CONTROL SYSTEMS FOR IORT APPLICATIONS AND ELECTRON THERAPY

A. Sarti (on behalf of the ARPG group)

Dipartimento di Scienze di Base e Applicate per l'Ingegneria
Sapienza Università di Roma

ACCELERATORS: MEDICAL APPLICATIONS

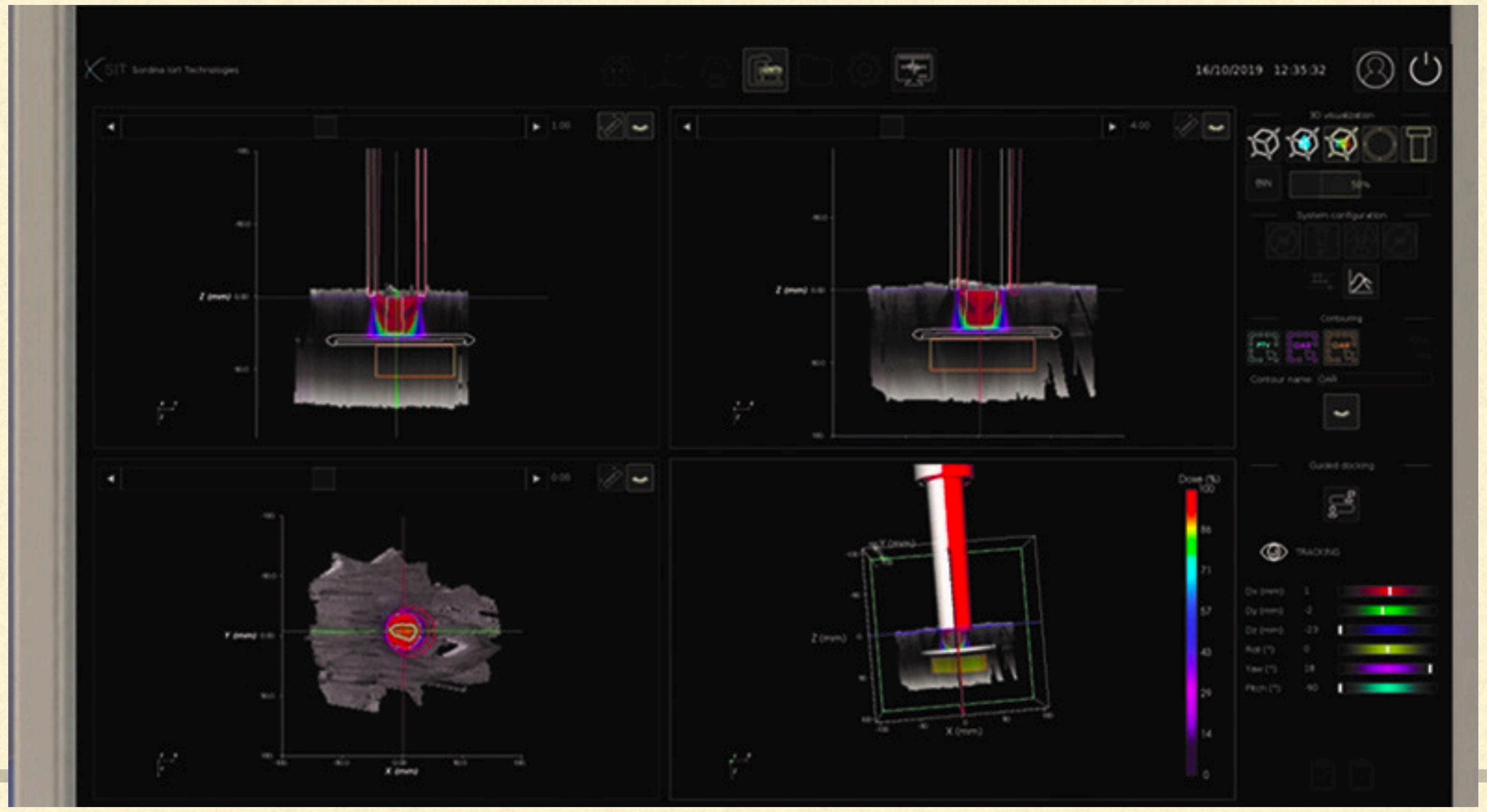
- Within the ARPG group, since almost 10 years, know-how has been gained in several applications of particle acceleration to medical physics.

- We started from protons and ^{12}C ions therapy, and then our interest moved also the acceleration/detection of neutrons. More recently we focused also on conventional RT (with photons in the ~10 MeV energy range) and the possibility to use electrons to overcome some of its limitations.

- The principle is always the same: a detailed knowledge of the mechanisms of interactions of primary and secondary particles with the patient tissues allows to plan the treatments (in order to deliver the needed dose to the tumour site, sparing organs at risk) and to monitor it (exploiting either primary or secondary products for the beam interaction with the patient)

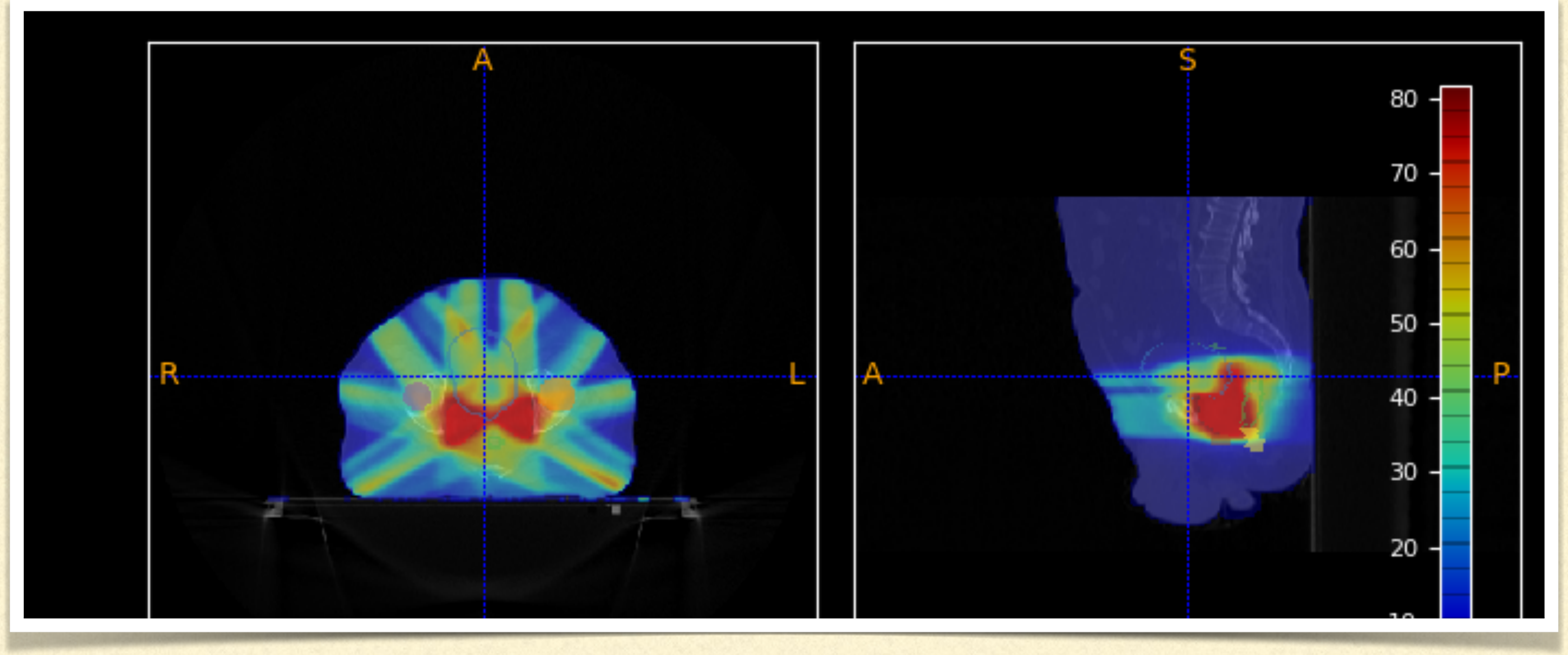
THE CURRENT CHALLENGES - IORT

Intra Operative Radio Therapy is nowadays performed using electrons of low energy [5-10 MeV] that are used to 'clean' an 'open' patient after its surgery to remove possible cancer tissue leftovers.. There is no real 'treatment planning' performed so far as the energy of the electrons is just dictated by the depth that one wants to 'clean', and **time is an issue** (.. open patient awaiting!).. First attempts, based on **analytical** models, are being implemented…



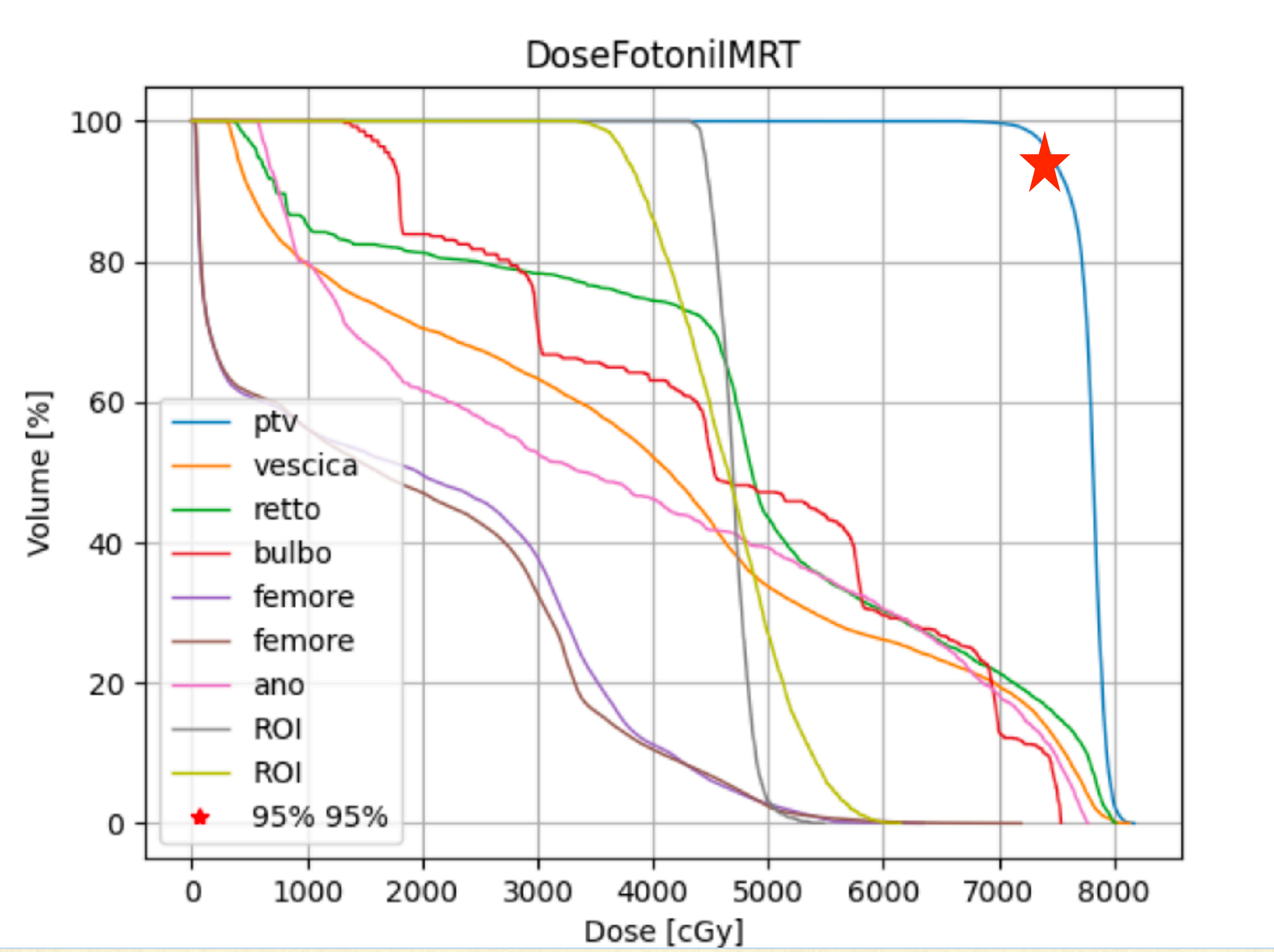
https://www.soiort.com/treatment-planning-system-tps/

THE CURRENT CHALLENGES - VHEE



The current way to 'deep' tumours (e.g. prostate cancer) is twofold:

- Photons (IMRT or VMAT): several photon fields are used to achieve a high conformity on the target volume (PTV, red) while trying to achieve the better sparing of OARs
- Protons (or even heavier charged ions, like ^{12}C or ^{16}O): have a 'ballistic' precision in the dose release, related to their interaction with matter mechanism (Bragg Curve, highly peaked dose deposition at the end of particle range in matter).



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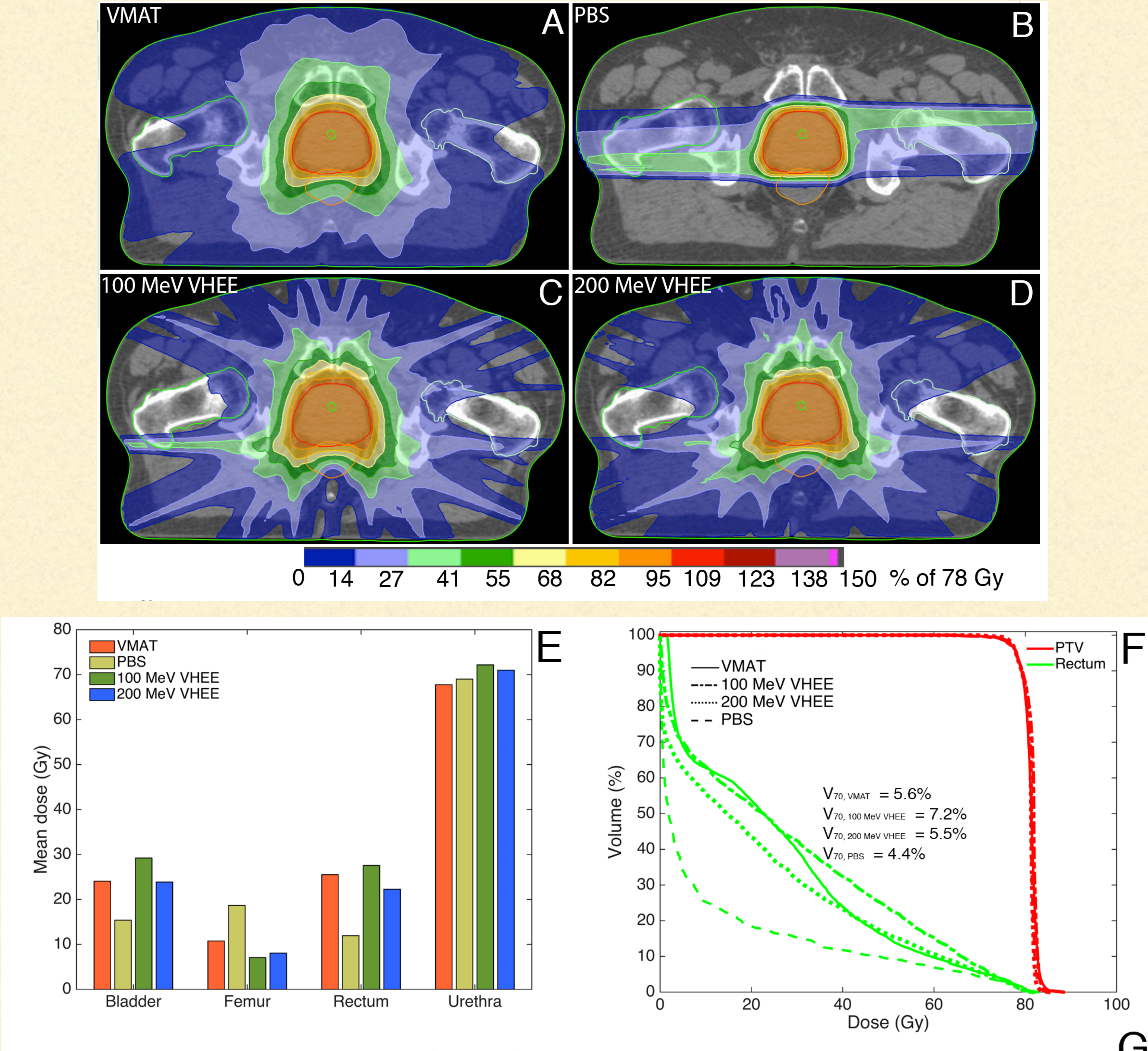
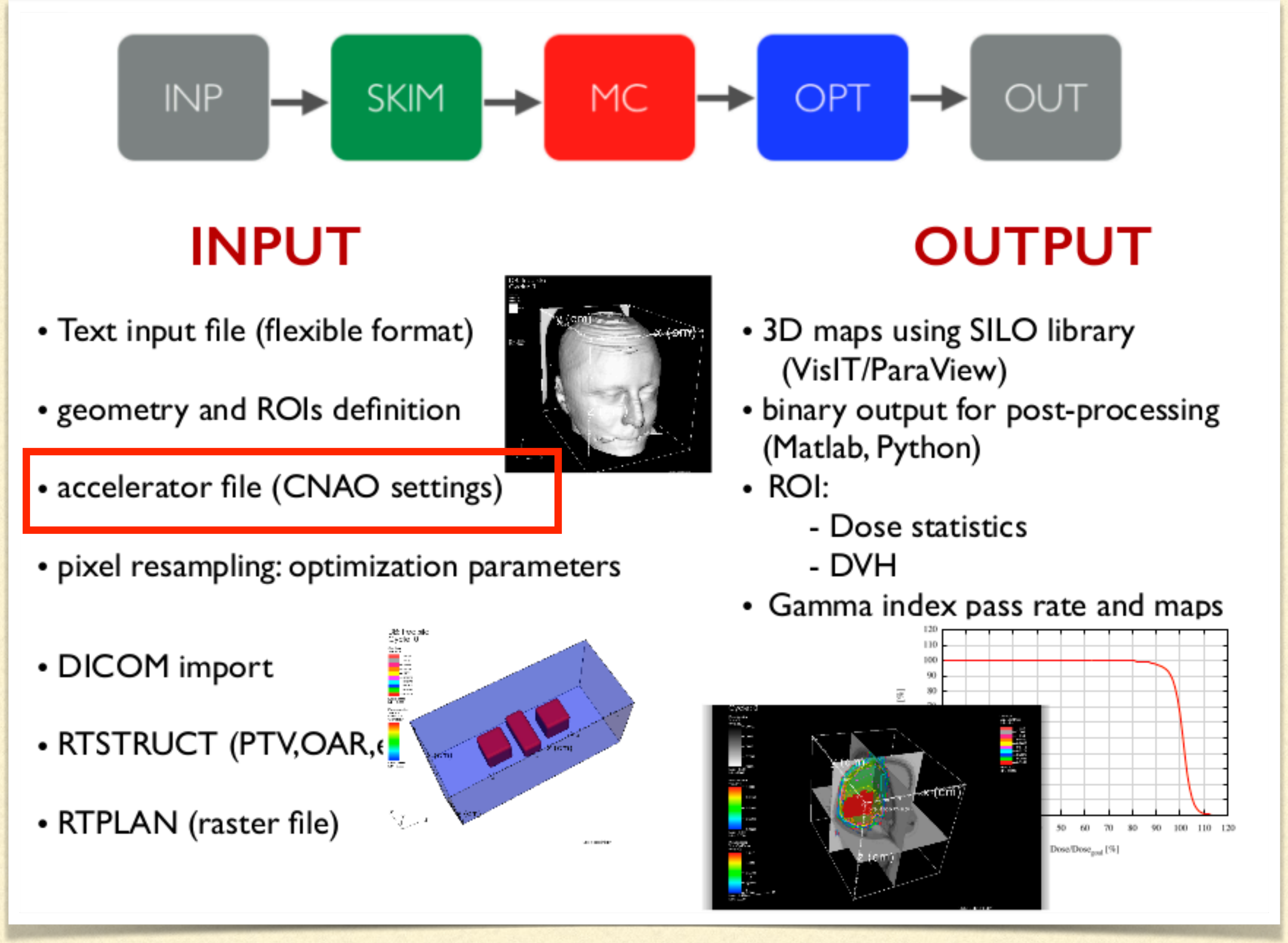
- To reach such depth, electron energies above 50 MeV would be needed (challenging for a delivery compatible with a treatment room of a clinical centre…) with several 'entry points' to avoid substantial dose to OARs…



Schueler et al, Phys Med Biol , 2017

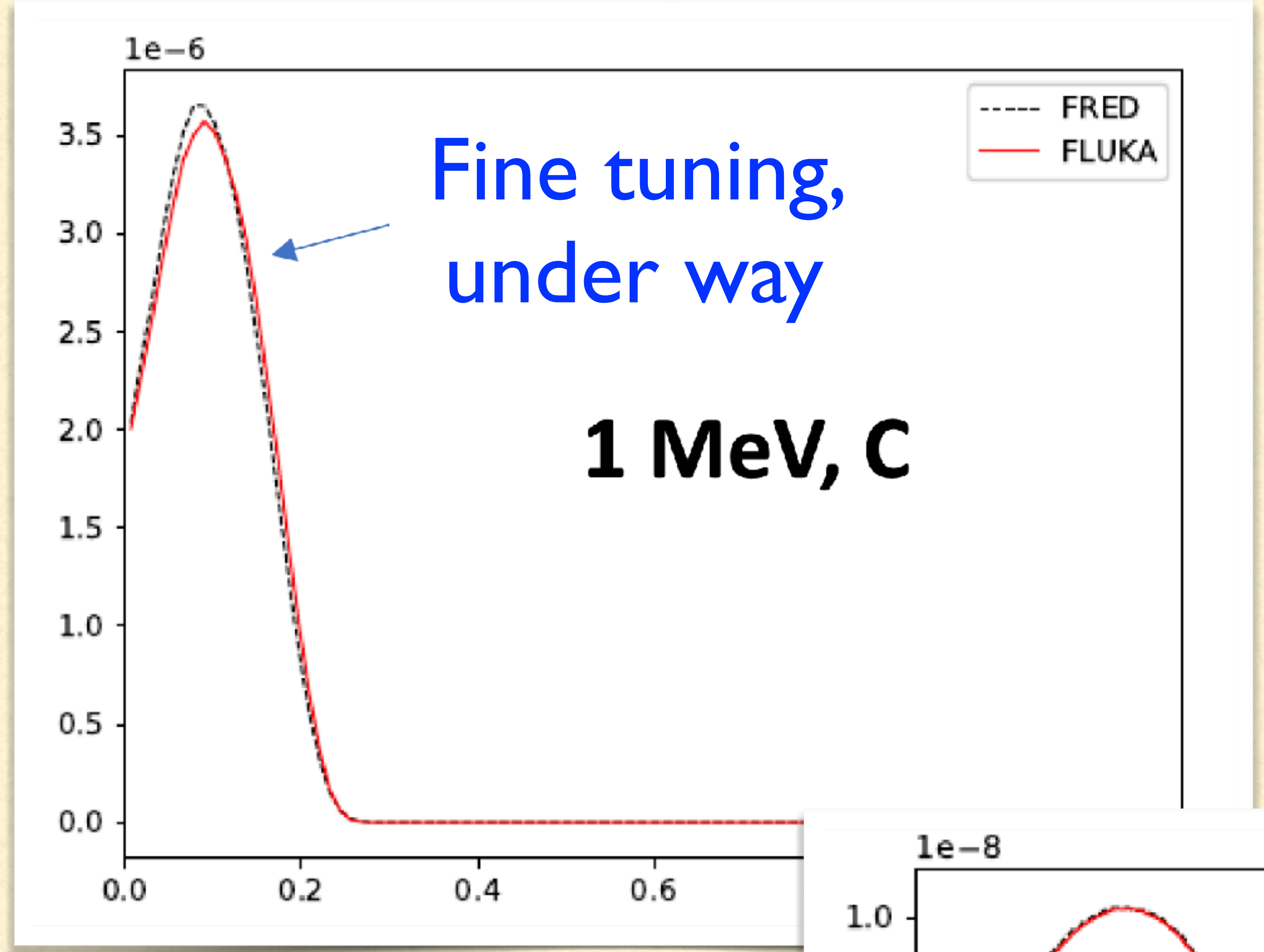
FASTER WITH A POWERFUL TOOL: FRED!



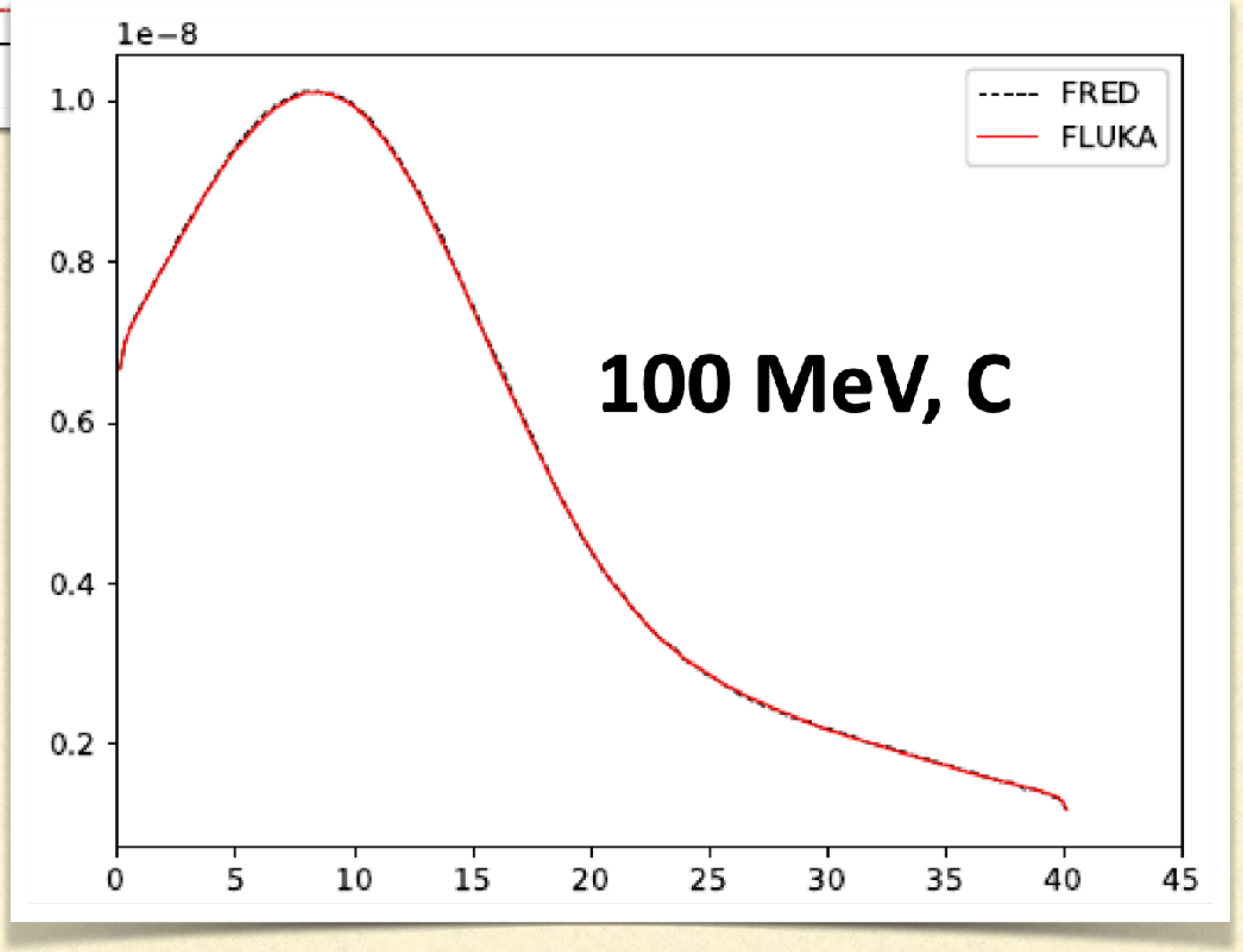
- Within ARPG a fast dose engine (FRED) that exploits the GPU technology has been developed:
  - Dose calculations can be performed in 1./1000 wrt standard tools (e.g. FLUKA)
  - Same accuracy of a standard 'full' MC in predicting the dose distribution
- Initially developed to handle protons, recently adapted to work with ^{12}C (M. De Simoni) **and electrons and photons (under development)**!

http://arpg-serv.ing2.uniroma1.it/arpg-site/index.php/research-projects/current-project/fred

TIME & ACCURACY: EM MODEL IMPLEMENTATION

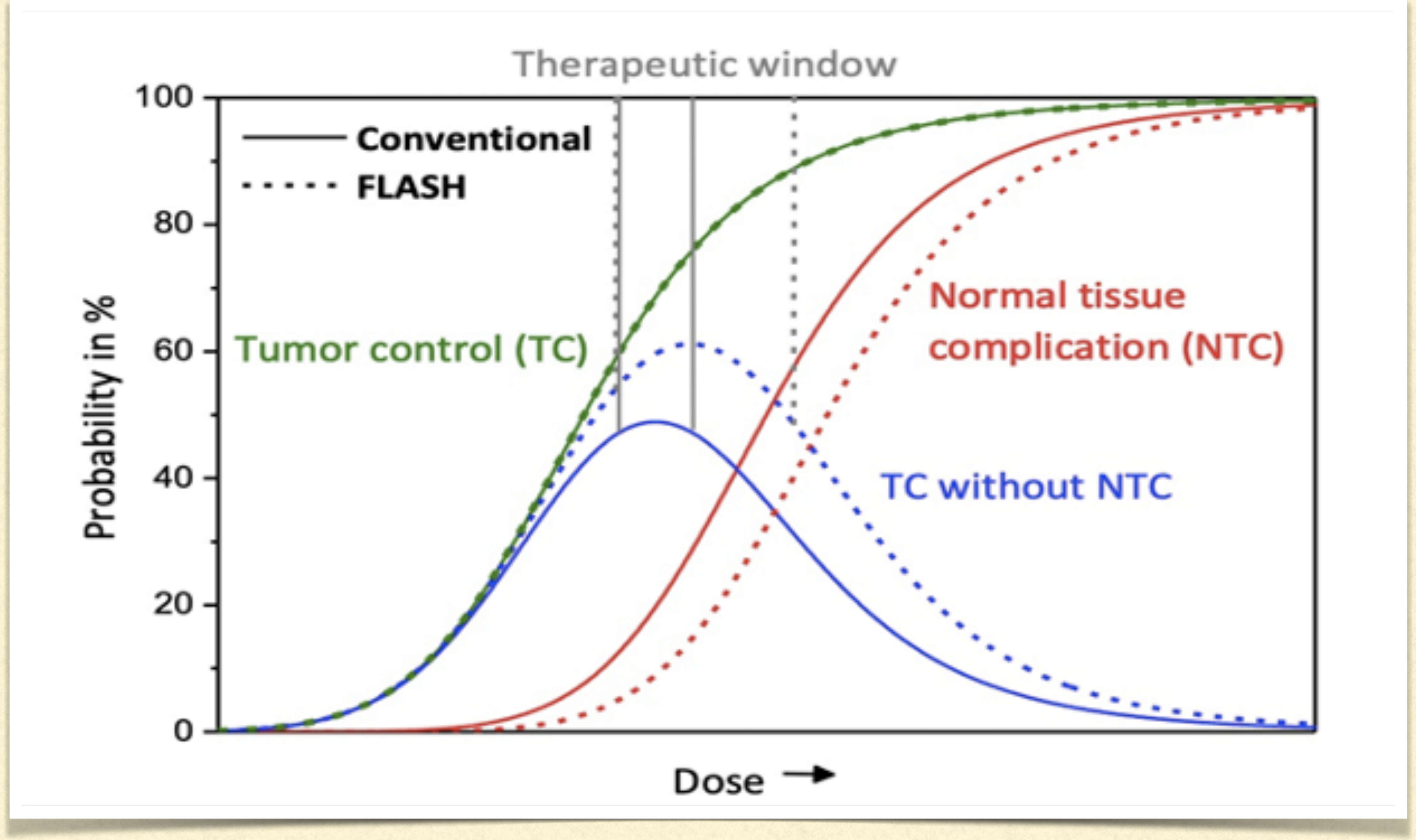


e⁻ on graphite (depth dose distributions)



- To fully profit from the speed of FRED..
  - .. EM interaction models have to 'ported' inside FRED / GPU framework & architecture .. not just a technical work: to simplify a model and maintain its accuracy is not an easy task.. requires deep knowledge of the underlying physics..
  - Benchmarking of FRED against 'standard' MC tools is crucial to validate its predictions…

THE 'FLASH' EFFECT



Author	Experiments	Model system	Type of radiation	Radiation fraction	Mean Dose rate	Comments
Favaudon *et al.*[2]	Mice	Lung fibrogenesis and blood vessels	4.5 Mev electrons	16 to 30 Gy of single fraction bilateral thorax	≥40 Gy/sec	The study showed a complete lack of acute pneumonitis and late lung fibrosis after bilateral thorax irradiation of C57BL/6 J mice with FLASH.FLASH prevented both activation of the TGF-b/SMAD cascade and acute apoptosis in blood vessels and bronchi.
Loo *et al.* 2017(Abstract)[27]	Mice	GI syndrome	20 Mev electron	10 to 22 Gy single fraction abdomen	>70 Gy/sec and >200 Gy/sec	Mice receiving 13–19 Gy, 29% survived 20 days after conventional vs. 90% after FLASH. LD50 of 14.7 Gy for conventional and 17.5 Gy for FLASH (16.6 Gy and 18.3 Gy for the 70 and 210 Gy/s cohorts, respectively)
Kim *et al.* 2017 (Abstract)[28]	Mice	Lung cancer model	NA	15 Gy single fraction to tumor	>50 Gy/sec	High dose Conventional radiation resulted in a rapid and reversible tumor vasculature collapse, which did not occur with high dose FLASH irradiation as determined by CD31 area densities, indicating that the biological effects differ between Conventional and FLASH.
Gruel *et al.*[4]	Mice	Brain cognition model	4.5 Mev and 6 Mev electron	10 Gy single fraction to whole brain	0.1 Gy/sec to 500 Gy/sec	Flash-RT neuroprotective effect is lost below 30 Gy/s but fully preserved above 100 Gy/s
Vozenin *et al.*[3]	Mini-pigs and cat	Skin	4.5 Mev and 6 Mev electron	25–41 Gy single fraction to normal skin and skin tumors	300 Gy/sec	Single dose FLASH-RT shows promise as a new treatment option for cat patients with locally-advanced squamous cell carcinoma of the nasal planum. Our results in pig and cats provide a strong rational for further evaluating FLASH-RT in human patients
Gruel *et al.*[5]	Mice	Brain cognition model	X-rad 225 photons	10 Gy single fraction to brain	37 Gy/sec	Preservation of memory at two and six months after a 10 Gy single dose FLASH-X-rays WBI delivered at a mean dose-rate of 37 Gy/s
Beyreuther *et al.*[29]	Zebra embryo fish	Embryonic survival, rate of pericardial edema and, rate of spinal curvature	224 Mev protons	0 to 42.5GY of single fraction	100 Gy/sec	Significant protective effect of proton Flash could be revealed neither for the survival nor for the morphological integrity of the zebrafish embryos. Solely for the rate of pericardial edema, a significantly reduced effect was found at the 3rd and 4th day after 23 Gy proton Flash compared to conventional proton irradiation
Buonanno *et al.*[30]	Human lung fibroblast cells	Clonogenic assay, DNA damage and senescence	4.5 Mev protons	0,5,20 Gy	0.05, 100 or 1000 Gy/s	To characterize the clonogenic cell survival depending on the proton dose rate, cells were exposed to different doses delivered at 0.05, 100 or 1000 Gy/s. The survival curves for all three dose rates followed a typical exponential decay trend with the dose. Although a slight difference between the low (0.05 Gy/s) and the two FALSH dose rates (100 and 1000 Gy/s) can be observed at the highest dose tested (10 Gy) the trends were not statistically different
Bourhis *et al.*[31]	Patient	Skin tumor	5.6 Mev electrons	15 Gy single fraction		First FLASH-RT treatment was feasible and safe with a favorable outcome both on normal skin and the tumor
Gruel *et al.*[32]	Mice	Brain cognition model	6 Mev electrons	10 to 14 Gy of single fraction whole brain	>100 Gy/sec	FLASH did not cause radiation-induced deficits in learning and memory in mice, did not impair extinction memory. FLASH produced lower levels of the toxic reactive oxygen species hydrogen peroxide, did not induce neuroinflammation
Simmons *et al.*[33]	Mice	Brain cognition model	16 or 20 Mev electrons	30 Gy single fraction whole brain	300 Gy/sec for 16 Mev or 200 Gy/sec for 20 Mev	FLASH is associated with reduced cognitive deficits, less loss of hippocampal dendritic spines

- Recently 'in-vivo' experiments have demonstrated that very high dose rates (x1000 wrt conventional RT) are able to achieve the same TC probability while significantly reducing the NTC (from 80% in 'deep organs' to 60% for the skin)

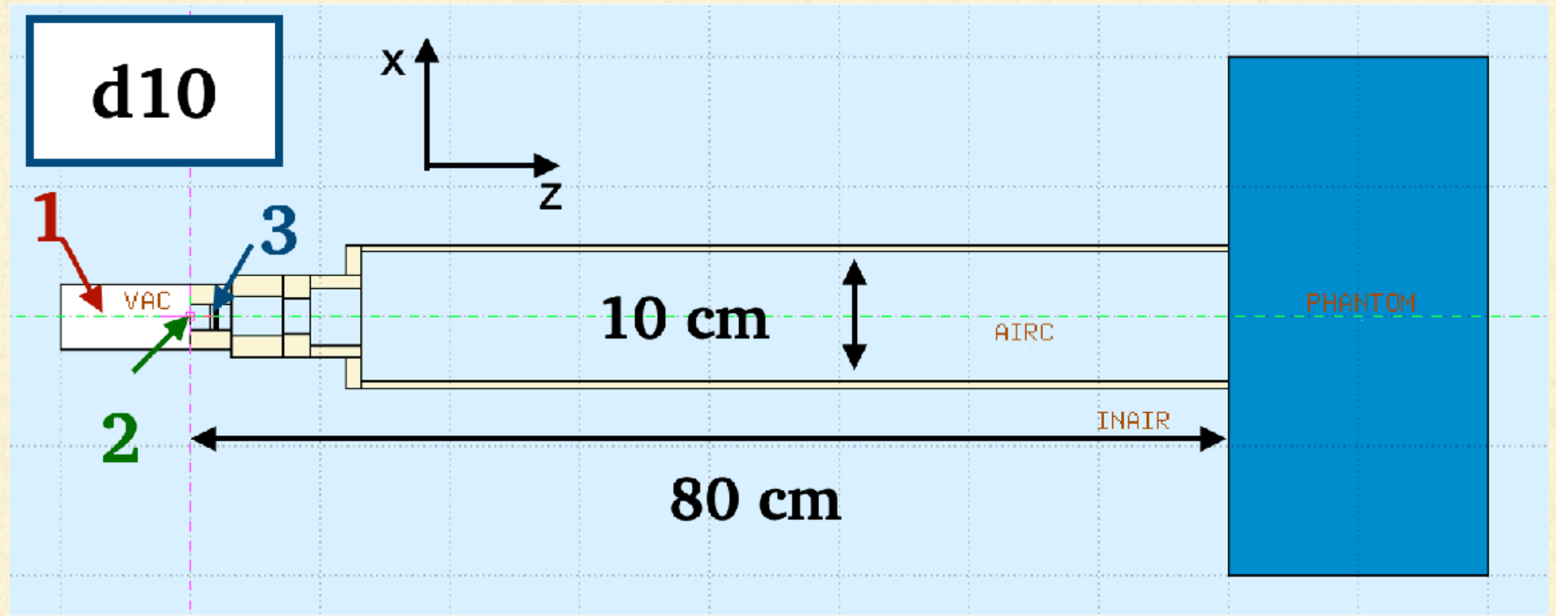
DEVELOPING A TPS FOR IORT APPLICATIONS..

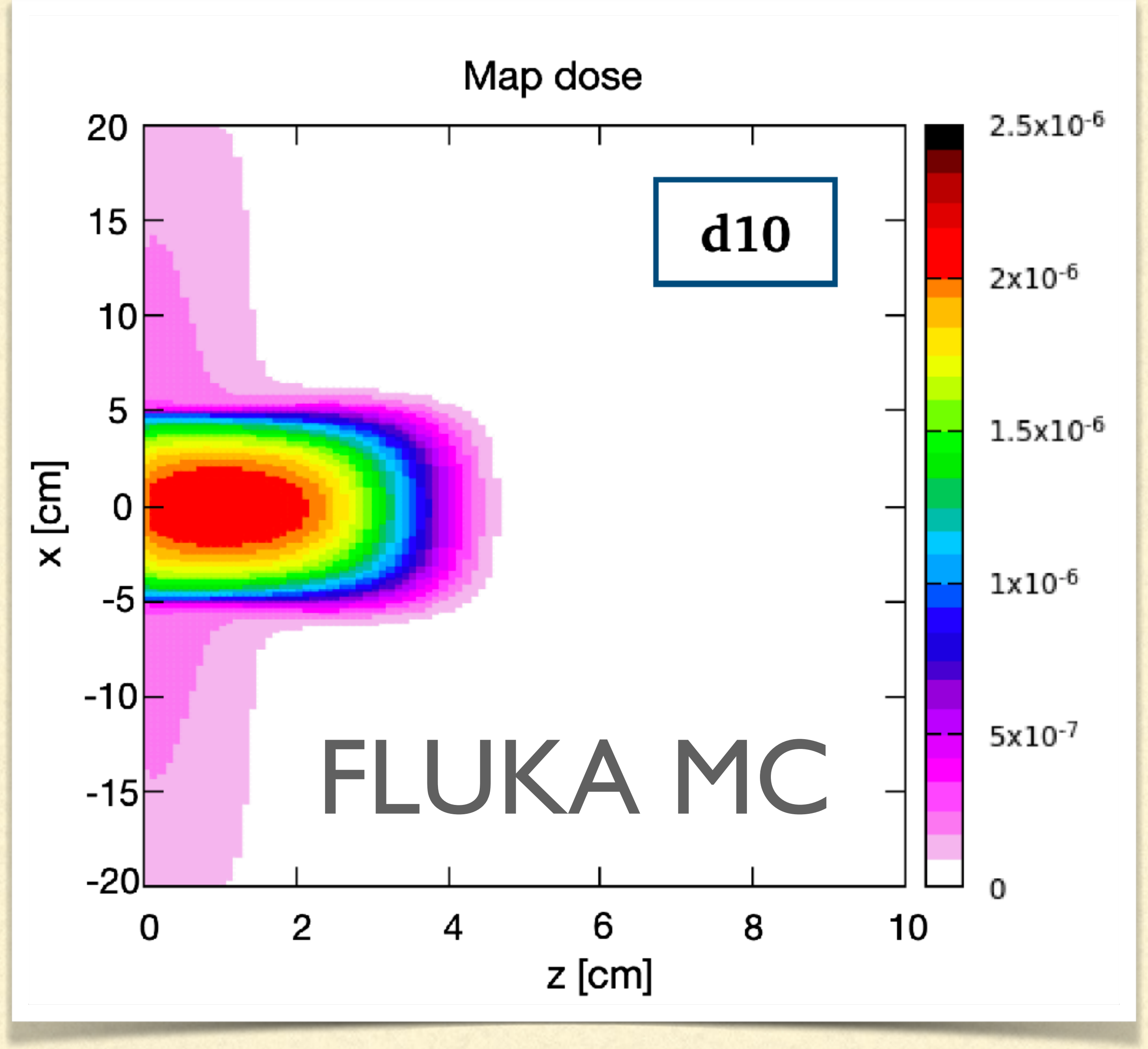
- The work will be carried out in close contact with SBAI department & SIT (Sordina Iort Technologies) in order to implement all the details of the machine used to deliver the beam

- The system needs to be capable of handling both ecographic and CT imaging input

- Flash and standard IORT conditions will be simulated using FRED, and **compared with the data of the machines currently being developed**… (E.g. Novac 11)

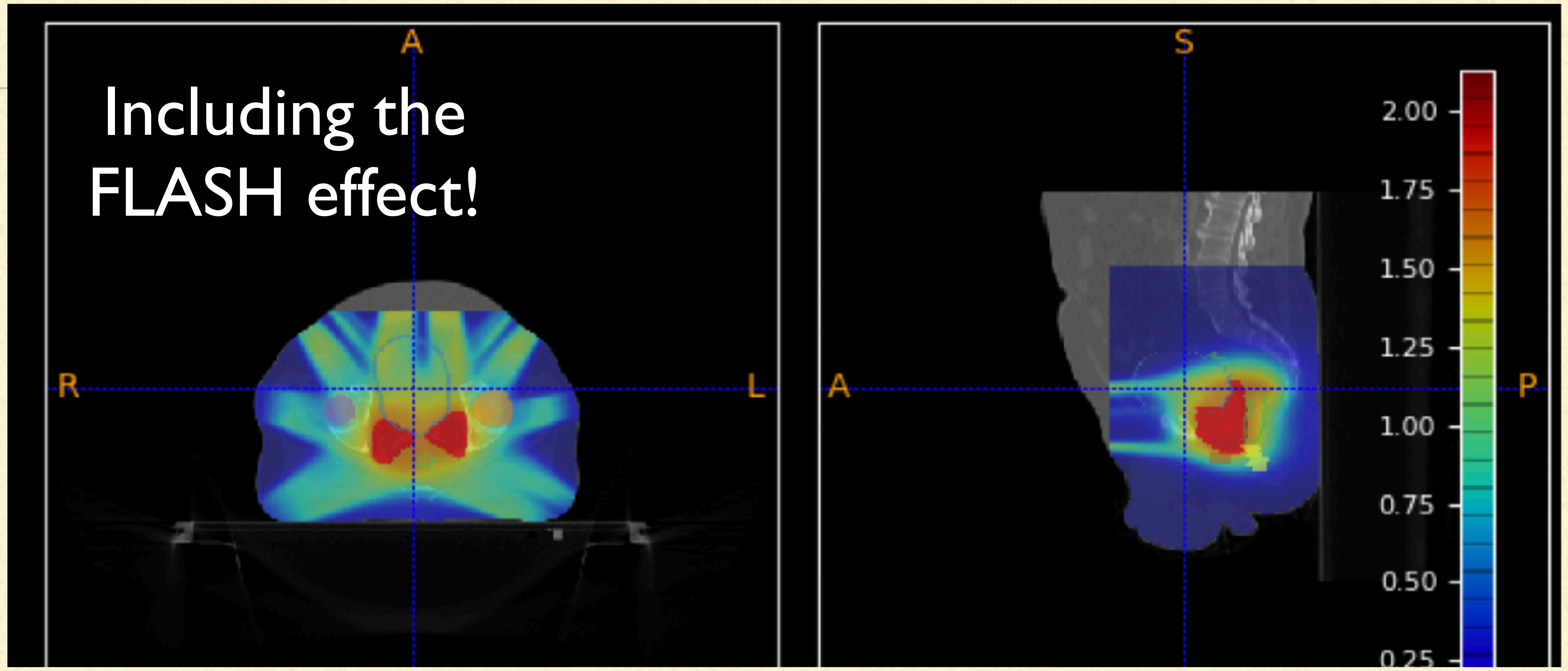
Novac 11

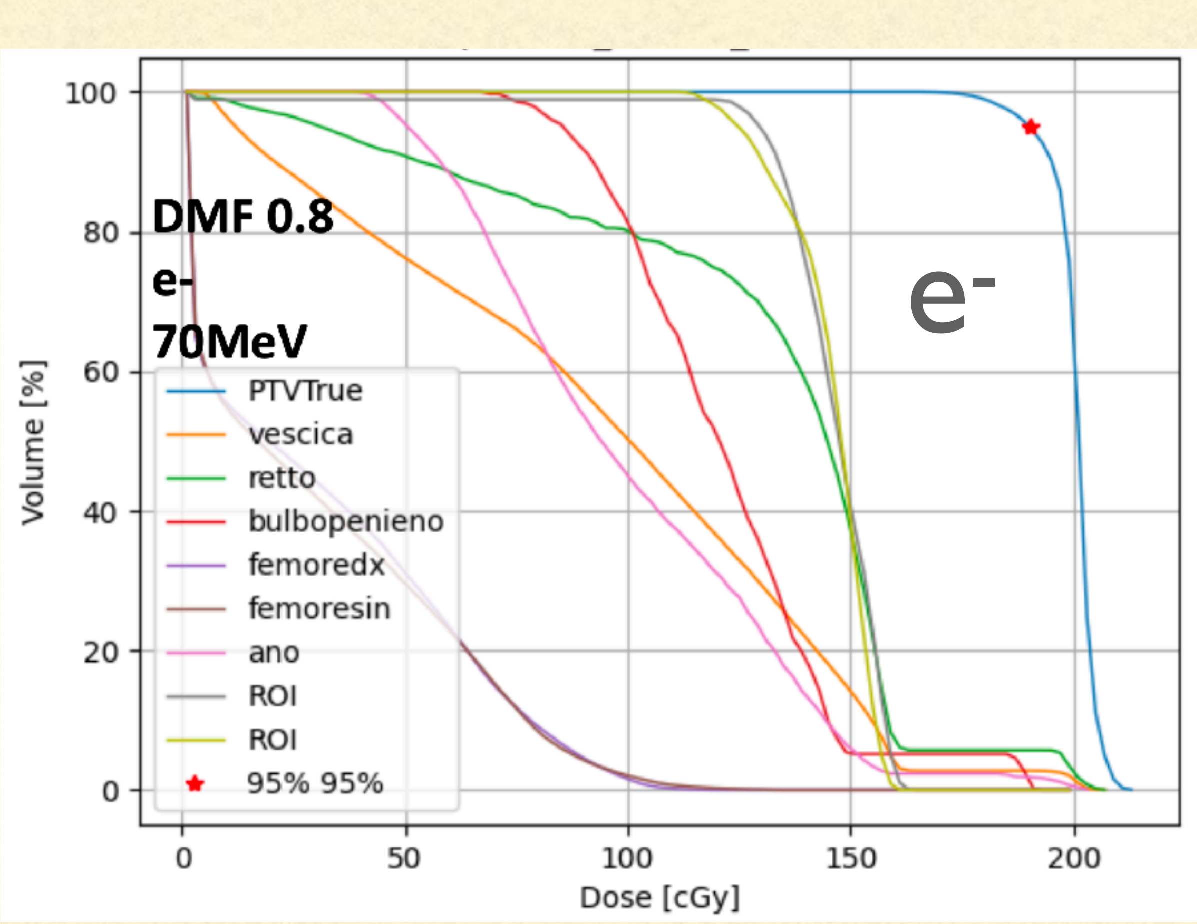


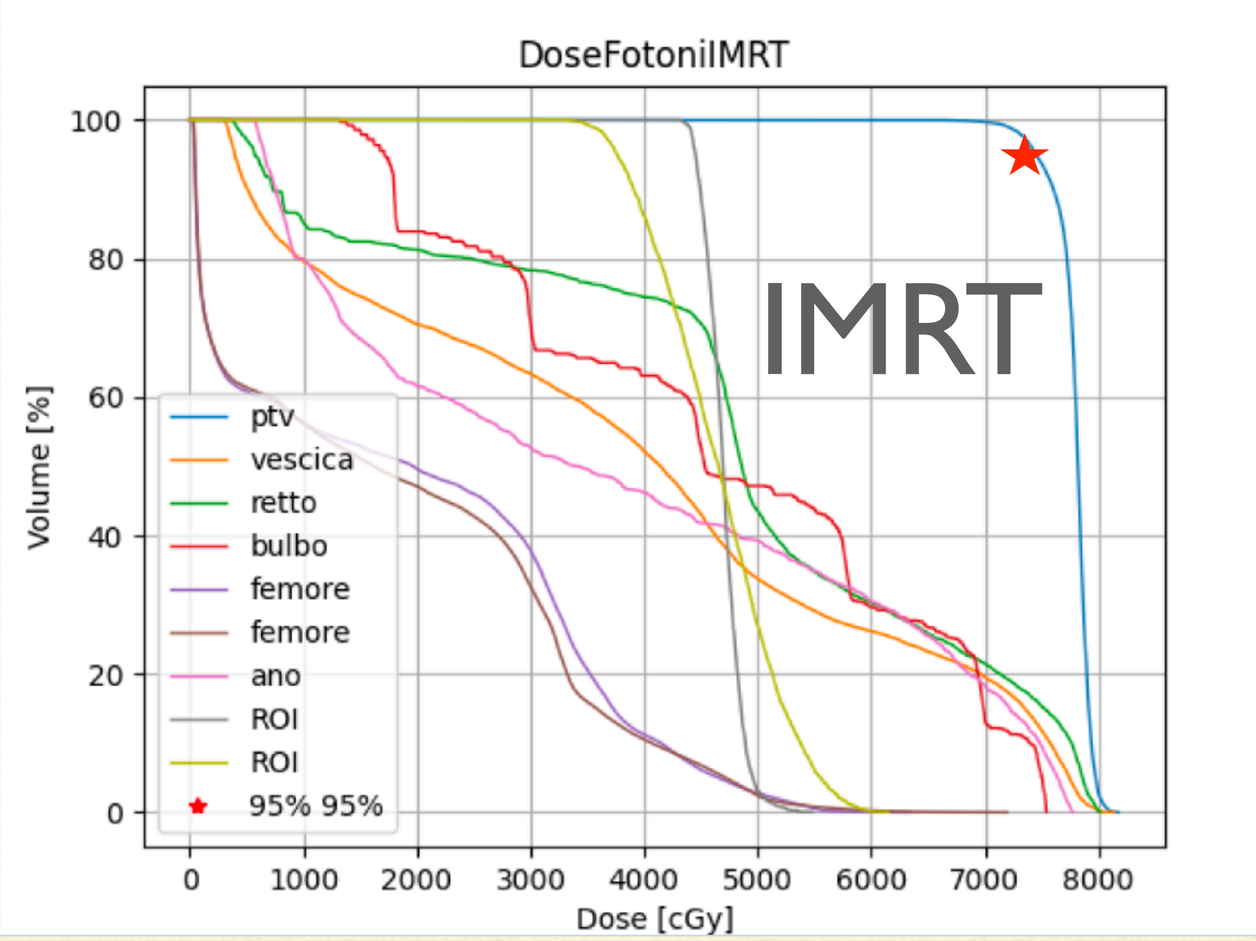


..AND A TPS FOR DEEP TUMOUR TREATMENTS

- Treating deep tumours with ‘high’ energy electrons comes with several advantages:
  - Reduced impact of morphological changes (wrt protons), reduced dose to OARs (wrt photons, implementing the FLASH approach), easiness in delivery!
- Proof of principle study just started using FLUKA, real TPS development attempt is about to start looking also at lungs and head&neck tumours as well…
  - A long road in front of us, just got opened..







SUMMARY

email: alessio.sarti@uniroma1.it
http://arpg-serv.ing2.uniroma1.it/arpg-site

- By joining the ARPG research group (Sapienza - SBAI dept.) one will have:
  - The chance to work with a lively group, that has a long standing experience in accelerator applications to the tumour treatment field, developing tools and performing a research activity in close collaboration with the SBAI accelerators group and the SIT
  - The opportunity to develop the EM models, improving their accuracy in the fast engine, allowing to open a new path for the fast planning of RT and electron treatments.
  - The possibility to exploit a fast dose engine software tool (FRED) for the studies related to the implementation of treatment planning technologies in the field of electron therapy (both of low and high energy: IORT and deep tumours).