FLASH Radiotherapy with hIgh Dose-rate particle beAms

FRIDA

Seconda Giornata Acceleratori - Catania 2-3 marzo 2023

Andrea Mostacci
on behalf of the FRIDA collaboration

Outline

FLASH Radiotherapy with hIgh Dose-rate particle beAms

FLASH effect for radiotherapy

FRIDA project @ CSNV

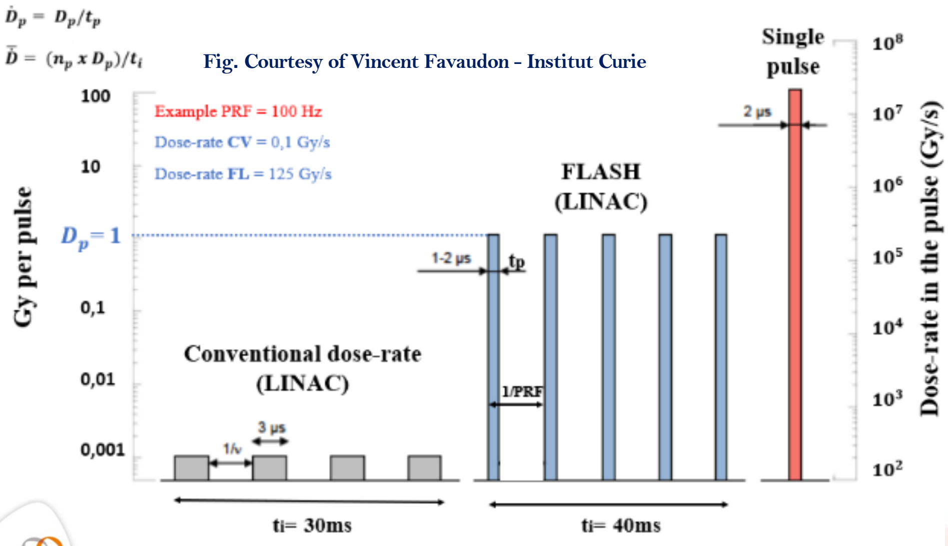
Beam Delivery

- Compact linac RF structures
- Improved power sources (pulse compressors)

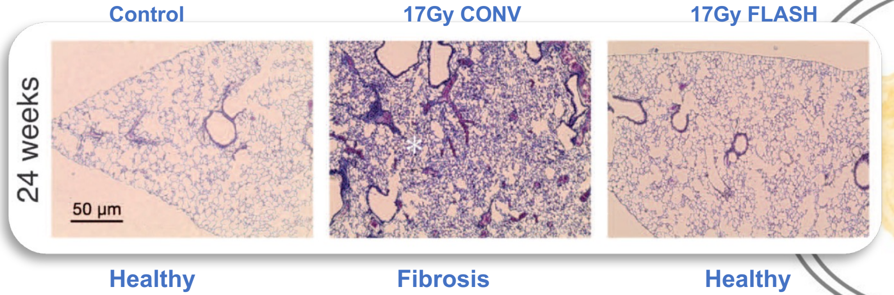
FLASH effect

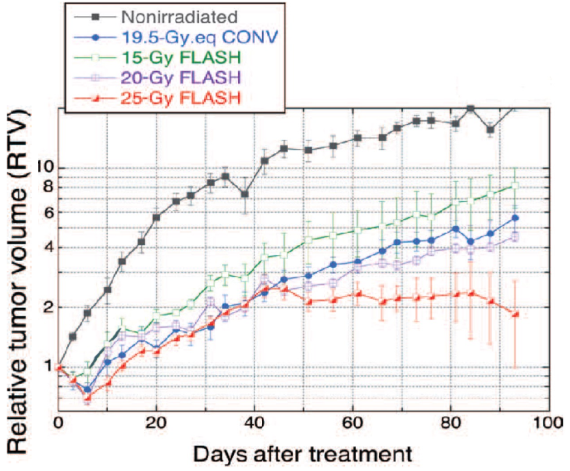
FLASH irradiation provides better protection on normal tissues while maintaining tumor killing effect compared with conventional dose rate irradiation

Temporal structure of energy deposition in the flash effect



V. Favaudon et al., *Science Translational Medicine* 6, 2014





Courtesy of L. Giuliano

FLASH effect

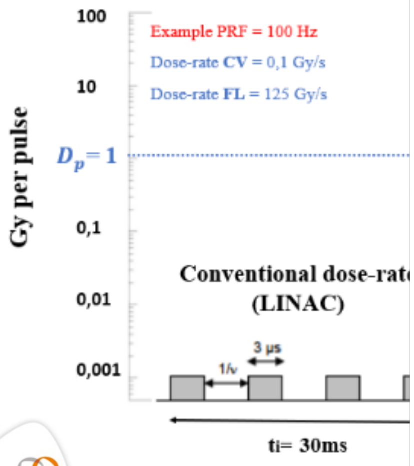
FLASH irradi e maintaining
tumor killing

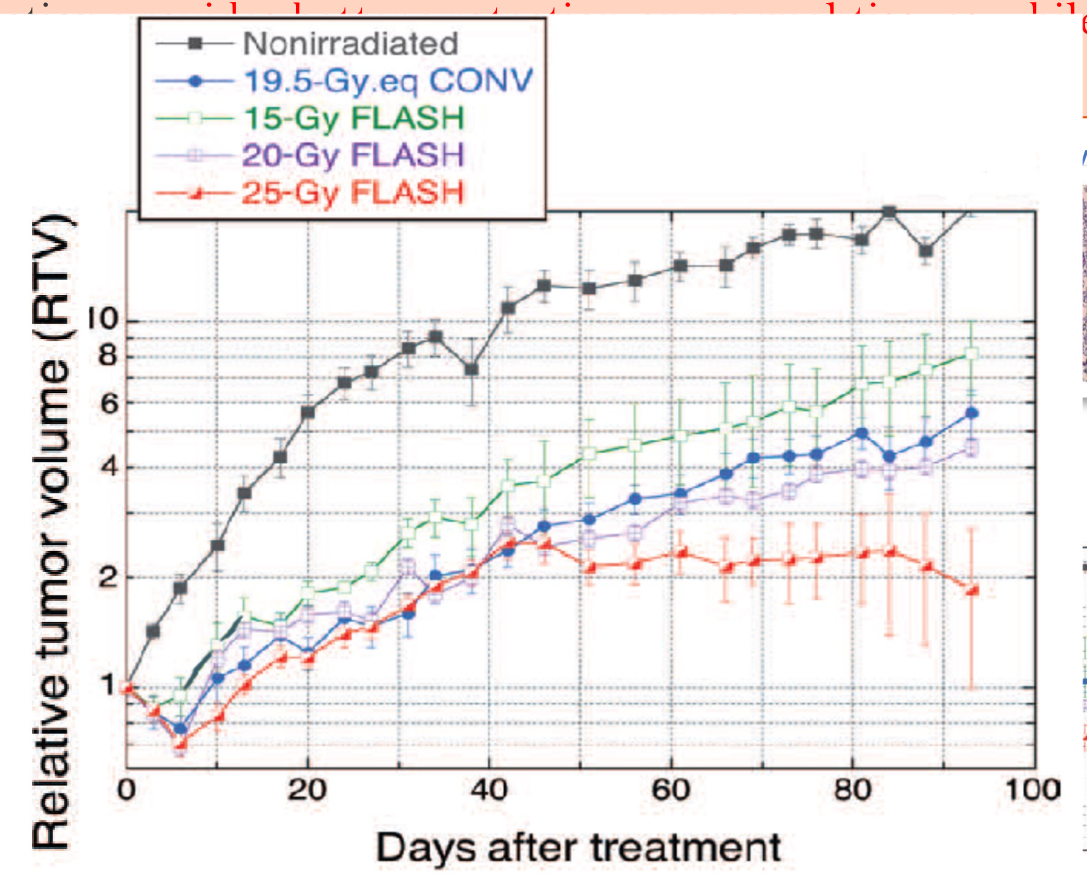
Temporal structure of ene

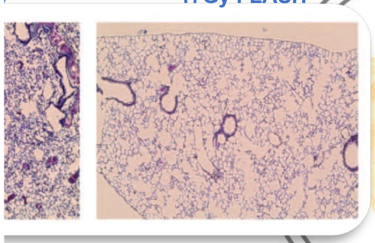
$\dot{D}_p = D_p/t_p$

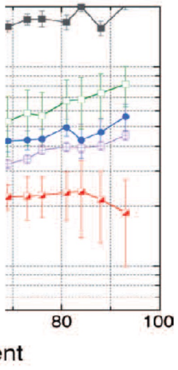
$\bar{D} = (n_p \times D_p)/t_i$

Fig. Courtesy of Vincent









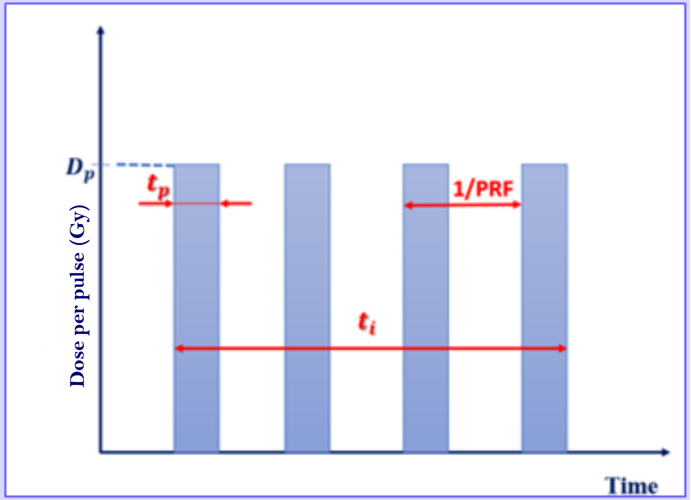
V. Favaudon et al., *Science Tr*

institut Curie

Courtesy of L. Giuliano

Definition of FLASH treatment parameters

FLASH effect depends on different inter-dependent parameters



- Total dose
- Dose per pulse — D_p
- Mean dose rate — $\overline{\dot{D}}$
- Instantaneous dose rate — $\dot{D}_p$
- Pulse length — t_p
- Pulse Repetition Frequency — PRF
- Number of the pulses — n_p

$$\dot{D}_p = D_p/t_p$$

$$\overline{\dot{D}} = n_p \times D_p/t_i$$

User interface

Example of irradiation:

Total dose = 12 Gy
D_p = 3 Gy

t_p = 4 µs
PRF = 100 Hz
n_p = 4

t_i = ~ 30 ms

$\dot{D}_p = 7{,}5 \times 10^5$ Gy/s

$\overline{\dot{D}}$ = 400 Gy/s

Courtesy of L. Giuliano

FLASH effect in a nutshell …

FLASH effect depends on different inter-dependent parameters

- Total dose
- Dose per pulse
- Mean dose rate
- Instantaneous dose rate
- Pulse length
- Pulse Repetition Frequency
- Number of the pulses

The mean dose-rate was initially used as a simplistic definition for FLASH irradiation (>40 Gy/s).

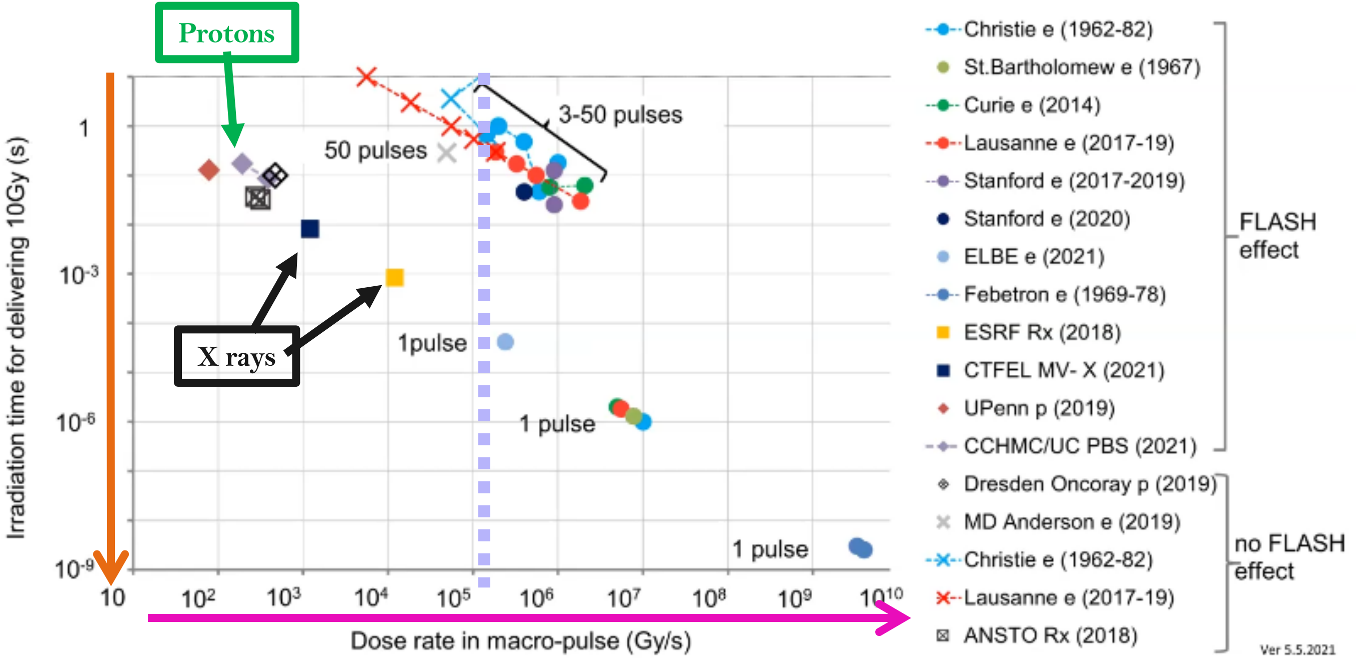
However, the instantaneous dose rate and the total treatment time appear to be the most critical beam parameters.

Friedl AA, Prise KM, Butterworth KT, Montay-Gruel P, Favaudon V. Radiobiology of the FLASH effect. Med Phys. 2022 Mar;49(3):1993-2013. Epub 2021 Sep 20.

Courtesy of L. Giuliano

Conditions to obtain or miss the FLASH effect

Available data on FLASH radiotherapy from **in vivo and in vitro experiments**



- **Highest dose rate in the pulse,**
- **Shortest irradiation time,**

highest is the FLASH effect.

Courtesy of
L. Giuliano

Montay-Gruel P, Acharya MM, Jorge PG, et al. Hypofractionated FLASH-RT as an effective treatment against glioblastoma that reduces neurocognitive side effects in mice. *Clin Cancer Res*. 2021;27(3):775-784.

Beam parameters to induce the **FLASH effect with *electrons***

FLASH effect depends on different inter-dependent parameters

- Total dose
- Dose per pulse
- Mean dose rate
- Instantaneous dose rate
- Pulse length
- Pulse Repetition Frequency
- Number of the pulses

Symbol	Description	Value
PRF	Pulse repetition frequency	> 100 Hz
t_p	Pulse width	0.1-4.0 μs
t_i	Total irradiation time	< 100 ms
$\overline{\dot{D}}$	Mean dose rate	> 100 Gy/s
$\dot{D}_p$	Instantaneous Dose-rate	$> 10^6$ Gy/s
D_p	Dose in a single pulse	> 1 Gy

Courtesy of L. Giuliano

CSN5 Call 2021 - FRIDA in a nutshell

From call proposal

The external beam radiotherapy research community is currently experiencing an exciting time: experimental evidence is growing, supporting the evidence of a considerable normal tissue sparing effect when treatments are delivered with dose rates much larger (100 times or more) with respect to the conventional ones. If confirmed, this so-called **'FLASH effect' has the potential to re-shape the future of radiation treatments especially with charged particles, with a significant impact on many oncology patients.**

The FRIDA project addresses several challenges posed by this potential revolution. A crucial task is represented by the mechanistic **understanding and modelling of the effect**. Another key ingredient is the necessary research and development phase in the acceleration and **beam delivery** fields to provide the required dose rates with a clinically acceptable precision. A final word on the FLASH effect will be said only if novel **beam monitoring** and dosimetry techniques capable of sustaining very high dose rates will be developed. Finally, software tools for **FLASH treatments planning** are needed to evaluate the technique potential and enable clinical applications.

Within INFN and **CSN5 activities**, the knowhow and expertise needed to make a step forward in this field are presently available. **Experiments will be carried out at FLASH beam facilities** that are (or will be in the near future) available, complementing the multiscale FLASH mechanism modelling efforts. LINAC and laser-plasma techniques will be applied to the delivery of FLASH e- and p beams. Detection and monitoring techniques will be developed and tested, as well as the implementation of software tools needed for the simulation and treatment optimization tasks. **All these contributions can be seen as steps towards the FLASH enabling technology**.

The FRIDA deliverables will place on solid grounds the future steps made when **aiming for the FLASH effect confirmation or disprove and its possible clinical implementation.**

The FRIDA organization

"WPO"
Coordination
P.I. A. Sarti

WP1
The FLASH mechanism
E. Scifoni (modeling)
G. Forte (bio experiments)

WP2
Beam delivery
A. Mostacci (e-)
G. A. P. Cirrone (p)

WP3
Beam/dose monitoring
A. Vignati (Beam monitoring)
G. Bisogni (Dose monitoring)

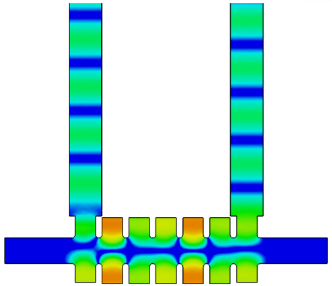
WP4
Treatment planning
A. Schiavi (Dose sim/optim.)
M. Schwarz (Treatment planning)

Units
CT –F. Romano
LNS – G. Cirrone
MI – D. Giove
PI – G. Bisogni
RM1 – A. Sarti
TIFPA – E. Scifoni
TO – A. Vignati

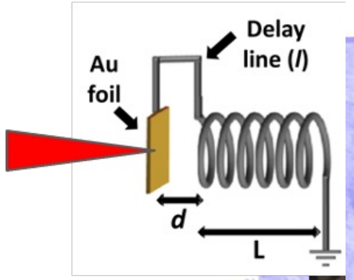
Courtesy of A. Sarti

WP2-Beam delivery: main activities

RF accelerated beams
- RF cavities — **RM1, LNS, LNF**
- RF source — **LNS, RM1, LNF**
- High current medium energy electron beams for medical applications — **Milano**



Laser Plasma accelerated beams
- Protons — **LNS, Milano, Queens Univ.**
- Electrons — **INO ILIL (CNR Pisa)**



Electron beam parameter list

Caveat: scaling to high energy the beam parameters for FLASH irradiation at 6-7MeV energy range (wide beams, large irradiation field)

	Description	Value
E	Beam Energy	7 MeV
PRF	Pulse repetition frequency	>100 Hz
t_p	Pulse width	4 µs
Q_p	Pulse Charge	400 nC
I_p	Pulse Current	100 mA
$\dot{D}_p$	In-Pulse Dose-Rate	$> 10^7$ Gy/s

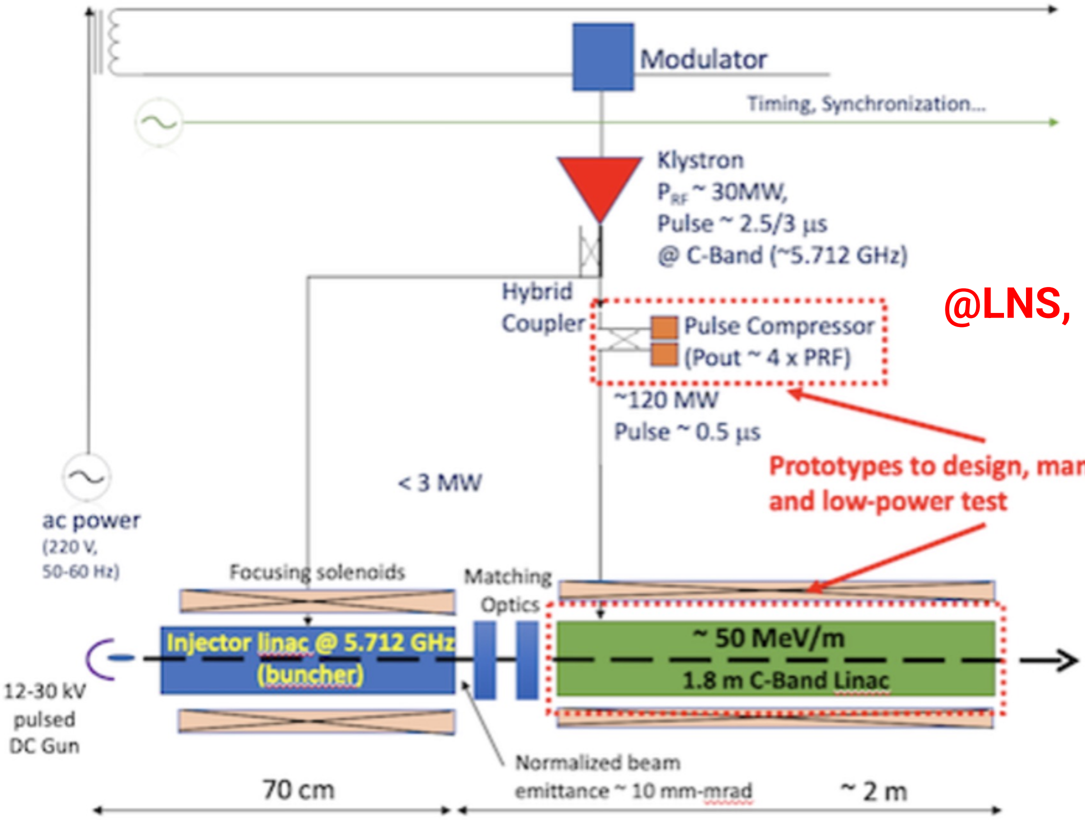
Meaurements with ElectronFlash at Curie Institut

	Description	Value
E	Beam Energy	60 - 130 MeV
PRF	Pulse repetition frequency	> 100 Hz
t_p	Pulse width	1 - 3 µs
Q_p	Pulse Charge	200 - 600 nC
I_p	Pulse Current	200 mA
$\dot{D}_p$	In-Pulse Dose-Rate	$> 10^7$ Gy/s

Courtesy of L. Giuliano

FRIDA proposal: layout

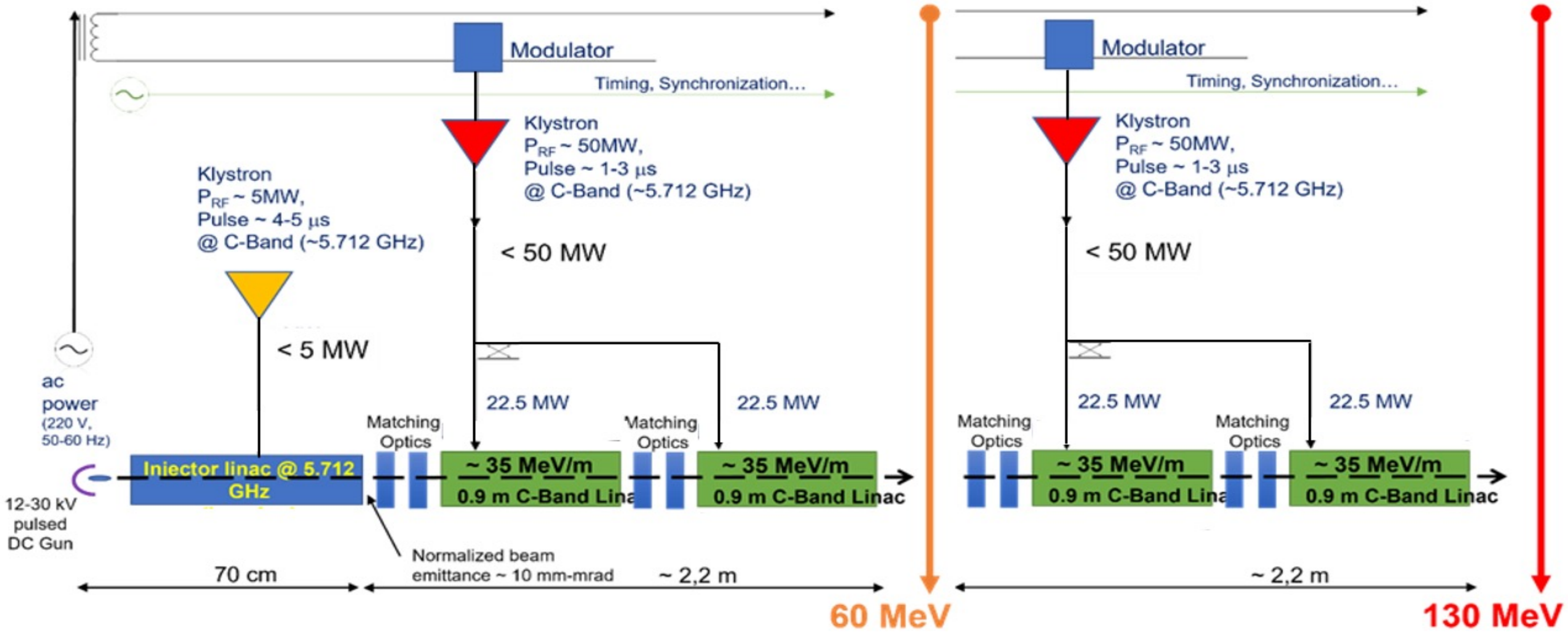
Compact C-band option



@LNS, LNF, RM1

@RM1, LNF, LNS

Update: 60-130MeV demonstrator



Main contributors: L. Faillace, L. Giuliano, M. Migliorati, L. Palumbo

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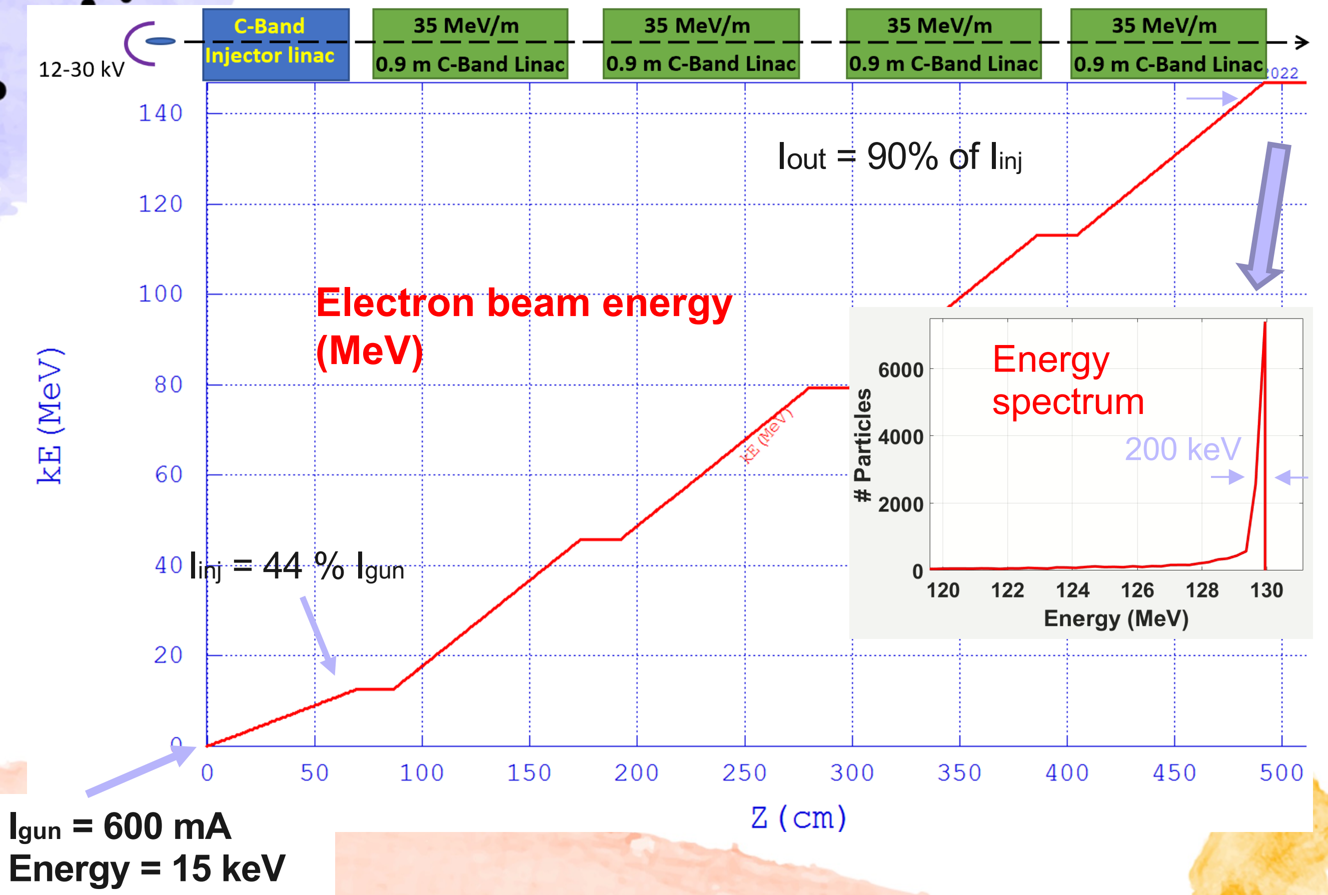
Beam Dynamics for the 130MeV demonstrator



Output e-beam >130 MeV and 200 mA output e-beam;

Input e-gun current = 600 mA;

No focusing solenoids needed;

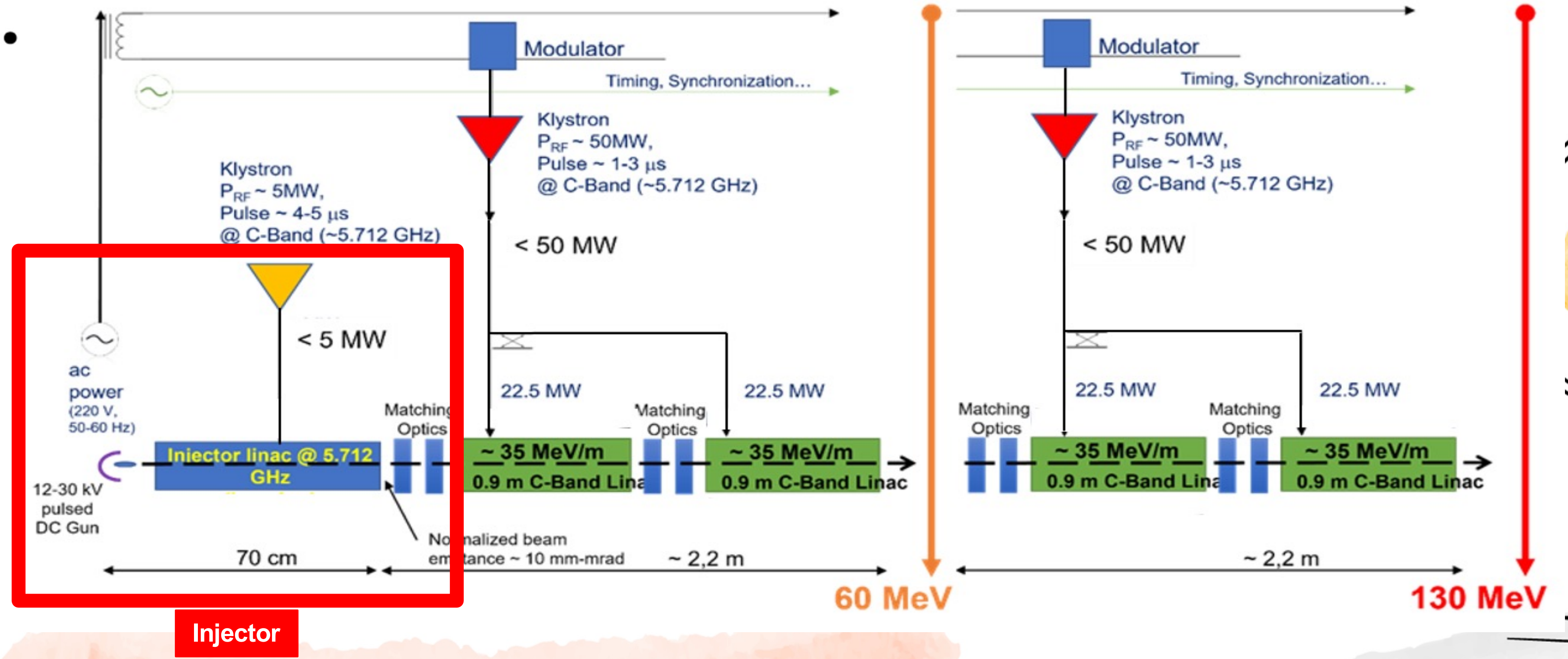
Total beam capture ~40%;

Lost e-current phase-space evaluated for required radiosafety protocols;

Very low energy spread 200 keV @ 130 MeV

Courtesy of L. Faillace

Update: 60-130MeV demonstrator



Main contributors: L. Faillace, L. Giuliano, M. Migliorati, L. Palumbo

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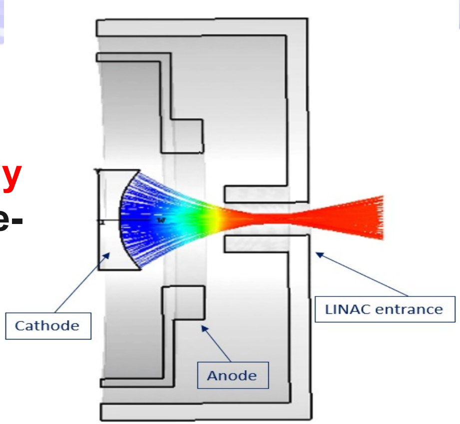
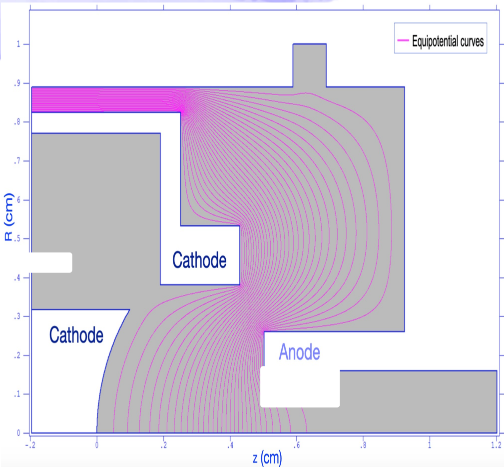
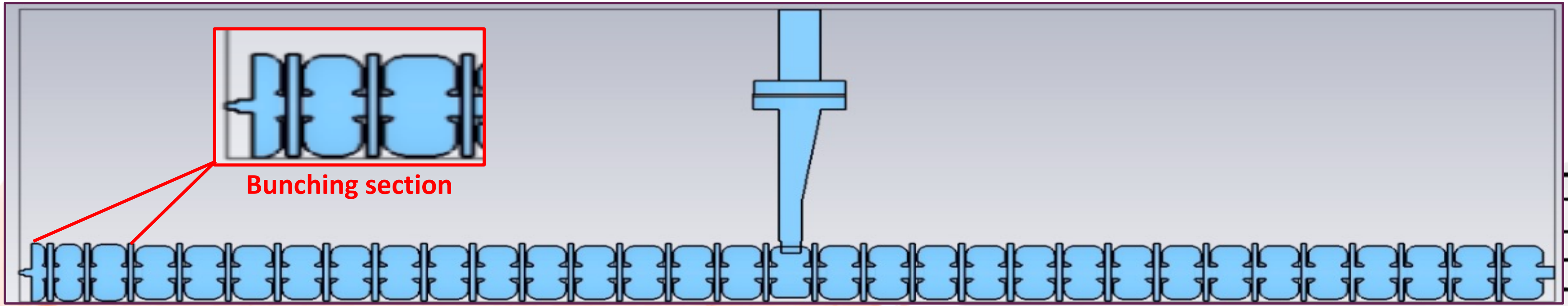
Accelerating structure: source and injector

Electron source: **pulsed DC thermionic gun** at 15 kV.

Injector Linac with matching section for **low-energy beam capture** (> 40%) and initial acceleration from e-gun up to **≈ 10 MeV and 200 mA** beam peak current.

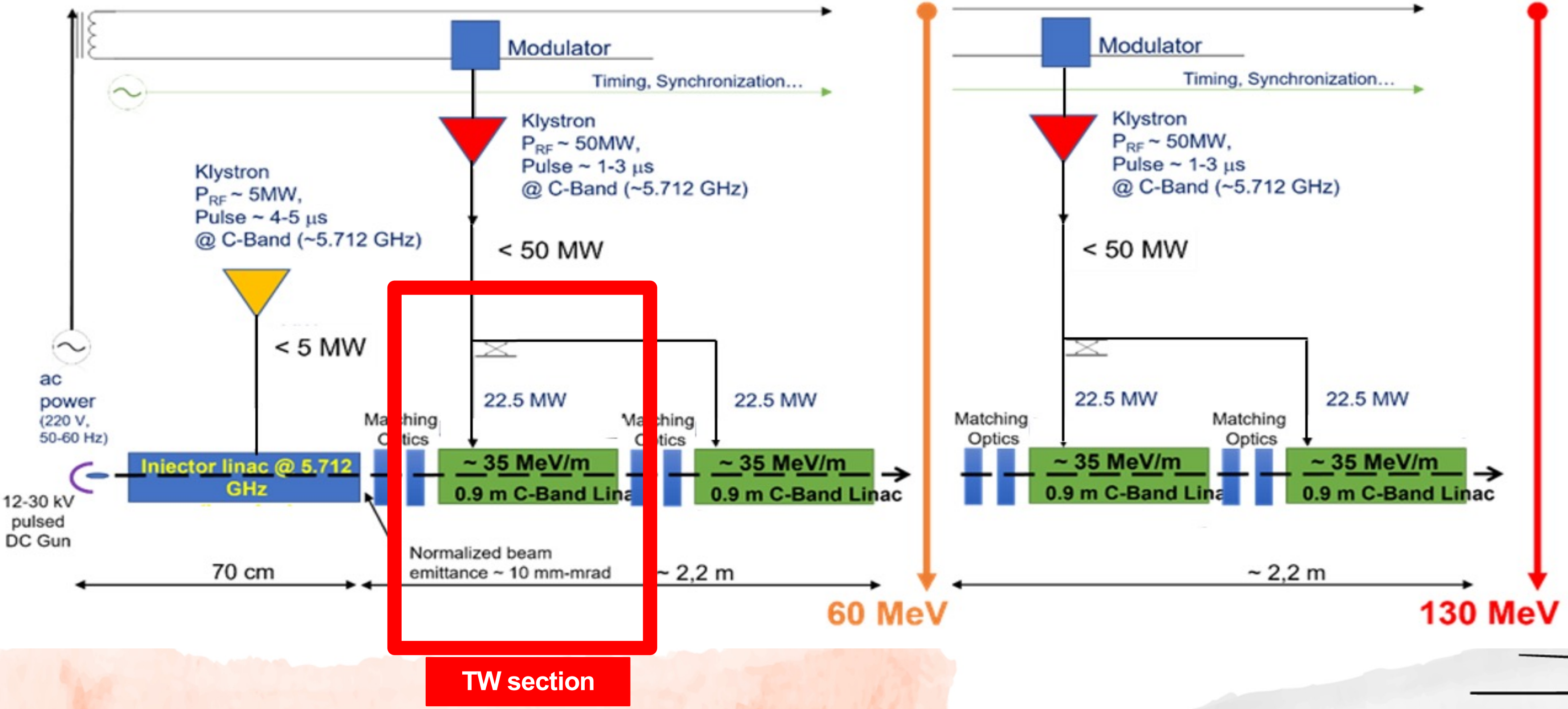






Main contributors: L. Faillace, D. Francescone, L. Giuliano, M. Migliorati, L. Palumbo

Update: 60-130MeV demonstrator



Main contributors: L. Faillace, L. Giuliano, M. Migliorati, L. Palumbo

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Accelerating structure: TW structure

Operating RF frequency: f_{RF} = 5.712 GHz in C-band;

Operating mode: TM010-like with $2\pi/3$ cell-to-cell phase advance;

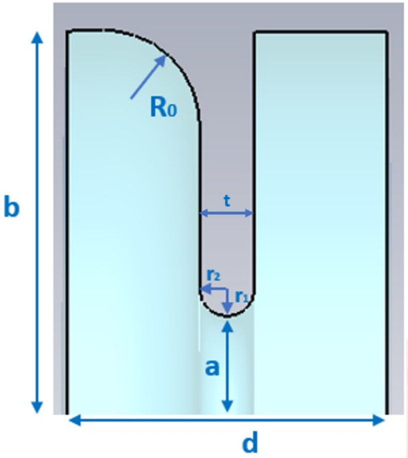
TW ***Constant Impedance***: Iris aperture radius a = 5 mm;

Structure Length: **0.9 m** (modularity) → MAX power/section ≈ 22.5 MW

Possibility of using pulse compressors and avoid one structure

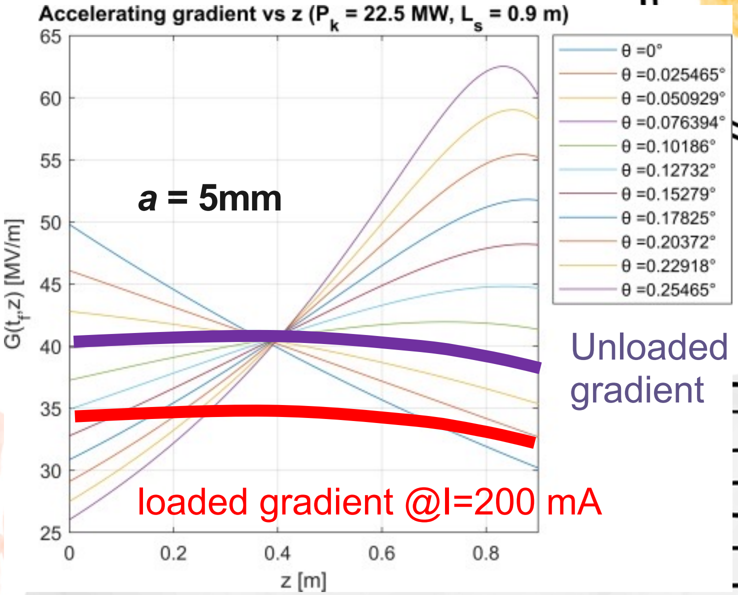
Symbol	Description	Value
E	Beam energy	50-250 MeV
t_p	Pulse width	1-3.0 μs
PRF	Pulse repetition frequency	> 100 Hz
I_p	Pulse current	> 200 mA
Q_p	Pulse charge	200 – 600 nC
D_p	Dose in a single pulse	219 Gy in ⌀30 mm
$\dot{D}_p$	Instantaneous Dose-rate	> 10^7 Gy/s

Single Cell design



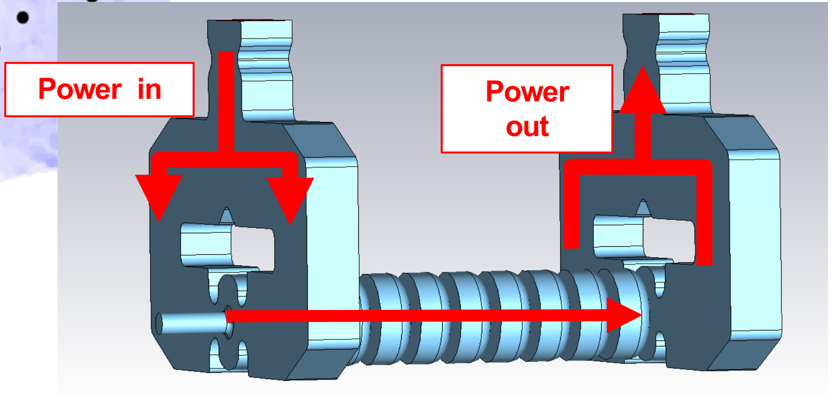
Single cell RF parameters

Parameter	Size [mm]
a	5
b	21,03
d	17,45
t	3
R0	6
r1/r2	1.25



Main contributors: D. De Arcangelis, L. Faillace, L. Giuliano, M. Migliorati

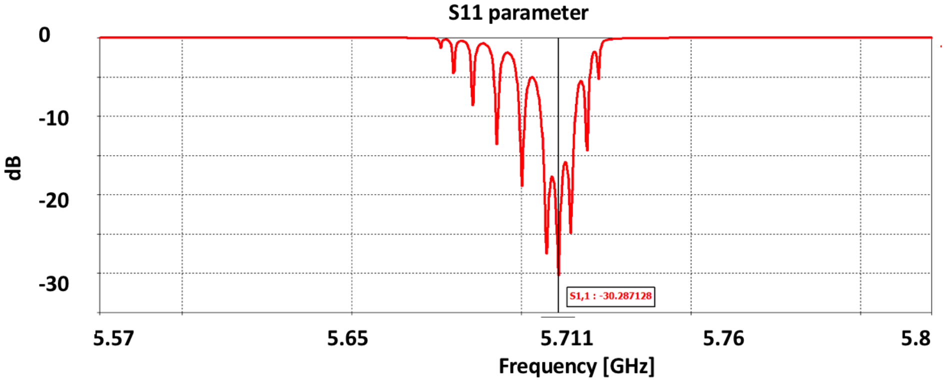
Accelerating structure: full RF design



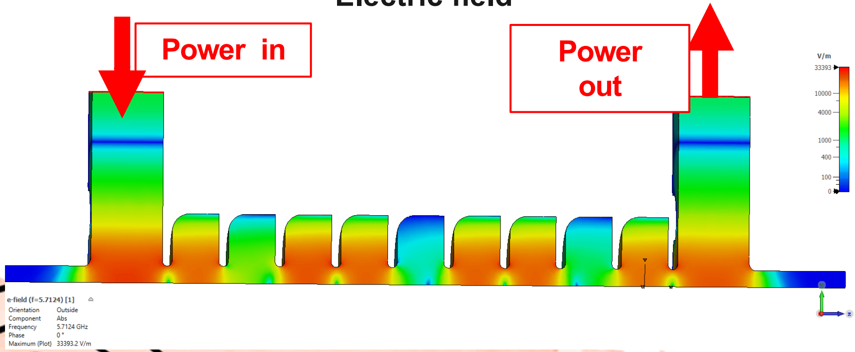
Dual-feed input and output RF power couplers;

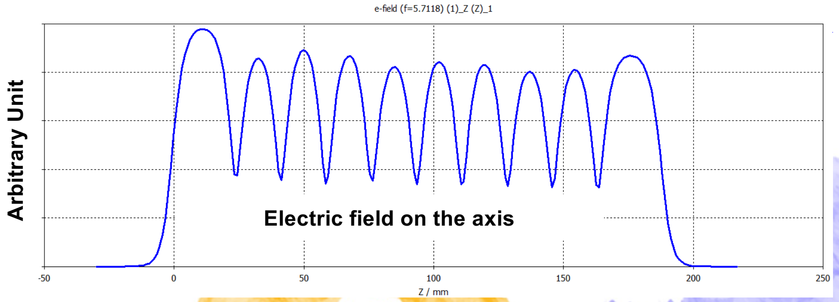
Iris aperture radius a = 5 mm;

Reflection Coefficient S11 = -30 dB at 5.712 GHz;



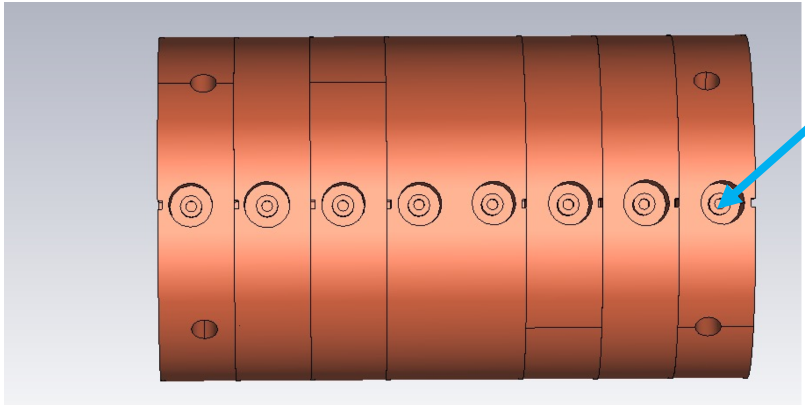
Electric field





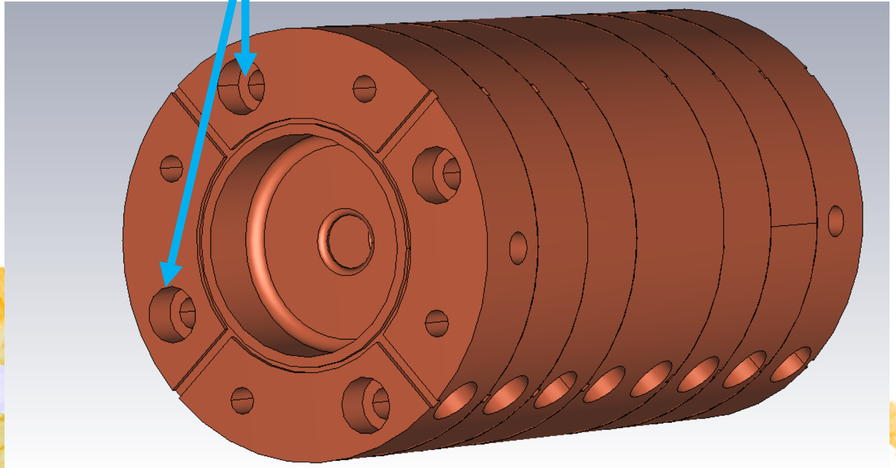
Main contributors: D. De Arcangelis, D. Francescone, L. Faillace, L. Giuliano, M. Migliorati

Accelerating structure: mechanical design

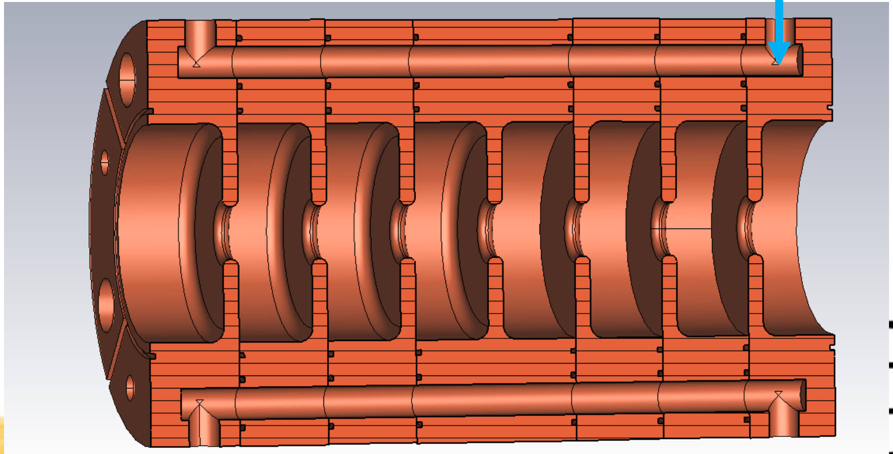


tuners

bolts to join the cells

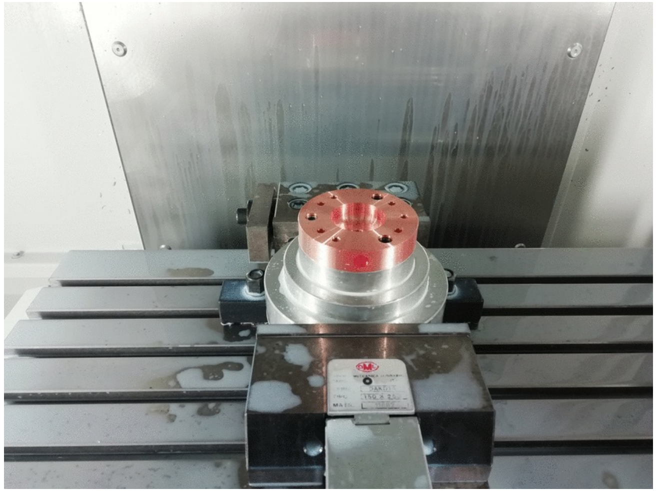


water for cooling



Main contributors: D. Alesini, L. Faillace, L. Giuliano, M. Magi, M. Migliorati

Accelerating structure: prototype realisation



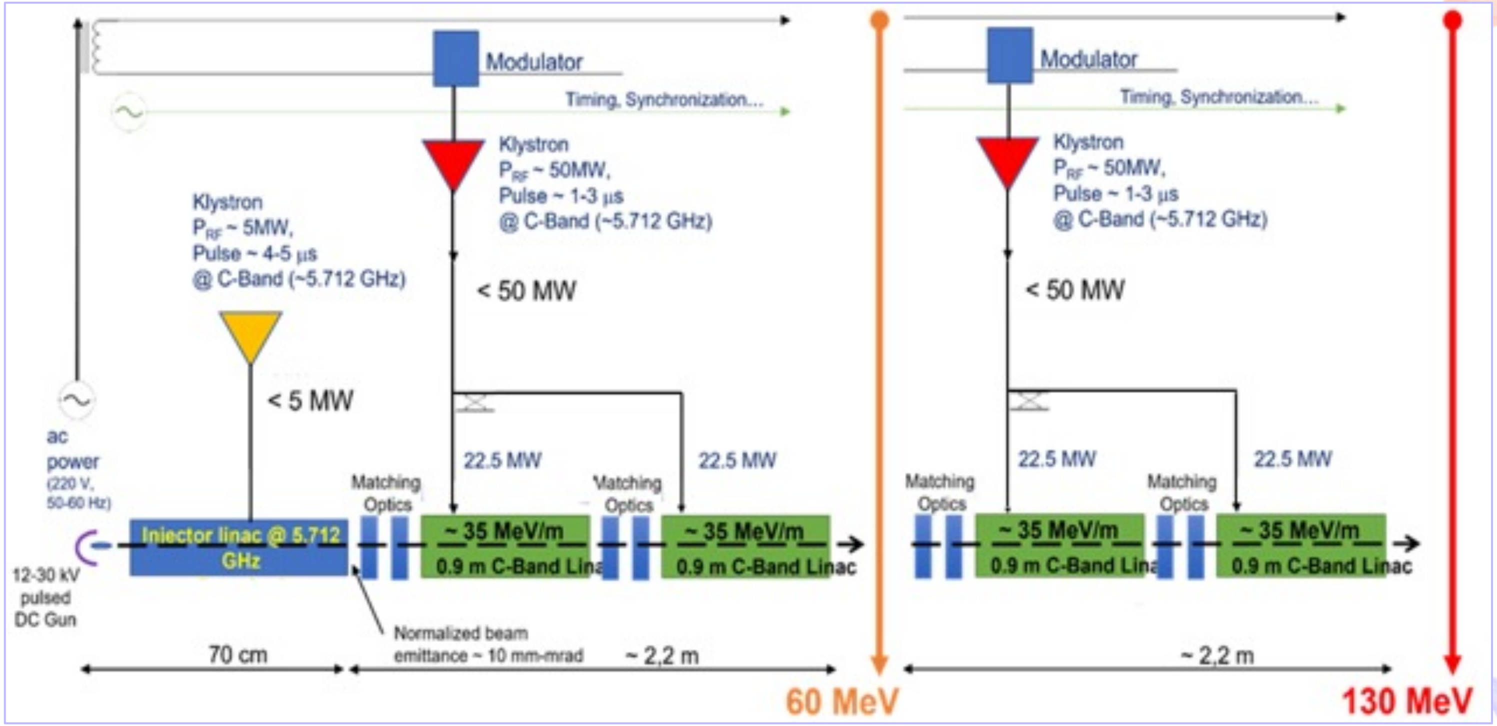
Main contributors: D. Alesini, L. Faillace, L. Giuliano, M. Magi, M. Migliorati

Design of RF structures workflow

• Baseline accelerating gradient: **≈ 35 MV/m**	**DONE**
• RF system (and pulse compressor characteristics)	**DONE**
• Average iris radius: **5 mm**	**DONE**
• Electromagnetic parametric study of the TW cell	**DONE**
• Effective shunt impedance optimization acting on the total length (and the iris tapering)	**DONE**
• Check of expected Breakdown rate (modified Poynting vector values @ nominal gradient)	**DONE**
• Design a realistic RF module including power distribution network	**ON GOING**
• Finalize the electromagnetic design (input and output couplers, final breakdown analysis)	**ON GOING**

Very High Energy Electron Linac layouts

Without pulse compressor



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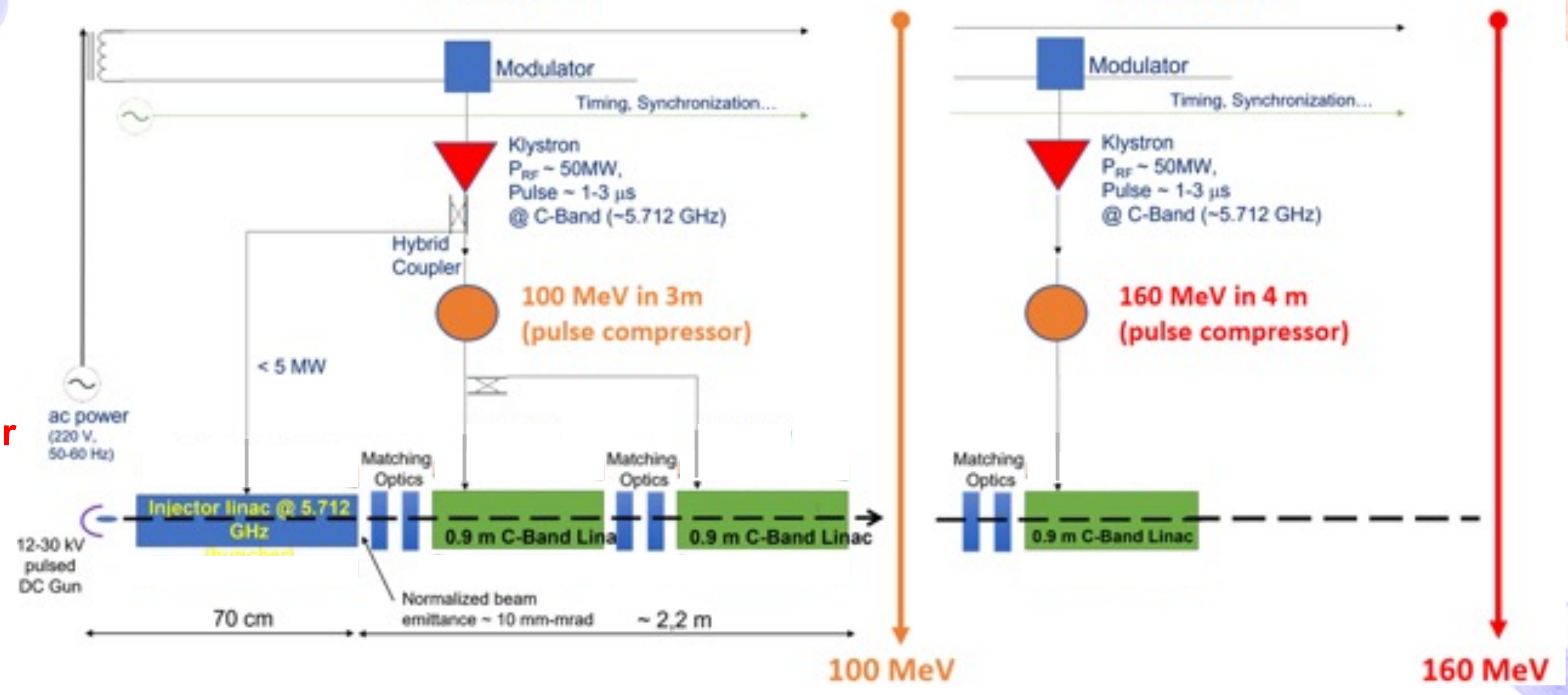
Very High Energy Electron Linac layouts

With pulse compressor



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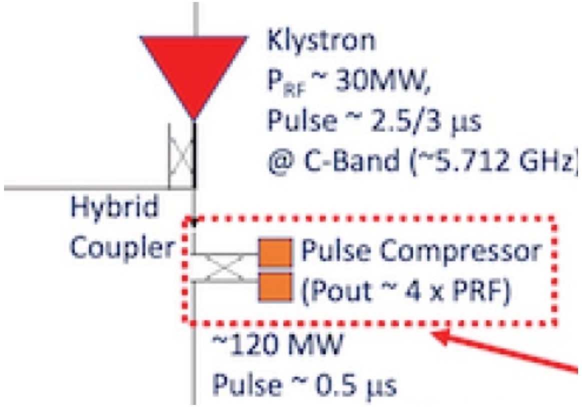
FRIDA proposal: pulse compressor



Doubling beam energy enhancing peak RF power at the expense of pulse width

Sub-tasks for the design of the pulse compressor

- Geometry and shape of the resonator definition
- RF Design of the RF pulse compressor
- RF simulation Report

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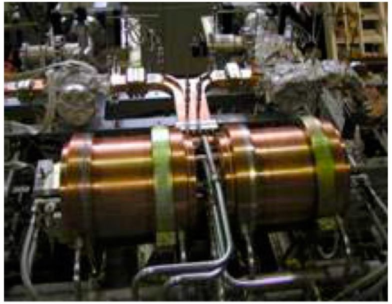
Istituto Nazionale di Fisica Nucleare
Laboratori Nazionali del Sud

Main Contributors: G. Torrisi, G. Sorbello, G. Mauro

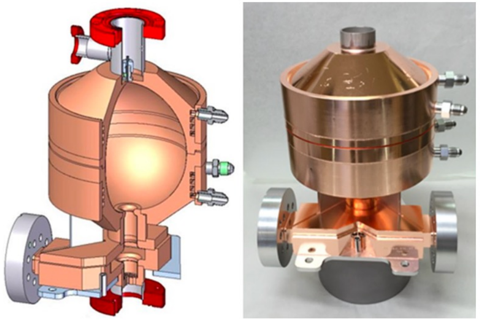
Pulse compressor: shape definition

Geometry and shape of the resonator definition



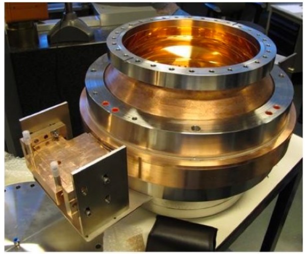
[**SKIP - A PULSE COMPRESSOR FOR SUPERKEKB** *THP61 Proceedings of LINAC 2004, Lübeck, Germany https://accelconf.web.cern.ch/l04/PAPERS/THP61.PDF*]

vs.



RF polarizer and single High-Q spherical resonator for new X-band SLED system *[J. Wang, S. Tantawi et al.,PRAB20, https://doi.org/10.1103/PhysRevAccelBeams.20.110401]*

vs.



single Barrel Open Cavity (BOC) pulse
R. Zennaro et al., IPAC2013,, WEPFI059 https://accelconf.web.cern.ch/ipac2013/papers/wepfi059.pdf C-BAND RF PULSE COMPRESSOR FOR SWISS FEL

main RF Pulse Compressor parameters

- resonant mode - Q-factor
- Coupling constant of the cavity / Reflection at the power coupler
- machining accuracy required
- maximum peak surface field (about 2 or 3 times higher than the acceleration field)

Main Contributors: G. Torrisi, G. Sorbello, G. Mauro

Pulse compressor: RF design

- design of **RF mode coupler** with reduced unwanted modes
- Investigation **RF power gain variation** as a function of the coupling constant ß of the RF compressor cavity
- obtain an optimal compromise between large coupling constant (high-power gain) and risks of **RF breakdown**
- reducing RF field around the edges, avoiding a large number of brazed parts, ***using if possible special joint-free open structures***
- **Transient** response
- **Thermal** studies, **Tuning** and **Multipacting**

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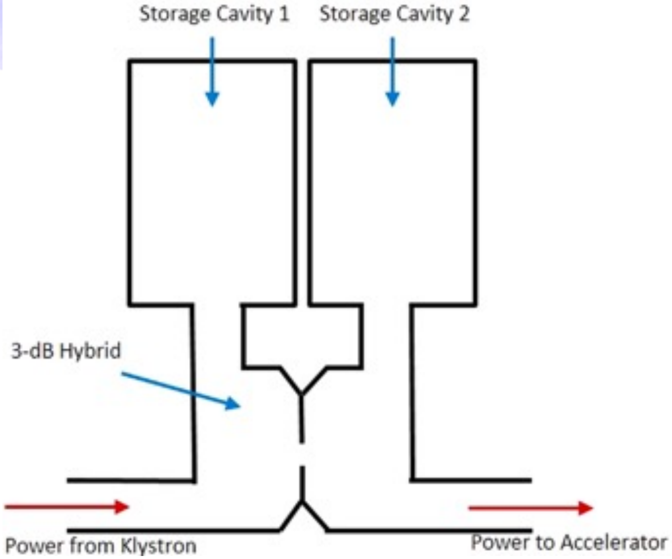
Main Contributors: G. Torrisi, G. Sorbello, G. Mauro

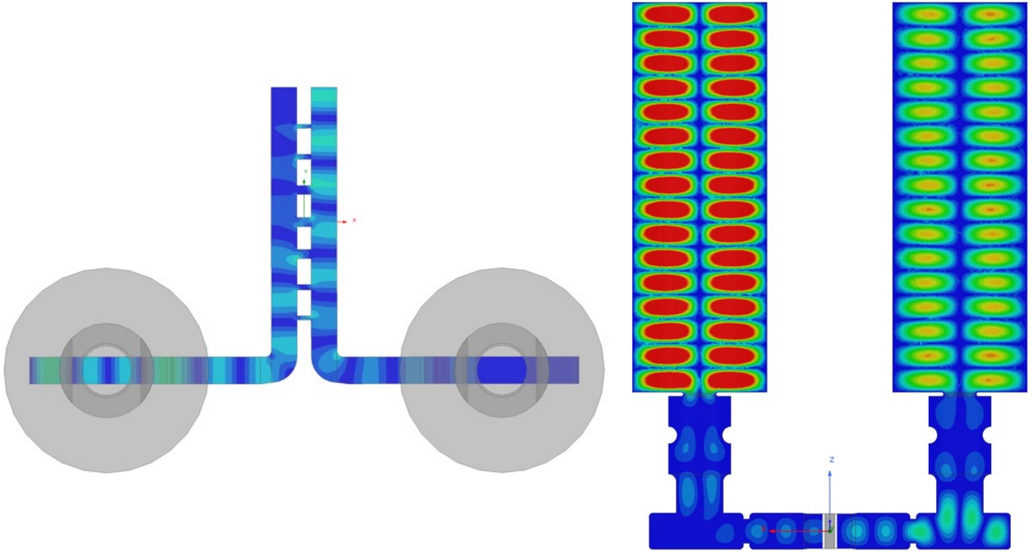
Pulse compressor: cylindrical cavity



Hybrid 3 dB coupler

Mode converter $TE10_{rectangular}$ to $TE01_{circular}$

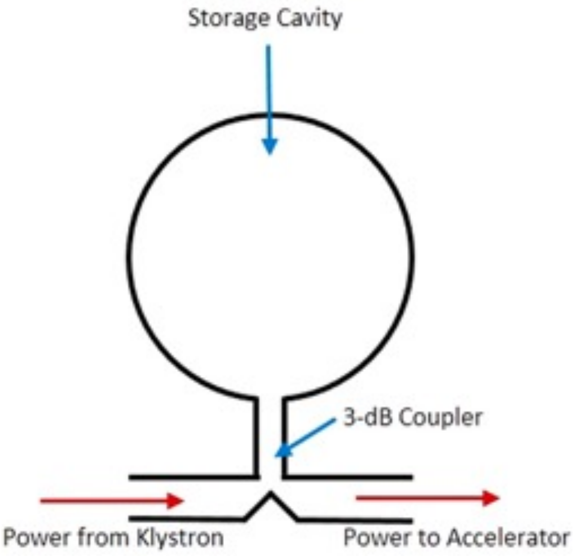
Storage cavity

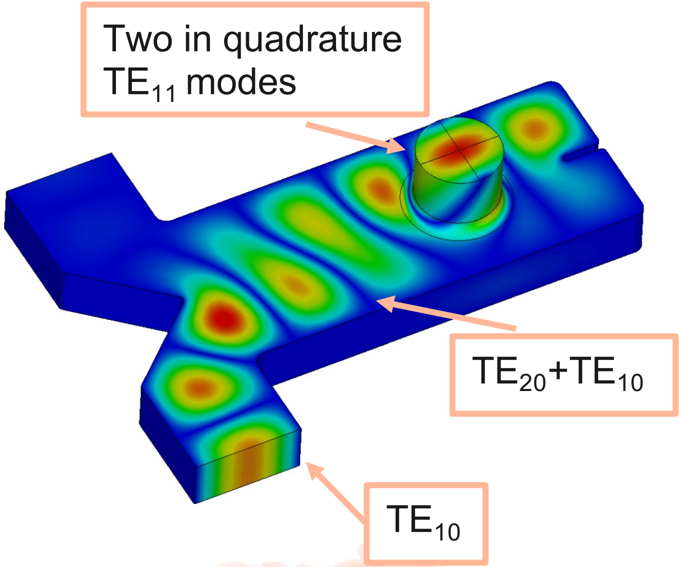


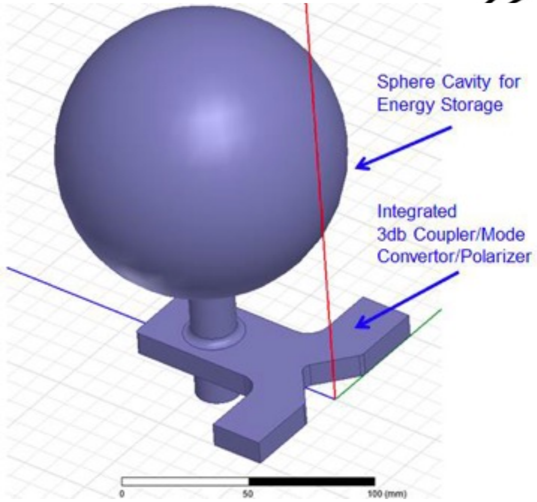
Total Dimensions: 507 x 326 x 702 mm^3

Main Contributors: G. Torrisi, G. Sorbello, G. Mauro

Pulse compressor: spherical cavity







works on two TE_{113} mode

Main Contributors: G. Torrisi, G. Sorbello, G. Mauro

Cylindrical cavity compressor: working principle

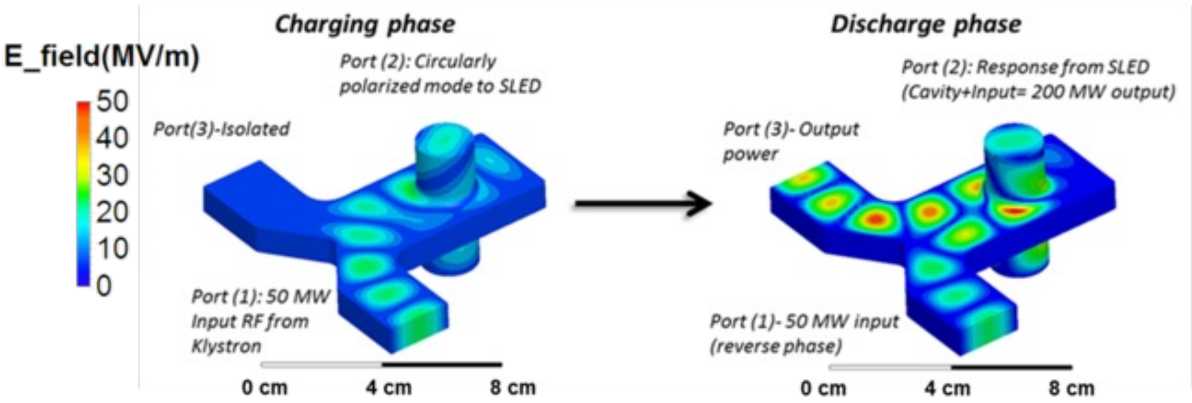
- Equal coupling to the TE_{10} and TE_{20} modes
- Isolation of the opposite port

❑ Each rectangular waveguide mode excite a TE_{11} mode

- Excitation in quadrature produces quasi circularly polarized wave

❑ TE_{11} modes excite degenerate TE_{114} modes of spherical resonator

- TE_{20} and TE_{10} emitted/reflected from the cavity cancel at input port



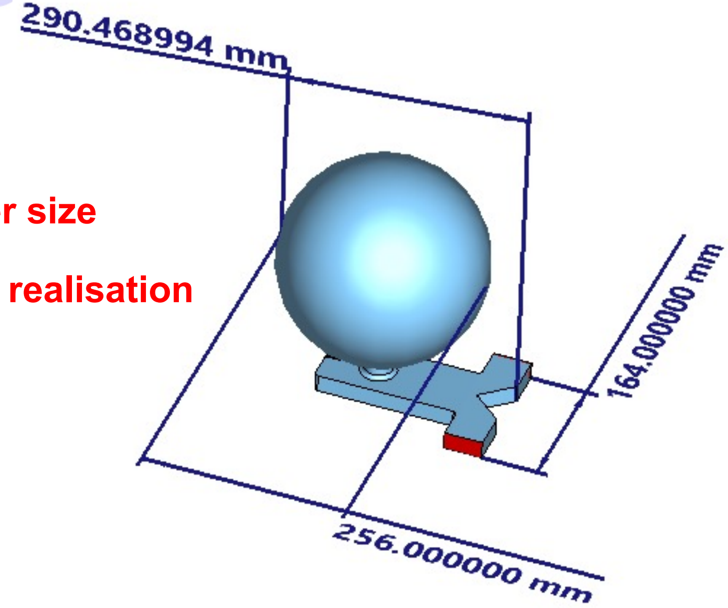
average power gain of 3.8

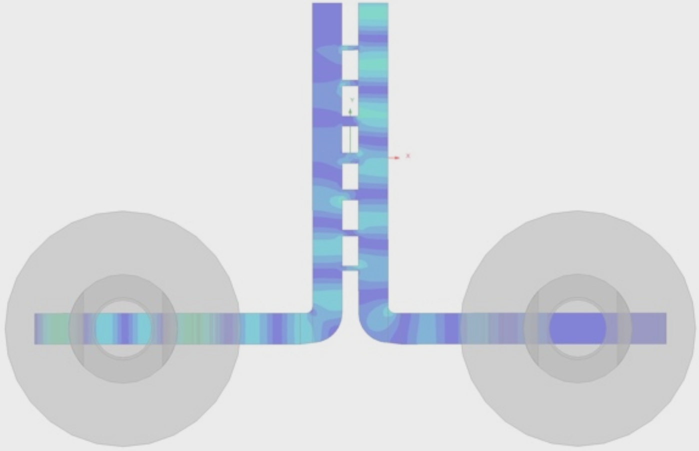
Main Contributors: G. Torrisi, G. Sorbello, G. Mauro

Pulse compressor: shape comparison

Smaller size

Easier realisation





Tot. Dimensions: 507 x 326 x 702 mm^3

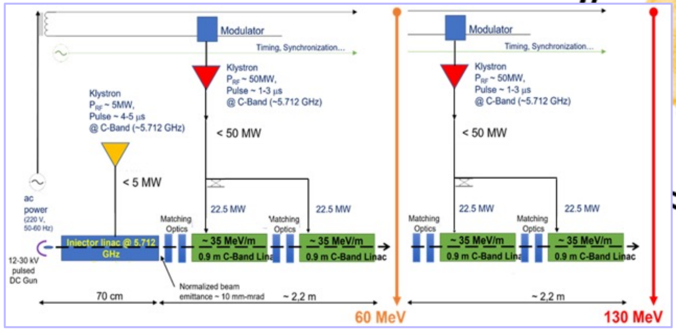
Main Contributors: G. Torrisi, G. Sorbello, G. Mauro

Conclusions

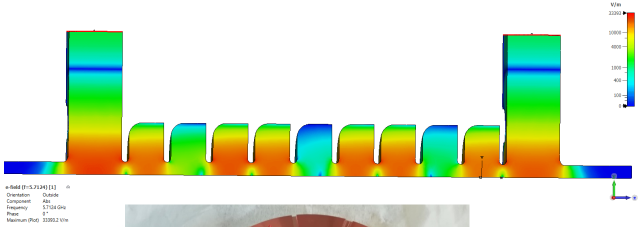
FLASH Radiotherapy with hIgh Dose-rate particle beAms

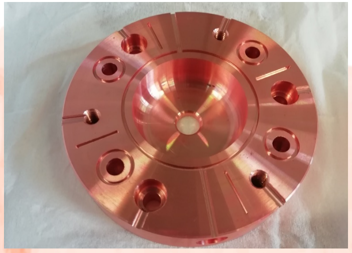
FRIDA aims to the FLASH effect confirmation or disprove as well as and its possible clinical implementation

Towards a Very High Energy Electron (VHEE) demonstrator

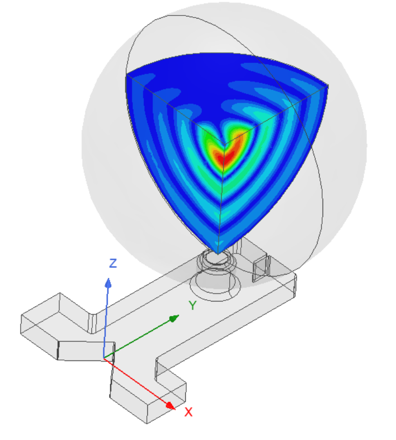


TW accelerating structure





Pulse compressor



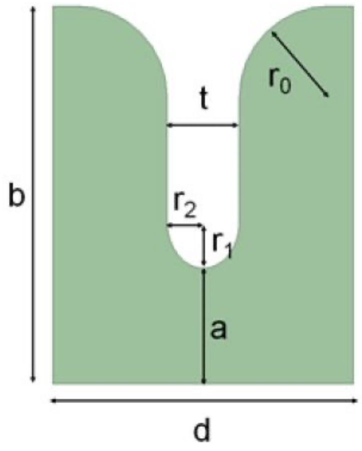
Thank you

FLASH Radiotherapy with hIgh Dose-rate particle beAms

Spares

FLASH Radiotherapy with hIgh Dose-rate particle beAms

RF parameters studies



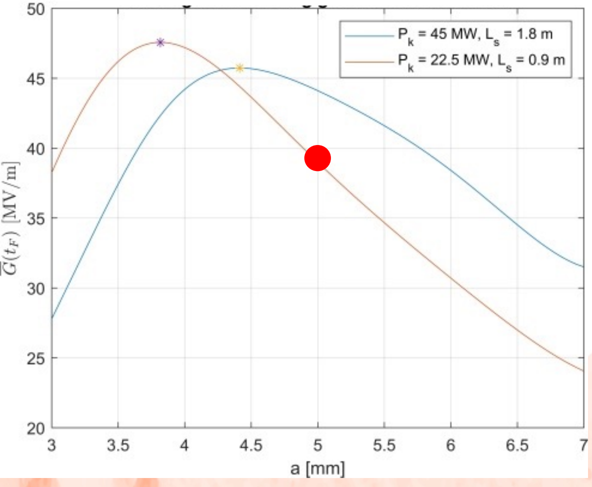
Structure length L_S **= 90 cm**;

Average gradient for $a = 5$ mm is equal to $\overline{G}$ **= 40 MV/m**, with an RF input power of P_{rf} **= 22.5 MW**;

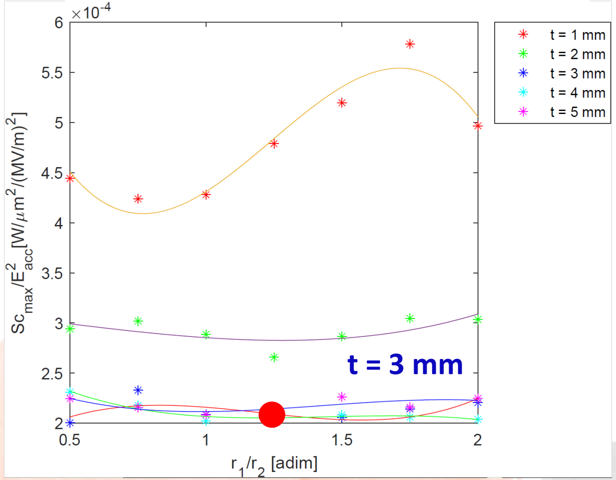
Modified Poynting vector S_c **below threshold of 2 MW/mm²**

Shunt impedance **R = 95 MΩ/m** for r1/r2 = 1.25 and t=3.

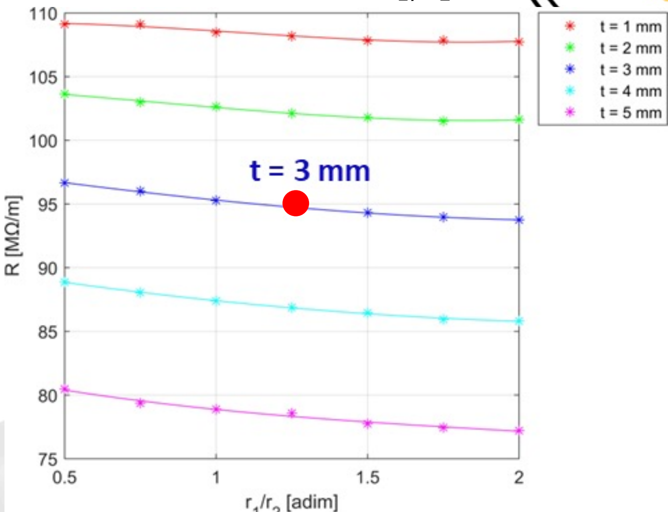
Average accelerating gradient vs iris radius



Modified Poynting vector S_c vs r_1/r_2



Shunt impedance R vs r_1/r_2



Courtesy of D. De Arcangelis