FLASH Therapy from Hadron Synchrotrons

IOP Particle Accelerators and Beams Conference
14th June 2024

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WHAT
is FLASH

1. Hadron Therapy, as compared to VHEE
2. FLASH Therapy, as applied to Hadron Therapy
3. UHDR Delivery Methods for Hadron Therapy

HOW
do we deliver FLASH?

4. Current Cyclotron FLASH Research
5. Current Synchrotron FLASH Research
6. Synchrotron Resonant Extraction

HOW
to design accelerators for FLASH?

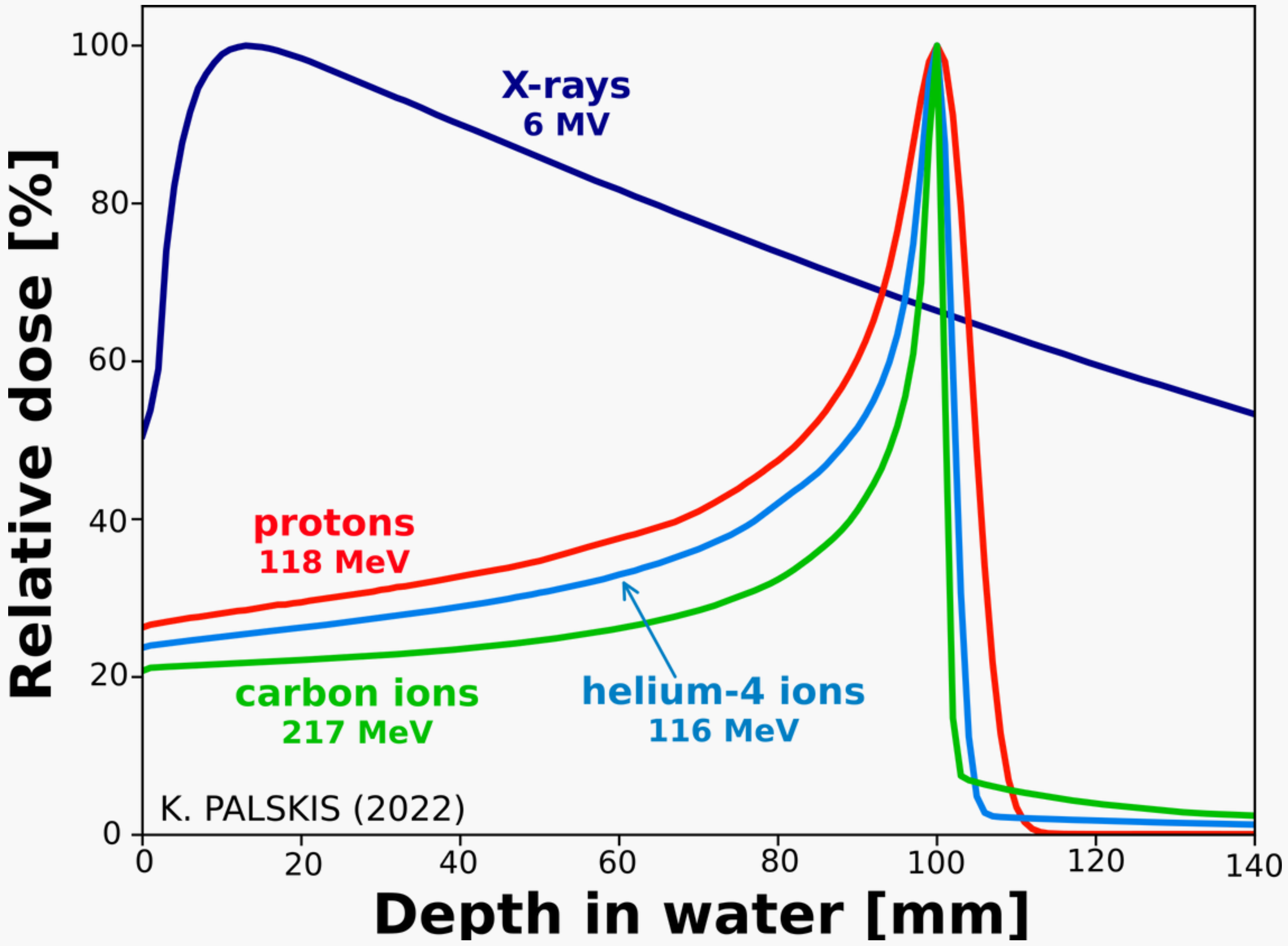
7. UHDR as Accelerator R&D Driver
8. NIMMS Study
9. LhARA Study

Hadron Therapy Overview

Protons & ions interacting with matter lose energy inversely proportional to their speed:

- Cumulative effect resulting in a peak
- Heavier ions have sharper peaks but experience nuclear fragmentation afterwards

$$-\frac{dE}{dx} = Kz^2 \frac{Z}{A} \frac{1}{\beta_{\text{rel}}^2} \left[\frac{1}{2} \ln \frac{2m_e c^2 \beta^2 \gamma^2 T_{\max}}{I^2} - \beta_{\text{rel}}^2 - \frac{\delta}{2} \right]$$



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For 10 - 30 cm depth, requires:

Species	Energy Range	Clinically Approved?
p+	60 - 220 MeV	✓
Helium-4 (2+)	60 - 220 MeV/u	✗
Carbon-12 (6+)	120 - 400 MeV/u	✓

Other ions tested, but each require dedicated trials.

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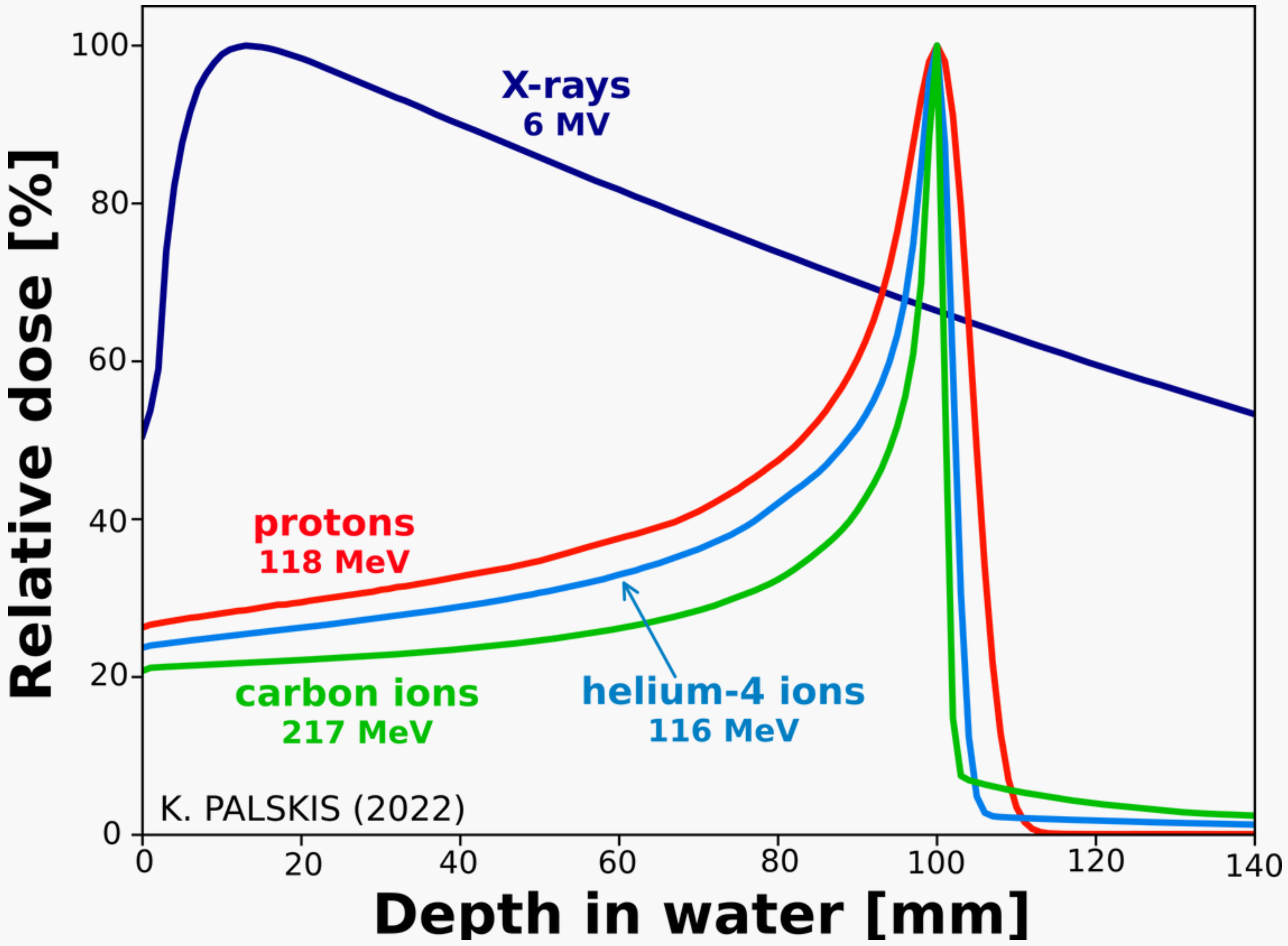

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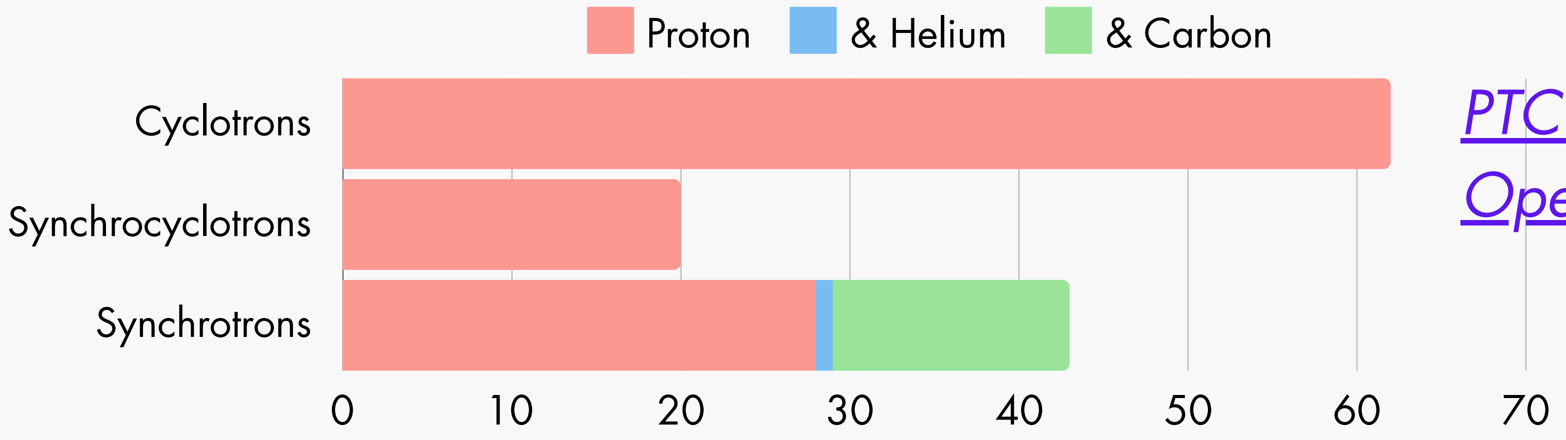


[*PTCOG - Facilities in Operation*]() (2024)

124 facilities providing ~1.5% of all radiotherapy treatments

Cyclotrons & SC:

~5 m diameter

40-80% extraction eff

Single energy

Single species

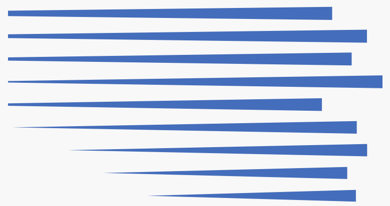
Synchrotrons:

~25 m circumference

90-90% extraction eff

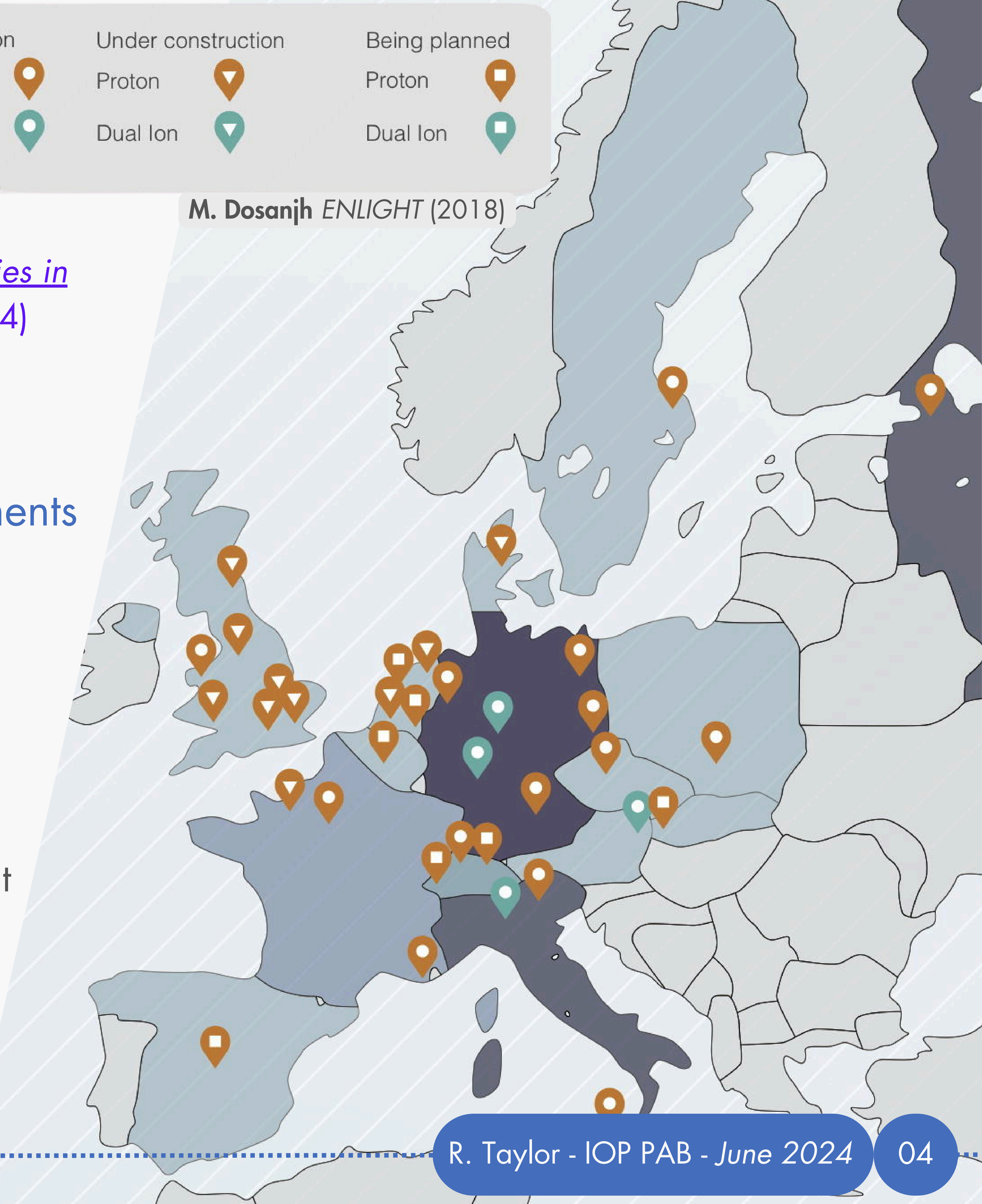
Range of energy

Range of ions



LINACs:

In development



M. Dosanjh *ENLIGHT* (2018)

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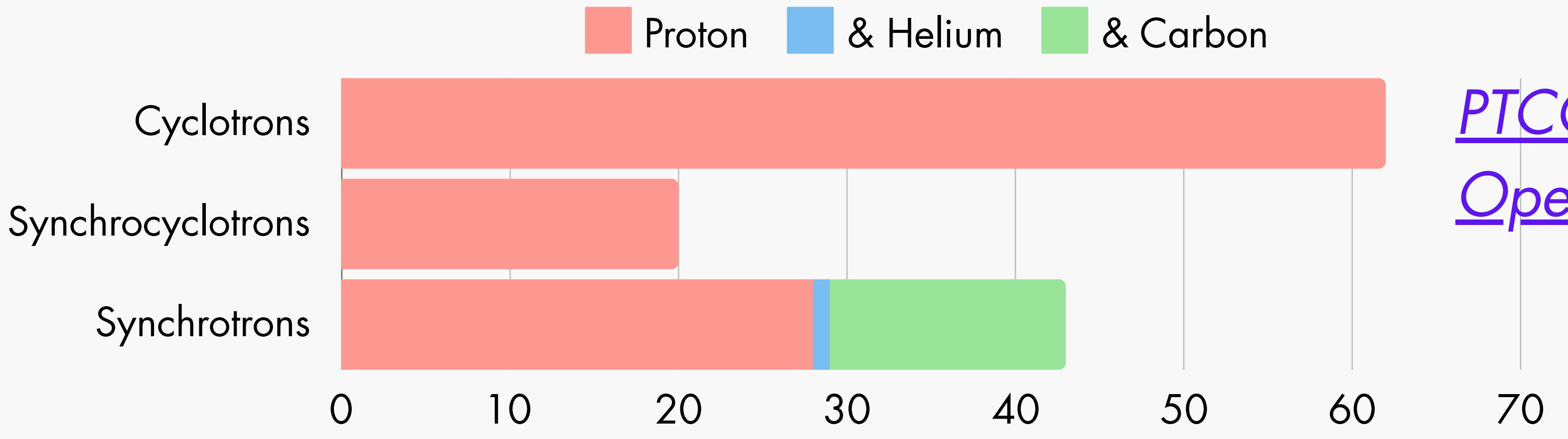

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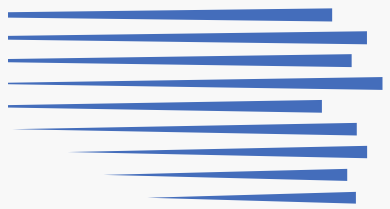

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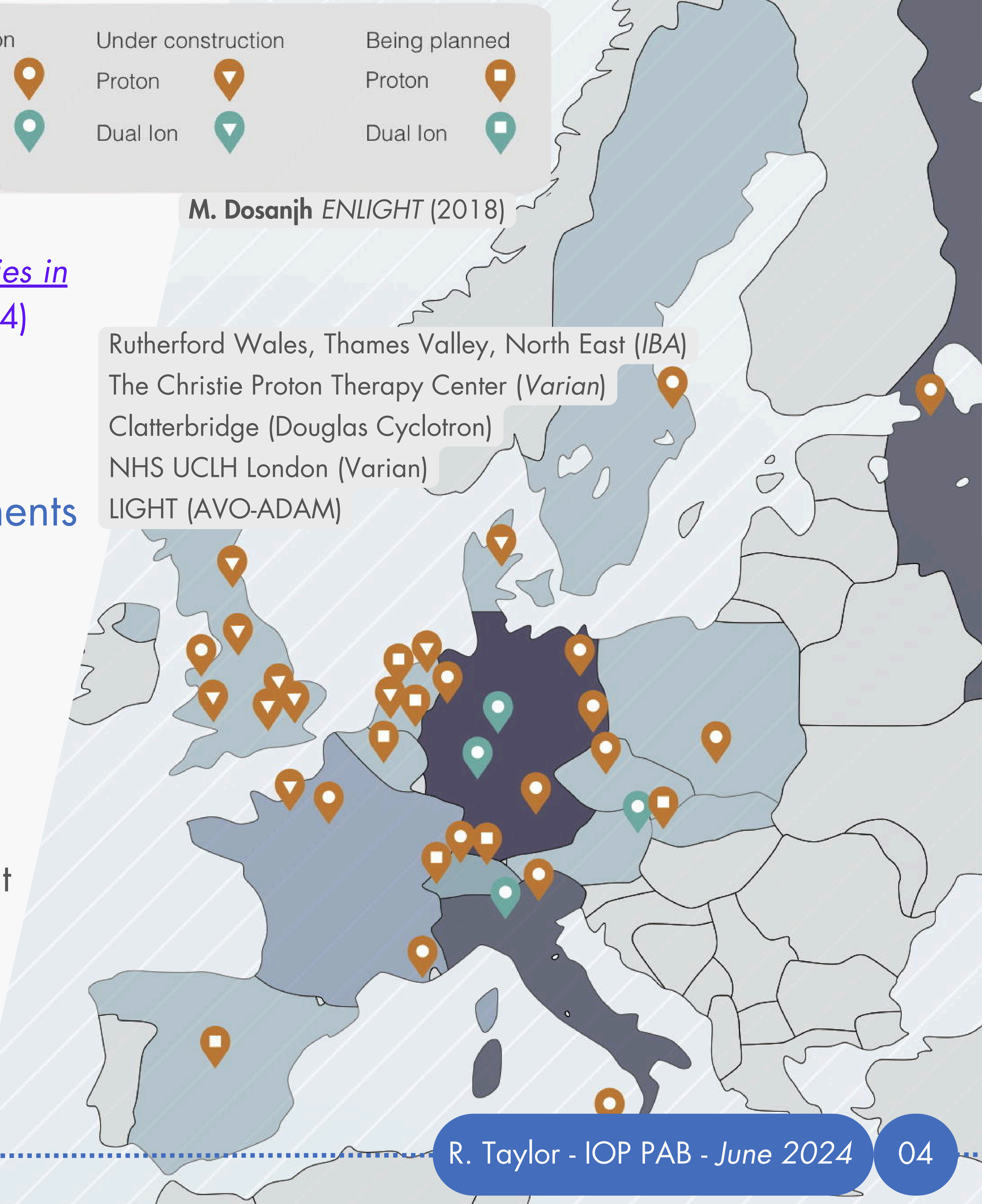

FLASH Therapy

High dose rate (>40 Gy/s) reduces ***toxicities*** *to* ***healthy tissue****, but preserves damage to tumour tissue.*
Potential to reduce side effects and number of fractions.

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Simplified Example:

Tumour volume: 1 litre **Total Dose:** 2 Grey
Minimum rate: 40 Gy/s **Corresponding spill length:** 50 ms

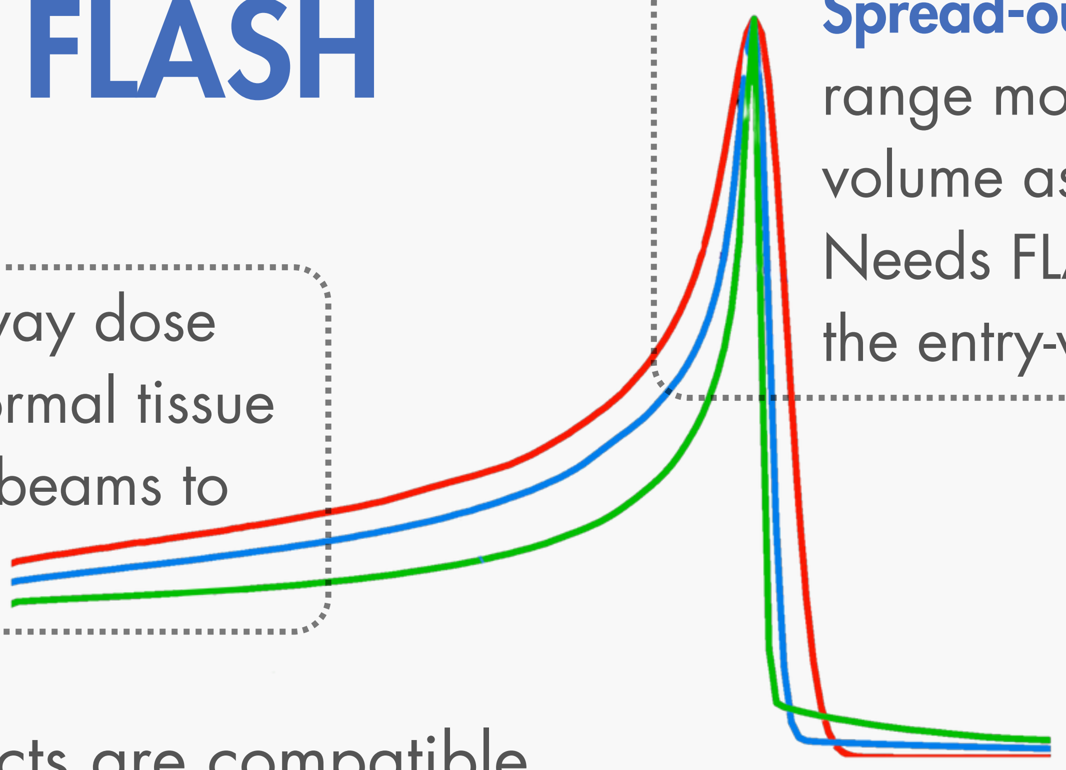
This would not necessarily result in FLASH. Heavily dependent on biological context, e.g. tissue type, oxygenation,

Tend to refer to Ultra-High Dose Rates (UHDR), to decouple from FLASH effect

Delivery of UHDR hadrons for FLASH

Longitudinal

Shoot-through, using the entry-way dose
- 8-10 Gy delivered to normal tissue
- Requires higher energy beams to go through patient



Spread-out Bragg Peak, with 3D range modulators to have depth in volume as a function of energy. Needs FLASH-compatible dose in the entry-way for protection.

Further data required to study if Bragg peak + FLASH effects are compatible
- Suitable experimental beamlines required for radiobiological research

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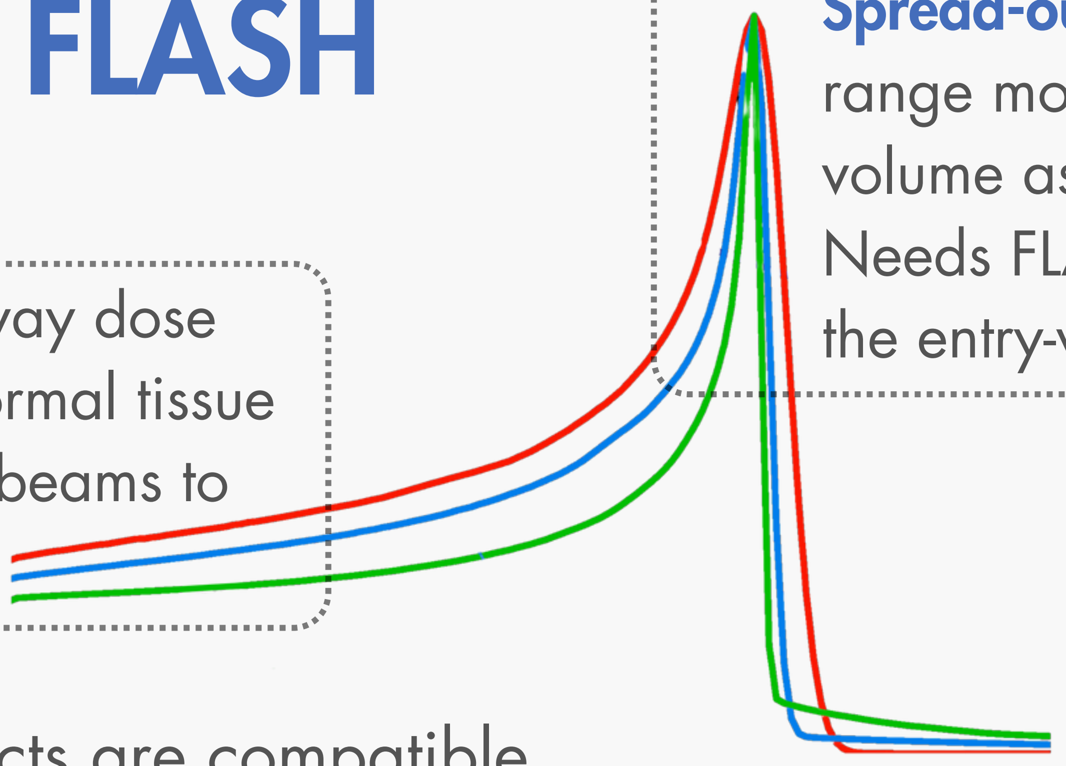

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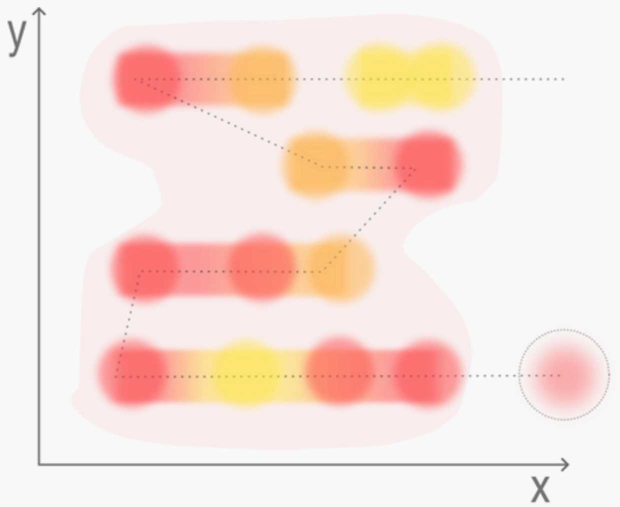
Transverse

Entire dose must be delivered within the time-frame.
Two active scanning methods, both requiring fast-responding quadrupole & scanning magnets.

Raster Scanning



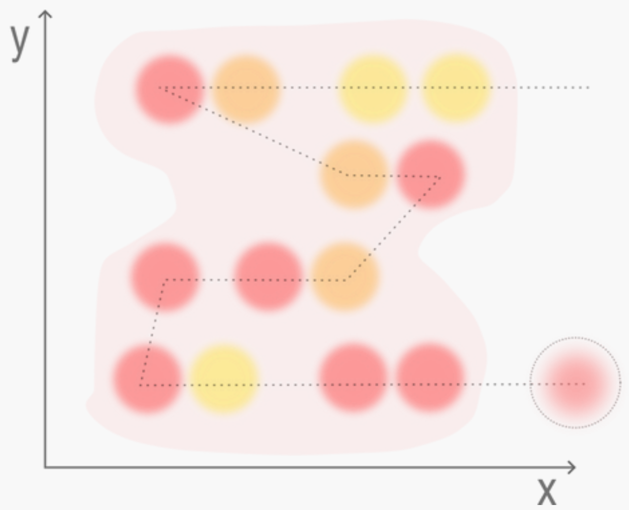
Dose rate non-obvious to define

Intensity variation:
By scanning slower

Dose profile:
Continuous < 100 ms

Constraints:
Uniform, low-ripple spill

Spot Scanning



Intensity variation:
With more shots

Dose profile:
Bursts of ~1 ms

Constraints:
Consistent between shots

UHDR extraction from cyclotrons

Primarily commercial

Varian

- ***FAST01*** clinical trial performed with modification of ProBeam cyclotron
- 7.5 cm x 20 cm treatment field at this volume
- 8 Gy in a single fraction at a dose rate of ≥40 Gy per second
- Transmission beam - no Bragg peak

E. C Daugherty. *FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases (FAST-01): Protocol for the First Prospective Feasibility Study* (2023)
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9893728/

Mevion

- HYPERSCAN Synchrocyclotron
- 1cm x 1cm cm field size
- 100 Gy/s and 200 Gy/s for 1 - 20 us
- Measured both at plateau and bragg-peak

A. Darafsheh. Feasibility of proton FLASH irradiation using a synchrocyclotron for preclinical studies (2020)
https://pubmed.ncbi.nlm.nih.gov/32452558/

IBA

- IBA ProteusOne synchro-cyclotron & ProteusPlus cyclotron
- 500nA for clinical FLASH kit, 800nA for physics tests
- Carbon and helium cyclotron in development (C400)

https://www.iba-worldwide.com/iba-and-particle-initiate-flash-proton-therapy-research-partnership

Y. Jongen *IBA C400 cyclotron project for hadron therapy* (2007)

UHDR extraction from synchrotrons

Resonant Extraction

With a revolution frequency of ~MHz, synchrotrons need multiple turns to get millisecond long spills from the machine

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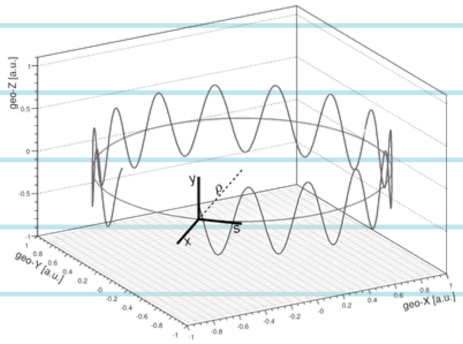
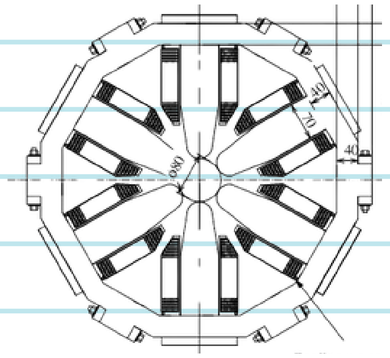
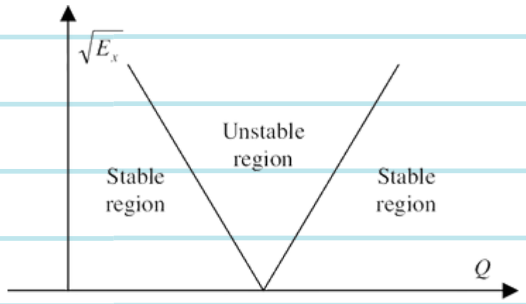
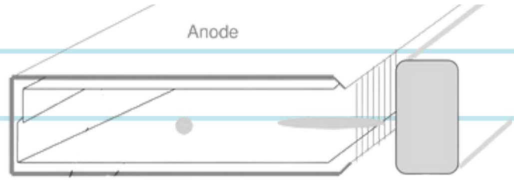
Resonant extraction requirements:

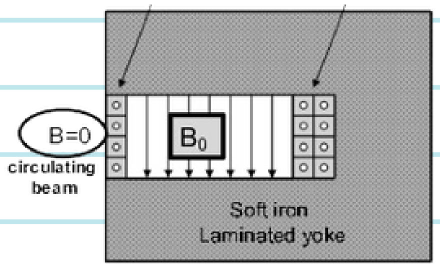
1. Horizontal Tune: Qx near 1/3 resonance
2. Strong Sextupole: To drive resonance
3. Excitation Method: Particles into resonance
4. Electrostatic Septum: Kicks high-amplitude particles
5. Magnetic Septum: Removes particles











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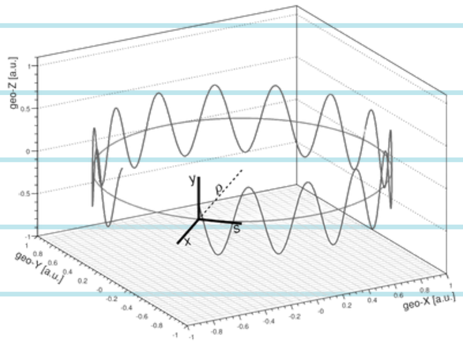
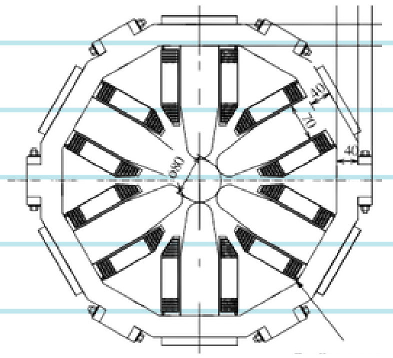


2. Strong Sextupole: To drive resonance



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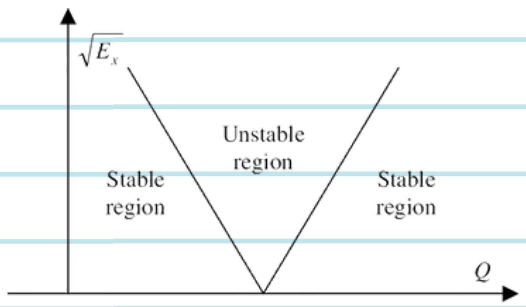
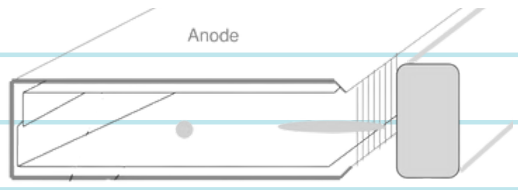
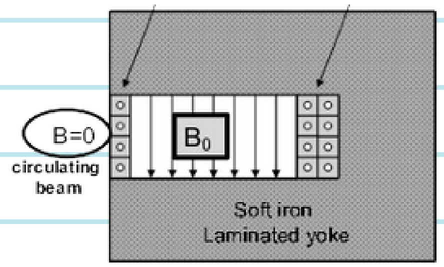
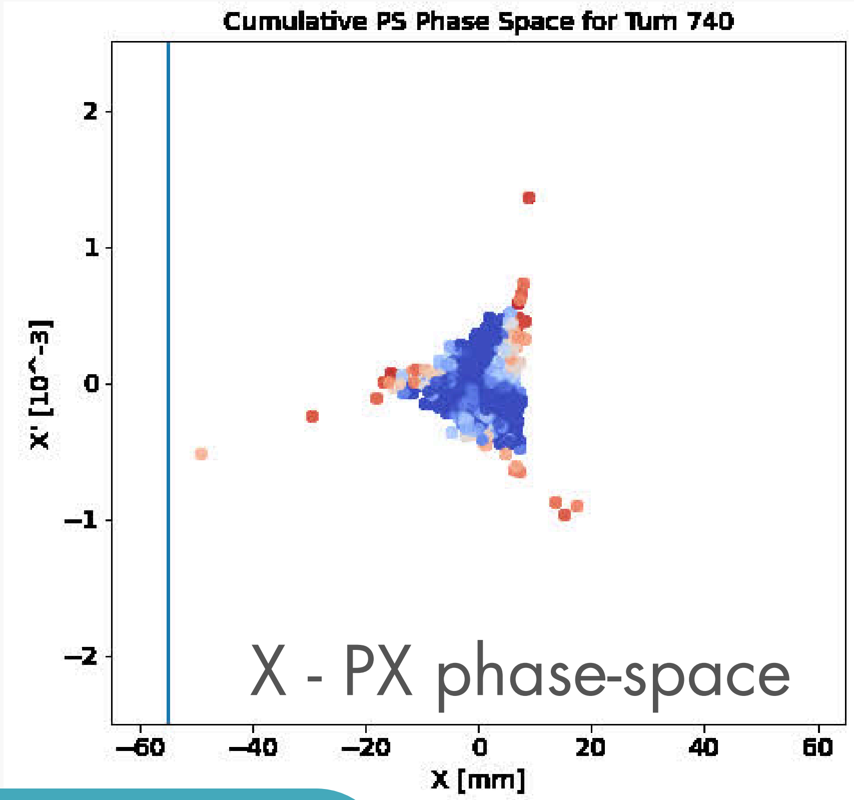


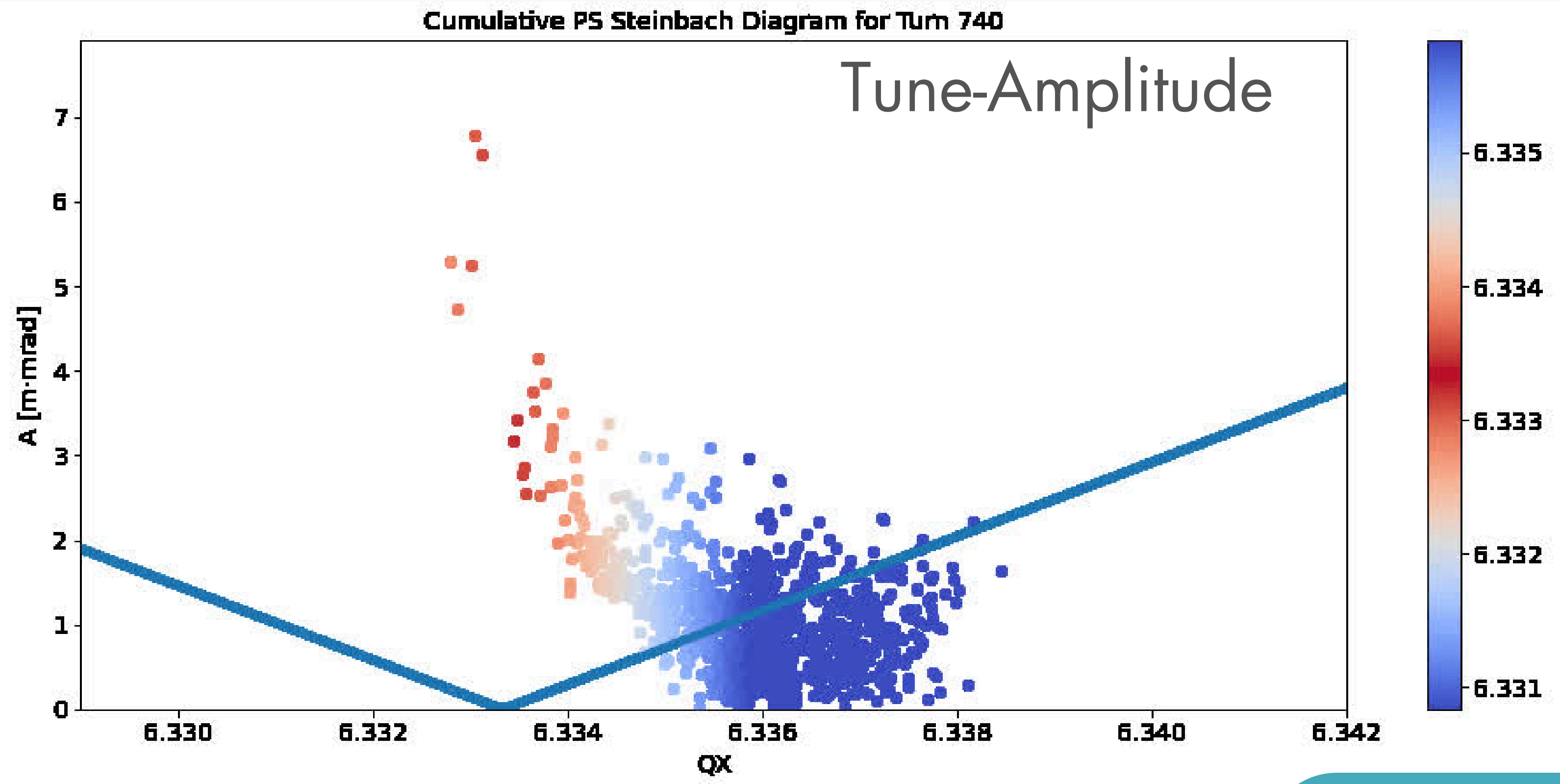
4. Electrostatic Septum: Kicks high-amplitude particles



5. Magnetic Septum: Removes particles







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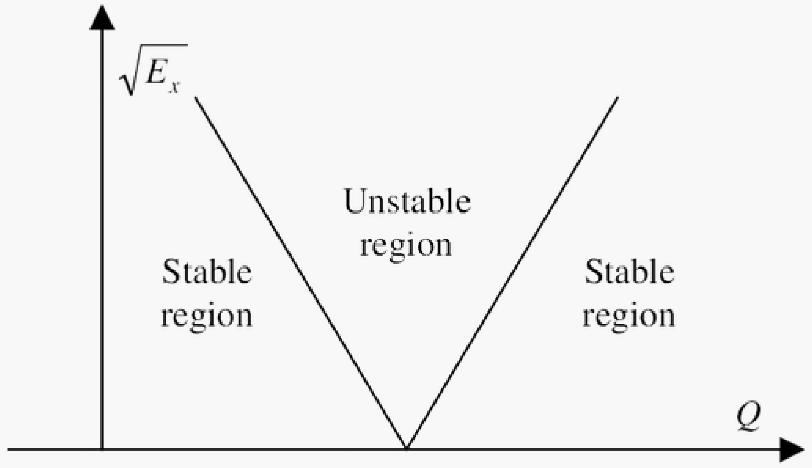
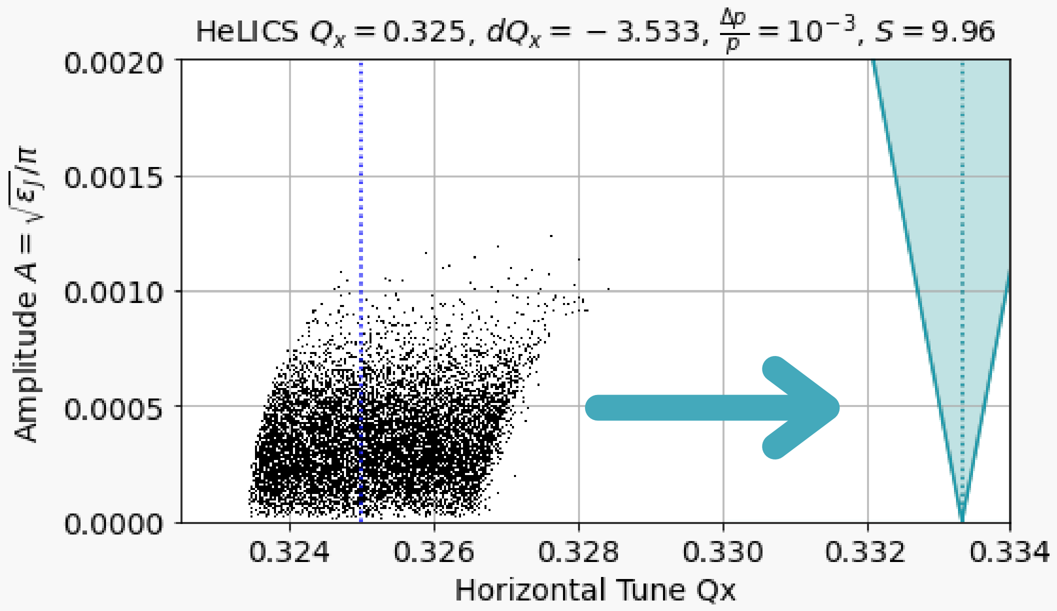
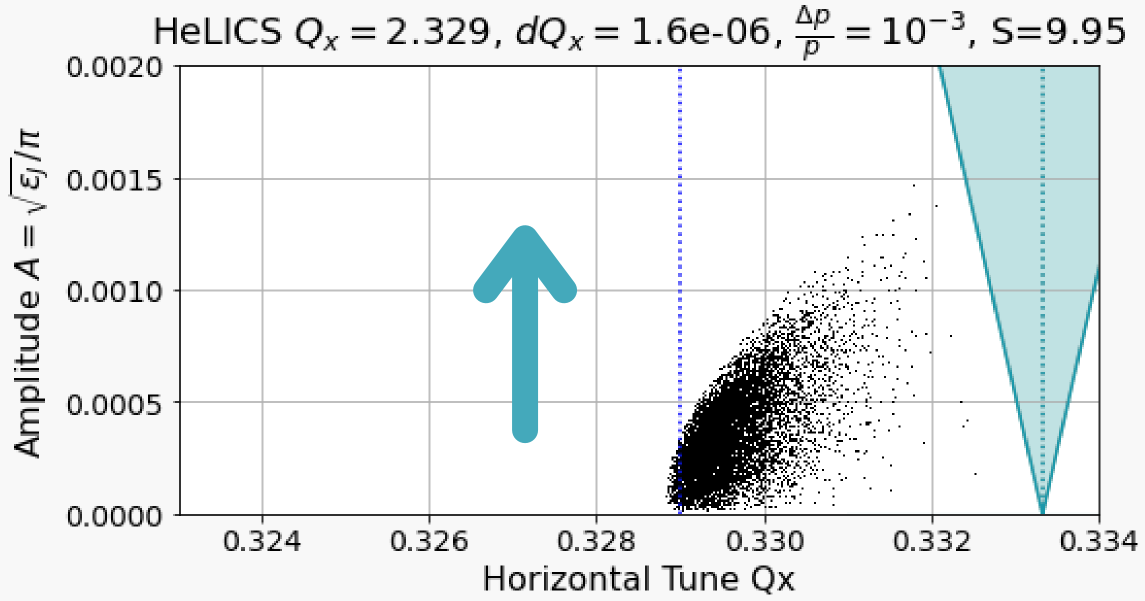


R&D limit of synchrotron UHDR is all in the excitation method of stable particles:

Momentum Driven



Amplitude Driven



<u>Betatron Core:</u> Increase momentum of beam/turn

Limits: Speed of push limited by chromaticity

<u>Quadrupole Driven:</u> Adjust tune of machine/turn

Limits: Current ripple & magnet ramp rate [T/m/s]

<u>RF Phase Displacement:</u> Ramp RF frequency/turn

Limits: Less stable at longer timescales

<u>Radiofrequency Knock-Out</u> (RF-KO):

Stochastic transverse excitation

- FM $\propto$ beam tune
- AM $\propto$ beam density

Limits: Voltage requirement exponentially increases

Feedback loops have limited resolutions

UHDR extraction from synchrotrons

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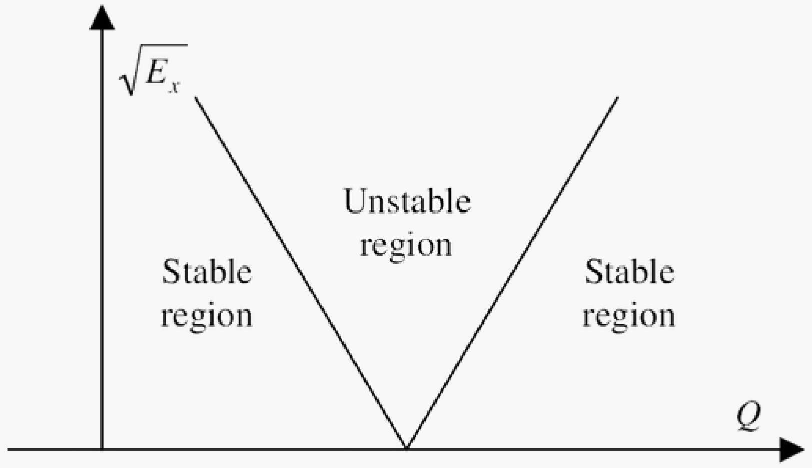

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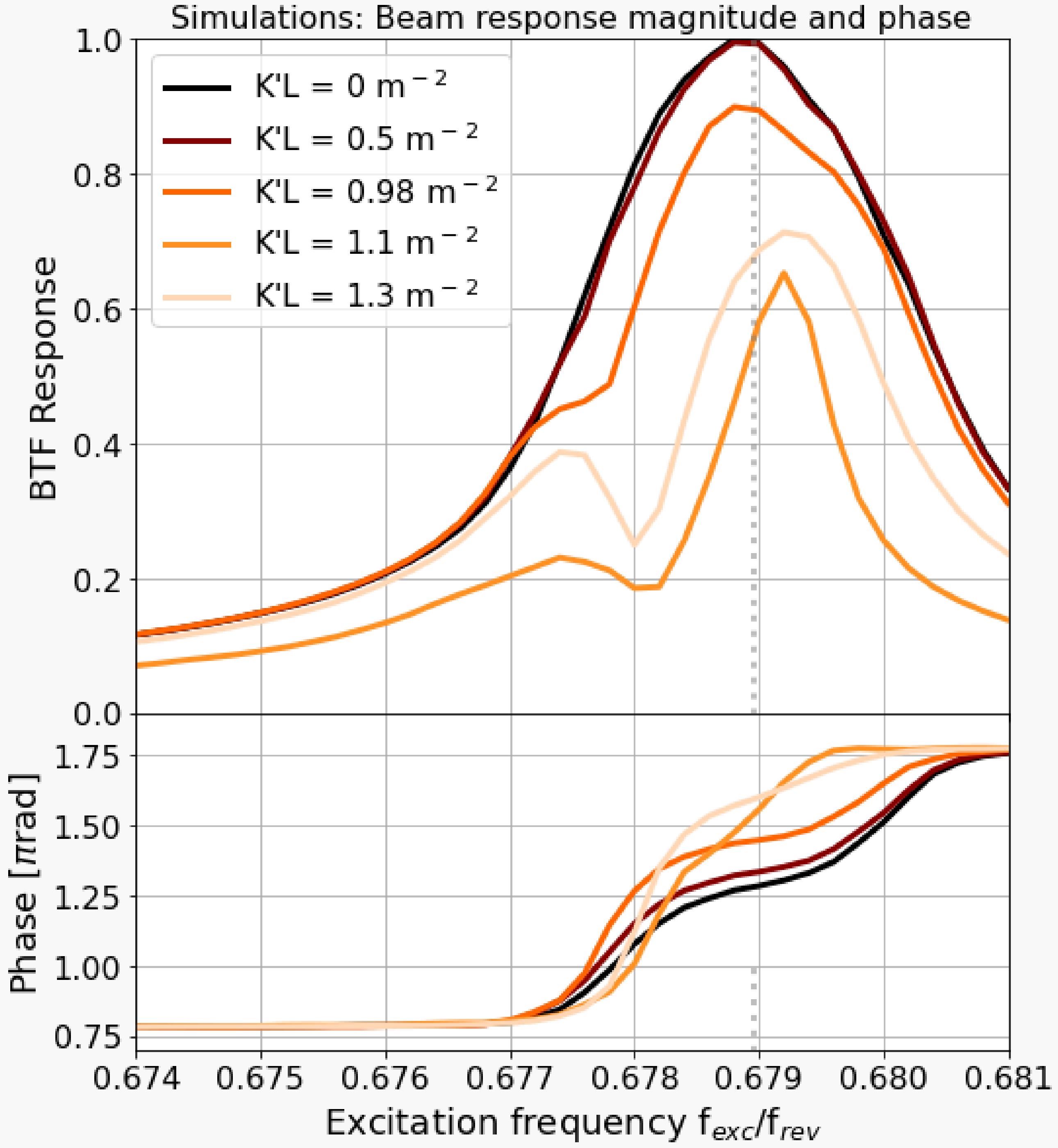

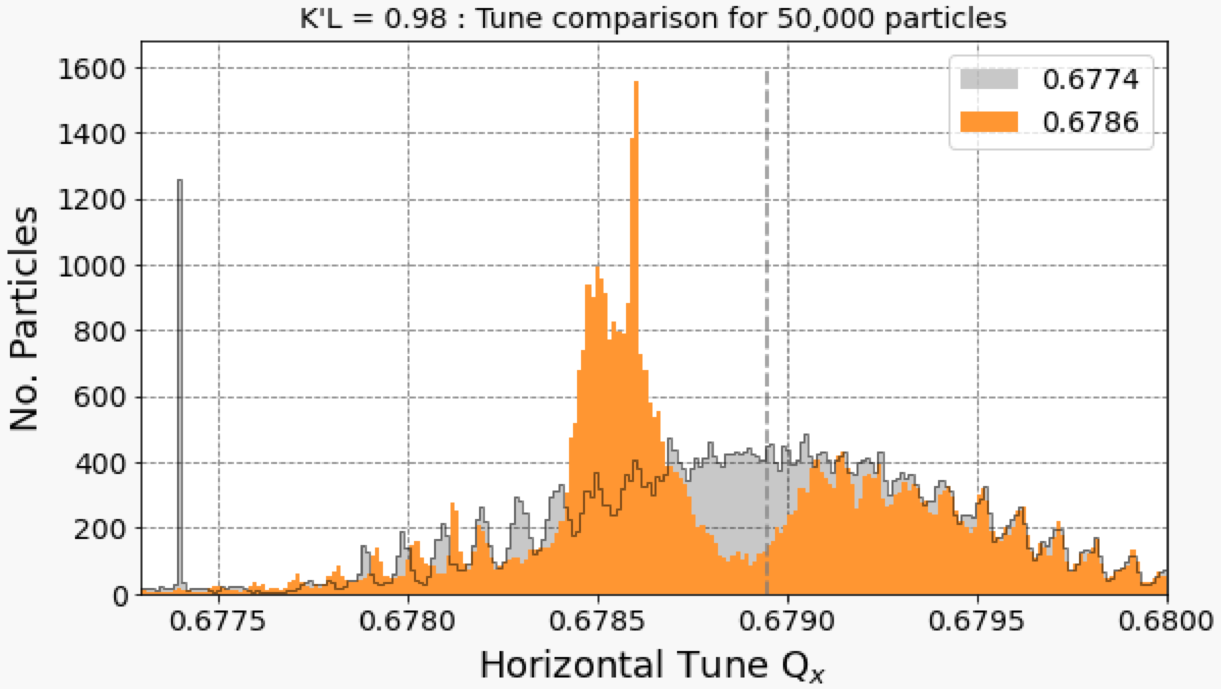

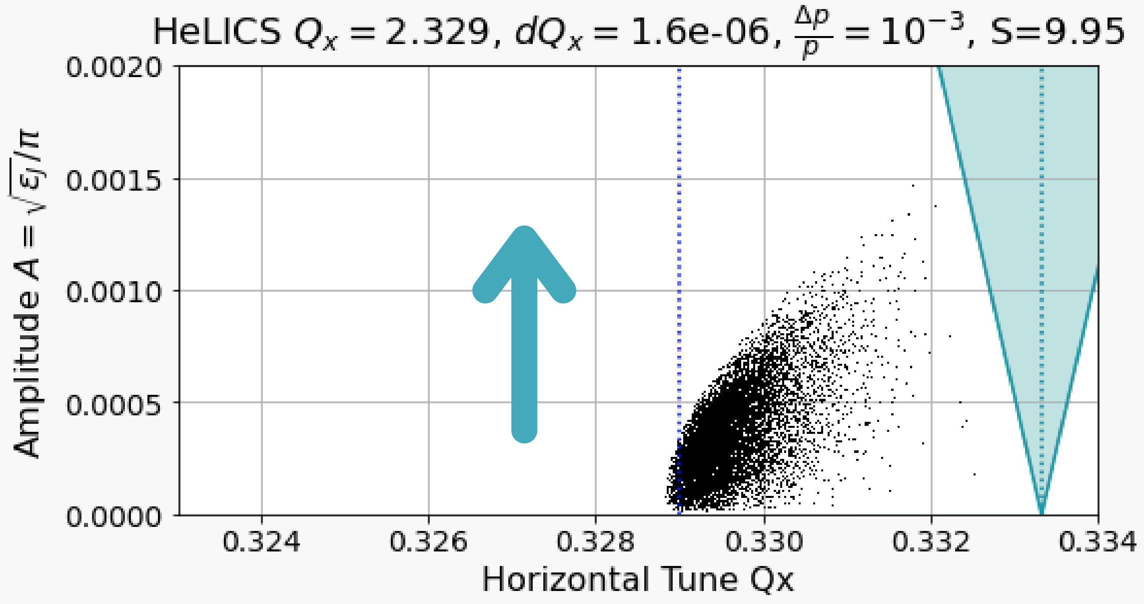

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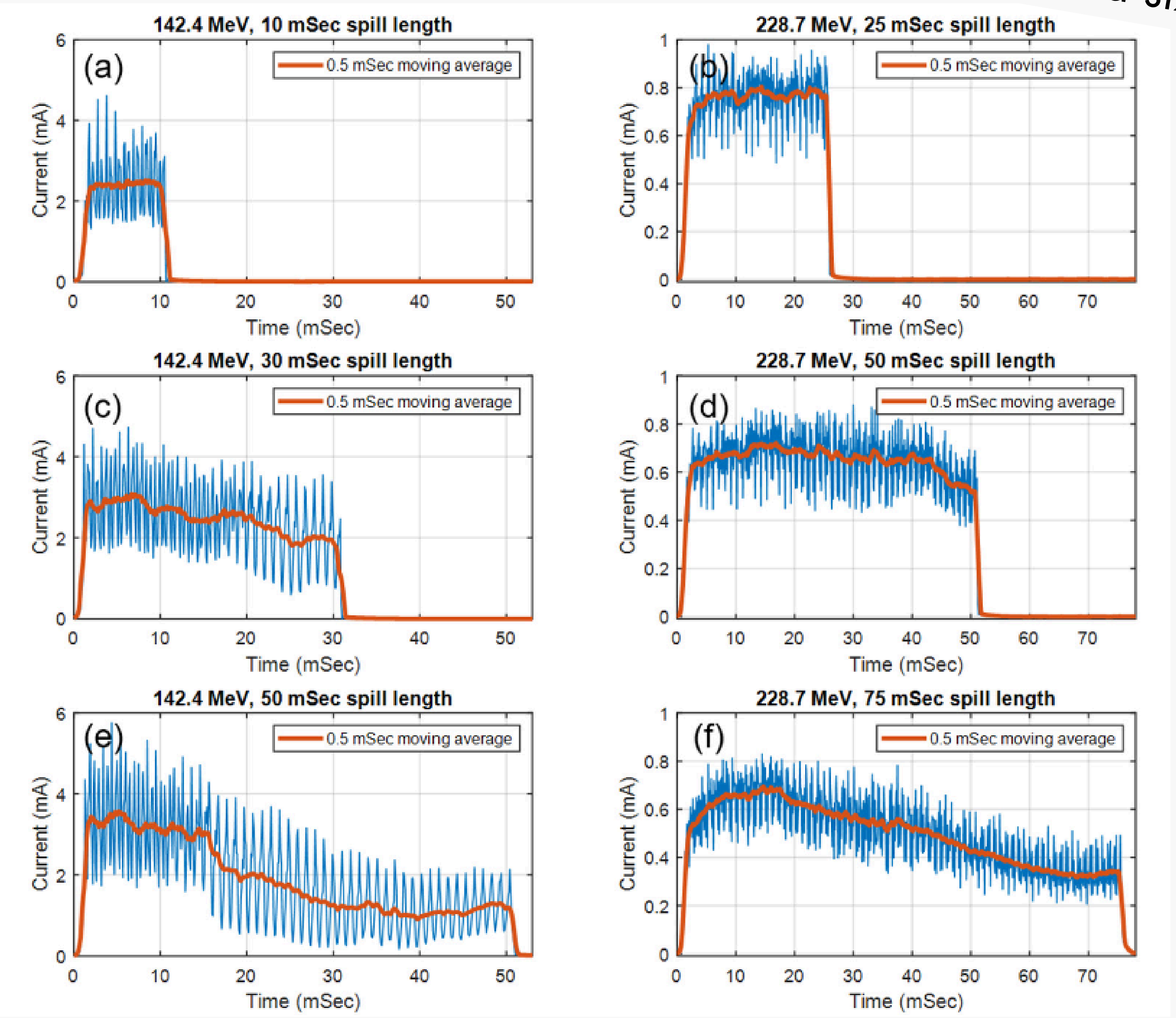
HITACHI

Continuous spill via RF techniques

Max 7x7mm^2 field size



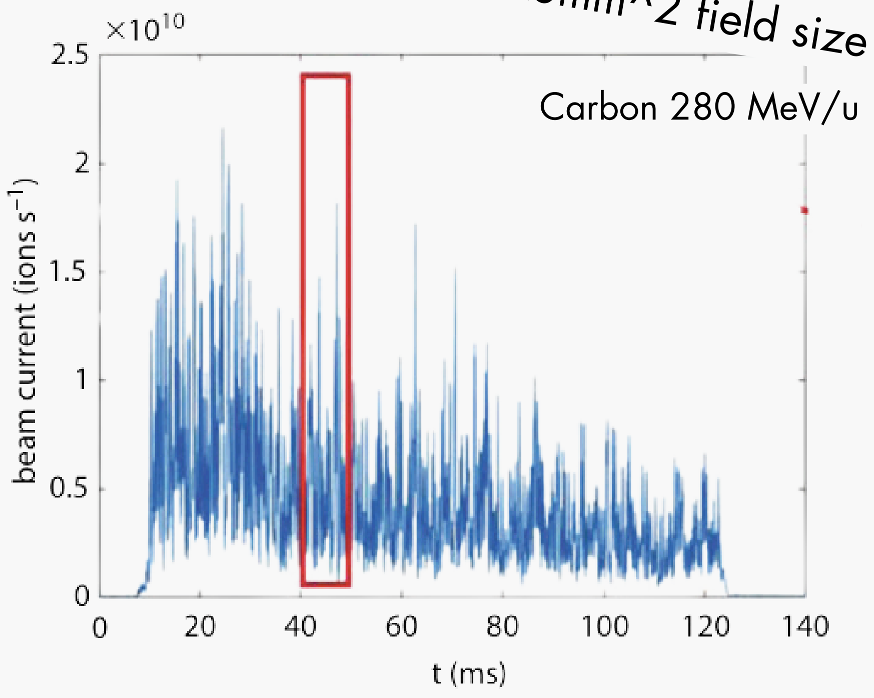
L. Yin *Feasibility of Synchrotron-Based Ultra-High Dose Rate (UHDR) Proton Irradiation with Pencil Beam Scanning for FLASH Research* **(2024)**

HIT - Heidelberg Ion Therapy Center

Continuous spill via RF-KO

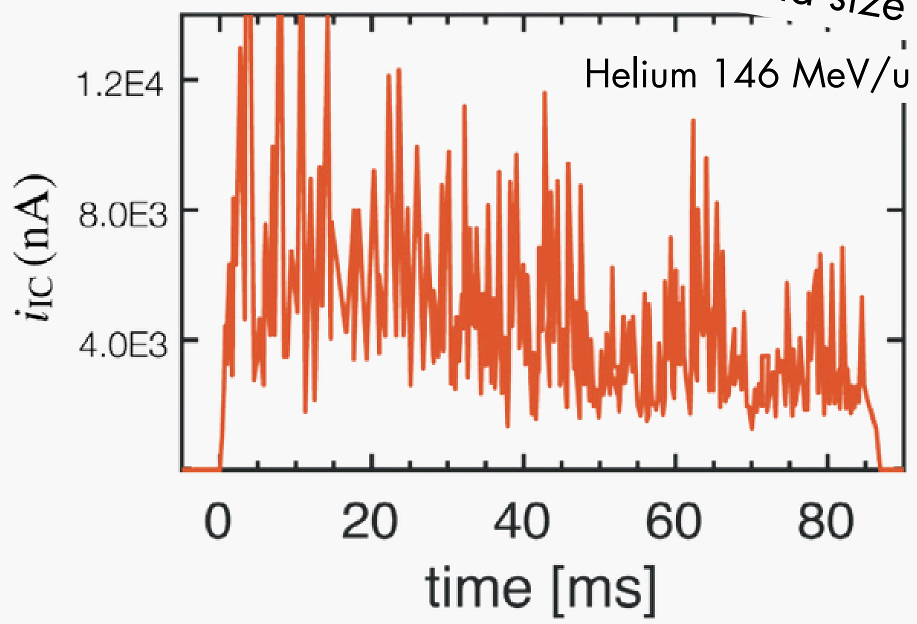
High fluctuations in spill ripple reduces minimum mean intensity to fulfil safety requirements.

Max 8x8mm^2 field size



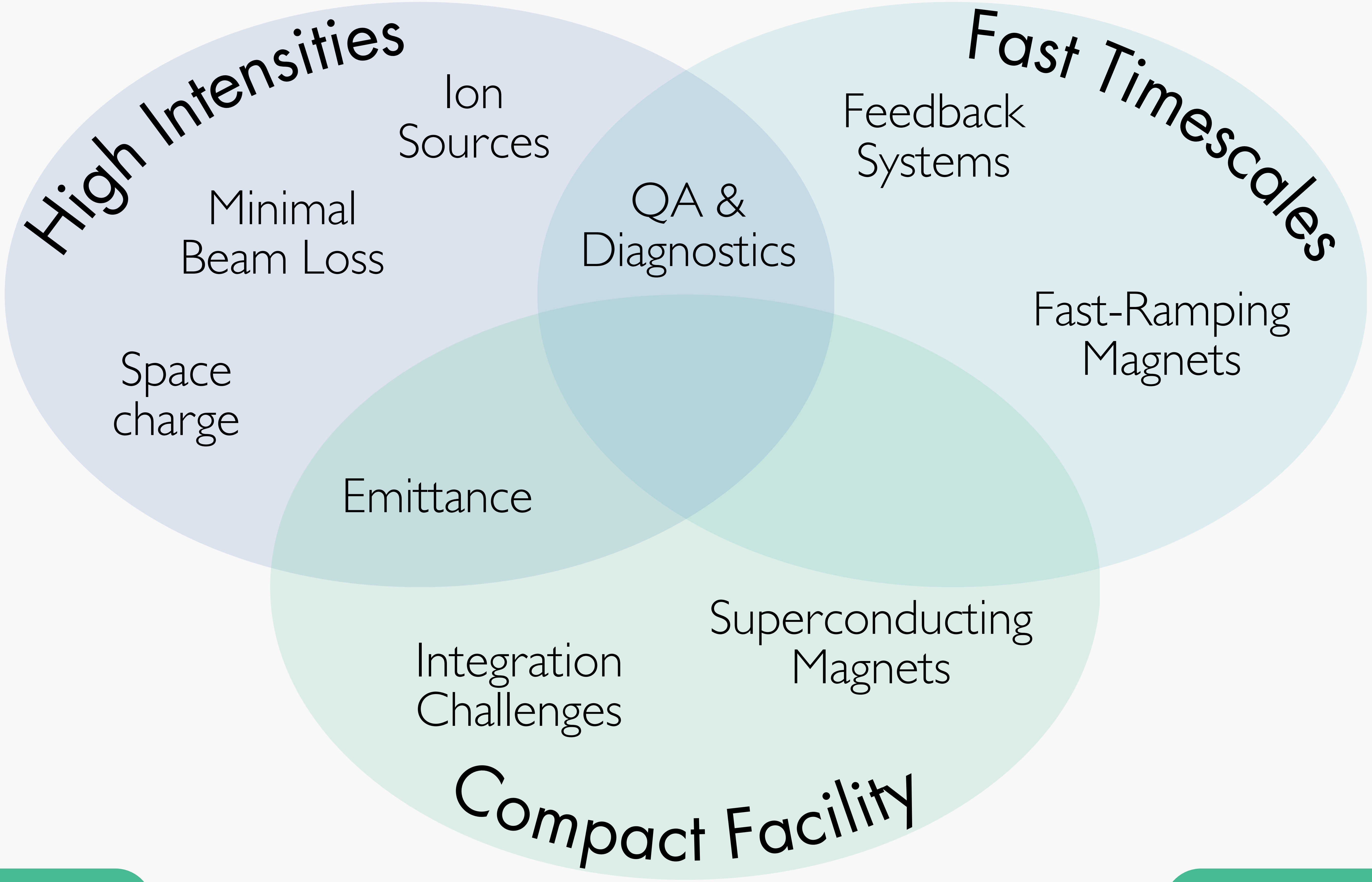
W. Tinganelli *Ultra-High Dose Rate (FLASH) Carbon Ion Irradiation: Dosimetry and First Cell Experiments* (2021)

Max 10x10mm^2 field size



T. Tessonnier *FLASH Dose Rate Helium Ion Beams: First In Vitro Investigations* (2021)

Ultra-High Dose Rate as Accelerator R&D Driver



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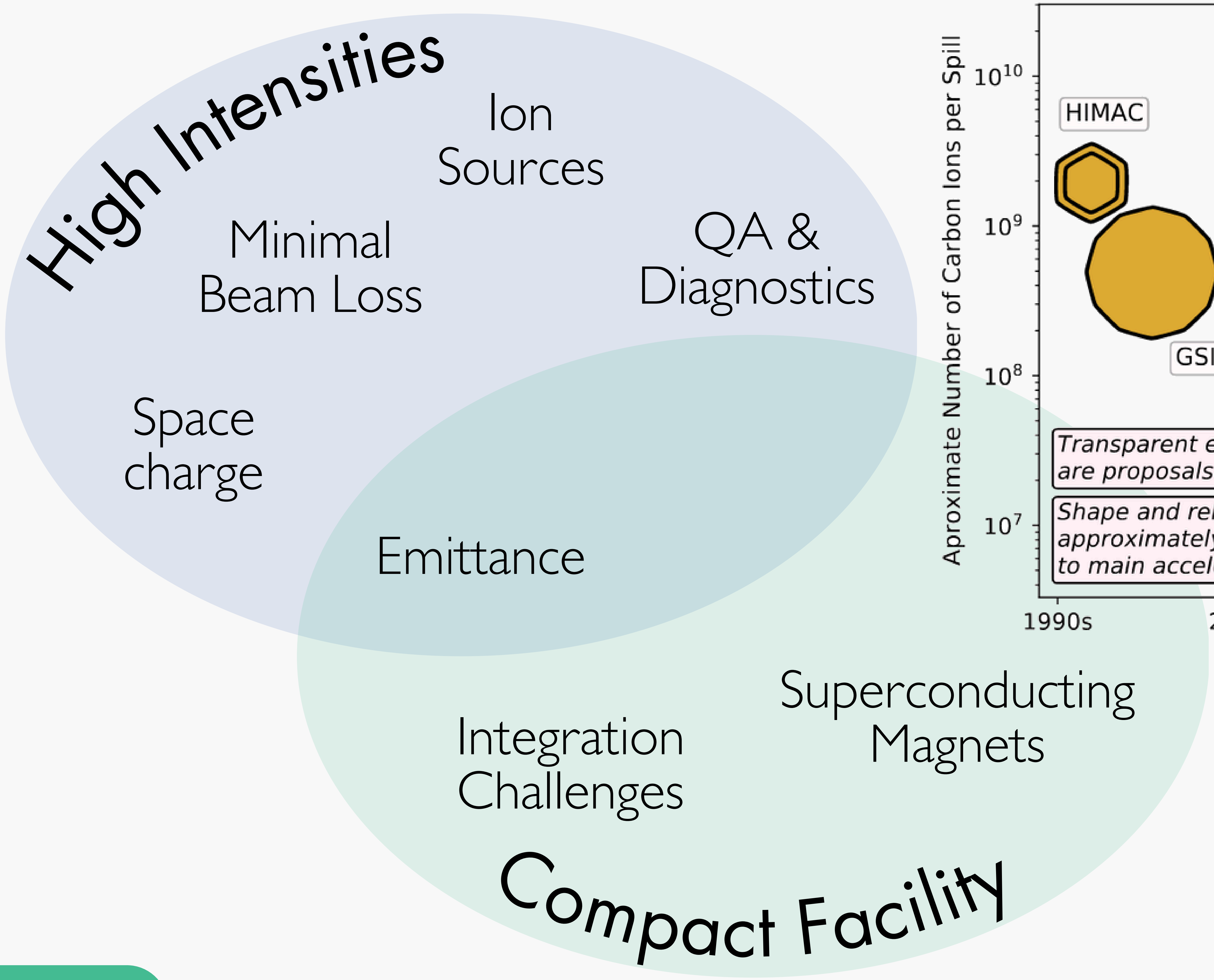
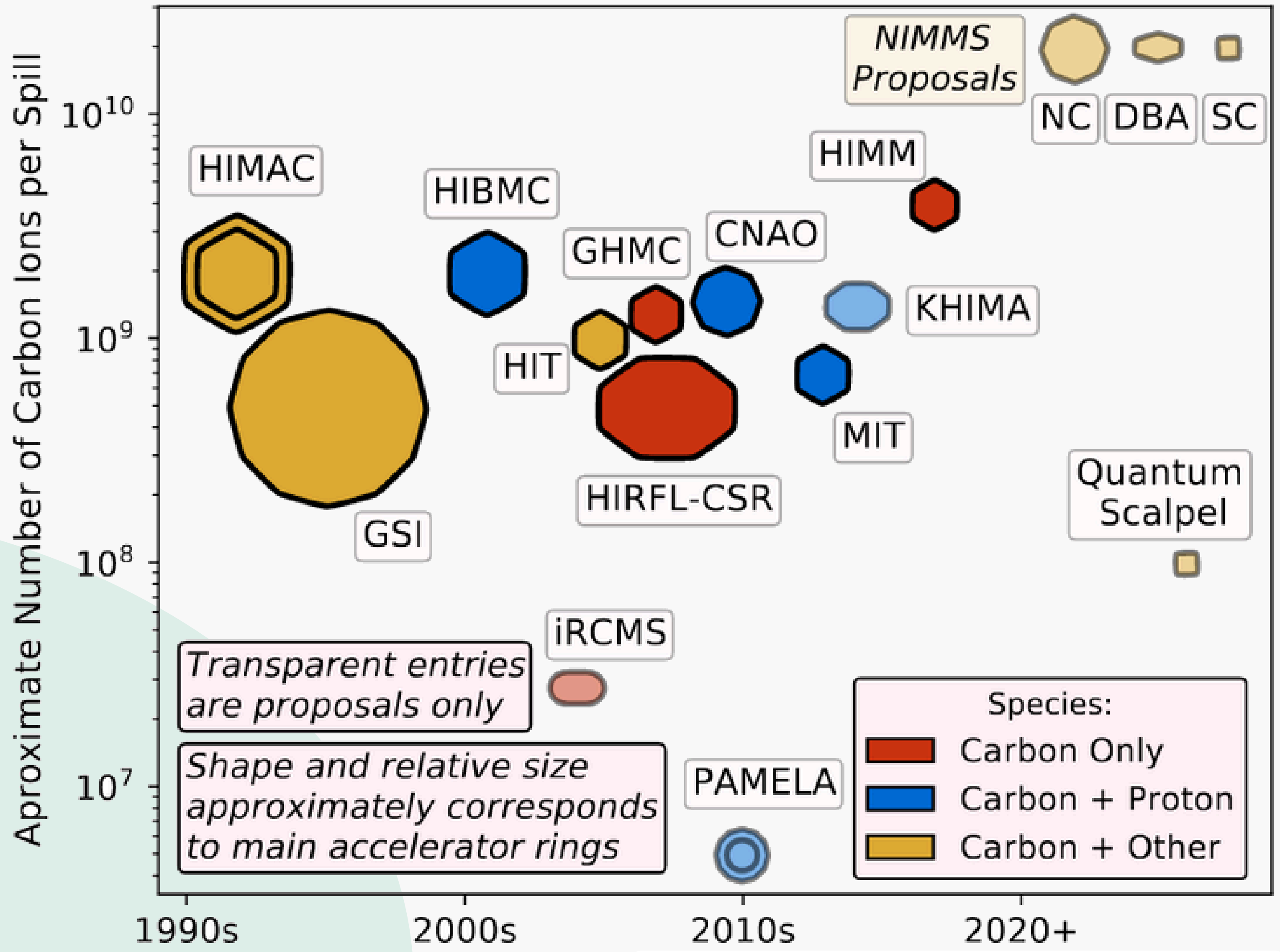




H. X. Q. Norman *Review of technologies for ion therapy accelerators* (2021) nimms

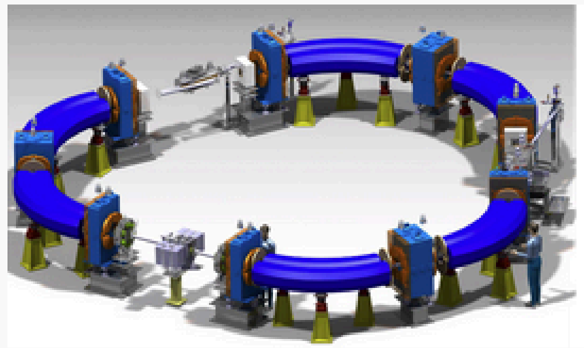
Next Ion Medical Machine Study

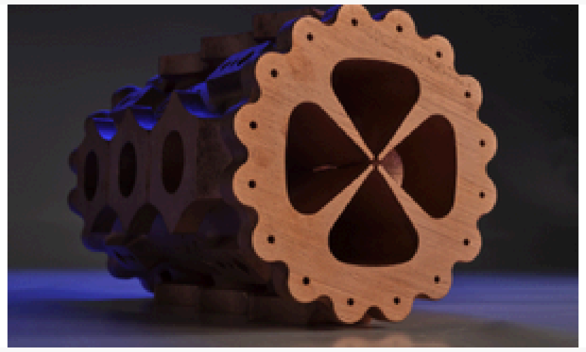
Open questions in hadron therapy encourages study into a new research and treatment facility:

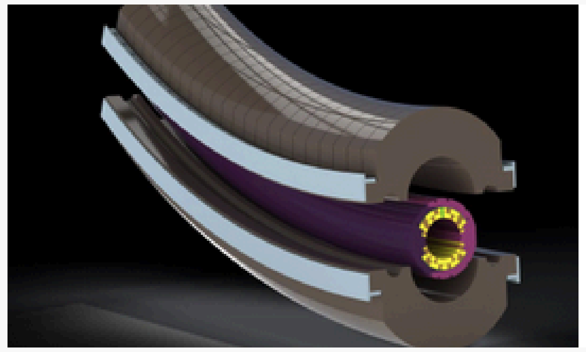
- Toolbox for accelerator technologies

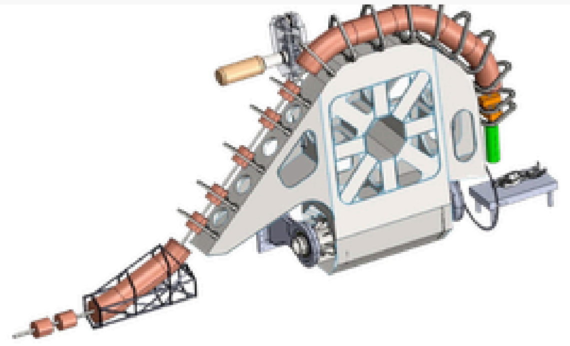
Two initiatives:

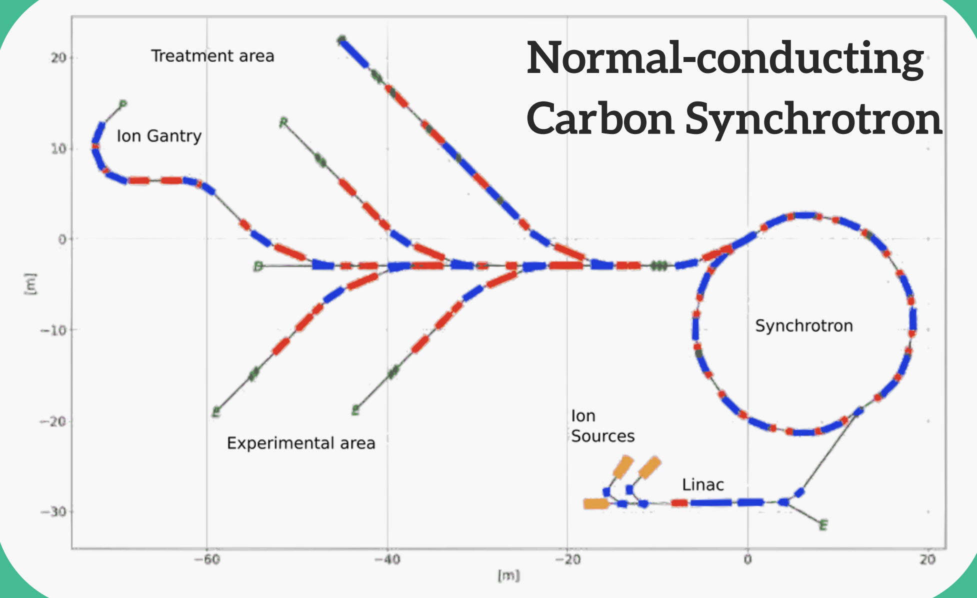
- SEEIIST - South East Europe
- Particle therapy center for the Baltics

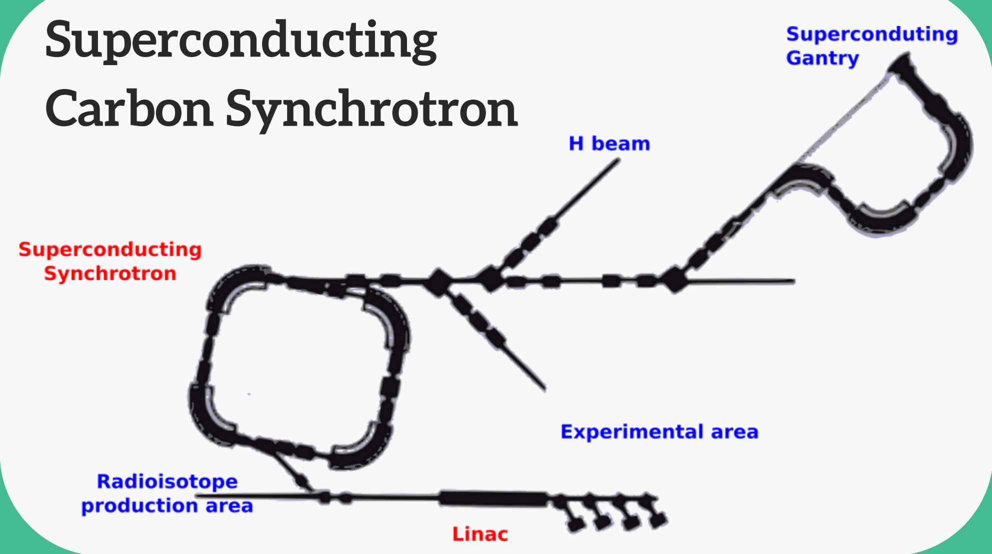

Synchrotron Accelerators

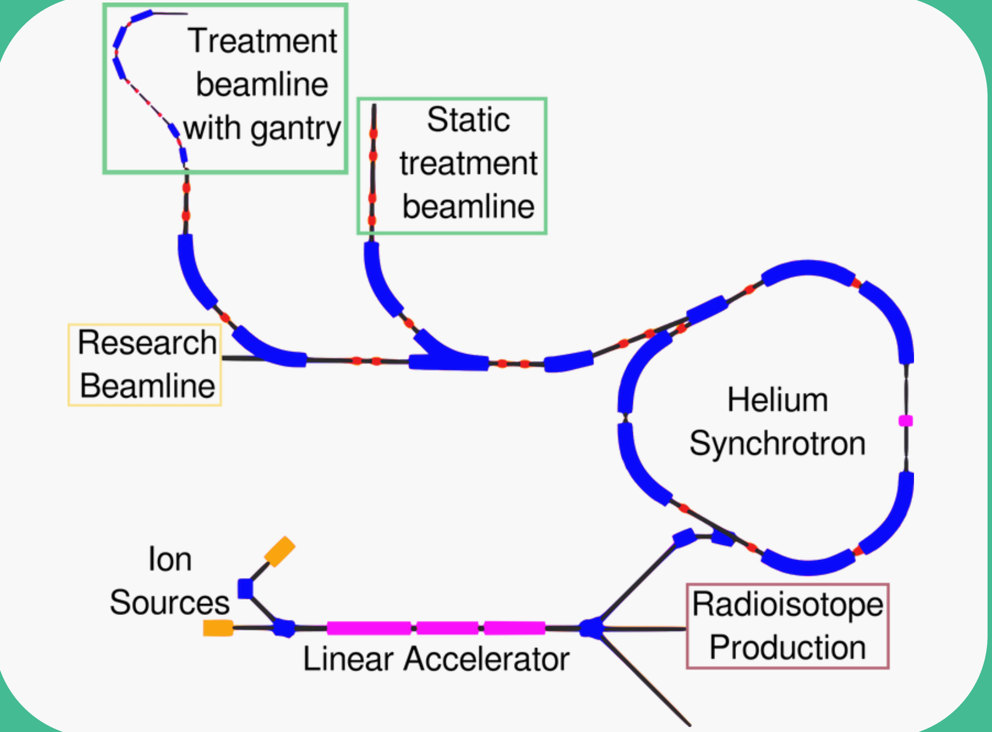

Linear Accelerators


Superconducing Magnets


Superconducing Gantries





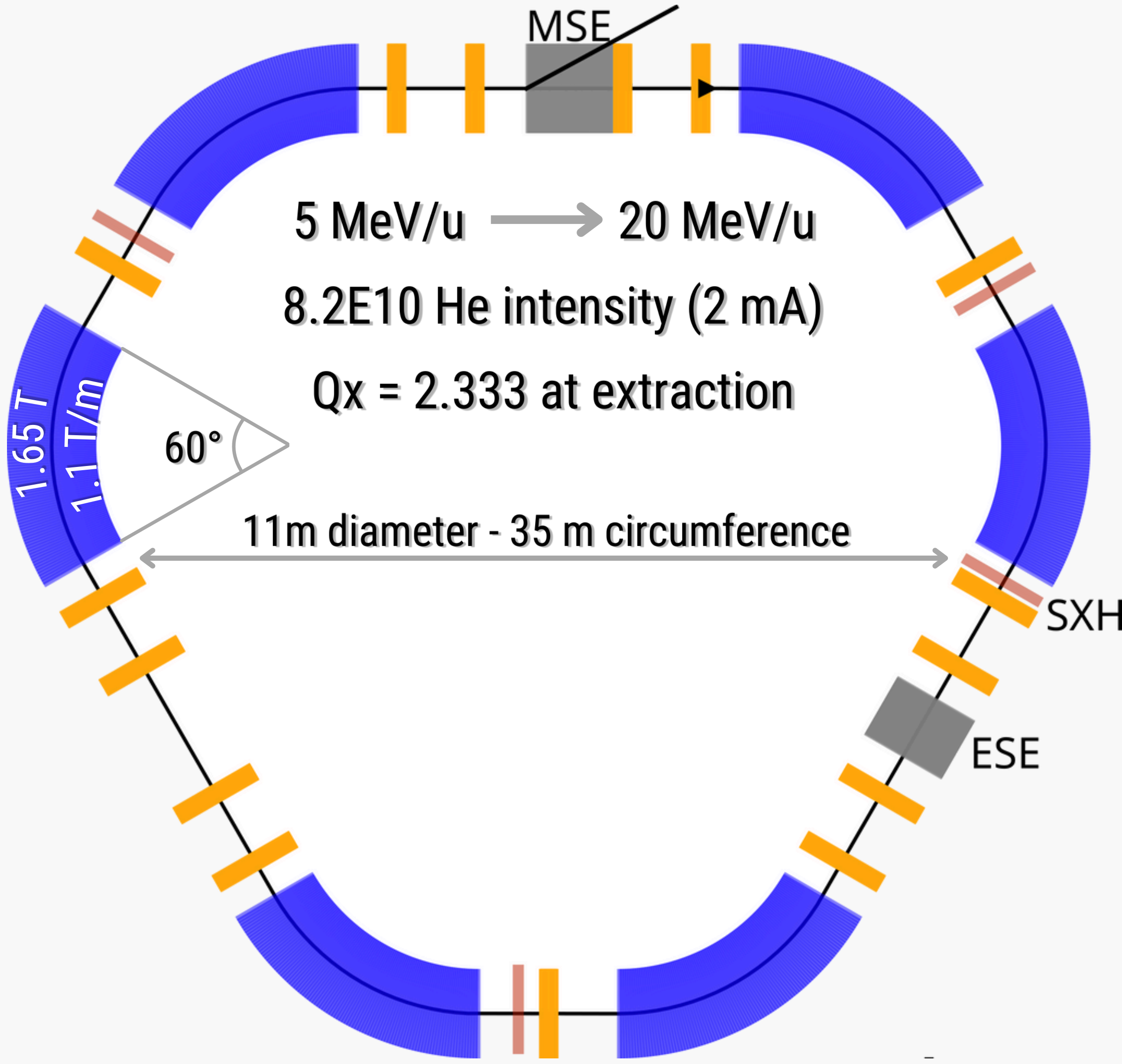


HeLICS: Helium Light Ion Compact Synchrotron

Accelerating protons for treatment, and helium ions for research. Planning installation for the Baltic states.

FLASH extraction inherent in the baseline design.

- 20x Multi-Turn Injection (MTI)
  - Higher emittance to reduce space-charge
- Exploring **continuous** and **burst** extraction for raster and spot scanning magnets.



Time [ms]	Turns	8 Gy	10 Gy
500	1,500,000	16 Gy/s	20 Gy/s
100	***300,000***	***80 Gy/s***	***100 Gy/s***
10	30,000	800 Gy/s	1000 Gy/s
0.00033	1	2.4E7 Gy/s	3.0E7 Gy/s

Delivering to volumes of ~5x5x5cm

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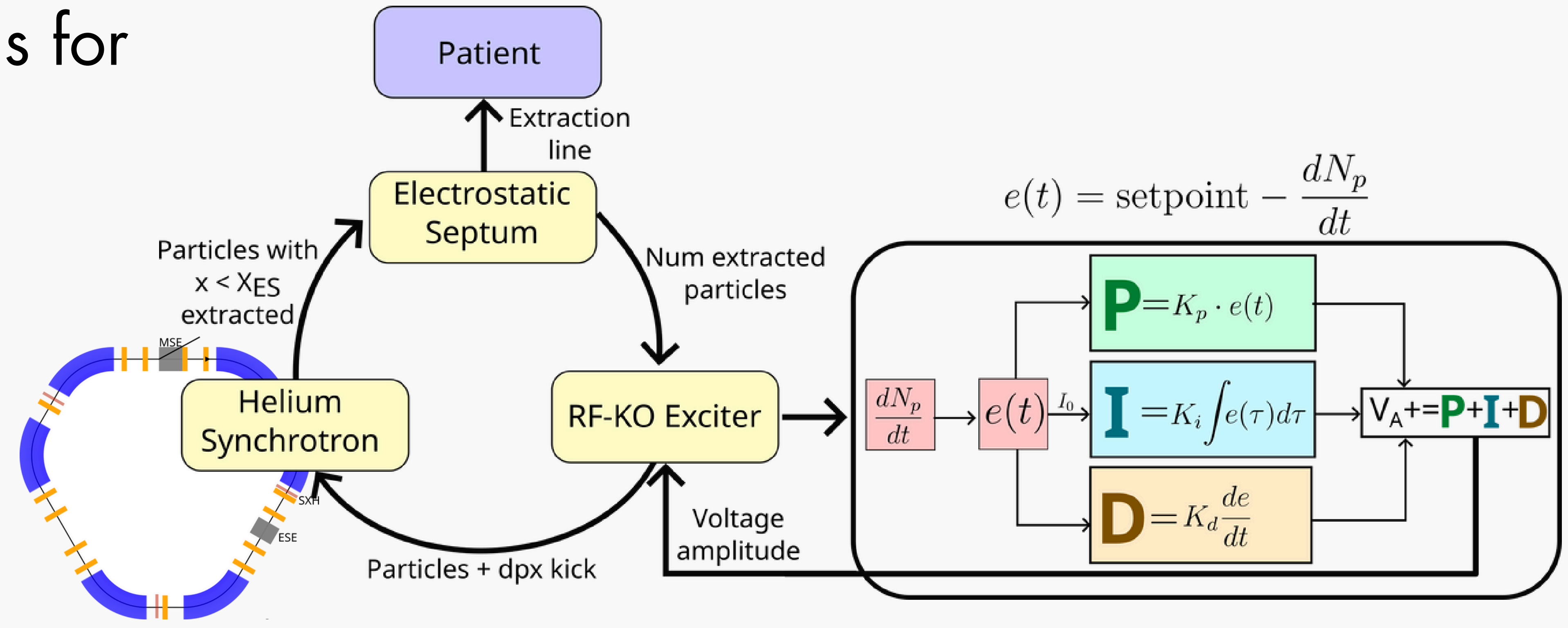
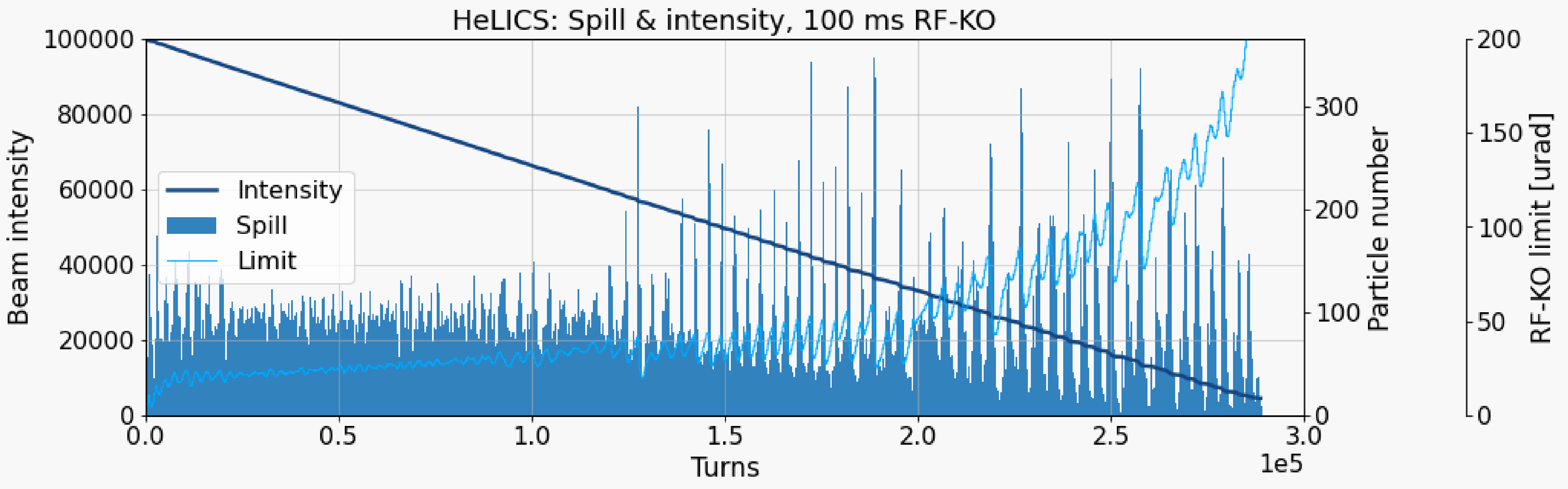
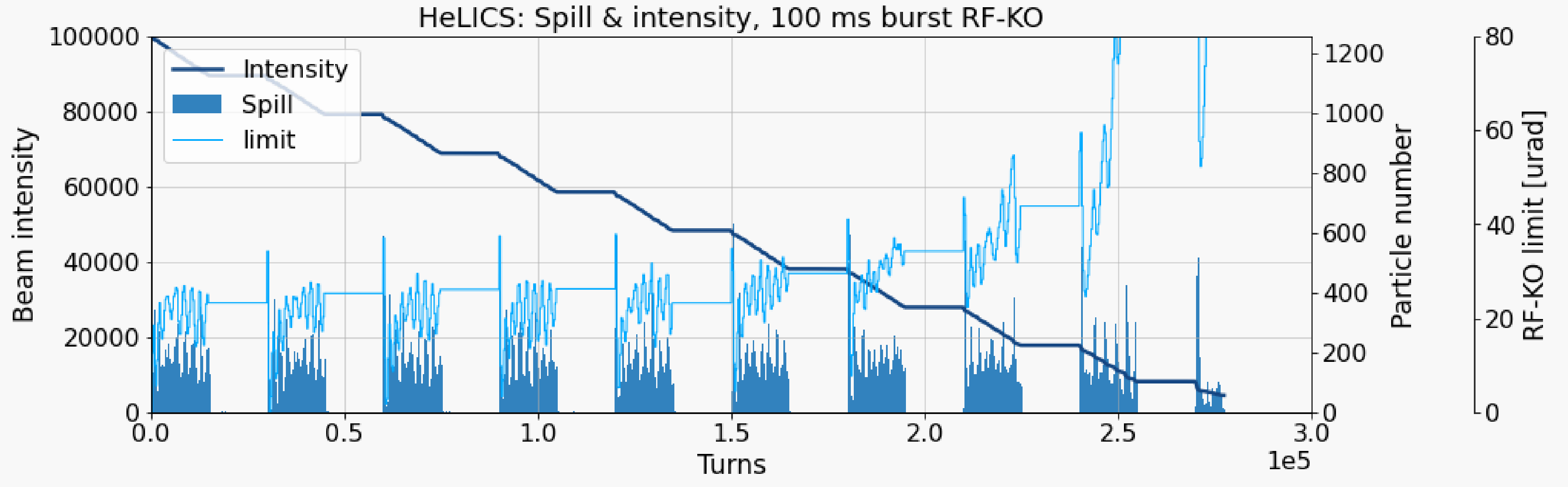


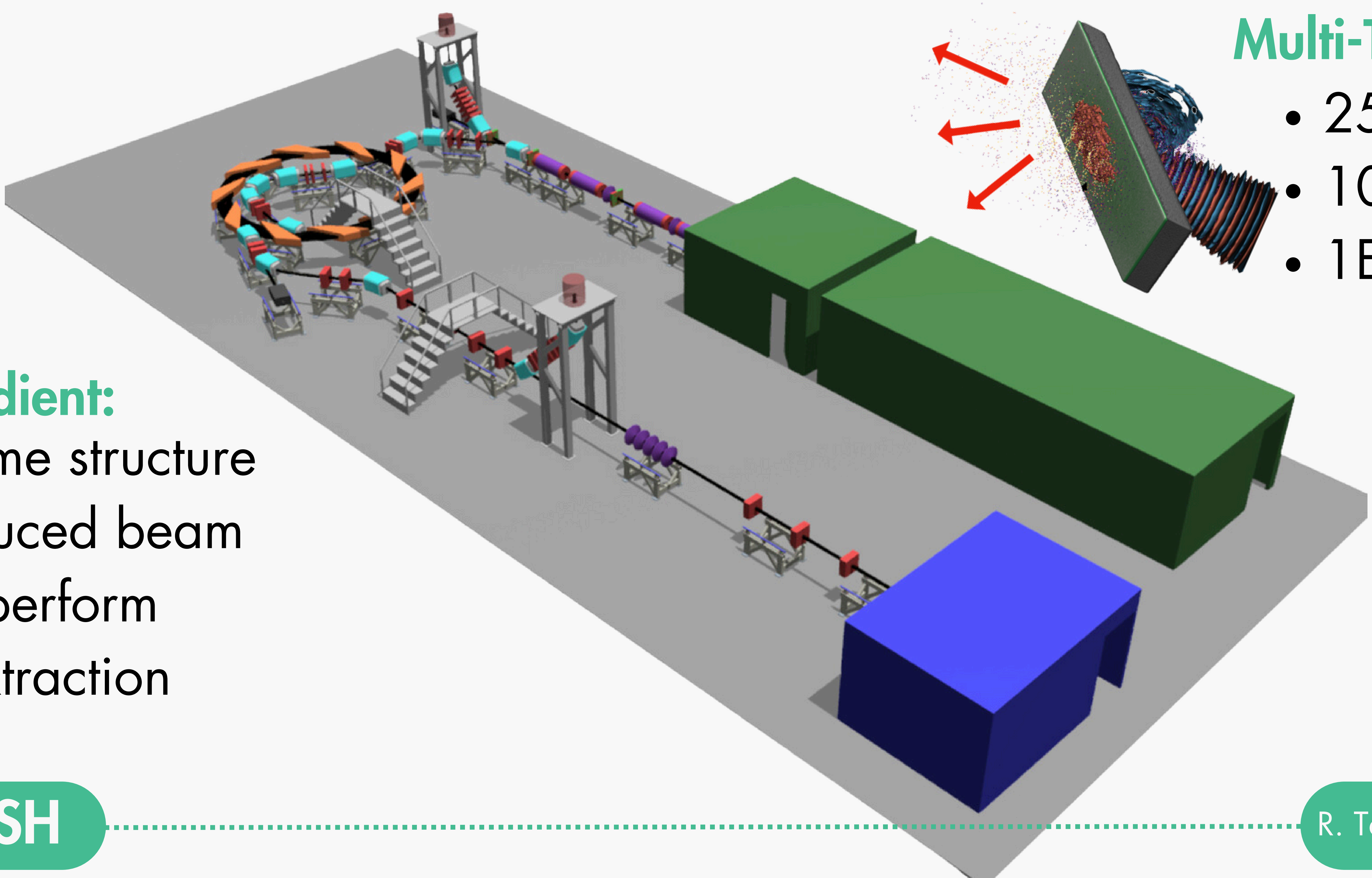




LhARA: Laser-hybrid Accelerator for Radiobiological Applications

Stage 1: 15 MeV in-vitro test bench for cellular radiobiology
Stage 2: 127 MeV (33 MeV/u ions) in-vivo for animal studies

Multi-TW commercial laser
- 25 fs pulses
- 10 Hz repition rate
- 1E10 ions per shot



Fixed-field alternating gradient:
- Maintain time structure of laser-induced beam
- Difficult to perform resonant extraction

FLASH at LhARA

mm - cm beam size

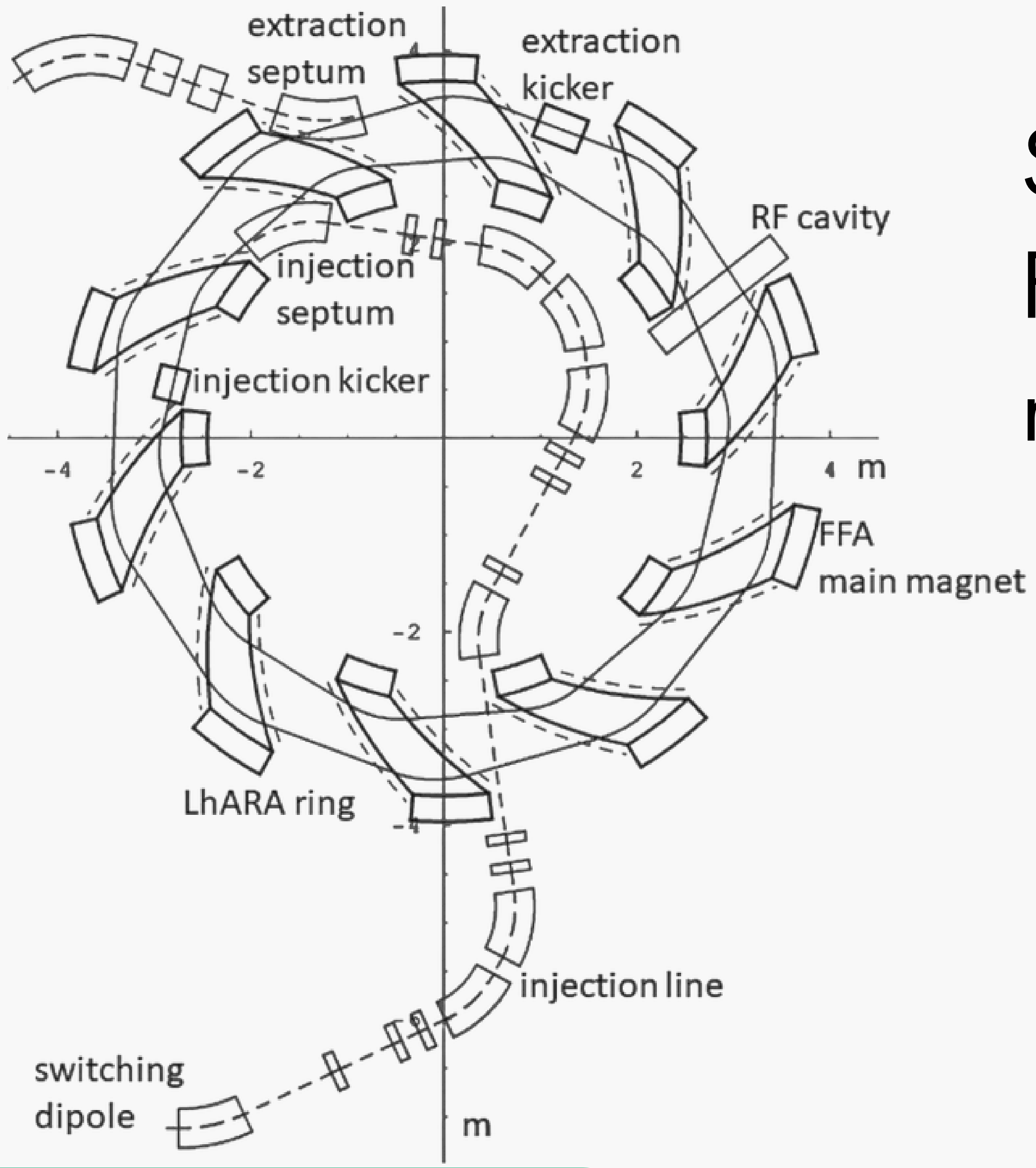
1E9 - 1E10 ions per shot

Real time monitoring

ns beam structure

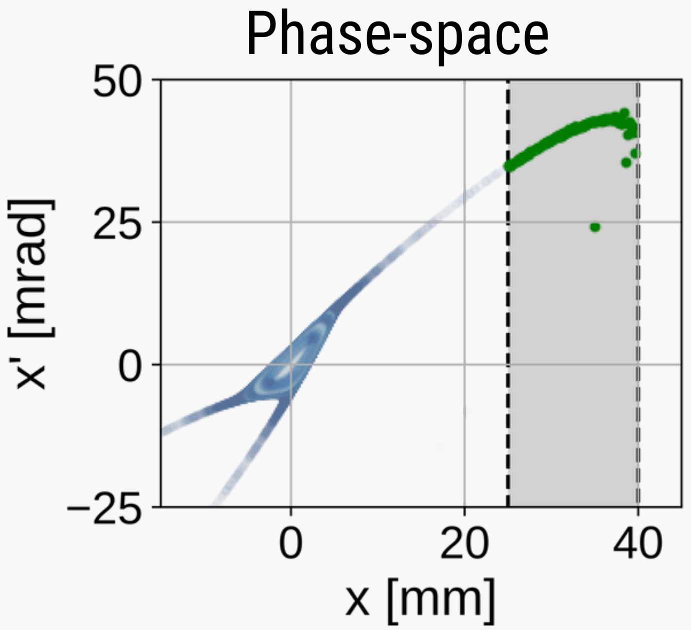
	127 MeV protons	33.4 MeV/u carbon
Dose per pulse	15.6 Gy	73.0 Gy
Instantaneous dose rate	3.8×10^8 Gy/s	9.7×10^8 Gy/s
Average dose rate	156 Gy/s	730 Gy/s

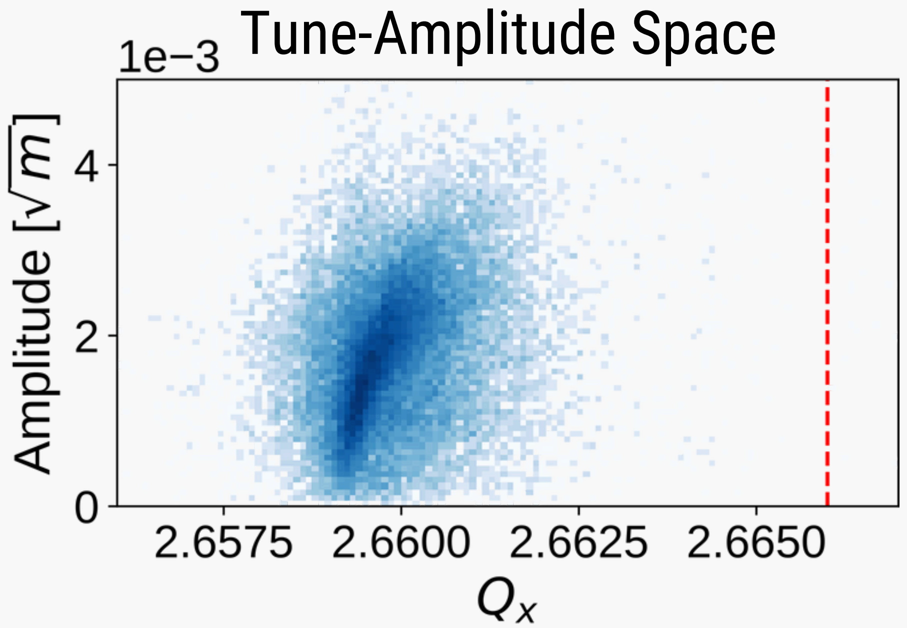
Galen Aymar *LhARA: The Laser-hybrid Accelerator for Radiobiological Applications* (2020)



Stage 2 baseline: one-turn extraction of provided short pulse

For flexible timescales: Resonant extraction is possible but requires adaptation of lattice geometry.





Also looking into mini beam delivery

Conclusions

The compatibility between **hadron therapy** and **FLASH therapy** is an active area of research.

The high energies needed to reach sufficient depths means **accelerators** are necessary for both **treatment** and **research** facilities.

Such accelerators need to reach **Ultra-High Dose Rates** to provide beams suitable for FLASH radiobiological research.

Active R&D is required for accelerators to reliably reach these high dose rates in a way that is **clinically approved**.

For synchrotrons, **advanced resonant extraction** methods need to be developed and tested to reach the required beam specifications.

The **next generation** of hadron therapy treatment machines are in development and actively incorporating FLASH R&D methods.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9544515/

- *beam type*
- *average dose rate (DR ave)*
- *pulse dose (D pulse)*
- *pulse dose rate (DR pulse)*
- *beam-on time*
- *tissue type*
- *tissue oxygenation*
- *minimum required dose, if any*
- *dose rate variations within the target volume*
- *dose rate variations within the irradiated healthy tissues*
- *optimal dose rate or range*
- *FLASH differences in differing linear energy transfer portions of the Bragg peak for ions*
- *timing matters of beam micro- and macrostructure*
- *fractionation*
- *dose conformity (or the lack thereof)*
- *dose distributions overlapping in space and time*
- *time interval(s) between these overlapping or nonoverlapping doses*
- *relative biological effectiveness*
- *FLASH differences between X-rays, electrons, and ions*
- *linear energy transfer aspects*