



First Performance Calculations for the Very High Energy Electron Radiation Therapy Experiment at PRAE

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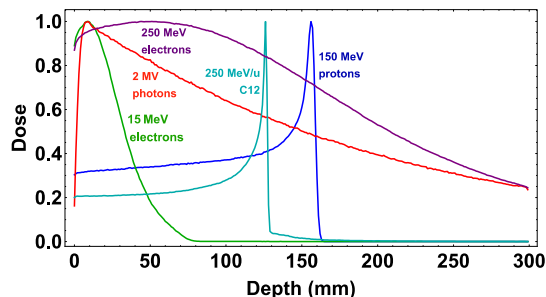


Figure 1: Dose profile for various particle beams in water (beam widths $r=0.5$ cm), [1].

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treatments in terms of doses delivered to surrounding healthy tissues [3]. This would allow to treat patients with VHEE beam directly or with innovative ways of dose delivery like Grid therapy mini-beams [4] or ultra-high dose rates FLASH beam [5], easier to produce with electron than with photon beams.

In the following sections we will present the first optics design and performance evaluation for a VHEE experiment at 70 MeV in the PRAE accelerator to deliver Grid therapy mini-beams and sub-millisecond ultra-high dose rates FLASH beams.

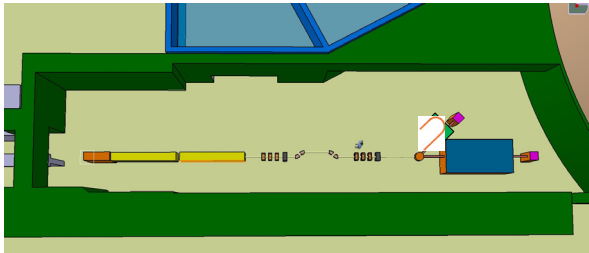


Figure 2: Schematic view of the PRAE accelerator (140 MeV) with the two experimental beam lines.

THE PRAE ACCELERATOR

The PRAE accelerator consists of a photo-injector, an acceleration section and two beam lines with the corresponding experimental setups: the subatomic physics and radiobiology research axes share the direct line and the instrumentation platform is located in the deviated line, as shown in Figure 2.

Table 1: PRAE Accelerator Performances

Parameters	
Energy	70 – 140 [MeV]
Charge (variable)	0.00005 – 2 [nC]
Normalized emittance	3-10 [mm mrad]
RF frequency	3.0 [GHz]
Repetition rate	50 [Hz]
Bunch length, rms	< 10 [psec]
Energy spread, rms	< 0.2 %
Bunches per pulse	1

A beam energy compressor section (ECS) follows the accelerating structure before separating in the direct (ProRad/Radiobiology) and the deviated line (Instrumentation). Two quadrupole triplets provide flexible beam optics to cope the different beam characteristics and operation modes depending on the application. The performances of the PRAE accelerator are summarized in Table 1. Detailed description of the accelerator and beam dynamics simulations is found in [6-7] respectively.

GRID OR MINI-BEAM THERAPY

One possible strategy to further improve the healthy tissue tolerance by using the concept of Spatially Fractionated Radiation (SFR) dose is the Grid or Mini-Beam Therapy (MBRT). In contrast to conventional RT the lateral dose-profile resulting of such grid-irradiation consist in a

pattern of high doses in "peaks " and low doses in "valleys".

Such techniques allow delivering large cumulative doses of radiation for treating the tumour, while reducing healthy tissue complications [8-9]. Remarkably high normal tissue dose tolerances (up to 100 Gy in one fraction) have been observed in in vivo biological experiments in the rat brain using SFR approaches that employ micrometric keV photon beams, as mini-beams (beam width of 400-700 μm) [10], which also produced significant tumour growth delay [11]. It is also evident that the advantages of VHEE beams for grid-therapy would benefit from the low lateral scattering and long penetration depth to allow the reduction of grid-size, up to sub-millimetric beams, and with direct magnetic collimation to construct the grid pattern. A theoretical proof of concept for this innovative approach in the treatment of brain-cancer has been recently explored [4] and some pre-clinical evaluation of other mini-beam approaches, such as proton MBRT [12] are being made at the Proton Therapy Centre at Orsay. To capitalise these initial encouraging results a first proof-of-concept with electrons will be made in PRAE.

First beam optics design calculated with the MADX program [13] is shown in Figure 3 to get transverse beam sizes ($\sigma_{x,y}$) of less than 700 μm with low beam divergence ($\sigma_{x',y'}$). The last dipole, indicating the starting of the instrumentation R&D platform, is not active in this case and for the sake of simplicity the ECS has not been taking into account.

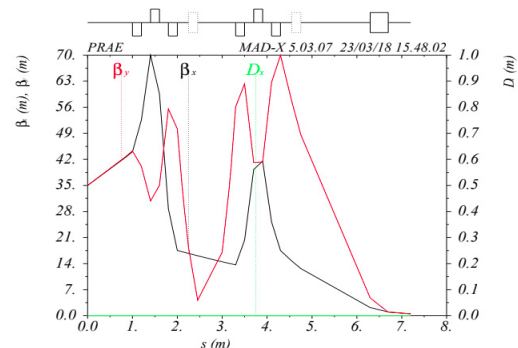


Figure 3: Beam optics design for mini-beam experiment at PRAE direct line without the ECS chicane and using two quadrupole triplets calculated with MADX.

Tracking simulations of a Gaussian bunch through the under vacuum accelerator beam line (Figure 3), an air gap of 10 cm and liquid water phantom of 3 cm depth has been performed with a Geant4 (Penelope module) based program BDSIM [14] for 70, 140 and 300 MeV. Results are illustrated in Figure 4 and summarized in Table 2. A benchmarking of the BDSIM results with MADX for the vacuum part and with the results with GATE (Geant4-based) in air and water has been made [15]. From these first results we could conclude that the mini-beam experiment is feasible but more promising using a higher-energy beam (>140 MeV). An extra focusing in air could be used to further

improve the Grid-pattern in depth. Some preliminary simulations of this extra focusing in air with BDSIM are on going.

Table 2: Transverse beam sizes and divergences sequentially at the accelerator vacuum window, after 10 cm air gap and 3 cm depth in water, for 70, 140 and 300 MeV.

Parameters	Energies [MeV]		
	70	140	300
$\sigma_{x,y}$ vacuum [μm]	166	170	170
	159	159	159
$\sigma_{x',y'}$ vacuum [μrad]	321	318	318
	318	323	323
$\sigma_{x,y}$ air [μm]	198	186	173
	183	182	162
$\sigma_{x',y'}$ air [μrad]	3141	1673	830
	3045	1868	801
$\sigma_{x,y}$ water [μm]	615	533	334
	646	561	350
$\sigma_{x',y'}$ water [μrad]	63511	37372	19934
	61522	36542	20162

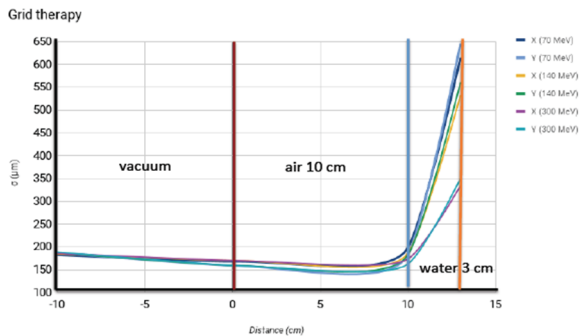


Figure 4: Beam widening for 70, 140, 300 MeV from end of vacuum window (0 in the horizontal scale), 10 cm air gap and 3 cm depth in water, calculated with BDSIM.

FLASH THERAPY

FLASH therapy experiments have been successfully tested with low energy electrons beams (4-6 MeV) only in small animals because of the low penetration of low-energy electrons. In 2014 the Institute Curie (IC) team demonstrated for the first time that FLASH irradiation spares normal lung tissue in mice from radio-induced fibrosis whilst leaving the anti-tumour efficiency unchanged [5]. The FLASH methodology consists of millisecond pulses of radiation (beam-on time ≤ 100 -500 ms) delivered at a high dose-rate (≥ 40 -100 Gy/s), hence over 2000 times faster than in conventional RT. Recently it has been shown that FLASH spares normal brain in mice from the loss of both memory and neural stem cells as endpoints [16]. Furthermore, on going studies using FLASH to cure non-operable squamous-cell carcinoma of the nasal planum in cats (shallow tumours fully irradiated by low energy electron beams). At the present time, melting of linear accelerator tungsten targets following high dose rate electron irradiation is a major technical problem preventing use of photon beam for FLASH irradiation of deep tumours [17]. The IC team is currently investigating the biological effect of FLASH treatment using protons beam (proto-FLASH) and the results of the first experiments are under analysis [18]. VHEE radiotherapy could be the most suitable to treat deep

tumour targets in FLASH conditions with distinct beam entrances.

A preliminary study of the beam optics and performances in PRAE direct beam line has been made for two different scenarios for FLASH tests in small animals:

- Sparing brain from radiation-induced loss of stem cells: round transverse beam sizes of around 10 mm with a dose of 10 Gy with beam on time 100 ms (5 bunches at 50 Hz), i.e. 10Gy/s [16].
- Sparing lung from radiation-induced fibrosis: transverse beam sizes of around 26 mm in horizontal and 18 in vertical with a dose of 15 Gy with beam on time 500 ms (25 bunches at 50 Hz), i.e. 30 Gy/s.

Beam optics with MADX and BDSIM simulations for these two cases has been calculated with the same methodology that for the mini-beams and the results for the BDSIM simulations are shown in Figure 5.

Concerning the beam intensity required to cope with the necessary dose rates (10 and 30 Gy/s), taking into account the corresponding transverse beam area for these two scenarios (1x1 and 1.8x2.6 cm²) and the mass stopping power value in liquid water for electrons at 70 MeV [19], 0.05 and 0.36 nC/s respectively are needed.

FLASH therapy

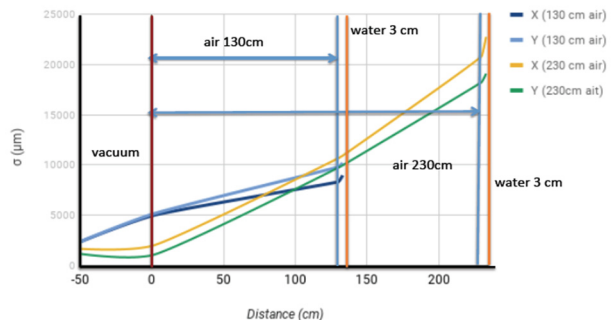


Figure 5: Beam widening for 70 MeV from end of vacuum window (0 in the horizontal scale), 130/230 cm air gap and 3 cm depth of water, calculated with BDSIM.

OUTLOOK AND PERSPECTIVES

A preliminary beam optics design and performance simulations for having a radiobiology experiment with Grid mini-beams and FLASH ultrahigh dose rate delivery treatment modalities at PRAE have been made. The results are encouraging and a deeper technical feasibility study is ongoing in order to demonstrate experimentally these innovative treatment modalities.

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