Dr. Miriam Brosi

Helmholtz Young Group Investigator proposal

Beam Dynamics and Collective Effects in the Generation and Propagation of Structured Beams for Advanced Accelerator-based Radiotherapy

Introduction

Particle accelerators nowadays play a vital role in a multitude of scientific fields. They have become highly complex over time and with them the field of accelerator physics. New developments are continuously pushing the understanding and the technological limits towards increasingly extreme beam properties. In electron accelerators, this includes ultra-short pulses at high intensities in linear accelerators or free electron lasers as well as transversely narrow pulses for ultra-low emittance synchrotron light sources. The extensive research conducted today aims for a deep understanding of the involved beam dynamics occurring in these extreme beam conditions and the required diagnostics. The extreme conditions lead to strong effects caused by the coexistence of many particles in the densely populated pulses. This is summarized under the term collective effects. They describe self-interaction of particles within the beam as well as the interaction with the environment, both of which are dependent on the detailed particle distribution. The study of collective effects is an active research topic and has been the main focus of my research in the last years.

At the same time, the current development of two advanced approaches in accelerator-based radiotherapy (RT) pushes in the same direction of high intensity beams with temporal or spatial structuring. FLASH RT is based on the delivery of very high doses in short pulses and Microbeam RT focuses on spatially fractionated beams. In both methods, a significant widening of the therapeutic window is observed. The resulting normal tissue sparing effect is expected to improve treatment outcomes and reduce overall toxicity for the patients resulting in a better quality of life after treatment. The beam properties used for FLASH and Microbeam RT go beyond the prediction and beam diagnostic capabilities in conventional RT. One difficulty is the increasing non-linearity in the response of usual dosimetry methods at high dose-rates. The increased requirements on dosimetry as well as on the overall diagnostics and simulation of the beam dynamics in the accelerators used for beam generation open up new challenges and possibilities. At the same time, the extreme beam properties in the novel radiotherapy methods require to push the understanding of the involved complex beam dynamics and collective effects (Figure 1) in this active and exiting research field.

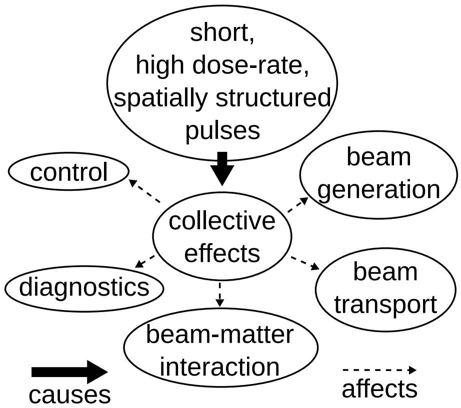

Figure 1: Areas to be influenced by collective effects.

The proposed project therefore aims at improving the understanding, predictability and control of the accelerator-based electron beams involved in FLASH and Microbeam RT. The entry point will be to extend the research on collective effects in accelerators to cover the beam properties required for FLASH and Microbeam RT, profiting from my expertise in this field. Subsequently, this project will expand the study beyond the particle accelerator into the beam-matter interaction up to the target tissue. The influence of collective effects during the transport from the accelerator through matter onto the target, which up until now was sparsely studied, will be explored in detail. Based on these studies, the effective relation of input particle distribution to the dose distribution on target will be explored. This enables, the attempt to solve the inverse problem, i.e. determining the required input distribution for a desired dose distribution on target. First tests of targeted beam shaping will be a part of this project. With this kind of control, the outcome of the project will be a significant contribution to FLASH and Microbeam RT as well as to the general advancement of accelerator physics.

Contents

1 Research Goal and Expected Outcome

The extreme pulse properties in FLASH and Microbeam radiotherapy lead to several open questions to be answered. The high dose-rates achieved have a strong effect on the underlying mechanisms: from the improved biological interaction with healthy tissue being the main advantage and driving point, to the increased non-linearity in dosimetric measurements, high requirements in beam based diagnostics, and the presence of complex dynamics and self-interaction leading to collective effects in the accelerator-generated particle beams. Collective effects in radiotherapy beams have yet to be investigated. Thinking further, collective effects acting on the beam can lead to significant deformations of the charge distribution and therefore of the produced dose distribution, resulting in the need for mitigation or compensation and ideally shaping of the generated RT pulse. Which, under certain conditions, might be extendable to generate modulated beams for these novel radiotherapy methods directly in the accelerator.

The main goal of the proposed project is to provide a fast and comprehensive assessment of radiotherapy beam properties and the resulting deposited dose on target as well as improved control thereof. Due to the high flexibility of electron research accelerators this project primarily focuses on electron based beams, with the possibility for transfer later on to heavier particles.

The following four objectives are selected:

I. Increased predictability of RT beam properties on target by development of start-to-end simulation including collective effects

II. Improved insight into the influence of temporal or spatial pulse modulation on detection and diagnostics to provide recommendations for applicable methods depending on beam parameters

III. Exploring the possibilities and defining the physical limitations of accelerator-based pulse shaping and modulation

IV. Investigating methods and algorithms solving the inverse problem, i.e. calculating the required initial beam distribution from a desired beam shape on target (based on I. - III.)

These objectives will be achieved by investigating the influence of collective effects on beam generation, beam transport, beam-matter interaction and diagnostics in novel electron radiotherapy methods with temporally and spatially structured beams. Therefore, different interactions of beam-particles with one another, described as collective effects, will be considered and incorporated into theoretical calculations and simulations of the transport of the particle beam from start-to-end, not only within the accelerator but also extended to the transport through matter (e.g., air or water) (objective I.). Furthermore, systematic studies on the dependence of different detection mechanisms and diagnostic tools on temporal and spatial pulse shapes combined with varying intensity will give insight into which diagnostic tools are suitable to aid in reliably delivering the desired conditions (objective II.). The investigation on the possibility to modulate the beam in the accelerator will pursue and compare different methods which will provide different temporal and spacial modulations. It will also entail studies on which modulations can be achieved on the final target when taking the transport through matter into consideration (objective III.). Employing the improved and extended simulation (from the first objective) to predict the resulting distribution on the target, might allow to consider the effects of the beam transport already during the generation of the beam. And if successful, this could enable the generation of a temporal and spatial particle distribution which preemptively compensates for the deformation expected during the propagation of the particle distribution from generation to the target. As a result, it would become possible to generate (within certain parameter limits) user-definable final particle distributions on the target (objective IV.).

The outcome of the project will firstly be the results achieved in the work packages aiming for the four objectives given above. This will directly contribute to the advancement of the novel radiotherapy FLASH and Microbeam RT by improving the reliability of the medically crucial distribution on target by improving the prediction, precise diagnostic and targeted control of the used particle beam. The planned start-to-end simulation tool will allow to determine the expected particle and therefore dose distribution on the medical target with higher precision. This is accompanied by a in-depth and profound recommendation on applicable diagnostic methods for complex RT beams, and how they can be complemented by incorporating shot-to-shot accelerator diagnostics into the standard diagnostic portfolio. The outcome of the investigation into targeted pulse shape control opens up new possibilities and approaches to generate the temporally and spatially modulated particle beams applied in novel radiotherapy methods.

Beside these direct outcomes, the project progresses the fundamental research on the interaction of high-intensity particle-beams with matter by considering collective effects. Furthermore, the project will contribute to the general field of accelerator science and give impulses for the research on energy efficient and sustainable accelerators in medical applications. Particularly for intense, short pulses which are inherently challenging, the project will contribute to improved diagnostics insight including shot-to-shot diagnostics and will provide a new simulation tool with a focus on collective effects in such beams. Furthermore, the project will advance the knowledge of possibilities and limitations for beam shaping to create spatially and temporally modulated beams and the understanding of the involved collective effects. The found method for solving the ”inverse problem” could provide improved diagnostics capabilities through back-propagation of measured particle distributions back to arbitrary upstream locations along the accelerator, providing for example an estimate of the emittance at the electron gun.

A wide variety of possible application fields in accelerator science come to mind. So could, for example, a transverse beam modulation find an application in the research on synchrotron radiation generated in free electron laser. The already mentioned method of back-propagating a measured particle distribution could be utilised similarly to ”virtual diagnostics” for plasma accelerators where diagnostics in the plasma cell is generally difficult. Furthermore, collective effects in beam-matter interaction become increasingly relevant for propagation of beams through plasma in plasma accelerators for higher intensities and shorter pulses.

In relation to energy efficient and sustainable accelerators, the project’s use of FLUTE with operation modes geared towards medical applications can serve as energy model for research of the energy profile of medical accelerators within the framework of KITTEN and a collaboration with the Energy Lab 2.0. This includes the possibility to study the energy consumption for the generation of RT beams and potentially allows to gain insights in the tolerable grid stability for medical applications relying on special beam conditions with tight tolerances.

In the medium to long term, the knowledge of critical parameters and understanding of involved physical effects, gained within this project, can be used to design energy efficient accelerators dedicated to medical applications such as FLASH or Microbeam RT.

2 Relation to the Helmholtz Program

This Helmholtz Investigator Group proposal directly contributes in the Helmholtz Program "Matter and Technology", realized in the Research Field "Matter", in the Topic "Accelerator Research and Development" (ARD). This topic falls precisely in the research activities at the Institute for Beam Physics and Technology (IBPT), home to the KIT electron accelerators.

One recent part of the subtopic 3 of ARD is the advancement of accelerator development by exploring novel use cases where radiotherapy is currently of high interest[1]. The research conducted in this project directly contributes to this topic with its main goal of furthering the accelerator physics side of novel radiotherapy methods like FLASH and Microbeam RT (as described in Section 1).

To generate such custom beams the project will explore and develop possible methods to modulate and control pulse shapes. This is augmented by evaluations of applicable diagnostics methods. The predictability of the particle distribution of these custom beams is improved by including collective effects into the beam dynamics at all stages from source to target in medical applications within this project. These three topics cover an important part of the ARD subtopic 3[2] ("Advanced Beam Control, Diagnostics and Dynamics") which is "*for all types of next-generation beams, the generation, detection, and control of ultrashort electron bunches*" because "*exploring the dynamics of custom beams at the forefront of today's technology is a prerequisite for the design of future high performance or compact accelerators.*"[2] For example, the "*reliable generation of attosecond to femtosecond electron pulses in free electron lasers*" is foreseen to be achieved by establishing "*improved start-to-end modeling considering all relevant aspects from the electron source dynamics to the mitigation of harmful collective effects.*"[2] Since the targeted intensities for FLASH RT lead to similar charge densities, albeit for longer bunches, the involved dynamics are similarly complex. The planned implementation of a start-to-end simulation including collective effects follows the same strategy.

A new research topic of strategic importance for IBPT as part of the Helmholtz Program "Matter and Technology" is the research into energy solutions for large-scale research infrastructures including the development and generation of efficient new beams for application in radiotherapy. To this end the institute initiated the KITTEN[3] framework together with the Energy Lab 2.0. By serving as a showcase for medical applications the project can contribute to this framework as discussed in Section 1.

Furthermore, KIT is partaking in the "Matter and Technology" topic on "Detector Technologies and Systems"[4] where the project could strengthen synergies with ARD. The project could benefit from preexisting expertise as well as serve as test-bed for detector developments by providing custom, e.g. spatially structured, beams. Possible collaborations are described in Section 7. A comprehensive placement of the project within KIT is given in the following section.

3 The Helmholtz Investigator Group within KIT

The Helmholtz Investigator Group is planned to be established at the Institute for Beam Physics and Technology (IBPT) at the Karlsruhe Institute of Technology (KIT). With the proposed project relying on the possibility to conduct systematic measurements on accelerators and particle beams, the IBPT will provide the ideal environment with easy and extended access for in-house researchers to its electron accelerators. Both accelerators serve as accelerator test facilities, which results in a high flexibility in beam conditions and the possibility to tailor operation modes to experimental requirements. To this end, the accelerators are equipped with extensive, state of the art diagnostics. The proposed project will build upon the flexibility by establishing dedicated operations modes with FLASH or Microbeam RT beam properties. Additionally, this will extend the portfolio of operation modes that can be provided at IBPT. The 2.5 GeV storage ring and synchrotron light source KARA (Karlsruhe Research Accelerator) provides short x-ray pulses. Additional operation modes have been implemented, for example, a short-pulse operation for the investigation of the dynamics in short bunches as well as the development and tests of novel, fast diagnostic methods. The second accelerator is the linear electron accelerator FLUTE [1]

[1] 9. Annual MT Meeting: `https://indico.desy.de/event/38765/contributions/152914/`
[2] ARD-ST3: `https://www.helmholtz-ard.de/e42986/e43194/index_eng.html`
[3] KITTEN: `https://www.ibpt.kit.edu/kitten.php`
[4] 9. Annual MT Meeting: `https://www.helmholtz.de/en/newsroom/article/platform-for-detector-technology-and-systems/`

(Ferninfrarot Linac- und Test-Experiment) which will be used for most experimental tests and studies within the project. It is designed to provide ultra-short electron pulses with an energy of around 6 MeV after the low-energy section and with energies of up to 50 MeV and bunch lengths down to femtoseconds after the full accelerator. The electron pulses in FLUTE are generated with a femtosecond chirped laser-driven photo-injector. Of great importance for the proposed project, is the recent implementation of a spatial light-modulator [2] which allows spatial and temporal shaping of the laser pulse and therefore control of the initial electron distribution. Additionally, a 50 MeV laser-plasma accelerator is being built as part of the ATHENA project. This will open the opportunity to test the developed simulation and diagnostic methods on a different type of accelerator and investigate the possibilities and limitations of LPA beams for radiotherapy in cooperation with the newly established group of Prof. Dr. Matthias Fuchs. Additionally, the project's outcome on back-propagation of particle distributions could support the research on LPA (as mentioned in Section 1).

The IBPT is part of the Accelerator Technology Platform (ATP) at KIT. The ATP combines KIT-internal expertise and infrastructures relevant for accelerator research, development and application. This includes among others experts and infrastructure on advanced detector technologies studying, for example, ultra-fast and radiation hard detection systems, which offers the possibility for collaborations on newly-developed detector systems, e.g. with the Institute for Data Processing and Electronics (IPE).

KIT offers a strong background in mathematical and computational science with the Scientific Computing Center (SCC) and the KIT Center ”MathSEE” (Mathematics in Sciences, Engineering, and Economics). For example simulation code the KiT-RT (Kinetic Transport Solver for Radiation Therapy) [3] simulation code has recently been developed by the research group Computational Science and Mathematical Methods (CSMM). Collaborations are envisioned and could add to the project with extensive experience in efficient implementation methods for complex physical processes in simulations tools.

With respect to the medical physics component of the proposal, the project is perfectly in line with the ideas of the recently established KIT-center "Health Technologies", strengthening the important component of accelerator research with respect to radiotherapy. Therefore, it is envisioned for the proposed group to contribute to the center. Another important opportunity is the research bridge "Medical Technology for Health (MTH)" as part of the longstanding strategic partnership with the Heidelberg University HEIKA (Heidelberg Karlsruhe Strategic Partnership). The details of planned collaborations are described in Section 7¸.

A joint master program in biomedical engineering in cooperation with the University Heidelberg is planned to start in the winter semester 24/25 strengthening this important research area by attracting young talents. The initiators behind this program would welcome my contribution towards lectures and supervisions of potential students. Additionally, members of the physics faculty such as dean of studies Prof. Dr. Quast and former vice-dean Prof. Dr. Husemann have declared their support for my involvement in a newly planned module of lectures on "physical foundations of technologies".

All of the above as well as the general wide variety of research fields at KIT promises multidisciplinary input and solution-finding in an inspiring, dynamic and nurturing environment for me to successfully establish myself as junior research group leader and for the project to provide an important contribution to accelerator science and towards the advancement of novel accelerator-based radiotherapy methods.

4 Current State of Research and Preliminary Work

4.1 State of the art: radiotherapy

Radiotherapy (RT) has always been a very valuable tool in cancer treatment [4]. In Europe, radiotherapy is recommended as part of the treatment plan for more than 50% of cancer patients [5]. Reducing side effects while maintaining or even enhancing treatment efficacy in the future will improve the quality of life of the patients. Radiotherapy uses ionizing radiation to damage the DNA within the tumor cells, which prevents the cells from reproducing and eventually leads to their death. The external beam radiotherapy (EBRT) is based on accelerator-generated high-energy beams delivering a targeted dose of ionizing radiation to the affected area. As some areas of healthy tissue are unavoidable irradiated the dose rate is carefully chosen to keep a balance between tumor control and normal tissue tolerance. The range between radiation doses that effectively destroy cancer cells while only causing minimal damage to healthy tissue and organs is called the therapeutic window [6]. A widening of this window is one of the main goals of present day radiotherapy research.

FLASH RT is a novel approach which focuses on short pulses with very high dose rates to enhance tumor cell lethality while minimizing damage to surrounding healthy tissue. In conventional external beam RT typically around 30 fractions with 1.8 - 2 Gy per fraction are delivered with a dose rate ranging from 0.2 to 20 Gy/min. For FLASH RT, dose rates of more than 40 Gy/s (=2400 Gy/min) were observed to be effective in combination with pulse trains shorter than 500 ms and a total dose of 10 Gy or more [6]. The resulting significant widening of the therapeutic window (see Figure 2) allows a higher dose per fraction than in conventional radiotherapy without causing severe side effects, such as acute normal tissue reactions or long-term complications. Several suspected mechanisms behind the beneficial FLASH effect [7] are being investigated. And while the exact mechanisms are not yet fully determined, the effect has been experimentally demonstrated for irradiation with photons, electrons and ions. The presented project will primarily focus on electron beams.

The high dose rates result in difficulties with standard dosimetry techniques showing deviations from the required linear detection efficiency [8]. So is, for example, the Fricke dosimetry nearly independent of does rate up to approximately 2 Gy per pulse, which is exceeded under FLASH conditions. Therefore, the primary standard for dosimetry in conventional electron RT is not applicable to FLASH RT. To this end, the effects leading to the observed deviations between expected and detected dose are under investigation and new dosimetry calibration procedures and detectors are being tested [9]. Recent work has, for example, included further investigations of ion-recombination in ionization chambers including improved ways of calculating the recombination correction factors [10]. In addition, systematic tests of possible, alternative detection mechanisms such as solid-state calorimeters and small-volume and active dosimeters were conducted [8], [11]. Active detectors and real-time diagnostics become increasingly relevant as well for beam monitoring as each of the few high dose pulses carries a non-negligible amount of the total dose described for treatment, increasing the required per shot accuracy as fluctuations in dose per pulse no longer average out. Besides the obvious need to establish accurate dosimetry methods, the prediction of the expected dose on target can be improved by including collective effects into the simulations. This will be described further in the state of the art: accelerators and collective effects section. For most standard medical accelerators the FLASH conditions are challenging if not impossible to achieve, requiring substantial improvement or the development of dedicated FLASH accelerators [12]. In the meantime, dedicated accelerator facilities with compatible beam conditions are employed as testbeds.

Another possibility to achieve reduced normal tissue damage are spatially structured beams used in **Microbeam Radiotherapy (MRT)** [13]. The spatial intensity modulation at the micrometer scale has shown the potential to widen the therapeutic window. The underlying biological mechanisms are suspected to have significant overlap with the mechanisms behind the FLASH effect due to the similarly high dose and dose rates in the micron-sized individual beamlets in the array of parallel microbeams [13]. Earlier studies with electron GRID radiotherapy [14] and recent studies with protons showed promising results in the sparing of healthy tissue [15]. Nevertheless, most studies on MRT have been conducted with X-rays. The unidirectional microbeams with spot sizes of 25 - 100 μm and a spot spacing of 50 -

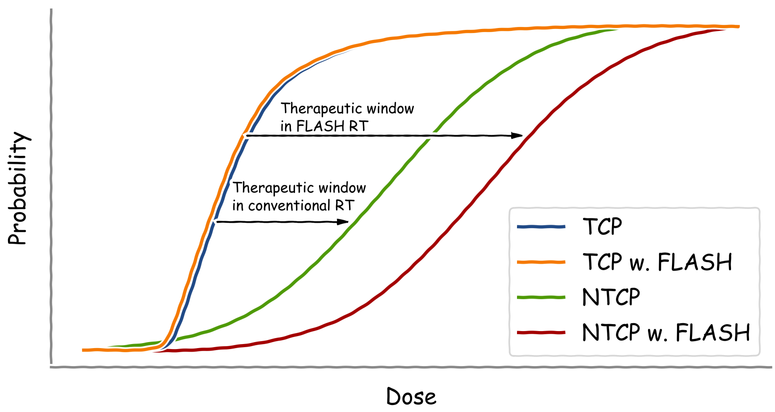

Figure 2: Sketch of the therapeutic window increasing as normal tissue complication probability (NTCP) is shifted to higher dose for FLASH RT and tumor control probability (TCP) remains.

200 μm are produced by inserting a multi-slit collimator into an x-ray beam with very small divergence produced at a 3rd generation light source [16]. This dependence on large infrastructure synchrotron sources is one of the main challenges in MRT today. With most research focusing on the modulation of the beam outside the accelerator close to the target area, accelerator-based electron beam modulation remains an open research question.

In summary, it can be concluded, that the high temporal or spatial structuring for both novel radiotherapy methods, FLASH RT and Microbeam RT, leads to an increased complexity in the diagnostics of the beam properties and the dose as well as in the generation. In addition to the capability to generate and diagnose beams for FLASH RT, also the beam dynamics under the extreme beam properties need to be investigated in great detail to understand and simulate the resulting effect on the beam properties on target.

4.2 State of the art: accelerators and collective effects

As discussed above, the requirements of new advanced radiotherapy methods on particle accelerators are high and current research on FLASH RT is consequently mainly performed on dedicated accelerator research facilities with a focus on electron accelerators. The additional advantage is the possibility to benefit from the flexibility in operation parameters, such as variable pulse length or intensity, and the higher degree in versatile instrumentation and diagnostics. This allows systematic studies and parameter mappings to assist the search for the best suitable parameter set for a widening of the therapeutic window. Furthermore, at current RT accelerators, the diagnostic measures focus mainly on the dose detected after the accelerator. The wide range of fast and accurate diagnostics available and employed in research accelerators opens up access to fast and extensive information on the beam properties, such as charge, energy, position, pulse shape, and more [9]. The proposed project will exploit this further than currently done to increase the extend of monitoring and control over the produced pulses and to provide recommendations on the most suited, complementary diagnostics methods for RT.

In general, research accelerators cover a wide variety of different use-cases and machine types, with circular and linear accelerators (linac) being the most common types. Overall, the beam properties can range from continuous beams to bunched beams consisting of particle packages (bunches), from MeV to several GeV or for colliders even TeV beam energies, from artificially elongated bunches with very narrow transverse sizes and divergence (ultra-low emittance [17]) to wider but ultra-short bunches down to femtosecond pulse durations [18]. For electron accelerators, the electrons are either generated via thermionic emission or with a laser pulse on a photo-cathode. The latter case provides control over the pulse length as well as the transverse distribution of the generated initial electron bunch by modulating the incident laser pulse [2]. This offers further possibilities for studies of spatially structured pulses and the possibility for accelerator-based beam modulation of radiotherapy beams will be investigated within this project.

In a continuous effort, research accelerators are characterized to a higher and higher degree with regards to a wide variety of effects including complex contributions to the beam dynamics such as collective effects. In general, the dynamics of accelerated particles is influenced by fields of different origin. External magnetic fields are applied for guiding and focusing the particle beams as well as external electromagnetic fields which are used for the basic acceleration itself but also for fast deflection in the context of diagnostics or for shaping the longitudinal charge distribution by so-called higher harmonic cavities resulting in complex shapes of the electromagnetic potentials. These dynamic boundary conditions lead to complex, non-linear dynamics of the accelerated particles. On top of this, self-generated electromagnetic fields act back on the particles and on the surrounding material. These self-interactions and interactions with the environment depend on the number and distribution of the particles within a bunch and are therefore often referred to as collective effects [19].

Each charged particle is surrounded by its electromagnetic field. The field interacts with all nearby materials such as a vacuum chamber, matter it passes through and also neighboring particles within the same bunch. These interactions can result in a force acting back on the charged particle leading to a change in movement direction or energy. The effective resistance that the charged particle experiences due to these interactions are described with frequency dependent impedances. Furthermore, in the same way one particle affects all neighboring particles, each particle is affected by the superposition of the fields of all other particles within the bunch. The resulting fields are referred to as wake fields and depend directly on the distribution of the charged particles in a bunch as well as on beam energy and the material properties of the surrounding structures. Both quantities are connected, as the impedance Z multiplied by the Fourier-transform of the charge distribution $\tilde{\rho}$ equals the Fourier-transform of the wake field V [19]:

$$V(t) = \int_{-\infty}^{\infty} \tilde{\rho}(f)\, Z(f)\, e^{i2\pi f t} \mathrm{d}f$$

This equation also directly shows, that depending on the shape and length of the particle distribution, the overlap in frequency with the impedance changes and therefore affects the resulting strength of the self-generated electromagnetic field.

Collective effects cause various issues in accelerator beam dynamics, such as emittance growth, energy loss, beam instabilities, overall degradation of performance and deformation of the temporal and spatial shape of the particle bunch. The mitigation and control of these effects is an ongoing topic in accelerator physics and advanced models and algorithms are developed to predict the influence of collective effects on the particle beams throughout the entire system. Collective effects have not been considered in the past in conventional accelerator-based RT due to the rather long pulses and therefore low momentary intensity and dose-rates. Furthermore, they are typically not included in calculations of the beam transport through matter often based on Monte Carlo or particle tracking. Common simulation tools include FLUKA, EGSnrc, BDSIM or the KiT-RT (Kinetic Transport for radiation therapy) framework designed for easy extendibility [3]. The inclusion of collective effects into the beam-matter interaction calculations is going to be an important topic within this project. Examples of collective effects with potential relevance for RT beams include space charge wake fields [20], coherent synchrotron radiation (CSR) [21] and resistive-wall wake fields [22] and are present in both circular and linear accelerators. The presence of these effects leads to instabilities like intra-beam scattering, the transverse mode-coupling instability [23], micro-wave instability [22] and the micro-bunching instability [24], all of which I have studied in electron storage rings in the past, as described in the following.

4.3 Open questions and challenges

Some of the aforementioned most pressing questions and challenges for accelerator-based FLASH RT and Microbeam RT are listed below:

- With the FLASH effect not yet fully understood, the optimal dose and dose-rate parameters are still to be determined.
- The high dose-rates result in a non-linear dependence in the dosimetry standards.
- Time resolved diagnostics to determine the shot to shot accuracy are required due to small number of high dose pulses.
- The expected influence of collective effects on the beam dynamics during generation as well as during the beam transport through matter in not commonly considered.
- The production of structured beams for Microbeam RT poses a challenge.

In general, a sound understanding of the effects involved in the dynamics of temporally and spatially structured RT beams is required for the generation, the propagation as well as the detection of the resulting high dose-rate pulses. Identifying the contributing collective effects and shedding more light onto their deforming influence is therefore crucial to accurately predict the particle-, and therefore, dose-distribution on target.

4.4 Previous relevant work on beam dynamics, collective effects and diagnostics by Dr. Brosi

In the last years, I have performed systematic studies of the longitudinal as well as transverse collective effects and instabilities influencing the bunch shape in all dimensions. The main goal was to investigate phenomena occurring under extreme operation modes to understand and circumvent resulting performance limitations while contributing to the general advancement of the field. The studied conditions included high charge in single bunches, dedicated short bunch-length operation modes at the storage ring KARA [25] and small transverse bunch-sizes in the ultra-low emittance synchrotron light source MAX

IV [22], [23], all conditions prone to instabilities leading to dynamic sub-structures in the charge density of the bunches. For the investigations, I conducted experimental studies and systematic simulations.

To evaluate the expected collective effects in the context of this proposal, simulations will be a valuable tool for which I have gained extensive experience in my previous research. For example, my studies of the micro-bunching instability, which occurs at bunch lengths in the order of several picoseconds or less, showed for example, an additional region of instability for certain parameters at lower bunch charge as predicted by the text-book equations [25]. To perform the theoretical calculations, I used the Vlasov-Fokker-Planck solver Inovesa [26], which simulates the longitudinal dynamics under the influence of the coherent synchrotron radiation impedance. To this end, the particle density distribution in the longitudinal phase space is calculated via the Vlasov-Fokker-Planck equation for each time step. I was involved in the scientific conceptualization of the code as well as testing the software and extensive benchmarking against measurements to assess the correctness of the results. Later, I extended the simulation to also include the influence of the geometric and resistive-wall impedance for studies of the micro-wave instability at MAX IV [22]. With these simulations I could very well reproduce the deformations in the longitudinal bunch shape observed experimentally (see Figure 3). This again proved the potential of Inovesa to simulate the temporal development of the particle density distribution under the influence of collective effects caused by different types of impedances. Another simulation method capable of calculating the development of a particle bunch under the influence of collective effects is particle tracking, where the individual particle paths are calculated opposed to the particle density in Inovesa. Using the particle tracking tool mbtrack2 [27], I could recently show in simulations as well as in measurements that for certain settings in the accelerator's magnetic lattice, a single-particle dynamics effect can be used to reduce the impact of the collective effect underlying the transverse mode-coupling instability [23]. This instability is caused by transverse wake fields and can lead to drastic beam blow ups resulting in complete loss of particles. The capability to prevent resulting particle losses reveals possible ways of combating this instability in future low-emittance electron storage rings.

Both simulation methods, particle tracking as well as phase-space density propagation employing the Vlasov-Fokker-Planck equation, are possible options to be explored for the planned calculations of the collective effect influence during the beam transport through matter. Furthermore, another viable starting point is based on the past work at CERN, to calculate beam-matter interaction using covariance matrices [28], which are a common tool used to transport beam properties along the accelerator.

For the proposed project, another important aspect in the investigation of collective effects are systematic measurements with a sufficiently high temporal resolution to resolve the resulting dynamics, be it separating the consecutive revolutions of a bunch in a ring based accelerator or resolving the shot to shot differences between consecutive bunches in a linear accelerator. I was part of the team that developed a new ultra-fast readout system, to study the influence of the micro-bunching instability on the emitted CSR and the deformation of the longitudinal bunch shape [29]. The system enabled time-resolved measurements of the CSR intensity emitted by each bunch at every revolution in the synchrotron [30], as well as the synchronization with an electro-optical bunch-profile monitor. The resulting synchronized measurements, together with my simulations using Inovesa, provided further insight, with a high temporal resolution, into the formation of sub-structures in the longitudinal bunch shape causing the observed fluctuations in the emitted CSR [31]. Based on my work, a feedback system has been designed at KIT with the goal to mitigate and control the micro-bunching instability [32].

My experience with the development of the fast readout system [29] as well as the utilization of multiple fast beam diagnostic systems and detectors, such as fast beam current transformers for time resolved

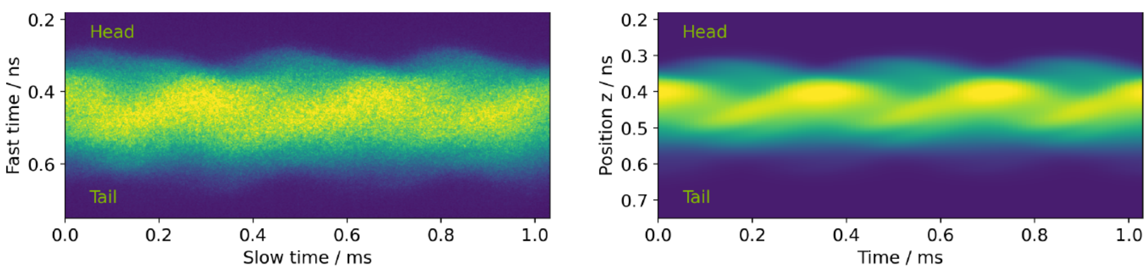

Figure 3: Measurement (left) and simulation (right) of the longitudinal bunch profile on the vertical axis and the temporal evolution on the horizontal axis.

charge measurements, beam position monitors, fluorescence screens, fast photo diodes, THz sensitive Schottky diode detectors [19] and more complex systems such as electro-optical bunch profile monitors [33], and synchrotron radiation monitors will be a great basis for the proposed experiments.

The extensive research conducted in the field of accelerator physics today aims for a deep understanding of the involved beam dynamics and collective effects especially in beams under extreme conditions, like short bunch lengths or high intensities and the diagnostics thereof. At the same time, with RT moving to beams with high temporal or spatial structuring for novel methods including FLASH RT or MRT, this research becomes more and more relevant, laying out the program for the proposed project.

5 Work Packages

To achieve the objectives, the work program is structured in the following work packages A-C:

<table>
<tr><td rowspan="6">WP A
Complex beam dynamics and collective effects</td><td rowspan="2">A1 Dynamics and collective effects in accelerator-based generation of temporally or spatially structured beams</td><td>A1.1 Cases study on collective effects in proposed dedicated RT accelerators</td></tr>
<tr><td>A1.2 Measurements and simulations of RT beams generated in FLUTE</td></tr>
<tr><td rowspan="3">A2 Beam-matter interaction for high intensity, temporally and spatially structured pulses</td><td>A2.1 Study existing models and simulations</td></tr>
<tr><td>A2.2 Simulation with existing models for FLUTE parameters (compare to WP B2.1)</td></tr>
<tr><td>A2.3 Extending model and simulation by incorporating collective effects</td></tr>
<tr><td colspan="2">A3 Implementation of start-to-end simulation including beam dynamics and beam-matter interaction</td></tr>
<tr><td rowspan="6">WP B
Systematic investigation on temporal and spatial pulse shape dependence of detection mechanisms and diagnostic tools</td><td rowspan="2">B1 For accelerator beam diagnostics</td><td>B1.1 Experimental tests (cf. to WP A1.2)</td></tr>
<tr><td>B1.2 Assess shot to shot resolution and provide recommendations for applicable methods depending on beam parameters</td></tr>
<tr><td rowspan="3">B2 For dose and dose-rate diagnostics (dosimetry)</td><td>B2.1 Exp. test dependence of different dosimetry methods on pulse-property</td></tr>
<tr><td>B2.2 Benchmark theoretical correction factors in dosimetry with respect to high dose rates</td></tr>
<tr><td>B2.3 Set-up 2D dose distribution measurement</td></tr>
<tr><td colspan="2">B3 Assess feasibility of 2D beam diagnostics outside of vacuum e.g., fluorescence screens</td></tr>
<tr><td rowspan="7">WP C
Beam modulation and beam shaping</td><td rowspan="2">C1 Exploration of methods for temporal and spatial shaping of pulses</td><td>C1.1 Simulation based on accelerator optics</td></tr>
<tr><td>C1.2 Experiment e.g., spatial light modulator</td></tr>
<tr><td rowspan="2">C2 Evolution of shaped pulses during transport</td><td>C2.1 Simulations based on results from WP A</td></tr>
<tr><td>C2.2 Experimental measurements at FLUTE</td></tr>
<tr><td colspan="2">C3 Investigation of methods and algorithms to calculate the required initial beam distribution from a desired beam shape on target (based on WP A3)</td></tr>
<tr><td rowspan="2">C4 Tests of generating custom dose distributions on target (simulation and experiment)</td><td>C4.1 Test of compensating the effect of beam transport</td></tr>
<tr><td>C4.2 Tests of generating custom (user-definable) final distributions</td></tr>
</table>

5.1 WP A - Complex beam dynamics and collective effects

As new, advanced radiotherapy modalities rely on high intensity, short and/or spatially structured particle beams, the influence of interactions between the beam-particles is significantly increased compared to conventional radiotherapy. Work package A will study the influence of these collective effects on the beam in the accelerator as well as during the beam transport through matter onto the irradiation target (Figure 4). The focus will be on the influence the collective effects have on the spatial and temporal particle distribution within the beam, and therefore how the distribution on the target is affected, which is an important parameter in radiotherapy.

Sub-work package A1 will focus on the beam dynamics during the beam generation in the accelerator. As first step (WP A1.1), a case study will be conducted. The influence of collective effects during the generation of beams for FLASH and Microbeam RT based on accelerator parameters of proposed accelerator designs for dedicated FLASH accelerators, e.g. [12], will be simulated. A combination of established accelerator simulation tools, such as ASTRA, AT or Ocelot will be employed as each includes different implementations of different sets of collective effects. WP A1.2 will use the linear accelerator FLUTE [1] at KIT as a testbed and compare measurements and simulations of different beam parameters resembling the desired radiotherapy beam properties. To this end, multiple different available operation modes in a wide parameter range will be evaluated to find a set of suitable conditions. Similar to WP A1.1, simulations of the beam dynamics will be conducted to understand and quantify the influence of of collective effects on the beam properties. Experimental measurements can be conducted with the existing, extensive accelerator diagnostic tools at FLUTE. The experimental measurements will overlap with the planned test in WP B1.1 on the applicability of accelerator diagnostics for these extreme beam properties.

The second sub-work package (WP A2) will focus on the influence of the extreme beam properties (high intensity, temporally and spatially structured) on the beam-matter interaction on the way from the accelerator to the target tissue inside the patient. In WP A2.1 existing models and simulation tools used in beam transport through matter calculations will be reviewed in detail to gain an overview of the effects typically considered, such as elastic and inelastic scattering, or bremsstrahlung. Based on preliminary research, it is expected that in most cases, purely the interaction of individual beam-particles with matter is considered and the influence of neighboring beam-particles is not included. In WP A2.2 corresponding simulations for a variety of possible beam properties generated at FLUTE will be conducted to evaluate the influence of the different interaction types. To this end, codes commonly employed in the radiotherapy and accelerator context will be used, such as BDSIM (based on Geant4) [34], EGSnrc [35], FLUKA [36] and the new KiT-RT framework [3]. WP A2.3 will investigate, in the context of beam-matter interaction, how the close presence of neighboring beam-particles and different possible interactions between the beam-particles themselves affect the passage through matter. To this end, collective effects known from accelerator physics, such as space charge, intra-beam scattering, transition or coherent synchrotron radiation effects and ion- or electron cloud effects (depending on the beam-particle type) are evaluated and their relevance depending on the chosen beam properties is estimated.

As next step (WP A3), the found effects will be incorporated into the calculations for the beam transport through matter and combined with simulations of the dynamics in the accelerator to create a start-to-end simulation. Multiple options on how the different simulations and calculations are to be combined will be evaluated. The goal is to find the best implementation method for beam propagation simulation through the accelerator and matter interactions not only for single particles but also taking into account collective effects. Possible methods, based on my experience in simulating collective effects in accelerators, include Monte Carlo simulations, particle tracking, phase-space density propagation by solving the Vlasov-Fokker-Planck equation, which originates from plasma physics, and the application of covariance matrices. for these methods, the influence of the surrounding beam-particles is often described as electro-magnetic fields, referred to as wake-fields and as impedances. As outcome of this work package a start-to-end simulation tool will be developed, which includes the consideration of collective effects in the accelerator as well as on the transport through matter to the target.

The successful completion of WP A will increase the predictability of the beam properties at the target and thereby deliver objective I.

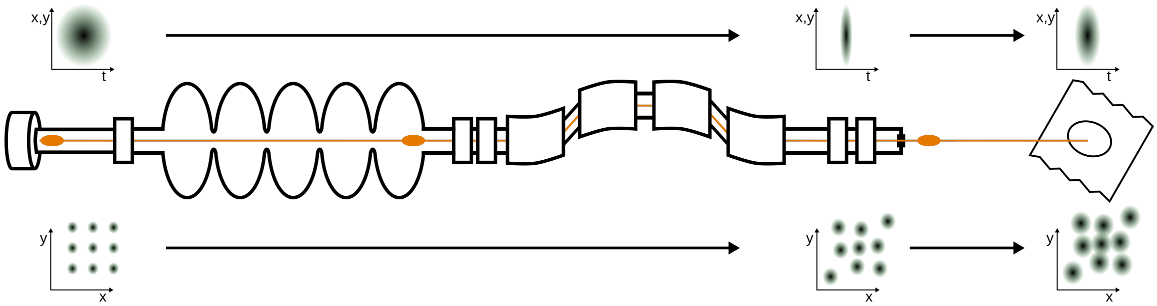

Figure 4: Sketch of evolution of short or spatially modulated particle distributions along the accelerator.

5.2 WP B - Systematic investigation on temporal and spatial pulse shape dependence of detection mechanisms and diagnostic tools

The extreme temporal and spatial beam properties not only affect the beam propagation but also increase the complexity of applicable detection mechanisms and diagnostic tools (for sketch with examples see Figure 5). WP B will systematically investigate how the performance and accuracy of different detection mechanisms and diagnostic tools depend on the temporal and spatial pulse shapes of the particle beams in FLASH and Microbeam RT.

WP B1 will focus on accelerator-based beam diagnostic. Different diagnostic tools, such as fast beam current transformers, beam position monitors, fluorescence screens and more complex systems such as electro-optical bunch profile monitors [33], synchrotron or transition radiation monitors among others, will be tested with regards to their suitability for and their ability to detect high intensity, temporally and spatially structured particle bunches with a high accuracy. Experimental measurements are planed in WP B1.1 and will be compared with simulations from WP A1.2. The measurements will give input for the assessment conducted in WP B1.2 to report on the potential of different diagnostic methods as support for RT beam diagnostics with the required adequate resolution and stability for medical applications. An additional focus will be in shot-to-shot capabilities of the diagnostic methods. Given the high dose per pulse in both advanced RT methods, the number of administered doses will be significantly smaller than in conventional RT. To still assure the application of the correct absolut dose, information on the individual pulses from shot-to-shot capable diagnostics would provide an significant advantage.

Work package B2 will focus on the effect the high dose rate, generated by the short pulses, has on dosimetry detectors. Experiments at other facilities have shown an increasingly non-linear detection efficiency for dose rates above 2 Gy per pulse [8], resulting in deviations between expected and detected dose. In WP B2.1, the ultra-short electron pulses generated in FLUTE and the ultra-short photon pulses generated at the KIT synchrotron light source with the electron storage ring KARA will be used for experimental tests of different dosimetry methods. The dependence on beam properties such as pulse length, intensity, transverse size, and energy will be evaluated. As starting point an advanced Markus chamber and the newly-developed flash-diamond detector, by PTW in Freiburg [11], will be tested towards their dependence on pulse length. Based on these measurements, also the recent developments of improved theoretical dosimetry correction factors for ion-recombination [10] can be validated using the ultra-short pulses at FLUTE (WP B2.2). Work package B2.3 will then investigate possibilities for measuring the 2-dimensional dose distribution. For testing the spatial resolution, the electron beam at FLUTE could be modulated in a first step by using for example collimators or potentially a mask at the accelerator exit.

As additional diagnostic of the 2-dimensional particle distribution after the accelerator, WP B3 will assess typical accelerator-based diagnostic tools such as fluorescence screens for profile monitors for the application outside the accelerator vacuum as preparation for WP C. In this context, also detector tests of new detector systems under development at KIT, for example radiation hard CMOS-pixel detectors [37], could be incorporated and tests at facilities with proton or ion beams (e.g., HIT in Heidelberg or the GSI in Darmstadt) could be conducted to extend the gained insights to other types of particles.

Completing WP B successfully will provide the experimental diagnostic setups required in WP C. At the same time, objective II will be achieved so that a recommendation can be given on diagnostic methods applicable for FLASH and Microbeam RT beams.

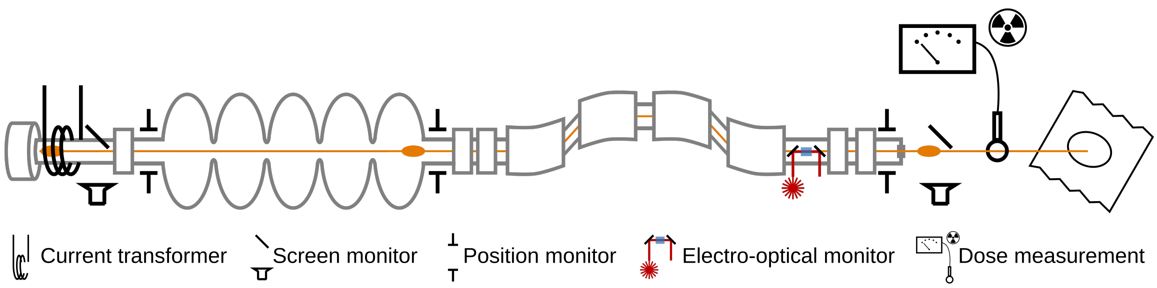

Figure 5: Sketch of multiple examples of diagnostic tools along the linear accelerator and outside.

5.3 WP C - Beam modulation and beam shaping

This work package aims to understand and push the physical and theoretical limitations of accelerator-based beam modulation and shaping for the application in radiotherapy, including solving the inverse problem to the beam propagation (Figure 6).

The first step (WP C1) will be to explore different methods for temporal and spatial manipulation of the beam shape and understand their limitations. This will be based, firstly, on simulations exploring a variety of options for different possible accelerator types operating as RT sources (WP C1.1). One general option could be, for example, to employ the accelerator focusing magnets to modify the bunch shape, by over- or under-focusing the beam at the accelerator exit. Secondly, in WP C1.2, different possibilities and limitations will be experimentally tested at FLUTE. This will include testing the option found in simulations in WP C1.1 as well as a method which sets-on even before the accelerator by directly generating a custom, initial charge-distribution. This is achieved by modulating the gun-laser spot on the electron-gun with a spatial light modulator set-up [2]. The spatial-light modulator allows the modulation of the spatial as well as the temporal shape of the laser pulse used to generate electrons on the photo-cathode of the electron gun. It operates by locally modulating the phase of the reflected laser pulse according to a pre-calculated hologram based on the targeted pulse shape and is currently being implemented at FLUTE [2].

The second step (WP C2) focuses on the investigation of the evolution of the initial modulated bunch shape during the transport through the accelerator and through matter on to the target. The investigation of the bunch shape evolution will consist of simulations (WP C2.1) based on the start-to-end simulation from work package A. The results will then be compared with experimental measurements in WP C2.2 employing the accelerator diagnostics and dosimetry detectors tested in WP B. The particle distribution will be measured at different positions along the accelerator as well as outside the accelerator after the passage through matter to make deformations and changes visible. These measurements will, furthermore, provide additional insight on which type of modulations can best be transported while maintaining the modulation.

Upon finishing WP C1+C2, the possibilities and physical limitations of pulse modulation and shaping will be understood and with this objective III is attained.

The next step, it then to investigate how and to what extend it is possible to generate a custom particle distribution and thereby a custom dose distribution on the target. To this end, WP C3, will examine possible methods and algorithms for calculating, based on a desired final distributions, the required, corresponding initial particle distribution in the accelerator (Figure 6). The goal can be also formulated as finding a solution to the inverse problem compared to the beam transport simulations conducted to predict the particle distribution on the target in earlier work packages. As this will build strongly on the results from work package A3, especially on the designed start-to-end simulation, the optimal methods will likely depend on the algorithm chosen in WP A3. Several possible methods come to mind, ranging from systematically mapping final distributions for a wide variety of initial distributions resulting in a type of catalog, over the analytical or numerical inversion of the transport matrix described in form of covariance matrices, up to employing machine learning algorithms trained on arbitrary bunch shapes propagated through the start-to-end simulation.

As final step (WP C4), when this connection between the final and the initial distribution is established, it will be combined with the beam modulation methods established in WP C1. Test will be contacted in simulations as well as experimentally at FLUTE. WP C4.1 will, as first step, employ the final method to compensate the effect the beam transport has on the pulse shape by considering any expected deformations already during the beam generation. And in WP C4.2, as final step, the capability of the method obtained in WP A3 will be tested to generate arbitrary, custom distributions on target and the limits in the achievable distributions will be explored.

With this, control over the particle and therefore dose distribution on the target will be achieved and the last objective (IV.) is fulfilled.

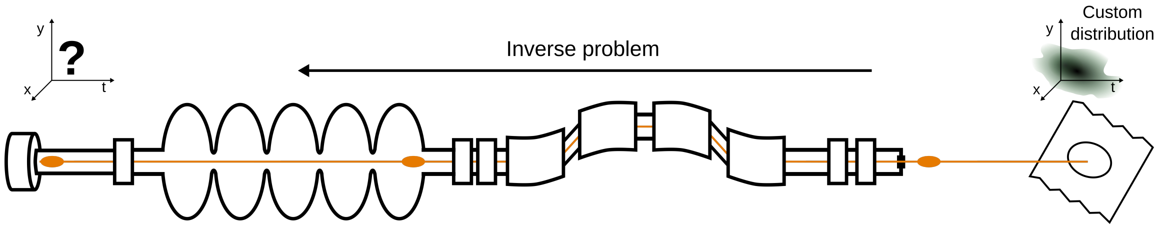

Figure 6: Sketch of the inverse problem to be solved to achieve custom particle distributions on target.

6 Work Plan

6.1 Time plan

The time line of the different work packages is displayed as a Gantt diagram in Figure 7. The individual work packages are color-coded according to the responsible team member. In the lower part of the figure, the planned time frame of each team member within the project is depicted. The exact time plan may be subject to change, depending on the research progresses. Any significant deviations from the original time plan will be communicated to the Helmholtz Association, in order to guarantee the best outcome for the project.

6.2 Group structure

The work program is designed for me as group leader and a total of 2 postdoctoral researchers and 2 doctoral students. There will be one postdoctoral researcher and one doctoral student in the first haft of the project and the same number in the second half, with a year overlap between the doctoral students in year 3 (see Figure 7 lower part).

To generally coordinate the work efforts and discuss outcomes and upcoming steps a weekly team meeting will be established. In addition, regular bi-weekly work package specific meetings will take place focusing on the respective challenges and problems to solve. For doctoral students, additionally, a weekly one-on-one meeting with me about their individual progress is intended which will give them the possibility to ask question in a more confidential and relaxed setting. In total, each team member should have no more than 3 regular meetings per week not including spontaneous discussions as well as more relaxed coffee break conversations.

The work of this project will be distributed, as described in the following, onto the planned group members with the time schedule shown in the graph in Figure 7:

Doctoral student (PhD 1) (starting between month 1 and 6, 3 years duration):
Research topic: Experimental study of the influence of advanced radiotherapy beam properties such as short bunch length, charge, energy and transverse size on accelerator beam dynamics, diagnostics and detected dose. The research will mainly focus on experimental measurements of the effects of extreme beam properties at the linear accelerator FLUTE accompanied by supporting simulations and will contribute to work packages A1.2, A2.2, B1 and B2.1.

Doctoral student (PhD 2) (starting month 25, 3 years duration):
Research topic: Investigation of theoretical methods and algorithms to solve the inverse problem of custom accelerator-based beam modulation for advance radiotherapy. The main focus will be the theoretic

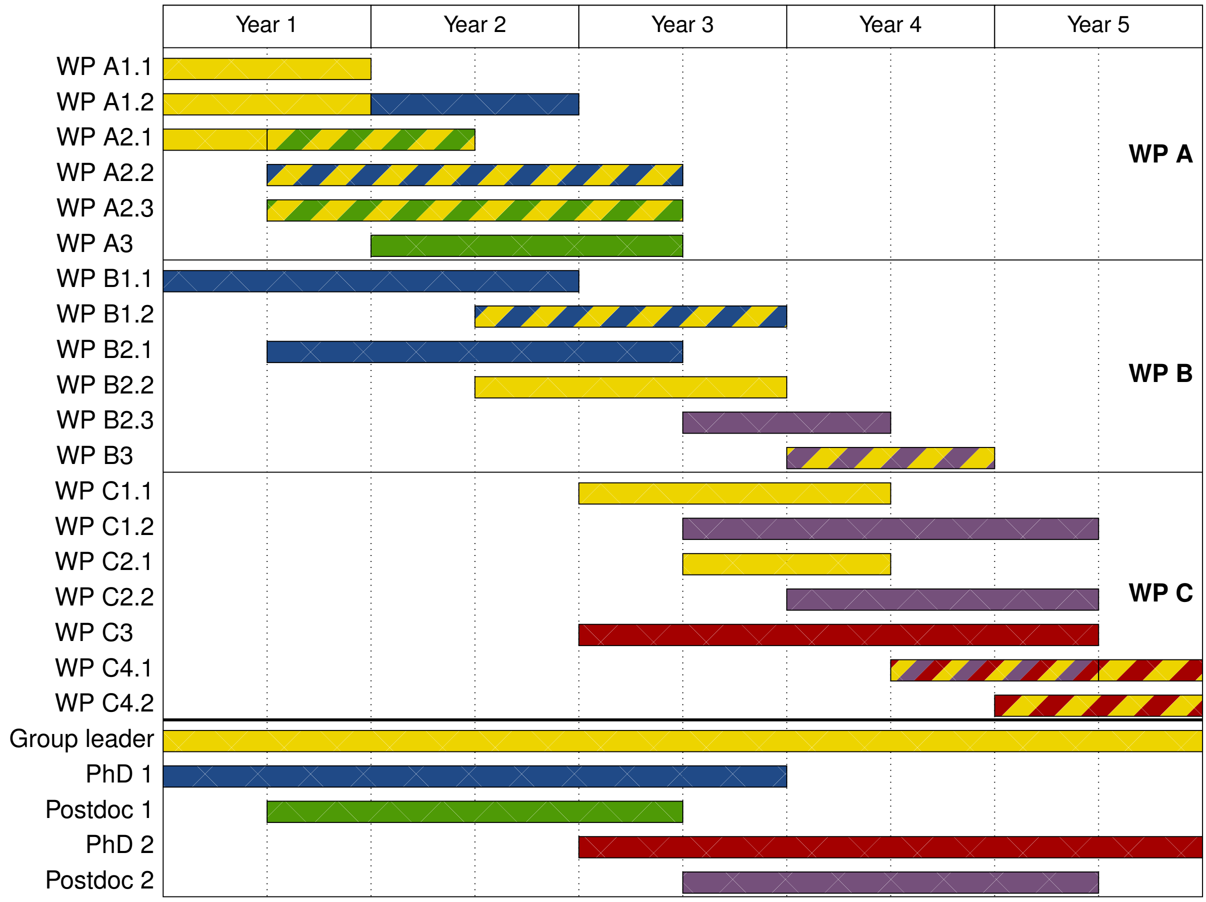

Figure 7: Time plan showing the individual work packages color-coded by responsible team member as well as the time frame of each team members within the project in the lower part.

work on a solution for WP C3 by finding an exploitable connection between the final particle distribution and the corresponding initial one. Therefore, the research will build on the start-to-end simulation from WP A3. It will likewise contribute to the simulation based tests while also closely collaborating on experimental tests in WP C4.1+4.2.

Postdoctoral researcher (Postdoc 1) (starting month 7, 2 years duration):
Research topic: Establishing start-to-end simulation for beam transport of accelerator-generated novel RT beams. This will entail exploring methods to propagate structured beams through the accelerator as well as through matter, including not only single particle to matter interactions but also considering collective effects during the beam transport through matter. The research will include the work on WP A2.1+2.3 and will be the main contributor for WP A3.

Postdoctoral researcher (Postdoc 2) (starting month 31, 2 years duration):
Research topic: Experimental exploration of temporal and spatial shaping of accelerator beams and 2D particle and dose diagnostics. This position will cover the experimental work on possibilities for accelerator-based beam modulation (WP C1.2). The work will furthermore devise 2D diagnostics for the particle and dose distribution (WP B2.3 + B3) enabling the experimental observation of the deformation of the beam modulations during transport (WP C2.2). The postdoctoral researcher will work with the doctoral student (PhD 2) on testing the algorithms for targeted beam shapes (WP C4.1).

Group leader (5 years):
Besides my planned involvement in lectures, I, as group leader, will coordinate and be involved in all work packages as discussion partner and supervisor. Furthermore, I will take on the following work packages partially or fully: A1.1, A2.1 (partially), A2.3 (partially), B1.2 (partially), B1.3 (partially), B2.2, C1.1, C1.2 (partially), C2.1, C4.1 (partially), C4.2 (partially).

In shared work packages, the work will be distributed by subtopic and a close communication will be maintained with the corresponding team member.

It is envisioned to give master students the possibility to contribute in different work packages. Possibilities would be, for example, in WP A3 (supervised by the first postdoctoral researcher) by testing different implementation possibilities for collective effects in beam-matter interactions, or setting up a new diagnostics system in the scope of WP B3 or also WP C2.2 supervised by the second postdoctoral researcher. It would offer a great opportunity for the postdoctoral researchers to gather experience in supervising students. Student assistants will support the project for example during experiments and measurement campaigns, with documentation, data organization or implementing specific data analysis scripts. This will, furthermore, be a good opportunity to get students involved and interested in the research field and can help attract students for Master thesis.

6.3 Research data management

This project will produce research data that covers a wide variety of data types, sizes and formats. Measurement data will originate from the multitude of accelerator beam diagnostic systems. The total amount of measurement data generated over the course of the 5 year project duration is estimated to be in the several TBytes range. This is mostly due to the multitude of diagnostics running during accelerator experiments combined with systematic parameter scans including imaging data from 2D profile measurements. Simulations will be conducted with multiple existing simulation tools like EGSnrc, FLUKA, ASTRA or Ocelot. Furthermore, results from theoretical calculations such as self implemented simulation tools are expected and will contribute to the resulting research data as well as the developed software tools themselves. Due to the use of particle tracking simulations and the possibility to run simulations on an HPC cluster, the estimated amount of simulation data is around several TBytes.

The file formats will depend on the diagnostic systems or simulation tools and can range from TXT, PNG, JSON or CSV to proprietary file formats or custom binary files. If the original format is not easily accessible and/or additional metadata should be saved with the original data, it will be converted to files of the hdf5 file-format (Hierarchical Data Format version 5). In the past, I have used this format extensively and it has proven to be very useful to store complex data. It is accessible with a wide variety of programming languages and provides the possibility for internal structuring of the stored data in groups with attributes. In this way, all the information from different sources required to evaluate measurement results can be bundled together, including metadata such as operational parameters of the accelerator. Furthermore, to keep the context of simulations and improve the re-usability, all the simulation input parameters and settings can be stored as metadata in the attributes of the hdf5-files. When software is built from scratch, the hdf5 file-format will be used directly. A consistent filename convention will be implemented including the date (human readable, ISO8601), a short name for the detector or simulation tool, and further information. Additional information relevant for later analysis or re-use of the data will be, as mentioned earlier, saved as metadata, either live during the measurement, for example, by reading accelerator parameters provided online from the accelerator control-system (EPICS) (including Unix timestamps) or, alternatively, added later in post-processing. All relevant accelerator settings, parameters or properties are by design saved continuously in a Casandra database. A corresponding post-processing workflow can be based on an existing Python framework developed by me which was successfully used to process more than 50 TByte of measurement data during my PhD studies.

To document experiments, the digital logbook ELOG will be used, which is used in multiple accelerator facilities as a documentation standard. Data files can be attached to the corresponding entries either directly or as link to files on a file server of the institute. For more extensive documentation, an instance of a wiki is available at the institute. Sub-spaces for individual teams can be created with corresponding access rights. There, information or discussions regarding multiple measurements or simulations can be stored. Within the framework of scientific research, regular comparisons between simulated and measured data will be performed to ensure consistency and increase data quality. Furthermore regular reference measurements at well known conditions are performed to characterize the detection chains. Regular meetings and discussions on the acquired data will be held to minimize human bias (four eyes principle). For the development of software a GitLab instance will be used. This provides a version controlled and simple possibility to save, transfer and jointly work on source codes. With the usage of GIT (distributed version control system), there is also the possibility to implement basic quality control mechanisms, e.g. git hook frameworks like pre-commit, which check the integrity of the source code before committing. For all python scripts the PEP8 coding-style convention will be respected.

For immediate storage during the runtime of the project, the data will be saved on the institute servers with backups which allow to manage the access rights via user-groups. In addition, to ensure minimal data loss, every personal PC of group members will be equipped with an external backup hard drive and each member will be instructed to perform regular backups.

For long-term storage and archival of data the multi-petabyte storage systems of the host institution (e.g. LSDF) including the archival on tape will be used. A minimum storage period of 10 years is default for these services.In addition, RADAR4KIT, a research data repository, can be used to bundle data and metadata, store and archive this data with the possibility to provide public access later on. For publications, high-level derivative data can be added as supplementary material on the journal web-page. For simulation data, from publicly available simulation code, the minimal set of parameters to recreate the data will be added. The corresponding full data sets can be published in KITopen via RADAR4KIT, receive a DOI and are open access. Software developed in the framework of this project is planned to be open-source and published on services such as GitHub.

Group members will be provided with the possibility to learn the usage of technologies regarding data management used for the project. Due to the continuous availability throughout the project and previous experiences with large data and software management, I will take on the task of coordinating the handling of research data for the project supported by the IT team of the host institute. Research data management within the project and used services will conform to the guidelines published by KIT ("Guidelines for Responsible and Sustainable Research Data Management at KIT (RDM Policy)") as well as the DFG code of conduct, and the EU open science policy.

6.4 Financial plan

The following section is a more detailed description of the financial plan given in the table in Annex 2.

6.4.1 Personnel costs

The personnel costs follow the DFG personnel rates from 2024. An annual rise of 3% is included starting already from the first year, to adjust for the potential starting date being in 2025.

To lead the proposed project, the funding for the position as junior research group leader is requested for the whole project duration of 5 years. The position will be filled by me, Dr. Miriam Brosi. For the proposed work program the funding for two doctoral students, two postdoctoral researchers, and several student workers is included.

The first doctoral student will be employed for three years on a 75% position and is planned to start shortly after the project start, latest after half a year (1-6 month after project start). The PhD thesis will be on the topic of: Experimental study of the influence of advanced radiotherapy beam properties such as short bunch length, charge, energy and transverse size on accelerator beam dynamics, diagnostics and detected dose. The candidate should have some experience in experimental work, including setting up and handling sensitive diagnostic hardware. This topic offers a round work package suited to result in a PhD thesis. It offers opportunities for the student to shape and combine different tasks according to their own vision to deliver the independent research results required for a dissertation, while still receiving the required guidance.

The second doctoral student will be employed for three years on a 75% position. This position should start in the beginning of project year three (24 month after project start). The work will focus on: Investigation of theoretical methods and algorithms to solve the inverse problem of custom accelerator-based beam modulation for advance radiotherapy. A candidate is envisioned with a background or strong motivation in mathematical methods and computational physics. For this project the doctoral student would have the possibility and time to evaluate different possible methods towards their feasibility for the project objective IV. while collecting experience and in-depth knowledge in all of them. This will result for the project in a good overview of the available methods while also providing the student with a broad knowledge for their following career steps.

The first postdoctoral researcher will be employed for two years on a 100% position and is planned to start after the first half of the first project year (6 month after project start). The planned work will include the incorporation of collective effects into beam-matter interaction and the implementation of a start-to-end simulation combining beam transport simulations in the accelerator with simulations of the transport through matter. A candidate with a strong background in many-particle systems, radiation transport through matter, or theoretical accelerator physics with experience in simulation programming is envisioned. The higher level of prior experience and knowledge required for this task, is more suited for a postdoctoral researcher position (compared to a doctoral student), which would furthermore allow the researcher to work as a more independent team member.

The second postdoctoral researcher will be employed with 100% for two years and is planned to start in the second half of the third project year (30 month after project start). Due to the experimental nature of the assigned work packages, an experimental physicist with an extensive background in fast, time-resolved diagnostics and detectors as well as short pulse physics would be suitable. Alternatively, an electrical engineer working in detector development for 2-dimensional pulse detection with some basic experience in accelerator physics would be a good fit. In order to ensure a continuous progress in this stage of the project, the tasks should be carried out by a postdoctoral researcher who, due to previous experience can more efficiently solve upcoming challenges. Additionally, the project will benefit from the contribution of prior knowledge in fields such as detector engineering At the same time, would the increased independence of the postdoctoral researcher allow them to define their own research profile and gain experience in supervision.

Additionally, some funds are requested to employ student assistants for a total of 3 years distributed over the project duration as required and interested students availability. The working time will be adjusted in such a way that the monthly salary corresponds to a “Minijob” (in 2024: €538/month maximum net salary) according to the customary rates for student assistants at KIT (in 2024: without completed master degree, €13.25/h netto). This results in a maximum of 40 working hours per month. The tasks will include support for setup, execution and documentation of experiments.

6.4.2 Material costs

Besides the accelerators, diagnostic tools and equipment already available at the host institute, the funding for the following items are requested. Two different dosimeter types will be bought for systematic and comparative measurements under different beam conditions and pulse lengths. The Advanced Markus Chamber is a plane-parallel ionization chamber with a small sensitive volume, suited for high dose per pulse conditions. The second selected detector is the flashDiamond, a synthetic single crystal diamond detector, recently developed for ultra-high dose rates. The detectors are from PTW Freiburg GmbH and were specifically selected to be compatible with the electrometer and slab phantom from the same company available at the institute. For measuring the 2-dimensional dose distribution, radiographic films will be used, for example GAFCHROMIC EBT3 or Kodak EDR2. Since the films are consumables, multiple boxes (à €1000) will be required. A total cost of €10000 is estimated over the project duration. A humidity logger in the experimental hall will be used during beam propagation measurements in air. An estimate of €1000 is requested to this end. For complementary electronics accessories, such as signal cables, adapters and connectors for detector readout and power supplies a fixed amount of €7000 is estimated. An additional €5000 is requested for supplementary readout electronics such as amplifiers or attenuators for detector signals as well as trigger signals from the accelerator systems. Mounting materials to e.g., build mounts for detector systems or other constructions required for experiments are estimated with a total of €5000 during the project duration. Optical components are planned with €10000 to cover lenses, mirrors, mounts, and further laser laboratory supplies for the experiments with the spatial light modulator. A dedicated PC is forseen as control and read-out station for the experiments. This will allow a fast handling and post-processing of results including the augmentation with additional meta-information. Portable hard drives will be used to quickly transfer working copies of the results for further analysis.

6.4.3 Travel costs

The participation in relevant conferences and workshops will enable the communication and discussion of results as well as help with establishing new connections and give access to the latest developments. For the travel to international conferences an average cost of €2500 is allocated, which also contains conference fees (e.g., typically around €700 for the international particle accelerator conference (IPAC)) and assumes a total trip duration of 6-7 days. For national travels an amount of €1500 is estimated to cover travels of up to 6 days. For me, in the role of group leader, an average of one international and one national trip per year is envisioned. For each doctoral researcher one international trip and two national trips are allocated within their contract duration, this could include a summer-school within Europe, e.g., Cern Accelerator School. For each postdoctoral researcher two international trips are planned. For all potential master students together, a total of three national trips to the DPG spring meetings are planned, to give them the possibility to present their research for the first time to a wider community out-side the university setting.

7 Cooperations and Communication

The closest cooperation will be with the Institute for Beam Physics and Technology (IBPT) led by Prof. Dr. Anke-Susanne Müller. This will provide access to the accelerator test-facilities FLUTE, KARA, as well as the planned storage ring cSTART and a laser-plasma accelerator under construction in the group of Prof. Dr. Matthias Fuchs.

The Accelerator Technology Platform (ATP) at KIT will provide an extensive infrastructure for accelerator research as well as a close connection to the detector development at the Institute for Data Processing and Electronics (IPE) at KIT. The envisioned cooperation with the IPE, includes the provision of unique beam conditions for tests of fast, 2-dimensional particle detectors under development while evaluating their applicability for diagnostics in beams with advanced RT modalities.

The Heidelberg Karlsruhe Strategic Partnership with the research bridge “Medical Technology for Health (MTH)” results in a close connection with the Heidelberg Ion-Beam Therapy Center (HIT) at the University Hospital Heidelberg and the German Cancer Research Center (DKFZ). This will provide the possibility for experimental studies with protons or ions at the experimental area of the accelerator complex at HIT. A collaboration is planned with Prof. Dr. Oliver Jäkel (HIT and Division Head of “Medical Physics in Radiation Oncology” DKFZ) and Prof. Dr. Dr. Jürgen Debus (i.a. Scientific-medical Director HIT and Medical Director “Klinik für Radioonkologie und Strahlentherapie”).

First discussions on a possible collaboration with Prof. Dr.-Ing. Christian Graeff (Deputy Research Director of the Department of Biophysics) and Dr. Lennart Volz from the GSI Helmholtz center for Heavy Ion Research have been started.

Discussions with Prof. De Carne at Institute for Technical Physics (ITEP) at KIT are ongoing on the topic of energy efficient and sustainable accelerators for medical applications, and spin-off projects from this Helmholtz Investigator Group are planned in the future.

The participation in relevant conferences such as the International Particle Accelerator conference (IPAC) or the Flash Radiotherapy and Particle Therapy conference (FRPT) and smaller workshops will enable the communication and discussion of results as well as help to establish new connections and provide access to the latest developments. Research results will furthermore be published in, preferably, open access journals and presented at Helmholtz meetings.

References

[1] M. J. Nasse, M. Schuh, S. Naknaimueang, M. Schwarz, A. Plech, Y.-L. Mathis, R. Rossmanith, et al. “FLUTE: A Versatile Linac-Based THz Source”. In: *Review of Scientific Instruments* 84.2 (Feb. 2013), p. 022705. DOI: 10.1063/1.4790431.

[2] M. Nabinger, A.-S. Müller, M. Nasse, C. Sax, J. Schäfer, C. Widmann, and C. Xu. “Transverse and Longitudinal Modulation of Photoinjection Pulses at FLUTE”. In: *Proceedings of the 13th International Particle Accelerator Conference* IPAC2022 (2022), 4 pages, 2.948 MB. DOI: 10.18429/JACOW-IPAC2022-TUPOPT068.

[3] J. Kusch, S. Schotthöfer, P. Stammer, J. Wolters, and T. Xiao. “KiT-RT: An Extendable Framework for Radiative Transfer and Therapy”. In: *ACM Transactions on Mathematical Software* 49.4 (Dec. 2023), pp. 1–24. DOI: 10.1145/3630001.

[4] J. Thariat, J.-M. Hannoun-Levi, A. Sun Myint, T. Vuong, and J.-P. Gérard. “Past, Present, and Future of Radiotherapy for the Benefit of Patients”. In: *Nature Reviews Clinical Oncology* 10.1 (Jan. 2013), pp. 52–60. DOI: 10.1038/nrclinonc.2012.203.

[5] J. M. Borras, Y. Lievens, and C. Grau. “The Need for Radiotherapy in Europe in 2020: Not Only Data but Also a Cancer Plan”. In: *Acta Oncologica* 54.9 (July 2015), pp. 1268–1274. DOI: 10.3109/0284186X.2015.1062139.

[6] M.-C. Vozenin, J. Bourhis, and M. Durante. “Towards Clinical Translation of FLASH Radiotherapy”. In: *Nature Reviews Clinical Oncology* 19.12 (Dec. 2022), pp. 791–803. DOI: 10.1038/s41571-022-00697-z.

[7] J. Atkinson, E. Bezak, H. Le, and I. Kempson. “The Current Status of FLASH Particle Therapy: A Systematic Review”. In: *Physical and Engineering Sciences in Medicine* 46.2 (May 2023), pp. 529–560. DOI: 10.1007/s13246-023-01266-z.

[8] F. Romano, C. Bailat, P. G. Jorge, M. L. F. Lerch, and A. Darafsheh. “Ultra-high Dose Rate Dosimetry: Challenges and Opportunities for FLASH Radiation Therapy”. In: *Medical Physics* 49.7 (July 2022), pp. 4912–4932. DOI: 10.1002/mp.15649.

[9] A. Schüller, S. Heinrich, C. Fouillade, A. Subiel, L. De Marzi, F. Romano, P. Peier, et al. “The European Joint Research Project UHDpulse – Metrology for Advanced Radiotherapy Using Particle Beams with Ultra-High Pulse Dose Rates”. In: *Physica Medica* 80 (Dec. 2020), pp. 134–150. DOI: 10.1016/j.ejmp.2020.09.020.

[10] K. Petersson, M. Jaccard, J.-F. Germond, T. Buchillier, F. Bochud, J. Bourhis, M.-C. Vozenin, and C. Bailat. “High Dose-per-pulse Electron Beam Dosimetry — A Model to Correct for the Ion Recombination in the Advanced Markus Ionization Chamber”. In: *Medical Physics* 44.3 (Feb. 2017), pp. 1157–1167. DOI: 10.1002/mp.12111.

[11] R Kranzer, A Schüller, A Bourgouin, T Hackel, D Poppinga, M Lapp, H. K. Looe, and B Poppe. “Response of Diamond Detectors in Ultra-High Dose-per-Pulse Electron Beams for Dosimetry at FLASH Radiotherapy”. In: *Physics in Medicine & Biology* 67.7 (Apr. 2022), p. 075002. DOI: 10.1088/1361-6560/ac594e.

[12] L. Faillace, D. Alesini, G. Bisogni, F. Bosco, M. Carillo, P. Cirrone, G. Cuttone, et al. “Perspectives in Linear Accelerator for FLASH VHEE: Study of a Compact C-band System”. In: *Physica Medica* 104 (Dec. 2022), pp. 149–159. DOI: 10.1016/j.ejmp.2022.10.018.

[13] H. Fukunaga, K. Butterworth, S. McMahon, and K. Prise. “A Brief Overview of the Preclinical and Clinical Radiobiology of Microbeam Radiotherapy”. In: *Clinical Oncology* 33.11 (Nov. 2021), pp. 705–712. DOI: 10.1016/j.clon.2021.08.011.

[14] A. Meigooni, S. Parker, J Zheng, K. Kalbaugh, W. Regine, and M Mohiuddin. “Dosimetric Characteristics with Spatial Fractionation Using Electron Grid Therapy”. In: *Medical Dosimetry* 27.1 (Mar. 2002), pp. 37–42. DOI: 10.1016/S0958-3947(02)00086-9.

[15] S. Girst, C. Marx, E. Bräuer-Krisch, A. Bravin, S. Bartzsch, U. Oelfke, C. Greubel, et al. “Improved Normal Tissue Protection by Proton and X-ray Microchannels Compared to Homogeneous Field Irradiation”. In: *Physica Medica* 31.6 (Sept. 2015), pp. 615–620. DOI: 10.1016/j.ejmp.2015.04.004.

[16] European Synchrotron Radiation Facility. *ESRF: Microbeam Radiation Therapy (MRT)*. URL: https://www.esrf.fr/home/UsersAndScience/Experiments/CBS/ID17/mrt-1.html.

[17] M. Apollonio, Å. Andersson, M. Brosi, R. Lindvall, D. Olsson, M. Sjöström, R. Svärd, and P. Tavares. “Improved Emittance and Brightness for the MAX IV 3 GeV Storage Ring”. In: *Proceedings of the 13th International Particle Accelerator Conference* IPAC2022 (2022), 4 pages, 2.876 MB. DOI: 10.18429/JACOW-IPAC2022-MOPOPT023.

[18] P. Tavares, E. Al-Dmour, Å. Andersson, J. Breunlin, F. Cullinan, E. Mansten, S. Molloy, et al. “Status of the MAX IV Accelerators”. In: *Proceedings of the 10th Int. Particle Accelerator Conf.* IPAC2019 (2019), 6 pages, 1.033 MB. DOI: 10.18429/JACOW-IPAC2019-TUYPLM3.

[19] M. Brosi. “In-Depth Analysis of the Micro-Bunching Characteristics in Single and Multi-Bunch Operation at KARA”. PhD thesis. Karlsruher Institut für Technologie (KIT), 2020. DOI: 10.5445/IR/1000120018.

[20] P. Amstutz and M. Vogt. “Microbunching Studies for the FLASH2020+ Upgrade Using a Semi-Lagrangian Vlasov Solver”. In: *Proceedings of the 13th International Particle Accelerator Conference* IPAC2022 (2022), 4 pages, 3.351 MB. DOI: 10.18429/JACOW-IPAC2022-WEPOMS037.

[21] M. Brosi, M. Caselle, E. Hertle, N. Hiller, A. Kopmann, A.-S. Müller, M. Schwarz, et al. “Online Studies of THz-radiation in the Bursting Regime at ANKA”. In: *Proceedings of the 6th Int. Particle Accelerator Conf.* IPAC2015 (2015), 3 pages, 1.047 MB. DOI: 10.18429/JACOW-IPAC2015-MOPHA042.

[22] M. Brosi, A. Andersson, J. Breunlin, F. Cullinan, and P. Tavares. “Time-Resolved Measurement and Simulation of a Longitudinal Single-Bunch Instability at the MAX IV 3 GeV Ring”. In: *Proc. IPAC'23*. 14th International Particle Accelerator Conference 14. JACoW Publishing, Geneva, Switzerland, May 2023, pp. 2642–2645. DOI: 10.18429/jacow-ipac2023-wepa020.

[23] M. Brosi, F. Cullinan, Å. Andersson, J. Breunlin, and P. F. Tavares. “Asymmetric Influence of the Amplitude-Dependent Tune Shift on the Transverse Mode-Coupling Instability”. In: (2024).

[24] M. Brosi. “Overview of the Micro-Bunching Instability in Electron Storage Rings and Evolving Diagnostics”. In: *Proc. IPAC'21*. International Particle Accelerator Conference 12. JACoW Publishing, Geneva, Switzerland, Aug. 2021, pp. 3686–3691. DOI: 10.18429/JACoW-IPAC2021-THXA02.

[25] M. Brosi, J. L. Steinmann, E. Blomley, T. Boltz, E. Bründermann, J. Gethmann, B. Kehrer, et al. “Systematic Studies of the Microbunching Instability at Very Low Bunch Charges”. In: *Phys. Rev. Accel. Beams* 22.2 (Feb. 2019), p. 020701. DOI: 10.1103/PhysRevAccelBeams.22.020701.

[26] P. Schönfeldt, M. Brosi, M. Schwarz, J. L. Steinmann, and A.-S. Müller. “Parallelized Vlasov-Fokker-Planck Solver for Desktop Personal Computers”. In: *Physical Review Accelerators and Beams* 20.3 (Mar. 2017), p. 030704. DOI: 10.1103/PhysRevAccelBeams.20.030704.

[27] A. Gamelin, W. Foosang, and R. Nagaoka. “Mbtrack2, a Collective Effect Library in Python”. In: *Proc. IPAC'21*. International Particle Accelerator Conference 12. JACoW Publishing, Geneva, Switzerland, Aug. 2021, pp. 282–285. DOI: 10.18429/JACoW-IPAC2021-MOPAB070.

[28] A.-S. Müller. *Description of Beam-Matter Interaction in the Covariance Matrix Formalism: Application to Modification of Emittance and Twiss Parameters -*. Tech. rep. Geneva: CERN, 2001.

[29] M. Caselle, L. E. A. Perez, M. Balzer, A. Kopmann, L. Rota, M. Weber, M. Brosi, et al. “KAPTURE-2. A Picosecond Sampling System for Individual THz Pulses with High Repetition Rate”. In: *Journal of Instrumentation* 12.01 (Jan. 2017), p. C01040. DOI: 10.1088/1748-0221/12/01/c01040.

[30] M. Brosi, J. L. Steinmann, E. Blomley, E. Bründermann, M. Caselle, N. Hiller, B. Kehrer, et al. “Fast Mapping of Terahertz Bursting Thresholds and Characteristics at Synchrotron Light Sources”. In: *Phys. Rev. Accel. Beams* 19.11 (Nov. 2016), p. 110701. DOI: 10.1103/PhysRevAccelBeams.19.110701.

[31] M. Brosi, T. Boltz, E. Bründermann, S. Funkner, B. Kehrer, A.-S. Müller, M. J. Nasse, et al. “Synchronous Measurements of Electron Bunches Under the Influence of the Microbunching Instability”. In: *Proc. IPAC'19*. International Particle Accelerator Conference 10. Geneva, Switzerland: JACoW Publishing, June 2019, pp. 3119–3122. DOI: 10.18429/JACoW-IPAC2019-WEPTS015.

[32] W. Wang, M. Caselle, T. Boltz, E. Blomley, M. Brosi, T. Dritschler, A. Ebersoldt, et al. “Accelerated Deep Reinforcement Learning for Fast Feedback of Beam Dynamics at KARA”. In: *IEEE Transactions on Nuclear Science* 68.8 (2021), pp. 1794–1800. DOI: 10.1109/TNS.2021.3084515.

[33] M. Reißig, M. Brosi, E. Bründermann, S. Funkner, B. Härer, A.-S. Müller, G. Niehues, et al. “Development of an Electro-Optical Longitudinal Bunch Profile Monitor at KARA Towards a Beam Diagnostics Tool for FCC-ee”. In: *Proc. IPAC'22*. International Particle Accelerator Conference 13. JACoW Publishing, Geneva, Switzerland, July 2022, pp. 296–299. DOI: 10.18429/JACoW-IPAC2022-MOPOPT025.

[34] L. Nevay, S. Boogert, J. Snuverink, A. Abramov, L. Deacon, H. Garcia-Morales, H. Lefebvre, et al. “BDSIM: An Accelerator Tracking Code with Particle–Matter Interactions”. In: *Computer Physics Communications* 252 (July 2020), p. 107200. DOI: 10.1016/j.cpc.2020.107200.

[35] I. Kawrakow and D. W. O. Rogers. “The EGSnrc System, a Status Report”. In: *Advanced Monte Carlo for Radiation Physics, Particle Transport Simulation and Applications*. Berlin, Heidelberg: Springer Berlin Heidelberg, 2001, pp. 135–140. DOI: 10.1007/978-3-642-18211-2_23.

[36] G. Battistoni, J. Bauer, T. T. Boehlen, F. Cerutti, M. P. W. Chin, R. Dos Santos Augusto, A. Ferrari, et al. “The FLUKA Code: An Accurate Simulation Tool for Particle Therapy”. In: *Frontiers in Oncology* 6 (May 2016). DOI: 10.3389/fonc.2016.00116.

[37] A. Dierlamm, M. Balzer, F. Ehrler, U. Husemann, R. Koppenhöfer, I. Perić, M. Pittermann, et al. “A Beam Monitor for Ion Beam Therapy Based on HV-CMOS Pixel Detectors”. In: *Instruments* 7.1 (Feb. 2023), p. 9. DOI: 10.3390/instruments7010009.