Hybrid ion and X-ray imaging in ion beam therapy: from model-based to data-driven approaches

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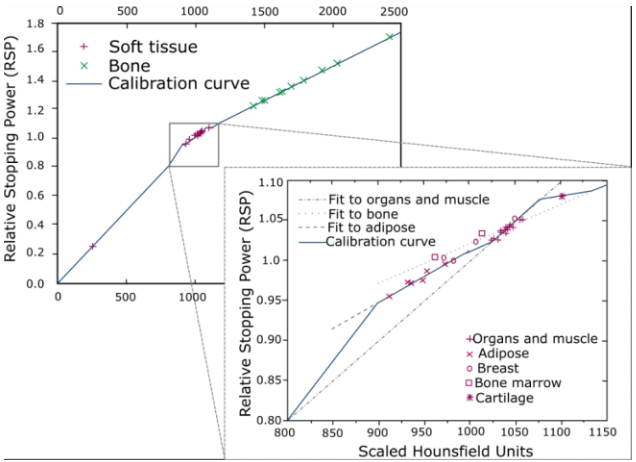
3rd ion imaging workshop - 13th October 2022 - Munich

Ion imaging in treatment planning

- Treatment planning in ion beam therapy is based on X-ray imaging but the native imaging technique for ion beam therapy is ion imaging
  - The X-ray CT image, expressed as Hounsfield Unit (HU), is semi-empirically calibrated into relative stopping power (RSP) to match the physical properties of the therapeutic radiation
  - The calibration curve is defined by piecewise linear fitting of the theoretical HU, parameterized based on experimental HU of tissue equivalent materials with known elemental composition, and theoretical RSP, calculated according to the Bethe-Bloch model
    - Uncertainties are associated to elemental composition, mass density and mean ionization energy of real tissue



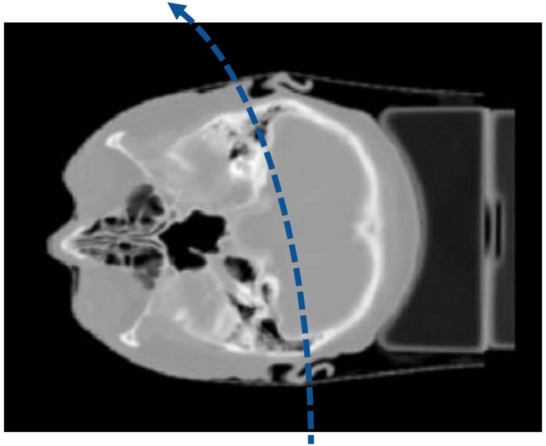
$$S/\rho \propto \frac{Z}{A}\frac{1}{\beta^2}\left(\ln\left(\frac{2m_e c^2 \beta^2}{I_m (1-\beta^2)}\right) - \beta^2\right)$$

ρ mass density, $\frac{Z}{A}\rho$ electron density, I_m mean ionization energy

Schneider et al. 1996 *Phys. Med. Biol.*

Ion imaging

- Ion imaging offers the promise of eliminating these inaccuracies by measuring the water equivalent thickness (WET) of the traversed object of interest
  - The WET (i.e., the ion radiography) is modeled as a line integral of the RSP (i.e., the ion image) along a certain concept of ion trajectory that depends on the detector configuration



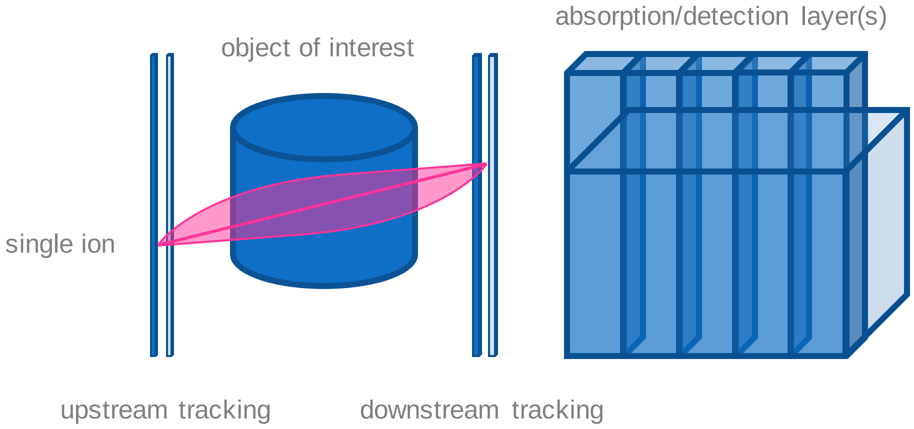
$$WET_i = \sum_j a_{ij} RSP_j$$

- The a_{ij} describes the intersection length/area/volume of the ion trajectory i with each voxel j
- The a_{ij} is the coefficient of the system matrix A that describes the forward-projection model $\overrightarrow{WET} = A * \overrightarrow{RSP}$ as a system of linear equations

List-mode detector configuration for single ions

- The scattering power of the ion is retrieved from the measurement of the position (or the position and the angle) prior and after the object of interest by means of single (or double) thin tracking layers

- The stopping power of single ions can be retrieved from:
  - Single absorption and detection block measuring the residual energy[1,2]
  - Multiple absorption layers interleaved by detection layers measuring multiple energy losses[3,4]



- Fast tracking layers can retrieve the scattering power and the stopping power from the time of flight of the tracked ion (i.e., 4D trackers) after the object of interest[5]

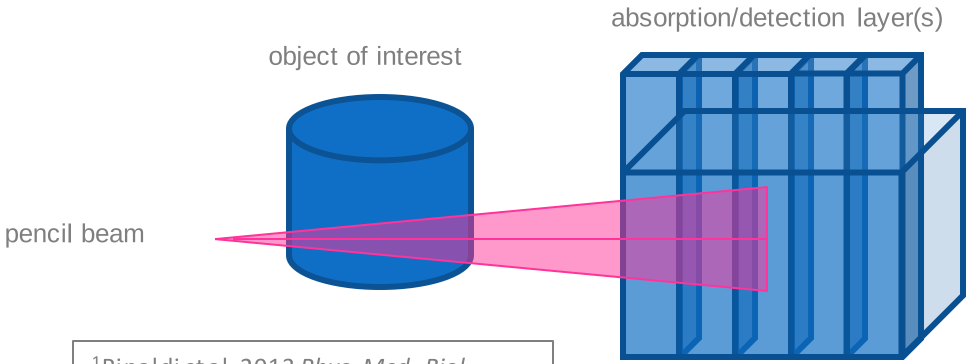
- The energy/range measurement is then converted to WET

Pioneer detector configurations
[1]Schneider and Pedroni 1995 *Med. Phys.*
[2]Sadrozinsky et al. 2004 *IEEE Trans. Nucl. Sci.*
[3]Pelmer et al. 1999 *Nucl. Instrum. Methods Phys. Res. A*
[4]Bashkirov et al. 2016 *Nucl. Instrum. Methods Phys. Res. A*

[5]Ulrich-Pur et al. 2022 *Phys. Med. Biol.*

Integration-mode detector configuration for pencil beams

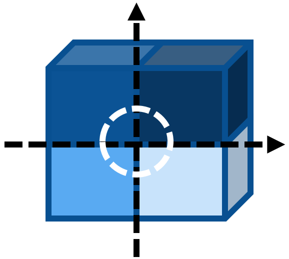
- The stopping power of single ions can be retrieved from:
  - Single absorption and detection block measuring the residual energy of the pencil beam
    - The mean energy/range is converted to WET
  - Multiple absorption layers interleaved by detection layers measuring multiple energy losses (i.e., the Bragg peak signal)[1] or single absorption and detection layer measuring the energy loss at multiple initial energies of the pencil beam[2,3]
    - The mixed energy/range is statistically resolved and converted to an histogram of WET components and occurrences (the mode WET component or the mean WET component are then selected)
  - Pixelated layers can statistically resolve also the scattering power of the pencil beam



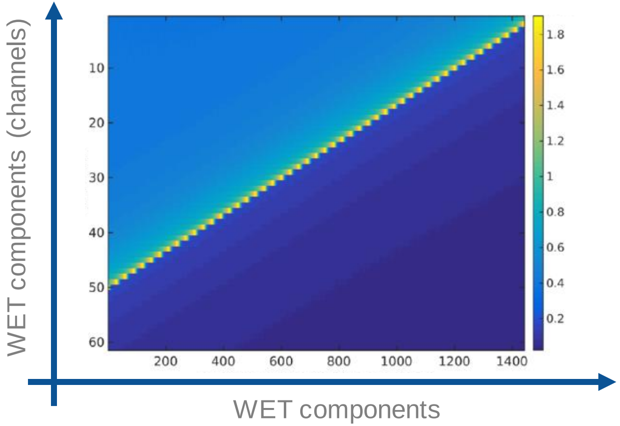
[1]Rinaldi et al. 2013 *Phys. Med. Biol.*
[2]Testa et al. 2013 *Phys. Med. Biol.*
[3]Telsemeyer et al. 2012 *Phys. Med. Biol.*

Integration-mode detector configuration for pencil beams

- In integration-mode detector configuration, the Bragg peak signal for each pencil is discretized according to the multiple layers (i.e., channels) or according to the multiple initial energies in a single layer



- Due to lateral inhomogeneity traversed by the pencil beam, the Bragg peak signal results in a linear combination of elementary Bragg peak signals
  - Linear decomposition[1,2] is applied to retrieve the WET histogram as WET occurrence for each WET component by solving the system of linear equations $\overrightarrow{BP} = LUT * \overrightarrow{WET}$
    - $\overrightarrow{BP}$ is the discretized Bragg peak signal
    - $\overrightarrow{WET}$ is the unknown vector of WET occurrences
    - LUT is the look-up-table of individual Bragg peak signals for each WET component

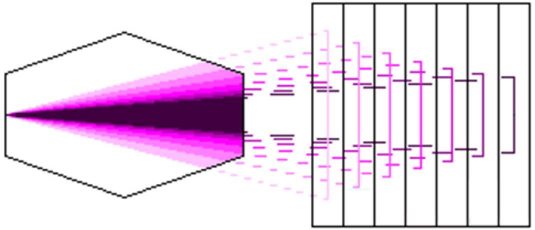


[1]Krah et al. 2015 *Phys. Med. Biol.*
[2]Meyer et al. 2017 *Phys. Med. Biol.*

Detector configuration and ion trajectories

- Due to the stochastic nature of the multiple Coulomb scattering, the ion trajectory of the single ion is known at the entrance and the exit of the object of interest but uncertain in between and thus, modeled according to a "spindle" Gaussian distribution
  - Maximum likely path (MLP) accounts for the scattering power of the single ion in list-mode detector configuration[1]
  - MLP approximation[2] or machine learning[3] can be adopted

- For integration-mode detector configuration, the typical concept of ion trajectory is the mean ion trajectory
  - As the nominal pencil beam dimension and direction are known, the model (in water) or the measurement (if available) of the scattering power corresponds to a flared conical Gaussian distribution for each WET component



- The model in water equivalent materials based on the X-ray CT image can be considered

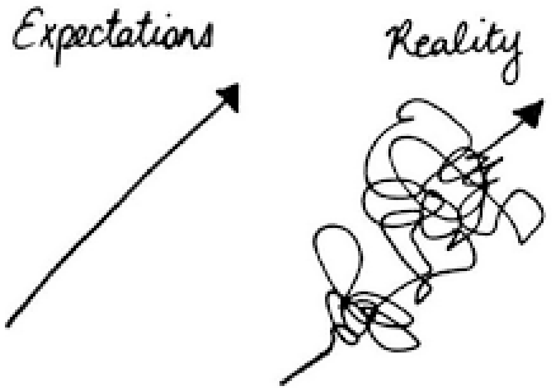
[1]Schulte et al. 2008 *Med. Phys.* [2]Collins-Fekete et al. 2015 *Phys. Med. Biol.* [3]Lazos et al. *2021 Phys. Med. Biol.*

Detector configuration and ion trajectories

- The concept of ion trajectory for different detector configuration plays a crucial role in the forward-projection model, which is a foundation in ion imaging

$$\overrightarrow{WET} \neq A * \overrightarrow{RSP_t}$$ (t for “ground truth”)

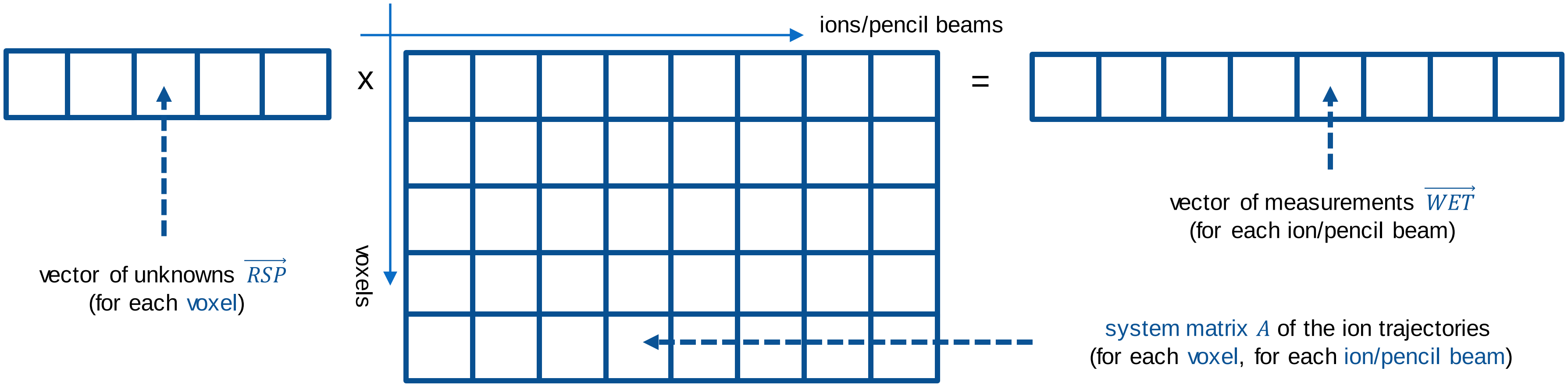
- However, in clinical scenarios the intrinsic inconsistencies of the forward-projection model are in the same order of magnitude of the inaccuracies of the semi-empirical calibration of the X-ray CT
    - The normalized root mean square error between the ion radiography and the forward-projection of the ground truth ion CT image is 1-2.5% for list-mode detector configuration and up to 2.5-5% for integration-mode detector configuration



Gianoli et al. *2020 Phys. Med. Biol.*

Tomographic image reconstruction

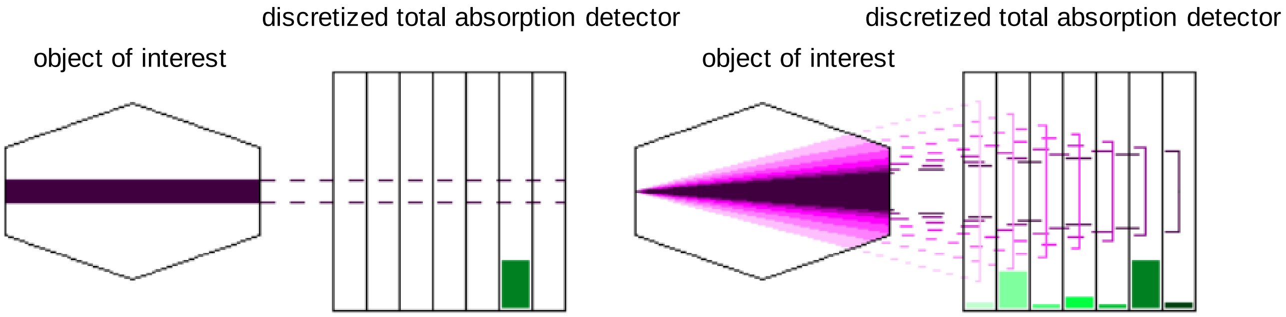
- Tomographic image reconstruction is applied to several ion radiographies, with projection angles covering 180°
  - The ordered subsets simultaneous algebraic reconstruction technique (OS-SART) coupled with total variation superiorization currently represents the state-of-the-art in ion imaging[1,2,3]
  - Information redundancy mitigates the intrinsic inaccuracies of the forward-projection model[4]



[1]Penfold et al. 2010 Med. Phys. [2]Meyer et al. 2019 *Phys. Med. Biol.* [3]Meyer et al. 2021 *Phys. Med. Biol.*
[4]Gianoli et al. 2019 *Phys. Med.*

Dedicated tomographic image reconstruction

- The model of the scattering power is included in the forward-projection model to make the forward-projection model more consistent to the ion radiography
  - For integration-mode detector configuration, the WET components are associated to the corresponding flared conical Gaussian distributions



Dedicated tomographic image reconstruction

- The simultaneous algebraic reconstruction technique (SART) is modified to handle the additional channel dimension[1,2]

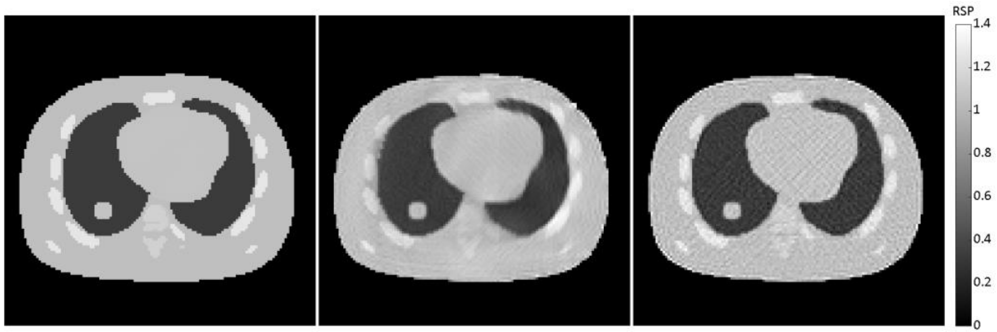
$$RSP_j^{n+1} = RSP_j^n + \frac{\sum_i \widehat{a_{ij}} \cdot \frac{\widehat{WET_i} - \sum_j \widehat{a_{ij}} \cdot RSP_j^n}{\sum_j \widehat{a_{ij}}}}{\sum_i \widehat{a_{ij}}}$$

- $\widehat{WET_i}$ is the sum of the WET components weighted for the WET occurrences

$$\widehat{WET_i} = \sum_k WET_{ik} x_{ik}$$

- $a_{(ik)j}$ is the conical Gaussian distribution for each channel k and thus, $\widehat{a_{ij}}$ is the sum of the conical Gaussian distributions weighted for the WET occurrences

$$\widehat{a_{ij}} = \sum_k x_{ik} a_{(ik)j}$$



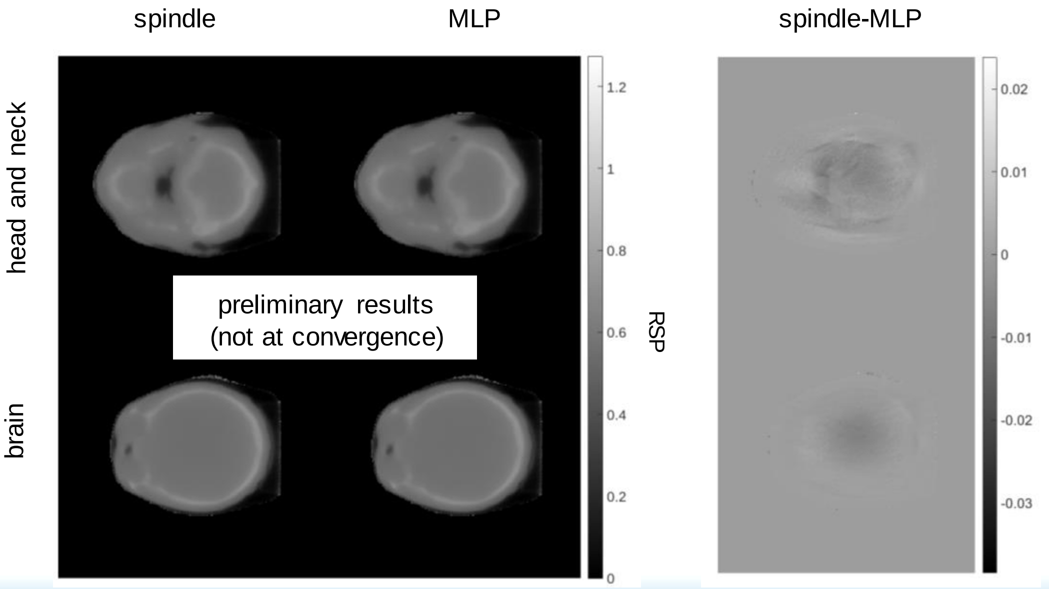
ground truth | Scatter-informed SART (WET histogram) | SART (mode WET component)

[1]Seller Oria et al. *2018 IEEE NSS-MIC* [2]Gianoli et al. 2019 *Phys. Med.*

Work in progress

- For list-mode detector configuration, the model of the scattering power to be included in the forward-projection model is described as "spindle" Gaussian distribution
    - The more consistent forward-projection model is expected to provide slightly better results than MLP

- The X-ray image can be used to model the scattering power in water equivalent materials (i.e., hybrid X-ray and ion imaging), also for integration-mode detector configuration
    - Master thesis project of Anagha Balaji (student of the Master program in Biomedical Engineering and Medical Physics at the Technical University of Munich) at the LMU Munich starting in October 2022

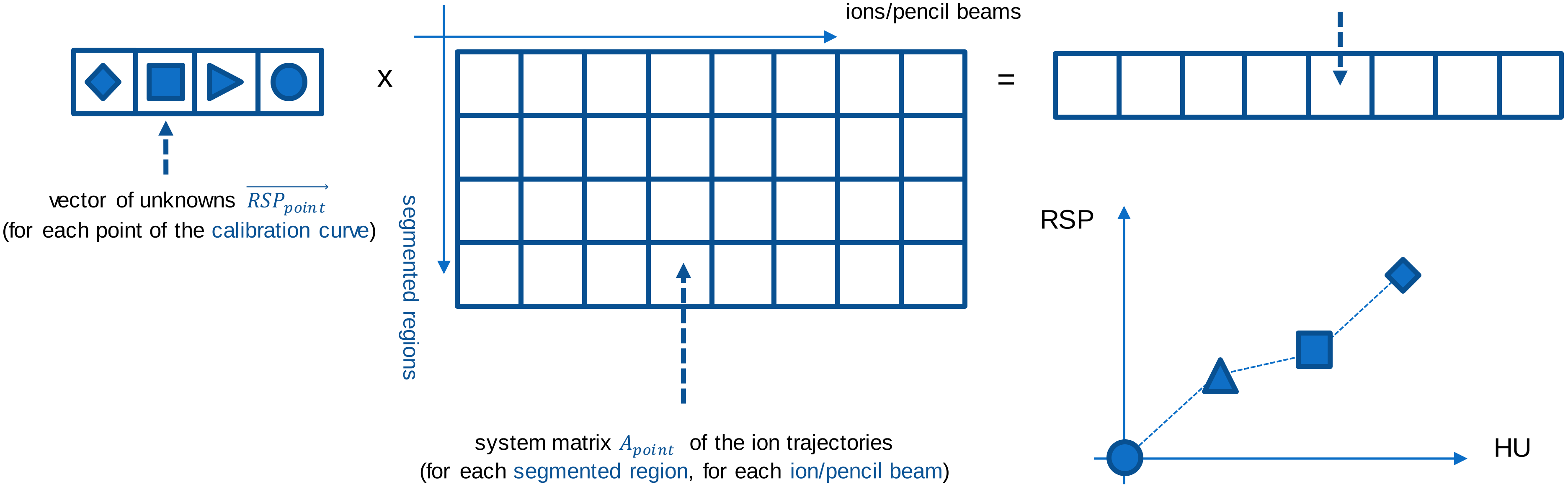


Optimization of the semi-empirical calibration based on ion radiographies

- The forward-projection model can be expressed in function of the calibration curve to optimize the X-ray CT image based on ion radiographies

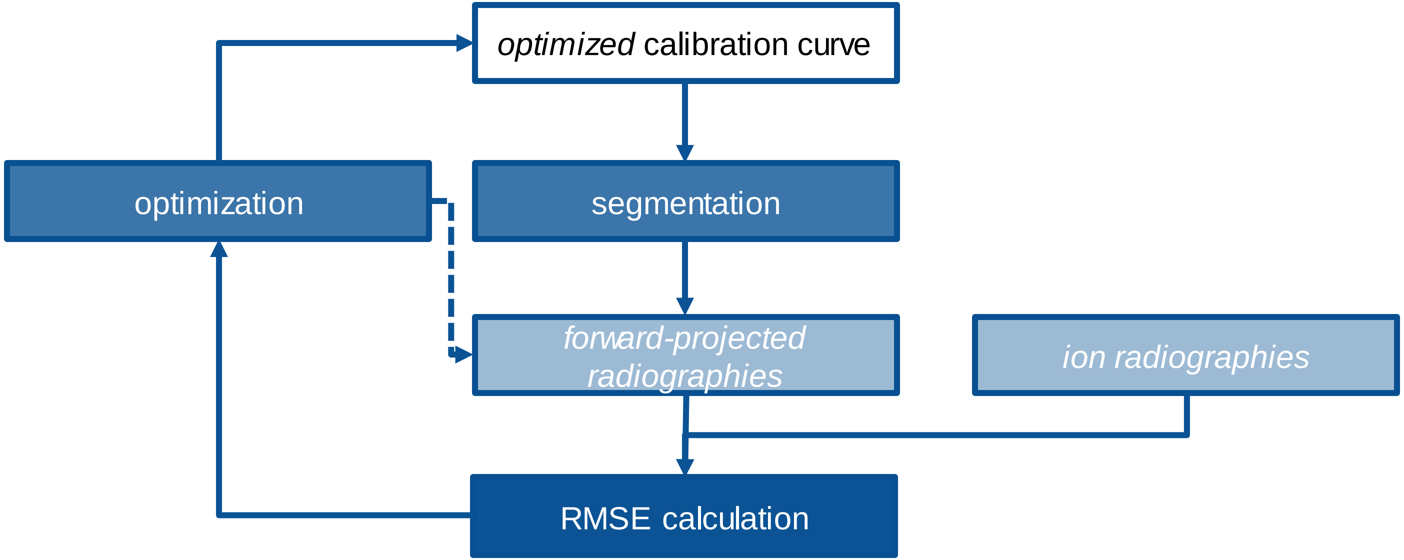
  - Reduced redundancy due to limited number of ion radiographies

vector of measurements $\overrightarrow{WET}$
(for each ion/pencil beam)



Optimization of the semi-empirical calibration based on ion radiographies

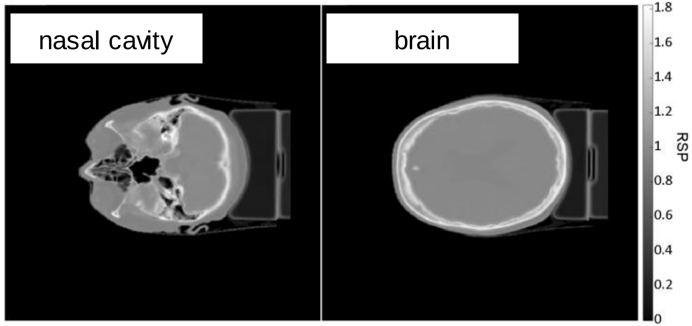
- This hybrid X-ray and ion imaging can be implemented as linear optimization, where the unknown is just the correction vector of the calibration curve and the system matrix embeds the inaccurately calibrated X-ray CT image[1,2,3,4] or as non-linear optimization, where the calibration of the X-ray CT image is iteratively corrected[5,6]

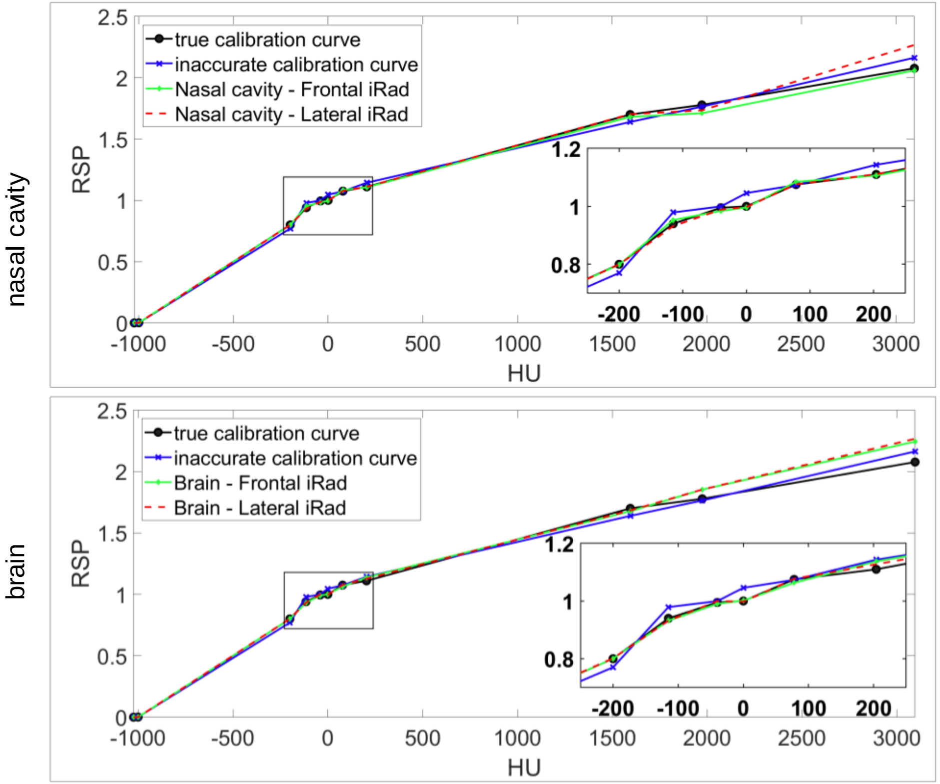


[1]Schneider et al. 2005 *Med. Phys.* [2]Collins-Fekete et al 2017 *Phys. Med. Biol.* [3]Zhang et al 2019 *Phys. Med. Biol.* [4]Krah et al 2019 *Phys. Med. Biol.*
[5]Doolan et al. 2015 *Phys. Med. Biol.* [6]Gianoli et al. 2020 *Phys. Med. Biol.*

Optimization of the semi-empirical calibration based on ion radiographies

- The forward-projection model for list-mode detector configuration is accurate enough to potentially minimize the calibration inaccuracies





Gianoli et al. *2020 Phys. Med. Biol.*

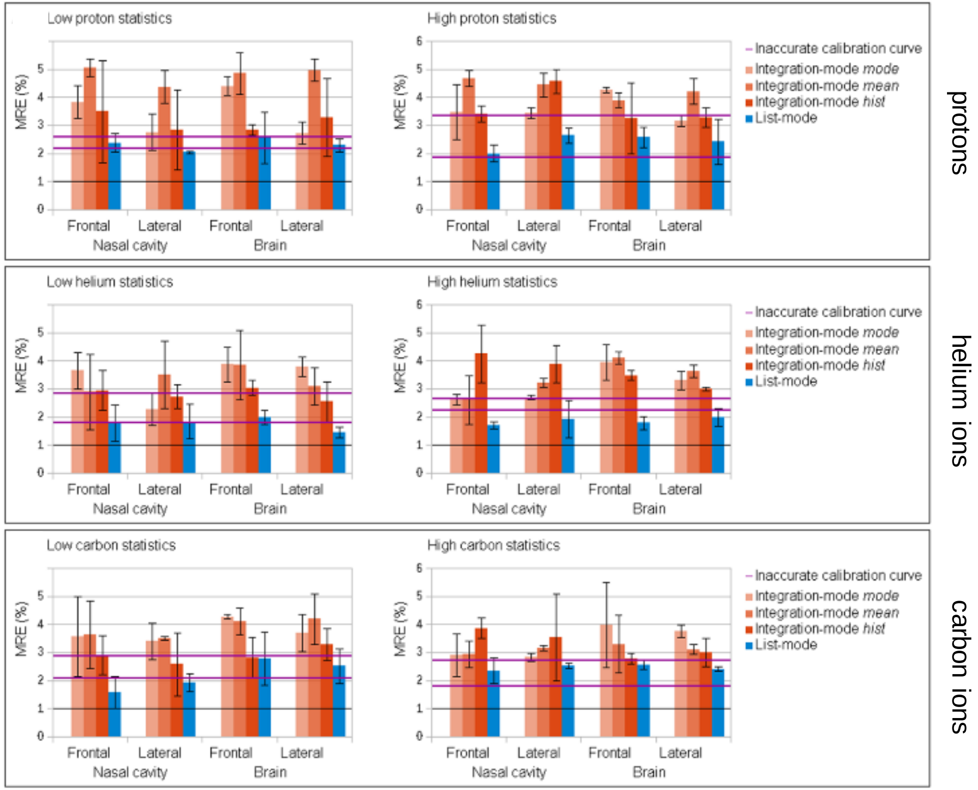
Optimization of the semi-empirical calibration based on ion radiographies

- The forward-projection model for integration-mode detector configuration is affected by intrinsic inconsistencies in the same order of magnitude as the calibration inaccuracies

    - Protons are penalized by larger scattering and beam spot size

    - Helium ions benefit from the compromise between scattering (and beam spot size) and statistics

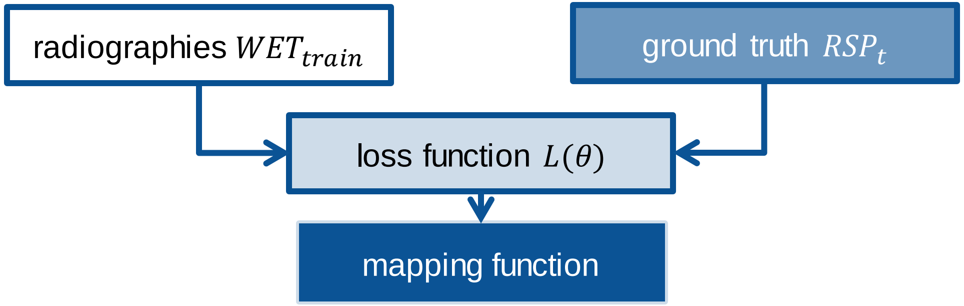
    - Carbon ions are penalized by the statistics



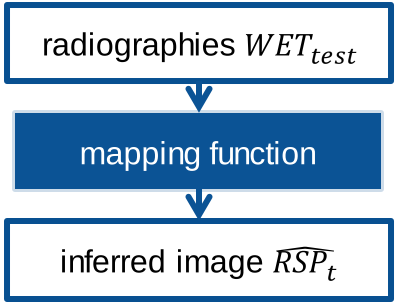
Gianoli et al. *2020 Phys. Med. Biol.*

Data-driven approaches

- Data-driven approaches based on supervised machine learning (ML) are proposed to overcome the intrinsic inconsistencies of the forward-projection model in clinical scenarios
  - Tomographic image reconstruction is typically based on non-linear and shift-variant mapping, as introduced by fully connected layers, down sampling (encoding) and up sampling (decoding)



$$\hat{\theta} = \arg min_{\theta} L(DNN(WET_{train}|\theta)|RSP_t)$$

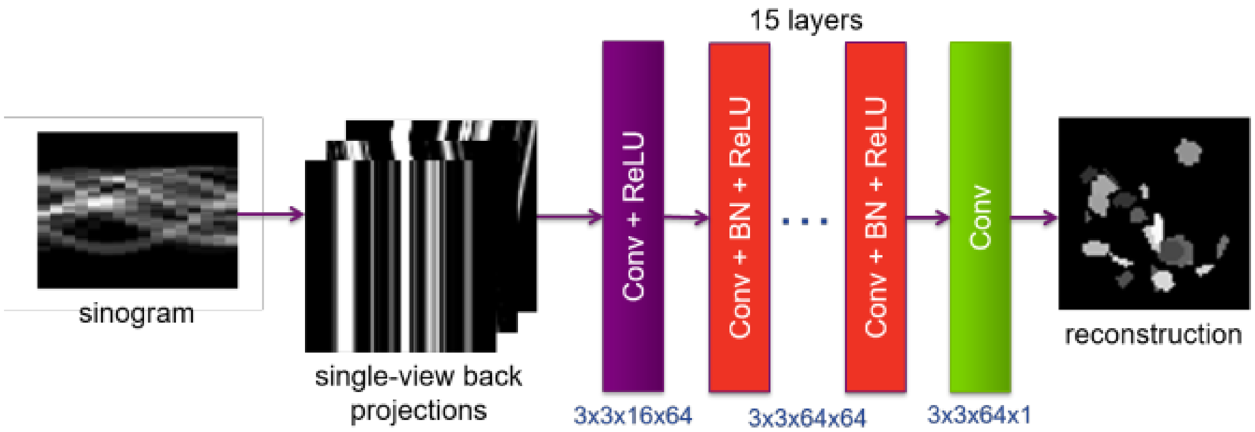


$$\widehat{RSP_t} = DNN(WET_{test}|\hat{\theta})$$

Wang et al. 2020 *Nat. Mach. Intell.*

Data-driven approaches

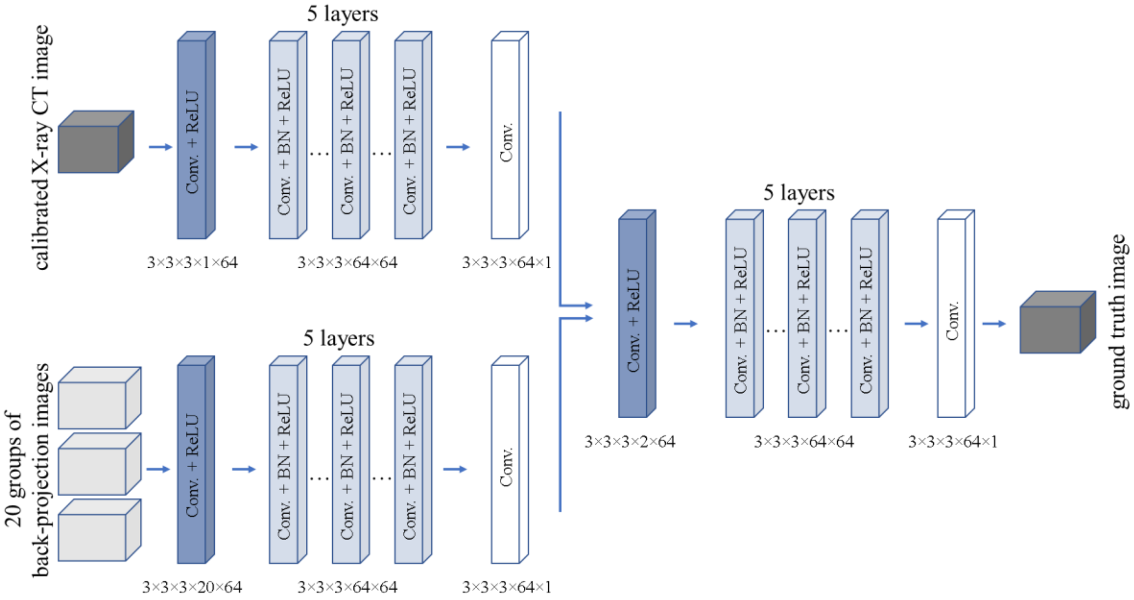
- Inspired by the ML literature about tomographic image reconstruction but extended toward hybrid X-ray and ion imaging
  - With the "deep back-projection", the geometrical relationship between the projection domain and the image domain is encoded in single-view back-projections that are stacked and fed as input to the convolutional neural network
  - The spatial invariance of the purely convolutional neural network is retained



Ye et al. 2018 *IEEE-GlobalSIP*

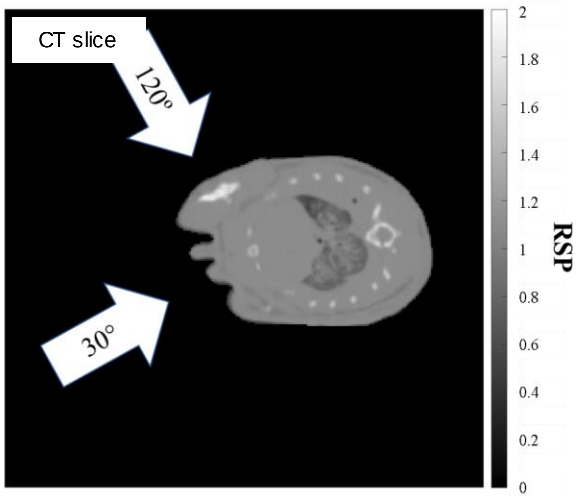
Data-driven approaches

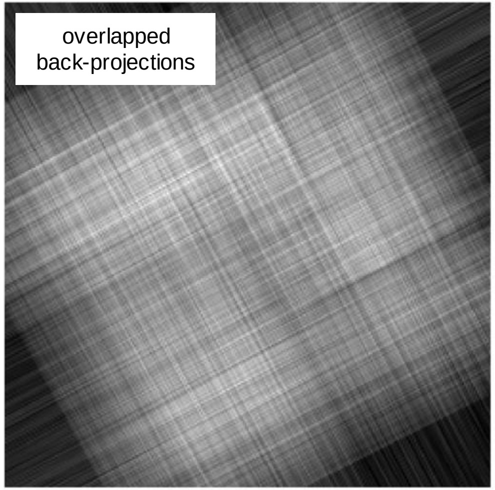
- The network is designed as a two input branches (one for the X-ray CT image and the other for the ion radiographies) followed by an integration branch
  - Two ion radiographies (two projection angles) are clustered according to the scattering angles of the ion trajectories (ten clusters for each projection angles)
  - Additive inaccuracies (up to 5% or 20%) applied to the ground truth calibration curve to simulate the inaccurate calibration of the X-ray CT image

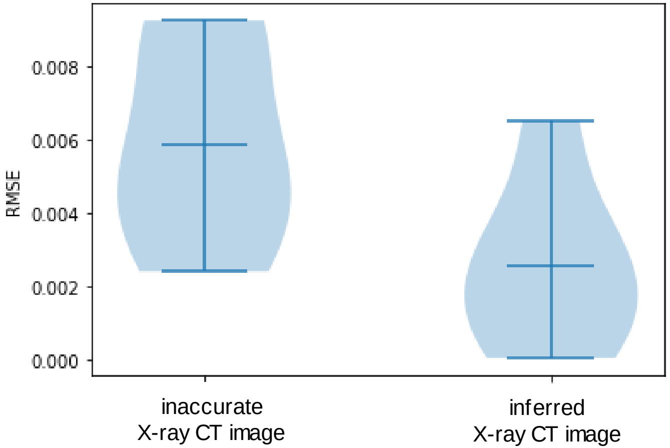


Work in progress

- Pre-clinical-like data (protons) for list-mode data (integration-mode data available)
- Synergism with the SIRMIO project "Small animal proton irradiator for research in molecular image-guided radiation oncology" → "*Proton imaging for small animals: status and perspectives*" (Prof. Katia Parodi)



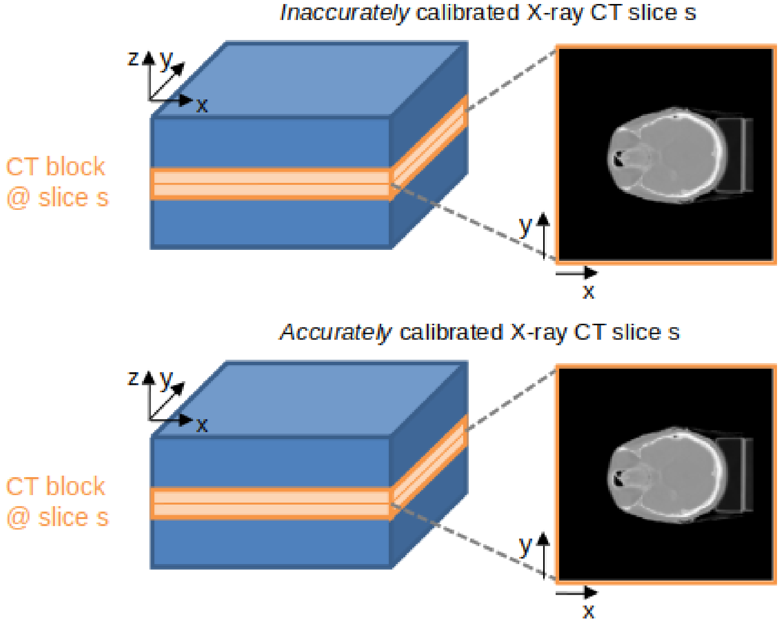


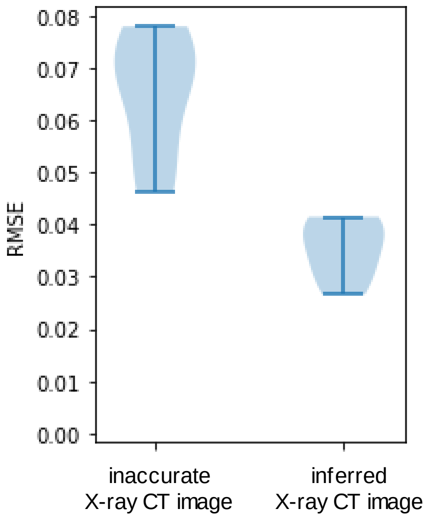


HiWi project of Marko Zlatic

Work in progress

- Clinical-like data (protons, helium and carbon ions) for list-mode data (integration-mode data available)
  - Training/validation/testing data randomly selected within available slices (“block” because of ion scattering)





PhD project of Ines Butz

The project - acknowledgments

- In November 2017 the project “Hybrid ImaGing framework in Hadrontherapy for Adaptive Radiation Therapy (HIGH ART)” was financed by the *Deutsche Forschungsgemeinschaft* (DFG) as “individual research grant”
  - Clinical translation from X-ray imaging to ion imaging is foreseen as combined X-ray and ion imaging and likely based on a limited number of ion radiographies acquired with integration-mode detector configuration
  - The combination of X-ray and ion imaging is envisioned not only for treatment planning but also for verification and adaptation → “*Evaluation of rigid and non-rigid changes in a small animal irradiation system based on proton radiographies: influence of detector performance*” (Dr. Prasannakumar Palaniappan and Prof. Marco Riboldi)




- In January 2022 the renewal of the project was confirmed
  - The idea of data-driven approaches for the combination of X-ray and ion imaging is put forward
- In September 2022 Ines Butz started working on the project as a PhD student

Gefördert durch DFG Deutsche Forschungsgemeinschaft