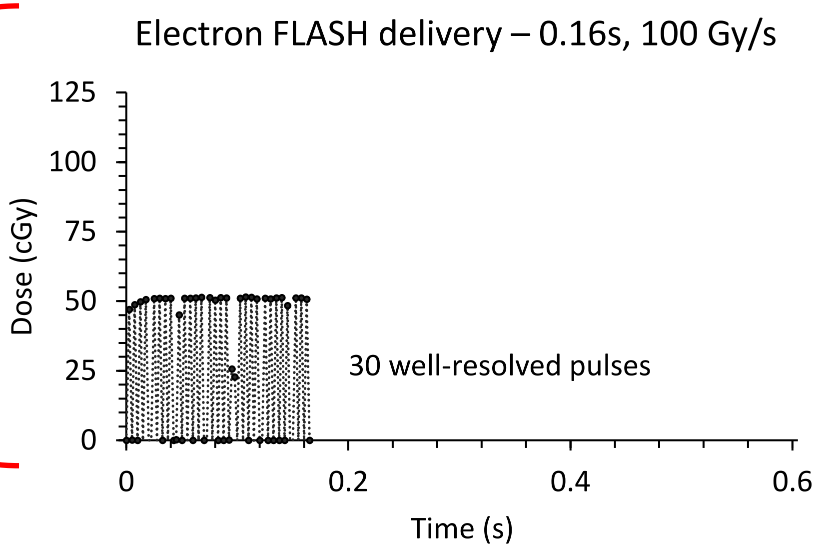


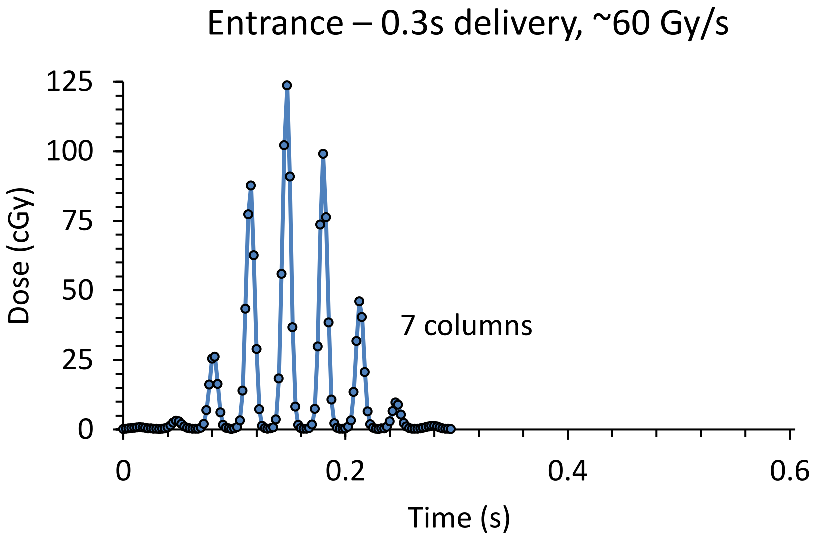




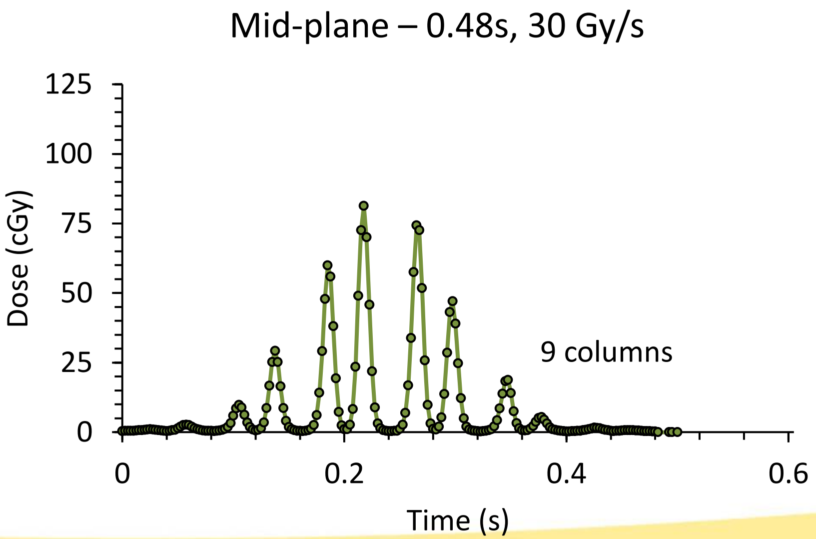
Poirier et al., unpublished

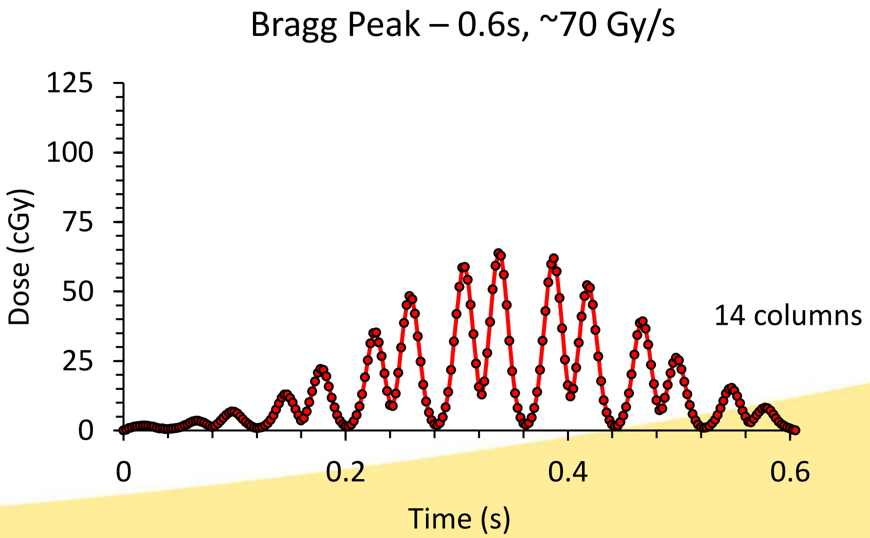
Scintillator results – dose vs time



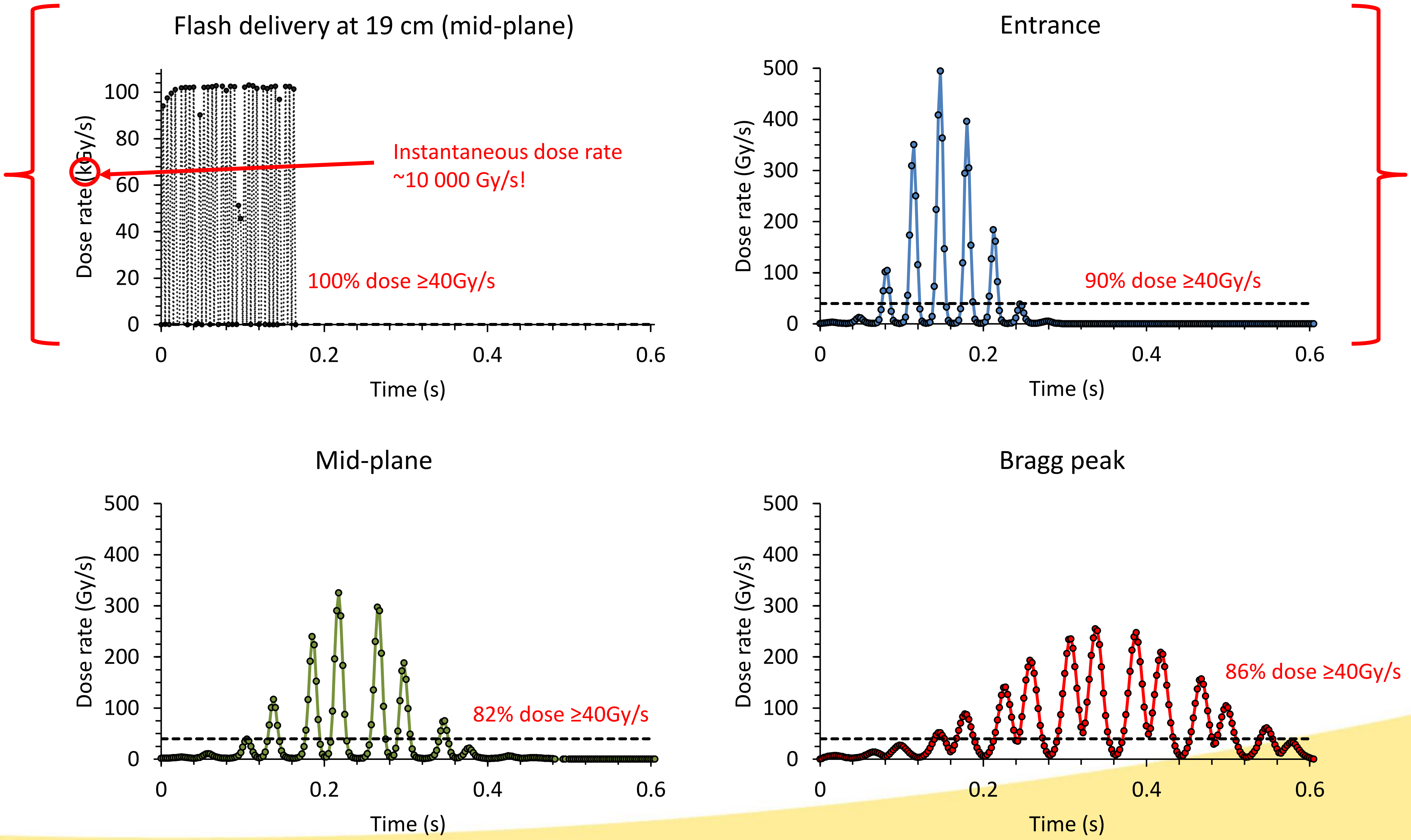


Preclinical studies and clinical trials



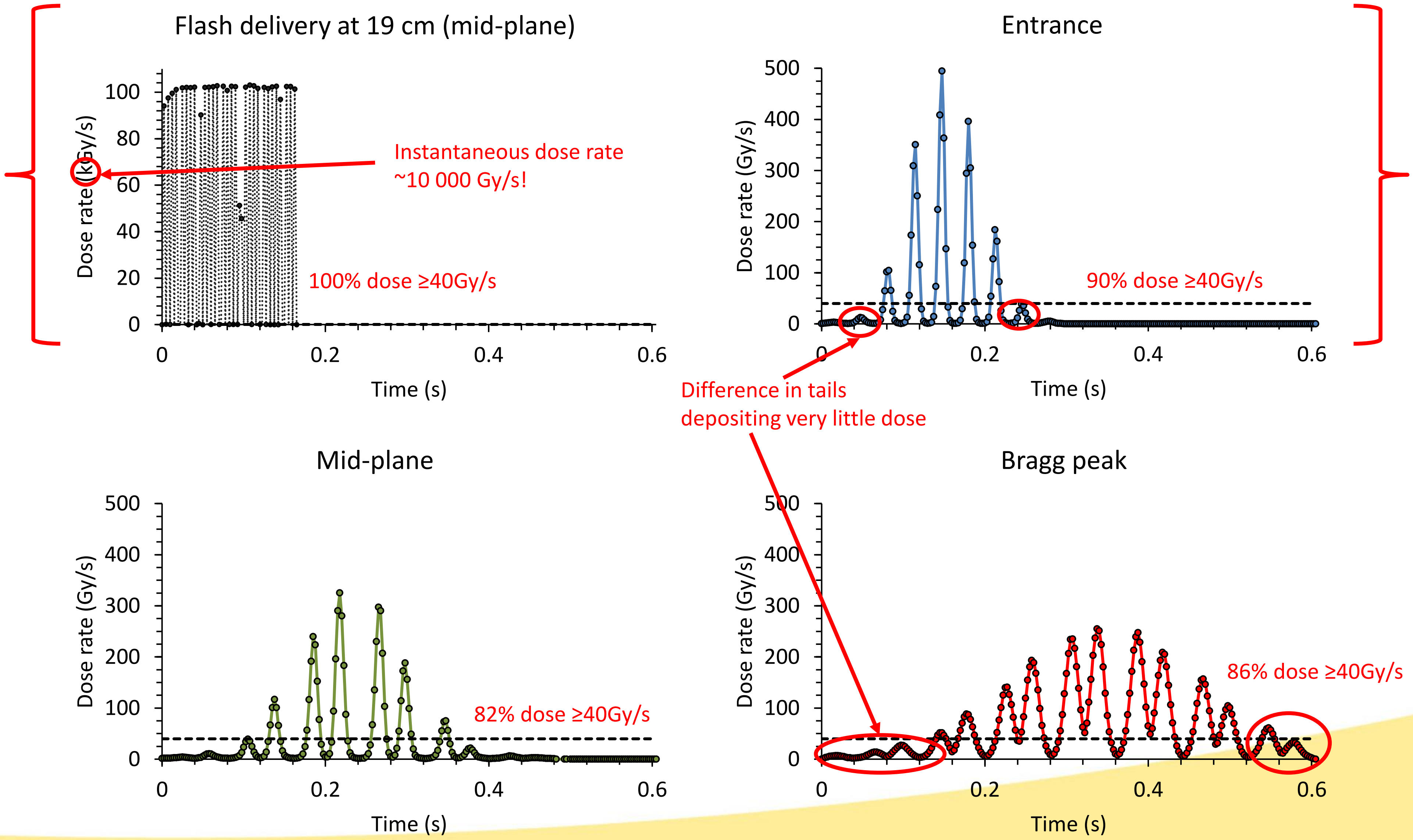


Scintillator results – dose rate vs time



Preclinical studies and clinical trials

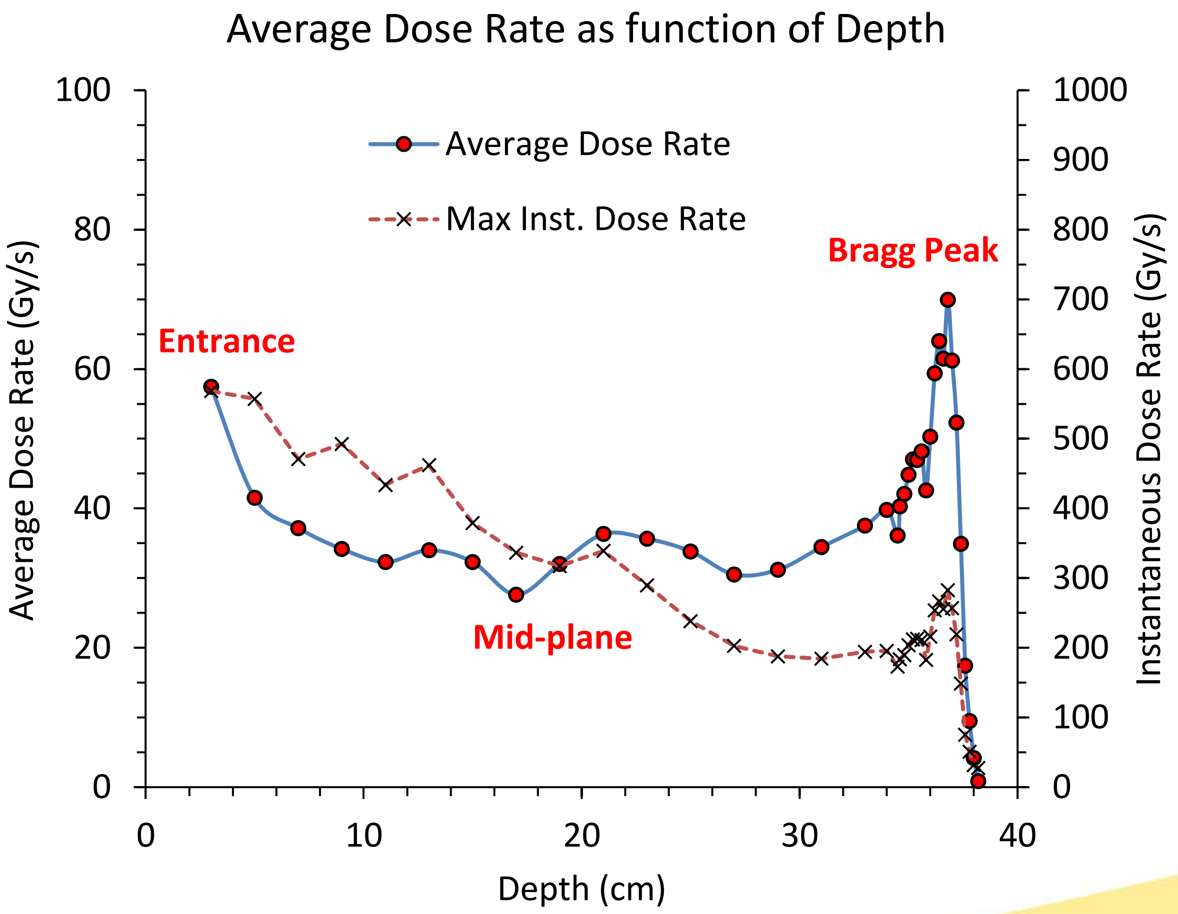
Scintillator results – dose rate vs time



Preclinical studies and clinical trials

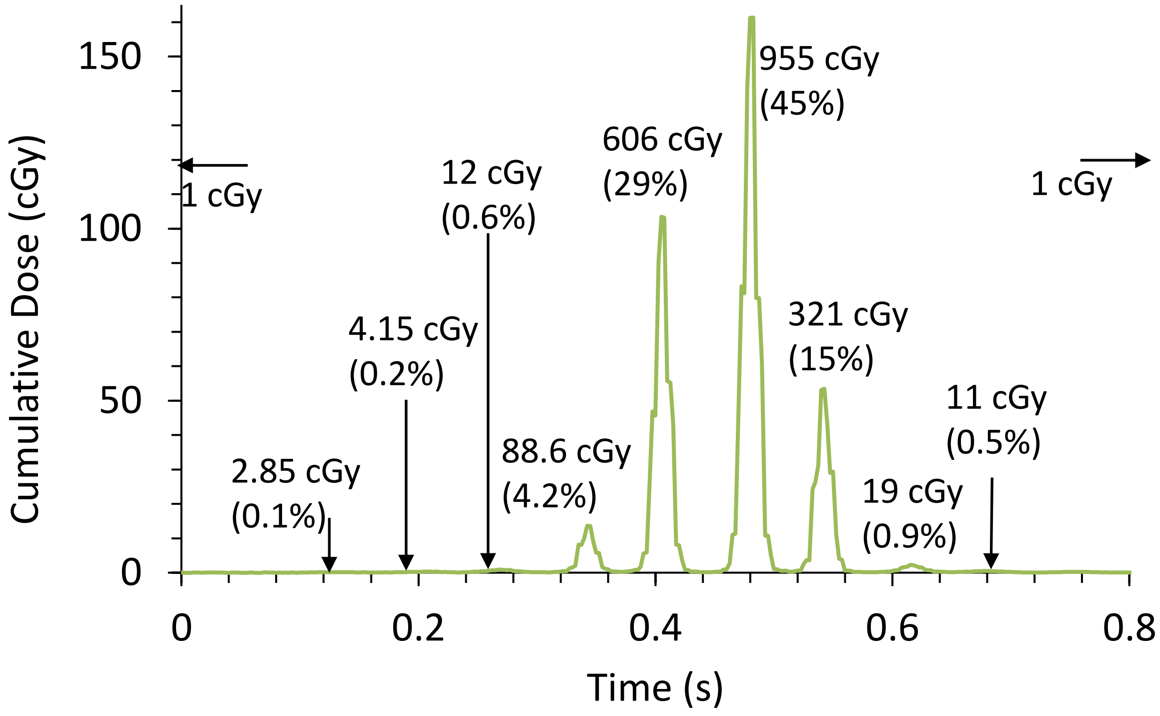
Scintillator results – dose rate vs depth

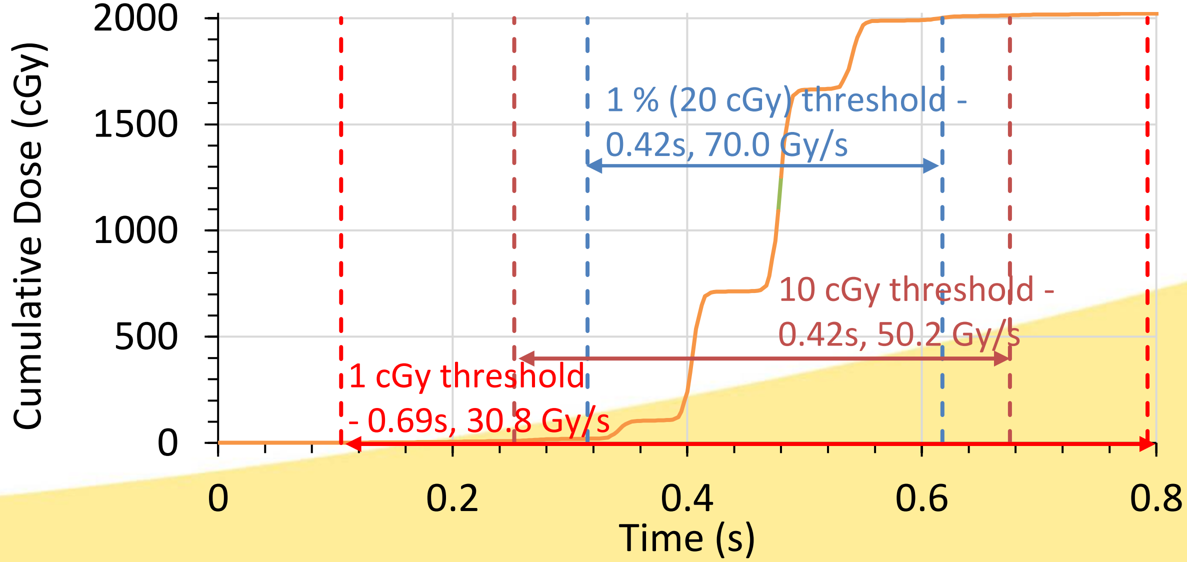
- Average Dose Rate:
  - Maximal at entrance and Bragg Peak
- Instantaneous dose rate:
  - Decreases consistently with depth
  - Minimal just before Bragg Peak (where OARs may be)
- Implications on clinically-realistic plans
  - Transmission plans: FLASH sparing concentrated on entrance
  - Bragg Peak plans: Longer delivery time, lower IDR may compromise effect



Open questions and further discussions

- Is there an instantaneous dose rate per “column” to trigger FLASH?
- Is there a threshold amount of radiation?
- Is there a maximum time between “columns” below which FLASH is lost?
- Do low-dose “columns” “spoil” the FLASH effect by lowering the average dose rate?
- **All these questions have biological answers that have yet to be studied**





Conclusions

- **Realistic** candidate plans for FLASH curative treatment of deep-seated tumors utilizes the **Bragg peak**
  - However, evidence from pre-clinical studies and clinical trials comes from **electrons** and **transmission protons**
  - Compared to Bragg Peak delivery, these have **higher instantaneous dose rate**
- Near the Bragg Peak, Dose & Instantaneous Dose **decreases**
  - Transmission FLASH used in extremity metastatic clinical trial
  - However, limited use for deep-seated tumors
  - Plateau region nearest bragg peak (where normal tissue is) has **worst** dose rate
- Average dose rate is still **poorly defined**
  - Highly dependent on threshold value used, with no clear biological justification
- **Future pre-clinical studies** should focus on studying the FLASH effect <u>near the Bragg Peak</u> & the impact of <u>delivery time characteristics</u>

Thank you!

I would like to acknowledge my collaborators:

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Questions

I would like to thank my collaborators

Sina *Mossahebi,* ***Kevin*** *Byrne,* ***Kai*** *Jiang, and* ***Amit*** *Sawant*