Opportunities and challenges in particle radiotherapy

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Physical and biological rationale of ion beam therapy

**Physical selectivity**
- Depth-dose profile (Bragg-Peak)
- ↓ lateral scattering ($Z>1$)

**Biological Effectiveness**
- Elevated local ionization density
- ↑ Relative Biological Effectiveness (RBE)
- ↓ Influence of tumour oxygenation (OER)

**Optimal differential effect at $Z = 6$**

**Parodi Habil Thesis 2008**


**Kraft Prog Part Nucl Phys 2000**
The technology evolution of ion therapy

From fixed beamlines and passive beam delivery...

... to rotating gantries and active beam delivery...

... to intensity modulated particle therapy (IMPT)

Clinical rationale of ion beam therapy

Is what we see what the patient receives?

Sources: http://www.schaer-engineering.ch/en/rptc.html14, GSI Darmstadt, A. Lomax, PSI

Nuclear Physics for Medicine Report, NUPECC, 2014
Treatment (re)planning uncertainties

**Patient model**
- Metal artifacts
- Image quality (CBCT)
- HU-SPR conversion
- Tissue-dependent biological parameters

**Dose calculation**
- Beam model
- Tissue heterogeneities
- Biological models

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**RBE models in treatment planning**

**Protons**
- Constant RBE = 1.1 clinically used
- Known RBE variations with LET
- Uncertainties of different models (typically based on LET$_D$ and $\alpha/\beta_x$)
- Unclear correlation to outcome

**Carbon ions**
- Variable RBE scheme (accounting for mixed field)
- Different models used in the clinics (LEM, MKM) based on different underlying assumptions
- Uncertainties of model predictions
- Unclear correlation to outcome

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Schuermann et al, MedPhys 2017, Special issue PT  
Willers et al, Radiother Oncol 2018

Giovannini, Mairani, Parodi, Rad Onc 2016  
Peeler et al, Radiother Onc 2016

Stewart...Scholz, MedPhys 2017, Special Issue PT
Interfractional anatomical changes

Bronchial carcinoma, $^1$H, MGH Boston

Parodi PhD Thesis 2004

Chordoma, $^{12}$C, GSI Darmstadt

Bortfeldt AAPM 2019

Intrafractional anatomical changes

Bert & Rietzel, Med. Phys. 2010
Mori et al, MedPhys 2017, Special issue PT
Mitigating range uncertainties in clinical practice

Usage of safety margins (non-isotropic) ≈ 2.5-3.5% + 1-3 mm

and conservative choice of beam angles

Paganetti, PMB 2012

Polf and Parodi, Phys Today 2015

Mitigating uncertainties in clinical practice

Different flavors of robust optimization including uncertainties in patient setup, range, biology

and different motion mitigation strategies (esp. gating and recanning) for moving organs (not covered in this talk)

Resch...Parodi, Dedes, Phys Med 2017
Imaging for patient model in ion beam therapy

More demanding than solutions in clinical use for photon therapy
Enhanced in-room (ideally at isocenter) imaging with SPR information
- On-board scatter-corrected CBCT
- On-rails (DE)CT
- Ion radiography/tomography
- Magnetic Resonance Imaging

On-board CBCT imaging for dose adaptation

Dose calculation requires CBCT intensity correction
1. Image level: Deformable Image Registration (DIR)
2. Projection level: scatter correction

81-95% profiles agree in range within 2 mm of rpCT calculation
Scatter-corrected CBCT

- Fast (< 10 s) scatter correction possible with deep learning
- Promising results for both correction methods at projection level (~ 10 ms / projection) and image level
- Space for improvement for more reliable dose calculation in ion beam therapy (e.g., connected to beam records)
- Similar results for synthetic CT generation from MRI
- However, SPR information not yet incorporated (enhancement with DE, pRAD, direct SPR conversion?)

Improved in-vivo SPR estimation: DECT

Dual Energy CT (DECT)
SPR from improved $\rho_{el}$ and $Z_{eff}$

$$SPR \propto \rho_{el} \ln \left( \frac{2m_e c^2 \beta^2}{(1 - \beta^2)} \right) - \beta^2$$

Planning study for surrogate trauma patients
Range differences SECT vs DECT of 1.5%, consistent with RMSE (2-3.5% vs 1%)
Improved in-vivo SPR estimation: DECT

Similar range differences reported for large scale patient cohort at Oncoray Dresden

Wolfahrt et al, IJROBP 2017

Almeida…Parodi.. Verhaegen, PMB 2018

V. Taasti PhD Thesis, Aarhus

Improved in-vivo SPR estimation: DECT

Integration & comparison of DECT to SPR & tissue segmentation in research version of RayStation

F. Dörringer, Master Thesis 2018

Ongoing work on accurate range characterization of biological tissue samples scanned in DECT

K. Niepel, ...G. Landry, K. Parodi, presented at PTCOG 2019
Ion radiography / tomography for:

- Direct (integral) SPR determination for patient-specific refinement of planning information (Schneider et al, Med Phys 2005, Schulte et al TANS 2012)
- Daily, low-dose image guidance for patient positioning (Cassette et al JACMP 2019)

Several detector concepts under investigation worldwide and discussion about optimal ion

Comparison of simulated (realistic) proton CT vs experimental DECT and SECT
Reduced errors (RMSE) for pCT (~0.2-0.5%) vs DECT (~0.5-0.9%) and SECT (1.6-2.7%)

Proton CT or dual-energy X-ray CT: which wins out for proton planning?

Proton imaging promises better than 1% SPR accuracy at dose ≤ 1-2 mGy

Dedes, ..., Schulte, Landry, Parodi, PMB 2019
Proton or heavier ion CT?

MC simulation of an ideal detector for proton, helium and carbon ion CT

Comparably better range accuracy than X-ray CT regardless of ion species

Reduced RBE for ion CT compared to imaging X-rays (according to RMF model*)


Fluence-modulated proton CT (FMpCT)

FMpCT achieves arbitrary image noise targets

Local reduction of imaging dose

Frequent dose verification within region of good image quality

Iterative optimization based on variance reconstruction and a Monte Carlo patient model

Dickmann,..., Parodi, Dedes, Landry, presented at AAPM 2019; Landry and Dedes DFG-funded Project
Make the invisible visible

Different emission mechanisms

Thermaoustic | Positron-annihilation gammas | Prompt gammas

"Ionoacoustic" range verification

First observed in passively scattered proton therapy

- **diffuse** local dose deposition
- **small** ionoacoustic signal amplitude
- **complex** range information

Revived interest in connection with pencil beam scanning

- highly **localized** dose deposition
- **enhanced** ionoacoustic signal amplitude
- **direct** range information

Trends of **high pulse intensity** for **new accelerators** like synchro-cyclotrons
(e.g., 6-7 μs FMHW, up to ~5pC/pulse @ 1kHz for IBA S2C2)
or possibility to **pulse isochronous cyclotrons**
(e.g, Jones et al Med Phys 2016)
“Ionoacoustic” range verification

Promising experimental campaigns and MC simulations at clinical energies

Sub-mm proton range retrieval accuracy and precision in water at few Gy dose with hydrophones

Expected (sub)millimeter range verification capabilities also in heterogenous patient anatomy, when using TOF and time reversal methods (with ideal detector properties)

Several investigations ongoing worldwide

Jones et al, Med Phys 2015
Lehrack, ...Parodi, PMB Letter, 2017
Jones et al, PMB 2018
Yu et al, Med Phys 2019

Investigation of high sensitivity and broadband detection systems

- Low pressure amplitudes challenging to detect (mPa vs. kPa/MPa for US imaging)
- Improvement of the signal-to-noise ratio to reduce the detection threshold (minimal dose)
- Broadband sensors: independent of the beam energy and sensor position w.r.t to the Bragg peak

Co-development of CMUT* sensors

- Collaboration with ACULAB
  Dr. Savoia - University of Roma Tre, Italy
- Dedicated CMUT design and front-end electronics
- Optimization of the sensor geometry based on a k-Wave simulation platform

First proof-of-concept at 20 MeV compared to conventional (PZT) transducers

*CMUT: Capacitive Micromachined Ultrasonic Transducers

J. Lascaud ...H. Wieser...Parodi, presented to IEEE IUS 2019
PET and PG range verification: Recent clinical implementations

In-beam monitoring of irradiation induced PET activity

Real-time detection of irradiation induced prompt gamma


Next-generation of hybrid detectors

Comparison of different detector technologies & geometries in collaboration with NIRS toward „Whole Gamma Imaging“

Lang, ..., Parodi, Thirolf, JINST 2014
Parodi, NIMA 2015
Integration in clinical workflow

Analytical PET calculation & ongoing integration of prompt gamma in a research version of Treatment Planning System “RayStation”

PET Calculation
PET Measurement
(data courtesy J. Bauer, J. Debus)

Dose PG & ongoing integration of prompt gamma

Pinto...Parodi, submitted
Pinto, Kröniger, ...E. Traneus, K. Parodi, ICCR 2016
Demo @ ASTRO 2018

Toward a new treatment planning strategy

Initial treatment plan Boosted spots Re-optimized treatment plan

Range retrieval accuracy and precision crucially depend on PB statistics and PG-dose correlation

DVH of the target and nearby OARs Dose average LET distribution

Tian...Parodi, Phys Med Biol 2018
The needed data for reliable signal predictions

**PET and PG production yields or cross sections**

**Tissue elemental composition (e.g., from DECT or MRI)**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>MR-DECT_{exp}</th>
<th>MR-NECT_{exp}</th>
</tr>
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<tbody>
<tr>
<td>CSF</td>
<td>0.66</td>
<td>0.66</td>
</tr>
<tr>
<td>GM</td>
<td>0.67</td>
<td>0.41</td>
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<tr>
<td>WM</td>
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<td>0.54</td>
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</tbody>
</table>

Horst et al, PMB 2019 (in press)

Verburg et al, PMB 2013

Berndt, Landry, ...Parodi, PMB 2017; Bauer ... Parodi, Radiother Oncol, 2018

**MRI-guided proton therapy?**

Robustness against anatomical changes restored with suitable beam angles

Acceptable accuracy of commercial pseudo HU generation after tuning bone values and accounting for internal air cavities, or AI-based

Ongoing computational and experimental work toward MR-guided proton therapy

Kurz...Parodi, PMB 2017

Maspero ...Parodi...Kurz PMB 2017;

Neppl, ...Parodi, Kamp, Acta Oncol 2019; Spadea et al IJROBP 2019

Schellhammer, Hoffmann et al PMB 2018
Going beyond p and $^{12}$C ions?

In-depth physical characterization of $^{16}$O and $^4$He ion beams to support extensive biological experiments and planning studies prior to clinical use.

**Open clinical questions**
- Which ion for which indication
- Advantages of mixed radiation ($\text{Ions} & \text{Photons, other combinations}$)

Tessonier, Mairani, ... Parodi PMB 2017a,b; Tessonier ... Parodi, Rad Oncal 2018; Horst...Parodi...Schuy, Phys Rev C 2019

New horizons in biological modeling

**Biological models for ion treatment planning**

RBE = 1.1 for protons?

Including OER modeling for cell killing painting

RBE model of helium ions?

Including oxygen enhancement ratio in ion beam treatment planning: model implementation and experimental verification

1 Nakai, Y Tsuchida1, W & M Greiner1, JU Berens1, A Maker1 and W Kettner
New horizons in biological guidance

Entering the new era of biological guidance

PET image guidance for stratification, therapy personalization and response assessment

New RT treatment schemes toward mixed ion approaches

Proton | Helium | Carbon | Oxygen
---|---|---|---
7 keV/μm | 50 keV/μm | 72 keV/μm

New horizons in small animal research

Bridging the gap: small animal radiotherapy research

Commercial irradiation platforms for photon RT

Emerging irradiation platforms for protons and heavier ions

Small animal irradiation platform performs preclinical proton studies

Xstrahl launches the new sarp beamline for proton, photon, carbon and flash pre-clinical experiments
The SIRMIO project
Small animal proton irradiator for research in molecular image-guided radiation oncology

Realize and demonstrate prototype system for
- precision, image-guided small animal proton irradiation
- integration in experimental beamlines of clinical facilities

- High beam quality
- Innovative image guidance beyond morphology
- Adaptive planning and delivery

Parodi et al, Acta Oncol 2019

New frontiers in RT
Widening the therapeutic window

Different radiation qualities
Source: NASA

LET (keV/μm)
Source: GSI

Radiation response enhancement
Kwatra et al 2013
Campbell, Decker 2017

Temporal fractionation (FLASH)

Girst et al 2016

Spatial fractionation (micro/minibeam RT)

Reduced damage of normal tissue

Increased tumour cell killing

Widening the therapeutic window
Laser-driven ion acceleration

From RF-accelerators (∼ kV/mm) to optical systems (∼ MV/μm)?

Sources: West German Proton Therapy Center & HIT Heidelberg

LION @ Center for Advanced Laser Application

Laser-driven proton source with new targets and beamline (AG Prof. Schreiber)

New detector prototypes (collaboration with Wollongong University, Australia)

Can provide instantaneous ultra-high dose rate (∼1Gy/ns) for FLASH investigations

Proton radiography

Ionoacoustics

PhD thesis S. Lehrack, S. Aldawood, S. Liprandi, M. Würl; project F. Englbrecht (ongoing)
Conclusion & Outlook

Treatment planning strategies can account for physical and biological uncertainties, however compromising achievable dose conformity.

*In vivo* dose / range verification remains an unmet challenge, although many approaches are possible before, during and after treatment.

Promising techniques for in-vivo SPR assessment and real-time range verification are close to / just starting clinical translation & evaluation.

Additional studies needed to improve biological models.

Reduction of uncertainties at planning & delivery stage will enable more effective dose delivery and likely impact clinical outcome.

More breakthroughs expected from new biological effects under investigation, for which new pre-clinical research platforms are emerging.

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www.med.physik.uni-muenchen.de

Further reading:
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- F. Verhaegen, MAASTRO
- T. Yamaya et al, NIRS
- S. Rit et al, CREATIS
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- A. Savoia, Universitá Roma 3
- M. Durante, U. Weber et al, GSI

Thank you for your attention