Hadrontherapy in 4D

Guido Baroni, Ph.D.
- Dipartimento di Elettronica Informazione e Bioingegneria, Politecnico di Milano
- Unità di Bioingegneria Clinica, Area Clinica, Fondazione CNAO
Presentation outline

Challenge of 4D therapy (respiratory correlated irradiation)
- X-ray radiotherapy inheritance
- Status and perspectives in particle therapy

4D treatment planning
- 4D imaging and motion modelling

4D dose delivery in particle therapy
- Experimental studies (local models)
- Prediction of daily anatomical changes (global models)

4D treatment verification
- Motion compensated in-vivo PET-based dosimetry
- 4D transmission imaging
**Challenge**: actively targeting a movable and deformable volume featuring variable kinematics and deformation patterns

- Combination of inter- and intra-fractional deviations
- **Tasks (on-the-fly):**
  1. **Target localization**
  2. **Treatment geometry adaptation** (beam direction, conformation)

Respiratory correlated (4D) therapy

![3D tumor traces on different weeks](image)

![Normalized amplitude](image)
Motion detection strategies
The X-ray radiotherapy heritage

✓ Direct tumor imaging
  ✓ Marker-based methods
    ✓ EM (Calypso\textsuperscript{TM}) [Balter et al. IJROBP 2005;61:933–37]
  ✓ Markerless
    ✓ Real-time X-ray image registration [Gendrin et al.
      \textit{Radiother Oncol} 2012; 102:274–80]

✓ Indirect tumor localization
  ✓ Correlation with surrogates
    ✓ Spirometric measurements [Hughes et al Radiother Oncol
      2009; 91: 336–41]
    ✓ Surface fiducials [Baroni et al., Radiother Oncol 2000;54:21–27]
(External) surrogates optical tracking and position correlation with inner anatomy is state of the art in photon therapy for:

- time resolved imaging for treatment planning
- breath-hold irradiation (motion suppression)
- respiratory gating (motion correlation, intermittent irradiation)
- tumor tracking (motion correlation, continuous irradiation)
Tumor tracking based on correlation models: the Cyberknife-Synchrony case

- Tumour tracking accuracy better than 1.5 mm [Kilby 2010]
- Correlation errors > 5 mm with breathing irregularities [Torshabi 2010]
Clinical effectiveness of tumor tracking (Cyberknife -Synchrony treatments)

(Riboldi et al, Lancet Oncol 2012)
From 4D X-ray to 4D hadrontherapy

- **4D imaging**
- **Treatment plan**
- **X-ray projections**
- **External surrogates + Correlation models**
- **Soft-tissue imaging**
- **Particle radiography**
- **Motion detection**

- **Magnet steering**
- **Lateral compensation**
- **Moving wedge**
- **Static wedge**
- **Depth compensation**
- **Offline PET imaging**
- **In-beam PET / prompt γ**
- **Treatment verification**
4D hadrontherapy

Current status

- Respiratory gating applied clinically with passive scattering (ext-int correlation)
- First cases with ion-beam active scanning reported for HCC patients (HIT) (ext-int correlation)
- No tumor tracking attempted clinically

Greatest caution motivated by

- 4D CT artefacts (uncertainties)
- Interplay effects (active scanning)
- Range uncertainties

What is needed

- Robust artefacts-free treatment planning
- Accurate tumor localization (local models)
- Estimation of daily global anatomical changes
Treatment planning: 4D CT artefacts

Motion monitoring in 4D CT based on **mono-dimensional signal**:  

- uncertainties in breathing phase detection

  Additional contribution to motion artifacts (besides irregularities)
4D CT – multiple markers and data mining techniques

(RPM phase)

(RPM amplitude)

(Multiple markers)

(IR markers)

(Gianoli et al, Med Phys 2011)
4D CT based on surface optical tracking: enrich information on rib cage kinematics

- Extract the 3D trajectory of non-corrrespondent surface points acquired with optical systems (deformable mesh registration) (Amberg 2007; Schaerer 2012)
- Synthesis of a multi-regional respiratory motion model for robust image sorting and/or for respiratory correlated delivery

- Principal Component Analysis (PCA)
- K-means clustering
- Self-Organizing Maps (SOM)

<table>
<thead>
<tr>
<th></th>
<th>PCA</th>
<th>K-means</th>
<th>SOM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson correlation coefficient*</td>
<td>0.90 ± 0.17</td>
<td>0.93 ± 0.06</td>
<td>0.91 ± 0.38</td>
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<tr>
<td>Root-mean-square error*</td>
<td>0.15 ± 0.10</td>
<td>0.11 ± 0.06</td>
<td>0.20 ± 0.12</td>
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</tbody>
</table>

Correlation with diaphragm motion (US) (median ± quartile)(5 subjects)
4D CT based on optical measurements: combining points and surface detection

- Novel system under development/testing combining real-time point-based with surface based acquisitions with high spatial and temporal resolution for redundant external surrogates acquisition. Applications in:
  - robust 4D CT (@CNAO early 2014)
  - combined/selectable point/surface patient set-up verification /respiratory gating / tumor tracking
Surrogate-less 4D MRI
Point-based motion modelling/model verification

Internal surrogate: MI

(...)

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Application of correlation models for **real-time tumor tracking** in particle therapy:

1. **Experimental validation** with scanned beams in clinical like scenarios:
   - **local correlation models**: accurate target positioning and beam tracking against interplay effects

2. Development of **global 4D models**
   - **daily 4D CT** estimation to reduce beam range uncertainties
Correlation models in particle therapy

Experimental setup:

- **Robotic phantom**
  - Reproduces thorax breathing expansion and inner target motion
  - Regular / irregular target trajectories (baseline drift, phase shift)
- **Optical Tracking System** (OTS)
  - SMART-DX100 (BTS Bioengineering)
  - Measures passive markers onto the thorax (f = 100Hz)
  - Includes external / internal correlation models (ANN, State model)
- **Treatment Control System** (TCS)
  - Receives target position (direct / estimated)
  - Modulates (direction and energy) the incident beam
- **Dose measurement**
  - 20 ionization chambers inside the target

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Commissioning of OTS / TCS integration:

- **Lateral** compensation (magnet steering in BEV)
- **Depth** compensation (dynamic wedge for energy adaptation)

(Fattori et al, TCRT, in press)
Accuracy of correlation models

<table>
<thead>
<tr>
<th></th>
<th>Regular State Model</th>
<th>Regular ANN Model</th>
<th>Baseline Drift State Model</th>
<th>Baseline Drift ANN Model</th>
<th>Phase Shift State Model</th>
<th>Phase Shift ANN Model</th>
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<tbody>
<tr>
<td>Type</td>
<td></td>
<td></td>
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<tr>
<td>MOTION TYPE</td>
<td>HORAX</td>
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<tr>
<td>PERIOD [S]</td>
<td></td>
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<tr>
<td>TARGET MOTION PERIOD [S]</td>
<td></td>
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<tr>
<td>TARGET MOTION AMPLITUDE (CC, AP, LR) [MM]</td>
<td></td>
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<tr>
<td>BASELINE DRIFT (CC, AP, LR) [MM/S]</td>
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<td></td>
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<tr>
<td></td>
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<td>4</td>
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<td></td>
<td>0.42</td>
<td>0.61</td>
<td>0.51</td>
<td>1.03</td>
<td>0.62</td>
<td>1.23</td>
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<td>0.34</td>
<td>0.27</td>
<td>0.41</td>
<td>0.78</td>
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<td>0.23</td>
<td>0.32</td>
<td>0.32</td>
<td>0.71</td>
<td>0.40</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Phase shift | 3 | 2.975 | 10, 5, 5 | 0, 0, 0
Dosimetric results

**Dose different wrt static irradiation**

- Static irradiation = beam fixed, static target
  - Measurement of nominal delivered dose
- ‘Interplay’ = beam fixed, target moving
  - Measurement of «motion blurred» dose

*(Seregni et al, PMB, 2013)*
Experimental set-up (CNAO, December 2012)

- **Robotic phantom**
  - Custom moving phantom featuring correlated external and internal motion along an hysteretic trajectory (25 and 18 mm peak to peak in lateral and vertical direction)

- **Optical Tracking System (OTS)**
  - Measured passive markers onto the ribs and internal target for control (f = 100Hz)
  - Included external/internal correlation models (ANN, State model)

- **CNAO-Dose Delivery System (DD)**
  - Received target position (direct/estimated) through proprietary interface
  - Applied beam direction correction (in-plane) as a function of target position deviation

- **Dose measurement**
  - Films scanned with proton pencil beam (single square film, 60 mm side)
Dosimetric results (films)

<table>
<thead>
<tr>
<th>Acq 1</th>
<th>Acq 2</th>
<th>Acq 3</th>
<th>Acq 4</th>
<th>Acq 5</th>
<th>Acq 6</th>
</tr>
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<tbody>
<tr>
<td>Static irradiation</td>
<td>OTS direct tracking</td>
<td>ANN prediction</td>
<td>State space model prediction</td>
<td>Interplay</td>
<td>Gating</td>
</tr>
</tbody>
</table>

Average flatness (omogeneity, [%])

<table>
<thead>
<tr>
<th>Acq 1</th>
<th>Acq 2</th>
<th>Acq 3</th>
<th>Acq 4</th>
<th>Acq 5</th>
<th>Acq 6</th>
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<tr>
<td>4</td>
<td>5.7</td>
<td>6.6</td>
<td>6.1</td>
<td>24</td>
<td>9.5</td>
</tr>
</tbody>
</table>

Average penumbra (principal axes, [mm])

<table>
<thead>
<tr>
<th>Acq 1</th>
<th>Acq 2</th>
<th>Acq 3</th>
<th>Acq 4</th>
<th>Acq 5</th>
<th>Acq 6</th>
</tr>
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<tbody>
<tr>
<td>9.2</td>
<td>9</td>
<td>9</td>
<td>9.2</td>
<td>19</td>
<td>9.1</td>
</tr>
</tbody>
</table>

* Field size: 6.3 and 6.9 mm (principal directions) respectively
From local to global 4D models

- **Local** correlation models *(target)* experimentally assessed

- Need to evaluate **WEL variations** *(dosimetric changes)* outside the **target**

Global 4D model

*adapt treatment planning 4D CT to the time of irradiation*
Global 4D model: general framework

**Model training**

- 4D CT
- 10x CT

**DIR**

- Reference volume (Mid Position)

**4D Model**

- 4D DVF
- 3D + ϑ

**Model estimate**

**current fraction**

Respiratory motion parameters
- Phase ϑ(t)
- Amplitude α(t)
- Baseline (f)

\[
\hat{s}_{\vartheta,\alpha} = \bar{f} + \alpha D_{\vartheta}
\]

Estimated CT (ϑ, α, f)

(Vandemeulebroucke et al. 2009; Fassi et al. 2013)
**CBCT studies**

**TREATMENT PLANNING**

- **4D CT** image acquisition
  - Estimation of a patient-specific **breathing motion model**
    - baseline (s)
    - amplitude (α)
    - phase (θ)

**PATIENT SETUP**

- In-room **3D CBCT** image acquisition
  - Estimation of daily tumor **baseline**

**DOSE DELIVERY**

- Dynamic acquisition of thoraco-abdominal **surface displacement** with optical systems
  - Estimation of a **breathing surrogate**
  - Extraction of respiratory **amplitude** and **phase** parameters
  - **Update** of the 4D CT motion model
  - **Tumor motion** tracking

*(Fassi et al, IJROBP, in press)*
CBCT study: sample traces

* Pixel spacing of CBCT projections = 0.8 mm/pixel
CBCT study: overall results

Total tracking error:

→ RMS error of tumor tracking in the CBCT projection plane
Global 4D model: can we predict a daily 4D CT?

**Modelling test**
→ intrinsic model errors DIR

**Tracking test**
→ tracking accuracy evaluation

**Rigid alignment Test**
→ for comparison
## Global 4D model: geometric results

<table>
<thead>
<tr>
<th>Patient</th>
<th>Experiment</th>
<th>Structure</th>
<th>COM distance [mm]</th>
<th>Hausdorff distance [mm]</th>
<th>Dice Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>GTV</td>
<td>Lungs</td>
<td>Trachea</td>
<td>Esophagus</td>
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<tr>
<td></td>
<td></td>
<td>GTV</td>
<td>Lungs</td>
<td>Trachea</td>
<td>Esophagus</td>
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<tr>
<td></td>
<td></td>
<td>GTV</td>
<td>Lungs</td>
<td>Trachea</td>
<td>Esophagus</td>
</tr>
<tr>
<td>P1</td>
<td>Modeling</td>
<td>0.40</td>
<td>0.42</td>
<td>0.36</td>
<td>0.50</td>
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<tr>
<td></td>
<td>Rigid</td>
<td>4.70</td>
<td>3.66</td>
<td>3.36</td>
<td>4.39</td>
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<tr>
<td></td>
<td>Tracking</td>
<td>1.58</td>
<td>0.78</td>
<td>1.01</td>
<td>0.84</td>
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<tr>
<td>P2</td>
<td>Modeling</td>
<td>0.51</td>
<td>0.15</td>
<td>0.46</td>
<td>0.21</td>
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<tr>
<td></td>
<td>Rigid</td>
<td>2.30</td>
<td>2.49</td>
<td>1.28</td>
<td>1.07</td>
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<tr>
<td></td>
<td>Tracking</td>
<td>1.82</td>
<td>1.05</td>
<td>1.98</td>
<td>0.96</td>
</tr>
<tr>
<td>P3</td>
<td>Modeling</td>
<td>0.13</td>
<td>0.14</td>
<td>0.34</td>
<td>1.19</td>
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<tr>
<td></td>
<td>Rigid</td>
<td>1.28</td>
<td>1.68</td>
<td>3.73</td>
<td>2.63</td>
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<tr>
<td></td>
<td>Tracking</td>
<td>0.87</td>
<td>2.78</td>
<td>2.19</td>
<td>2.09</td>
</tr>
<tr>
<td>P4</td>
<td>Modeling</td>
<td>0.52</td>
<td>0.15</td>
<td>0.45</td>
<td>0.36</td>
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<td></td>
<td>Rigid</td>
<td>3.93</td>
<td>2.63</td>
<td>1.57</td>
<td>1.75</td>
</tr>
<tr>
<td></td>
<td>Tracking</td>
<td>1.26</td>
<td>0.41</td>
<td>0.65</td>
<td>1.17</td>
</tr>
</tbody>
</table>

**Tracking Test:**
- Localization error (COM) = 1.4 mm (GTV), 1.3 \(\div\) 1.5 mm (OARs)
- Contour surface distance (Hausdorff) = 0.55 mm (GTV), 0.57 \(\div\) 0.53 mm (OARs)
- Volume overlap (Dice) = 0.83 (GTV), 0.87 \(\div\) 0.93 (OARs)
Global 4D model: HU difference

A) Motion state identification error

Patient P1

Patient P2

Patient P3

Patient P4

B) HU difference

Modeling

Rigid alignment

Tracking
Global 4D model: WEL results

Quantification of range variations

\[ \Delta WEL \text{ calculation} \]
Global 4D model: WEL results

A) Mean absolute $\Delta$WEL

- **Rigid alignment Test**
  
  $|\Delta WEL| = 1.6 \div 7.8$ mm
  mean($\Delta$WEL (GTV)) $\neq 0$ mm
  → Systematic variations

- **Tracking Test:**
  
  $|\Delta WEL| = 0.7 \div 1.4$ mm
  mean($\Delta$WEL (GTV)) $\approx 0$ mm
  → NO systematic variations

B) Signed $\Delta$WEL distribution

- **Overshoot**
- **Undershoot**
1. **Local correlation models** validated experimentally in scanned particle therapy
   - RMS tracking error < 1.5 mm
   - few % dosimetric deviation wrt static irradiation

2. **Global 4D models** can predict anatomy changes (preliminary)
   - Results are patient dependent
   - Systematic WEL variations can be compensated
4D treatment verification

Motion compensated PET imaging

- Off-line PET-based treatment verification for moving target
  - reduced count statistics due to time delay before acquisition
  - reduced count statistics due to 4D acquisition

illegible 4D PET images from commercial scanners
4D treatment verification

Motion compensated PET imaging: alternative strategies

✓ 4D MLEM (motion compensation through DIR in image domain)
✓ “4D Virtual PET” (Gianoli et al, TCRT, in press)
✓ Pre-reconstruction sinogram warping (anticipated motion compensation in sinogram domain)

![Image of PET imaging results](image.png)

Ideal PET image (NCAT phantom)  SW-MLEM  4D-MLEM

free-breathing PET  4D-MLEM

virtual 4D PET  SW-MLEM
Simulated 4D transmission imaging (image contrast through lung masking for lesion detection)

(courtesy of J. Seco)

(courtesy of MF Spadea)
4D eye motion monitoring (under development)

✓ Infra-red eye tracking technique for real-time 3D clipless eye motion monitoring (Fassi et al. JBO, 2012)
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