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POLITECNICO DI MILANO

Time-resolved strategies for tumor targeting at CNAO

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Presentation outline

Motion monitoring technology:

- ✓ Motion monitoring in 4DCT: sufficient as ground-truth ?
- ✓ How to improve ?

Clinical experience in respiratory gated treatments at CNAO

- ✓ Efficacy of device for motion suppression
- ✓ Redundant verification
- ✓ QA

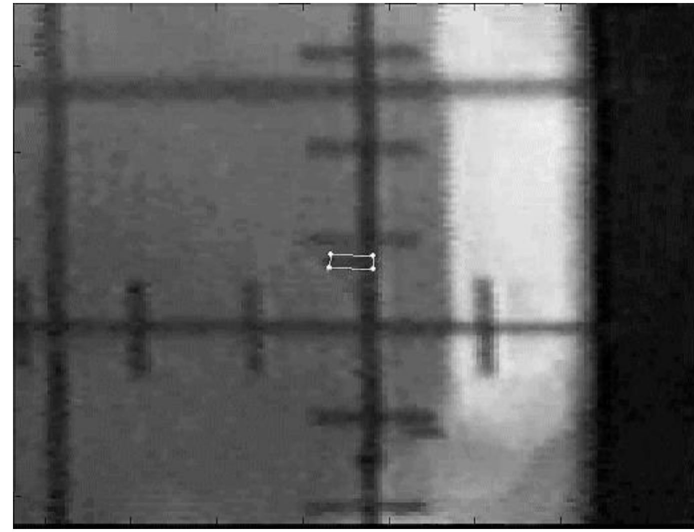
Motion modeling beyond tumor tracking

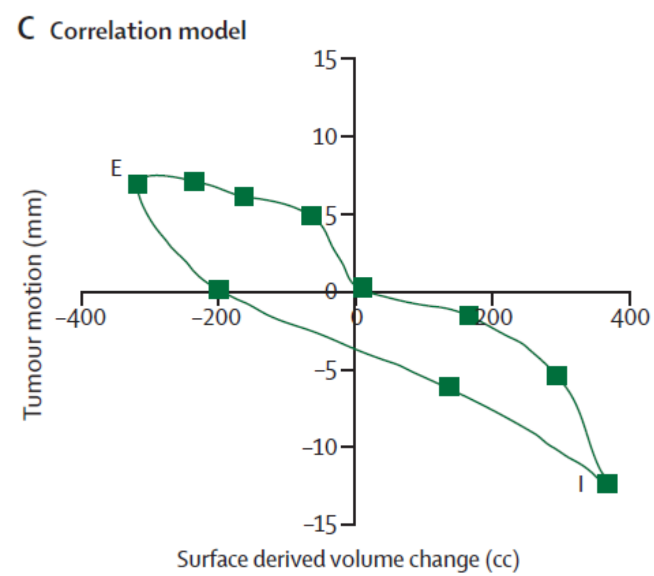
- ✓ Local motion models for tumor tracking
- ✓ Global motion models for adaptive strategies

Tumor motion detection

(Riboldi M., Orecchia R, Baroni G., Lancet Oncol, 2012, Review)

- ✓ Direct tumor imaging
  - ✓ Marker-based methods
    - ✓ X-ray [Shirato et al. *Cancer Sci* 2012;103:1–6, Review]
    - ✓ EM (Calypso^{TM}) [Balter et al. *IJROBP* 2005;61:933–37]
    - ✓ Positron emitters [Chamberland et al., *Med Phys*, 2011, 38:810–19]
  - ✓ Markerless
    - ✓ Ultrasound [Schlosser et al *Med Phys* 2010;37:6357–67]
    - ✓ Real-time X-ray image registration [Gendrin et al *Radiother Oncol* 2012; 102:274–80]
    - ✓ MRI [Fallone et al *Med Phys 2009;*36:2084–88]
    - ✓ 4D-PET [Parodi et al, *Med Phys 2009;36:4230–43*]
- ✓ 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]

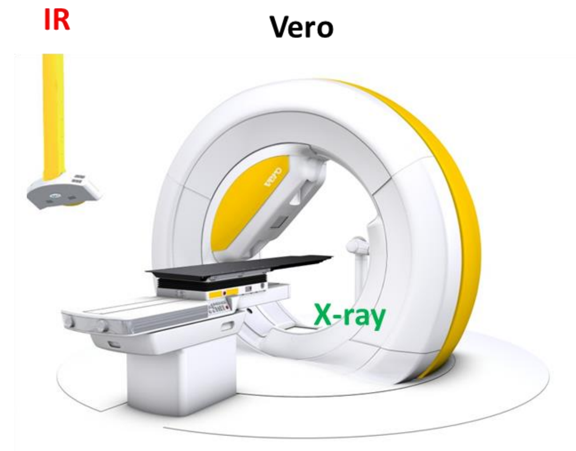


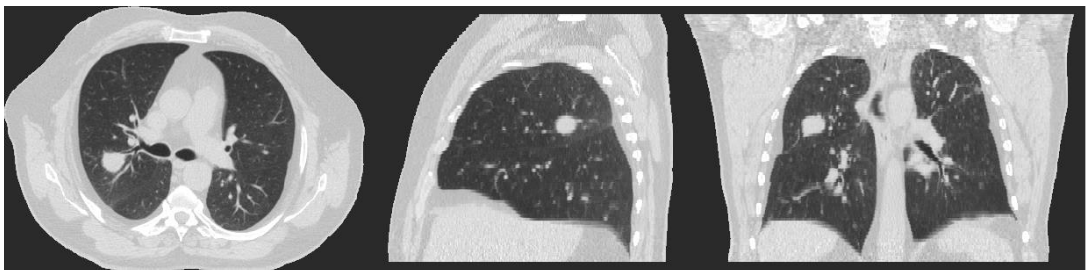


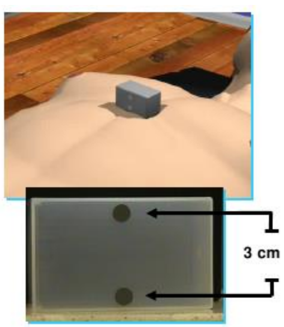
Respiratory correlated / compensated treatment planning and delivery: X-ray radiotherapy

(External) surrogates tracking and position correlation with inner anatomy is state of the art for:

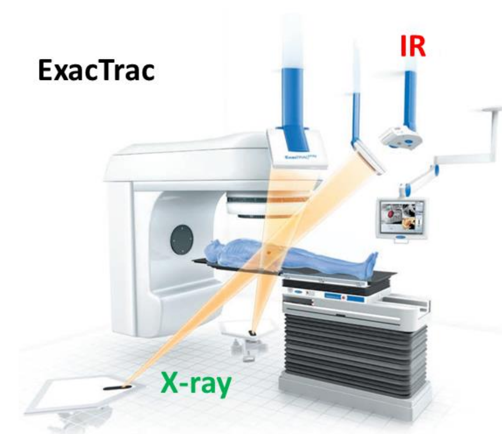
- ✓ time resolved imaging for treatment planning (X-ray and particle)(4D-CT)
- ✓ breath-hold irradiation
- ✓ respiratory gating
- ✓ tumor tracking







Lightweight reflective marker, distance-calibrated



4DCT quality

"Conventional/commercial" 4DCT:

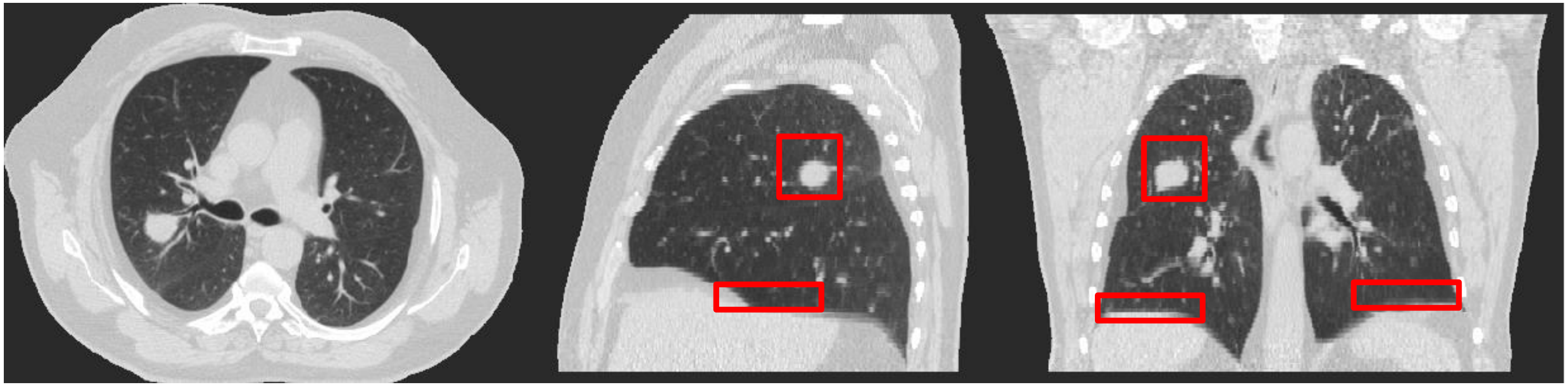
- ✓ relies on a single-dimension breathing signal
- ✓ performs a relatively low temporal resolution in clinical use
- ✓ is prone to motion artifacts resulting in deformation of critical structures

Nevertheless:

- ✓ feeds time-resolved treatment planning and delivery strategies
- ✓ feeds many motion models based on deformable image registration
- ✓ represents the ground truth for motion models assessment

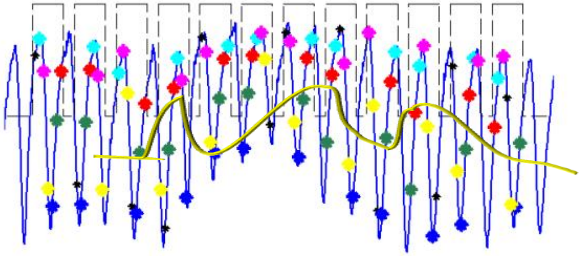
Then ?:

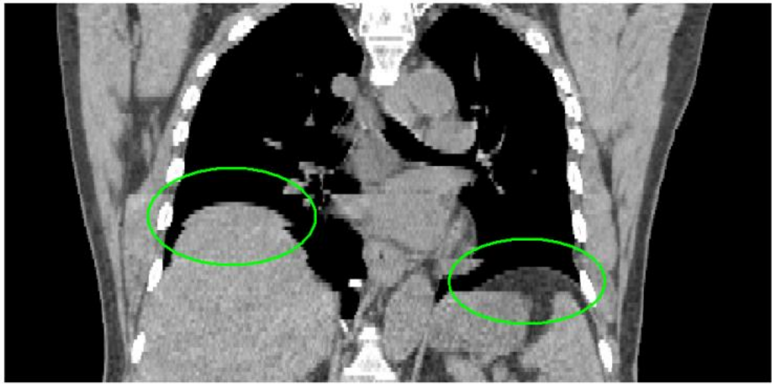
- ✓ Increase the complexity of motion monitoring during CT scanning
- ✓ Adopt more robust imaging modalities for motion description (4D MRI)



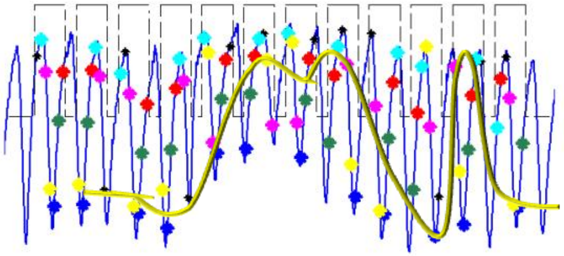
Robust 4DCT resorting – multiple markers

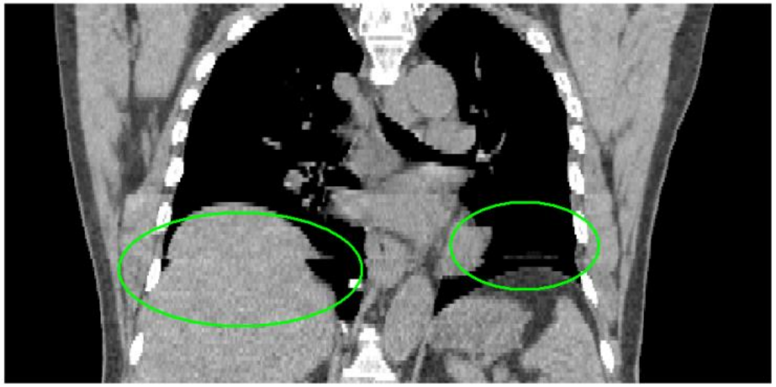
RPM phase



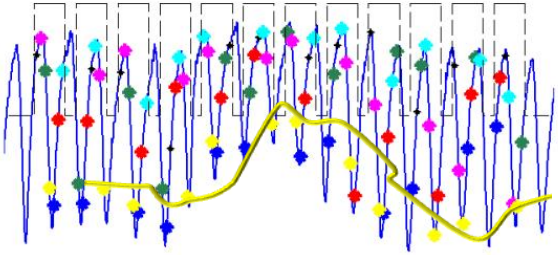


RPM amplitude





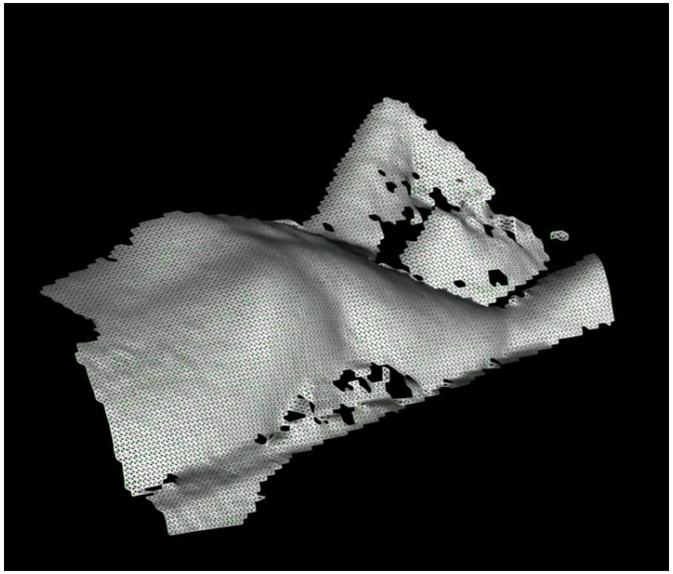
Multiple markers

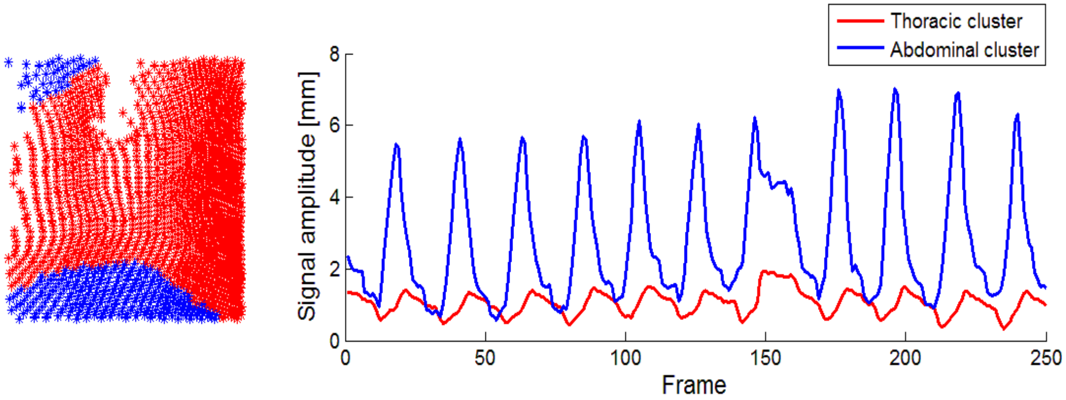


(Gianoli et al, Med Phys 2011)

4D CT based on surface optical tracking

- ✓ Extract the 3D trajectory of non-correspondent surface points acquired with optical systems (deformable mesh registration) (*Schaerer et al, PMB 2012*)
- ✓ Synthesis of a multi-regional respiratory motion model applicable for robust image resorting and/or for respiratory correlated delivery





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

Correlation with diaphragm motion (US) (median ± quartile)(5 subjects)

	PCA	K-means	SOM
Pearson correlation coefficient*	0.90 ± 0.17	0.93 ± 0.06	0.91 ± 0.38
Root-mean-square error* [mm]	0.15 ± 0.10	0.11 ± 0.06	0.20 ± 0.12

Hybrid marker- surface detection

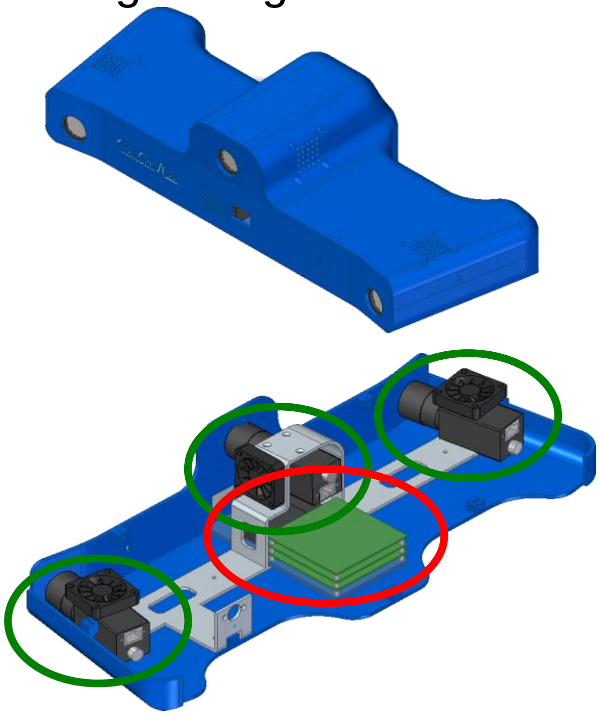
A Politecnico di Milano – CNAO joint project

Concept:

- ✓ Video-based marker detection and 3D reconstruction
- ✓ Video-based pattern light recognition and 3D meshing
- ✓ Single or combined working modality
- ✓ To be used for robust 4DCT and motion monitoring during treatment delivery

Technical features:

- ✓ 3 CMOS cameras (1280*920 resolution)
- ✓ 1 small-size low-heating speckle projector
- ✓ On-board power distribution
- ✓ Ethernet + USB connection
- ✓ Real-time recognition and 3D reconstruction



Hybrid marker- surface detection @CNAO

System installation and testing:

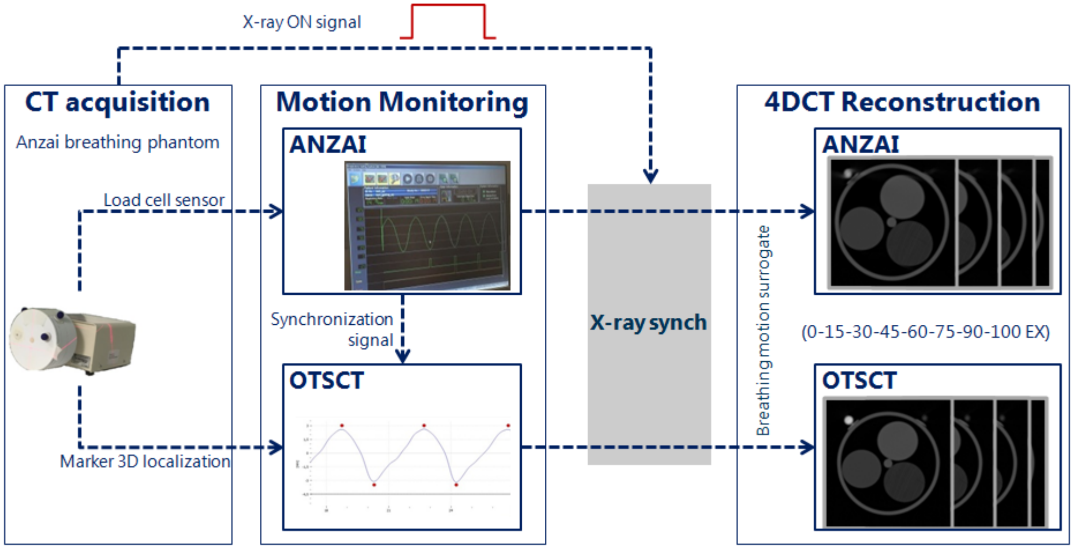
- ✓ Prototype installed in CNAO CT bunker (Siemens SOMATOM Sensation™)
- ✓ Siemens Open Gating Interface™ installed on CT
- ✓ Preliminary testing on system latency, marker 3D reconstruction accuracy and surface detection capabilities
- ✓ Protocol for synchronized use with Anzai™ system
- ✓ Comparison with Anzai-based 4DCT on phantom

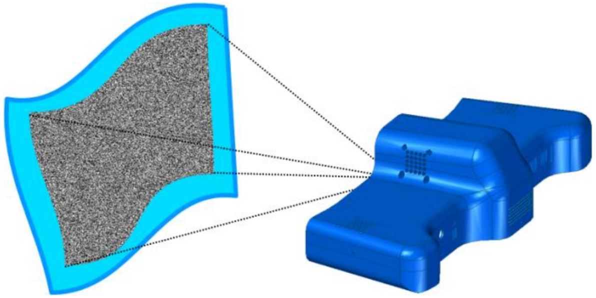
Hybrid marker- surface detection @CNAO

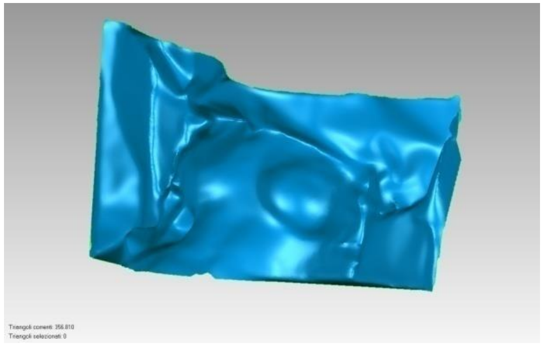
System testing results:

Technical Features – mean(std.dev)

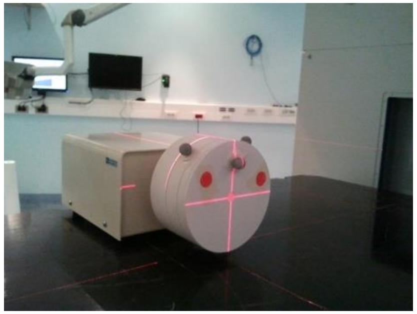
Frame rate (Hz)	30
3D accuracy (mm)	0.41 (0.36)
System latency (ms)	43.7 (2.6)

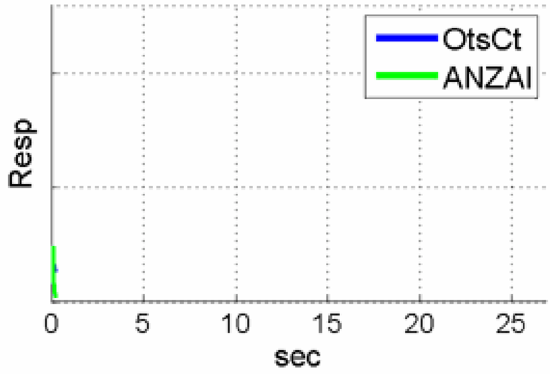


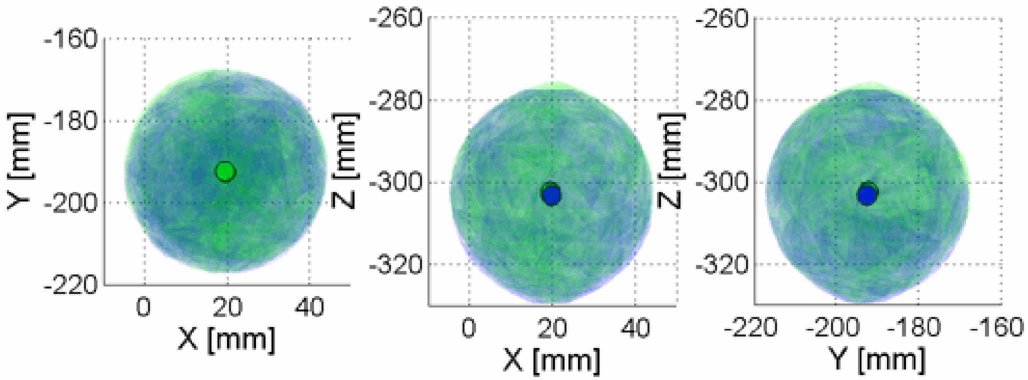




Synchronized Anzai-phantom 4D scanning







	ANZAI median (IQR)	OTSCT median (IQR)	Nominal
Range of motion (mm)	17.2 (0.18)	18.5(0.14)	20.0
(Results of spherical fitting)			
Radius (mm)	24.6 (1.57)	24.4 (1.47)	25.0
Residuals (mm)	0.05 (0.61)	0.01 (0.66)	

Results are presented as median (IQR)

- ✓ Comparable results on motion range and spherical fitting of inner phantom markers
- ✓ First few patient cases acquired with synchronized (Anzai and 1-marker OTS) CT scanning (Anzai-based as reference)
- ✓ Readiness to increase complexity of external surrogates for more robust image rebinning

Respiratory correlated carbon-ion therapy @ CNAO

Methods

- ✓ Started in 2014 with commissioning
- ✓ Gating associated with abdominal compression

Treatment planning

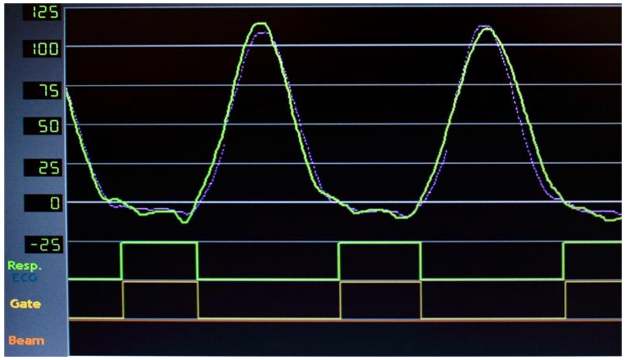
- ✓ 4DMRI for patient-specific assessment of of GTV motion (pancreas cases)
- ✓ 4DCT with Anzai belt
- ✓ Verification of GTV displacements at contiguous respiratory phases around End-of-Expiration

Treatment delivery

- ✓ Active beam rescanning (five layers rescans)
- ✓ Anzai system for detecting gating window
- ✓ Redundant verification by means of CNAO-OTS in treatment rooms

(Ciocca M., …. Baroni G., *Phys Med,* 2016)

	Sex	Age	Lesion site	Field	Sessions	Dose Tot [Gy]
P1	Male	67	Liver	2	12	55.2
P2	Male	61	Pancreas	2	8	38.49
P3	Female	22	Thorax	2	16	76.8
P4	Male	44	Pancreas	2	13	62.4
P5	Female	75	Pancreas	2	12	55.18
P6	Male	40	Vertebra (spine)	3	16	70.4
P7	Female	47	Liver	2	9	44.68
P8	Female	28	Angiosarcoma	2	16	70.4
P9	Female	74	Pancreas	2	12	57.6
P10	Female	75	Liver	2	12	57.6
P11	Female	76	Liver	2	12	55.2



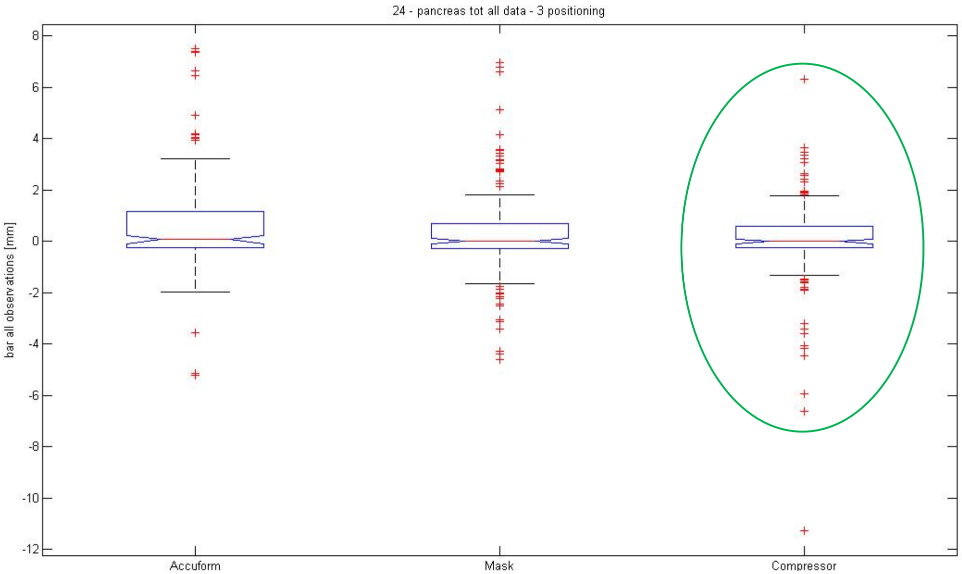
Respiratory correlated carbon-ion therapy @ CNAO

Preliminary 4DMRI motion assessment

- ✓ Prone and supine position
- ✓ Free-breathing, immobilization mask, abdominal compressor

- ✓ MRI sequences: Trufi,T2; Haste,T2
- ✓ Image-based 4DMRI reconstruction (Paganelli *et al*, Med Phys, 2015)
- ✓ Manual contouring on End-of-Inspiration, End-of-Expiration, Intermediate phase

- ✓ Overlay of segmentations
- ✓ Motion quantification

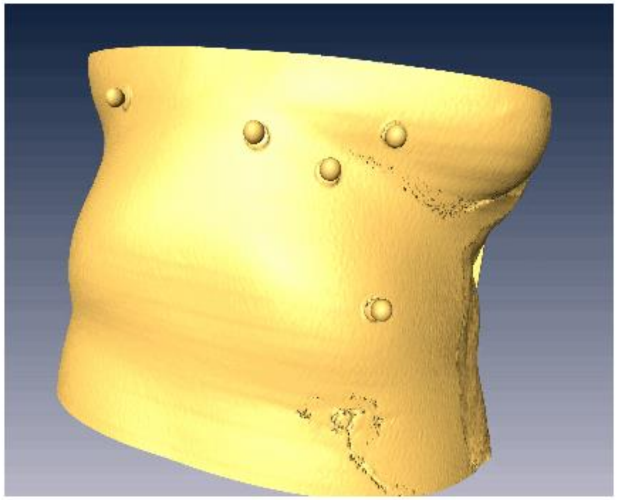


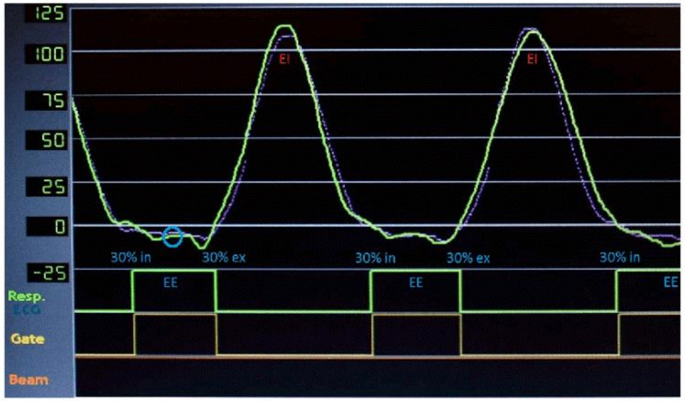
4DCT-based GTV motion assessment

- ✓ Manual contouring at End-of-expiration phase
- ✓ B-spline deformable registration applied for GTV contour propagation on -30% and +30% respiratory phase
- ✓ GTV (and relevant OARs when required) motion assessed for respiratory gated treatment verification
- ✓ Motion quantified as GTV (and OAR when relevant) centroid displacement

	30insp-0exhale	0exhale-30exp	100insp-0exhale
Median [mm]	0.91	0.80	4.89
IQ [mm]	1.73	1.51	1.76

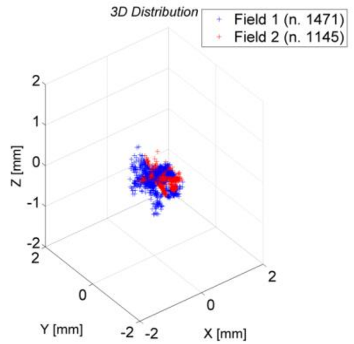
- ✓ Patient specific CTV-GTV margins optimized on patient-specific basis
- ✓ Dosimetric verification

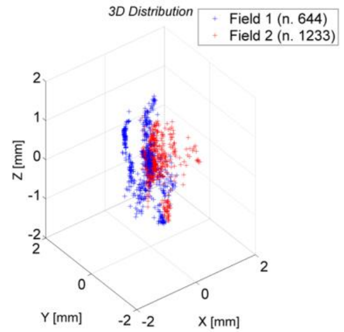


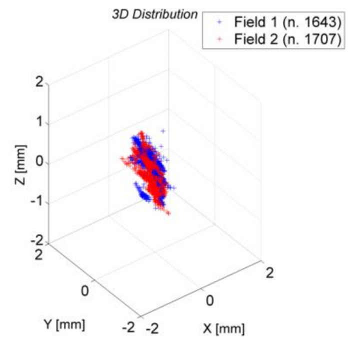


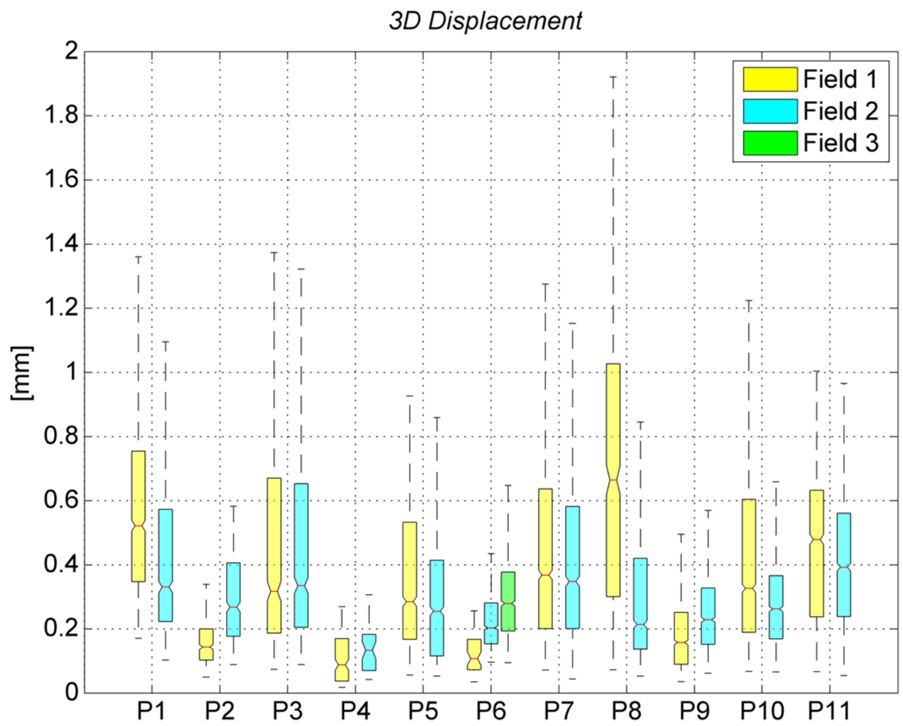
Optical tracking verification at delivery

- ✓ Surface landmarks position checked at each “beam-on” provided by Anzai system
- ✓ Submillimetric deviations observed in average
- ✓ Outliers within GTV-CTV margins consistently





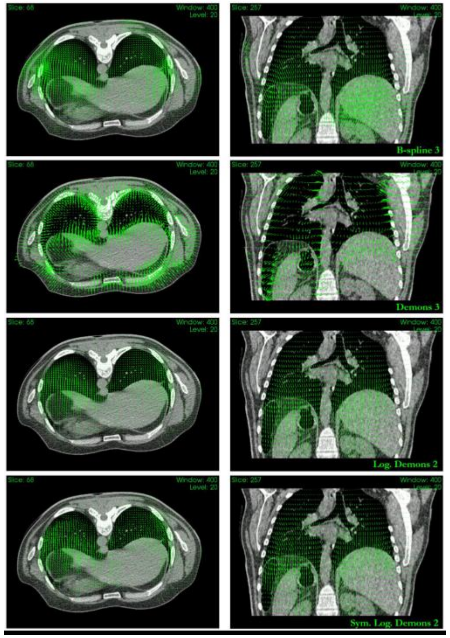




Respiratory correlated carbon-ion therapy @ CNAO

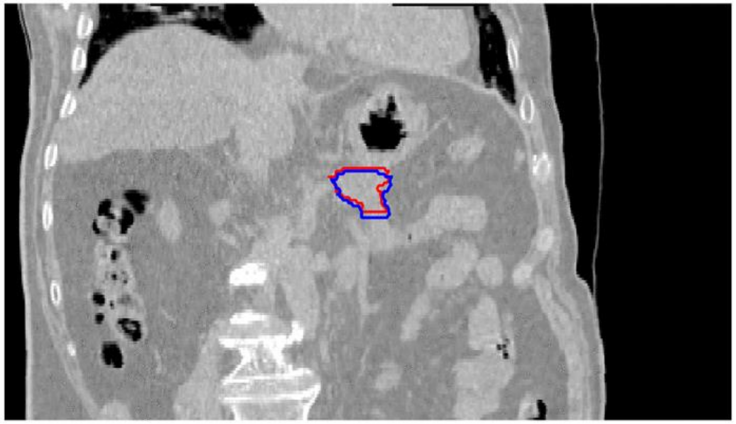
Model based QA of respiratory gated treatment

(Meschini G., …., Baroni G., *Phys Med*, 2017)



- ✓ Extract breathing surrogate signal (phase and amplitude)
- ✓ Feed global/local image-based model
- ✓ Estimate/track position of GTV (and other relevant structures) during “beam-on” phase (residual motion assessment)
- ✓ Propagate GTV (and other relevant structures) contour to beam-on phases
- ✓ Quantify motion and compare with margins
- ✓ Dosimetric assessment (*work in progress*)

30%



Time resolved delivery in particle therapy

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

1. **Experimental validation** with scanned beams

   → **local** correlation models (**target position**)

2. **Global 4D modeling**

   → **4D CT** prediction for range variation estimation

Tumor tracking in particle therapy – proof of principle @GSI

Experiment

- *Robotic ph*
  - ✓ Reproc ... ependent)
  - ✓ Regula
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  - ✓ Include
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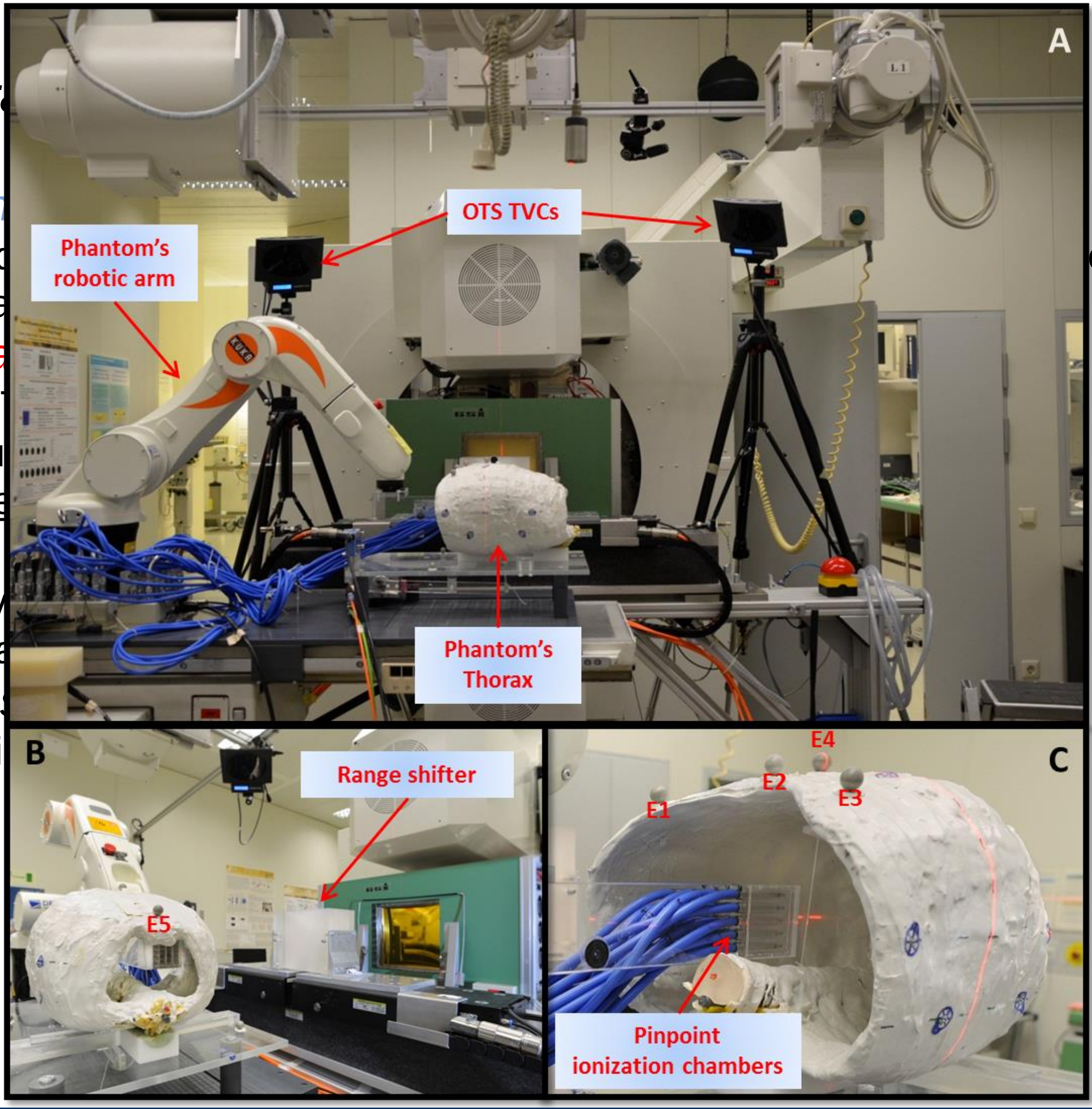
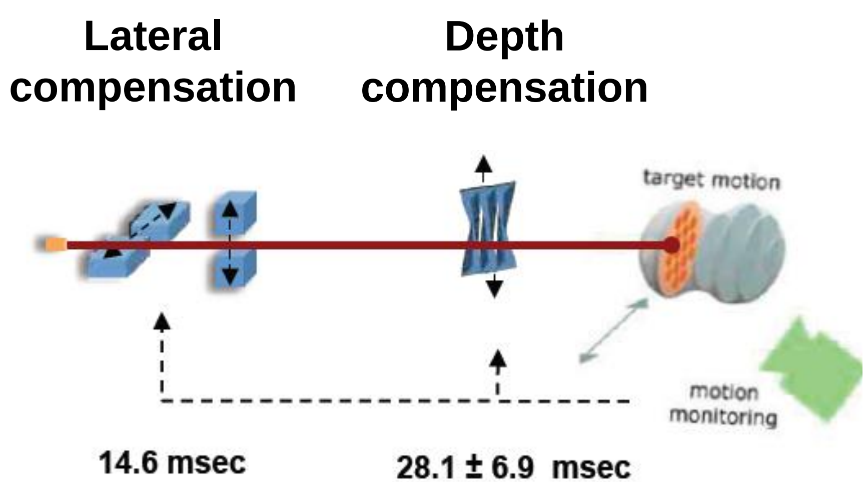


Latency compensation

Commissioning of OTS / TCS integration:

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



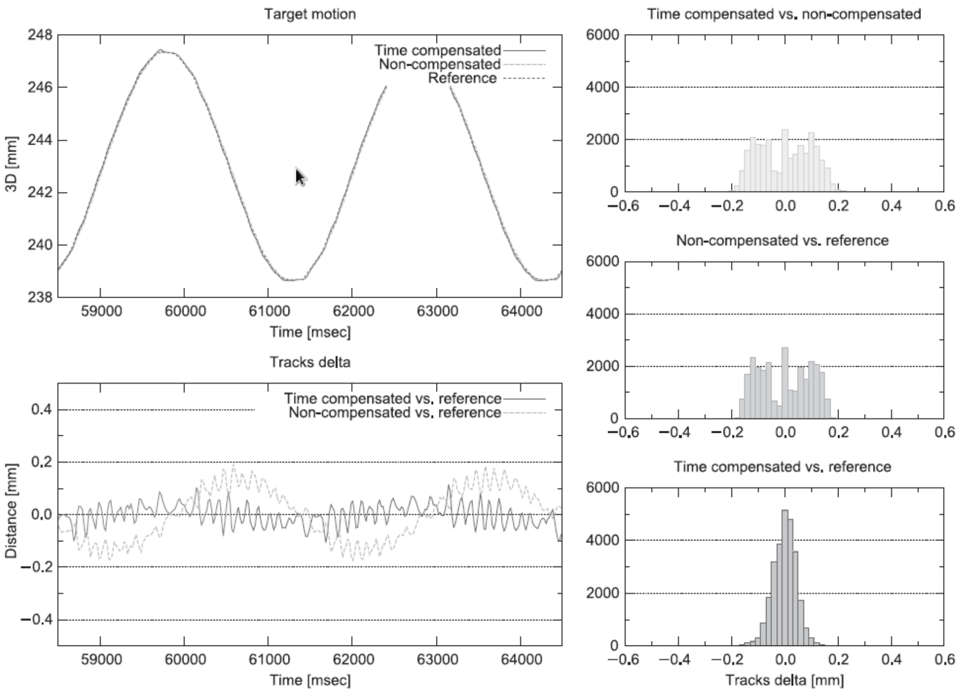
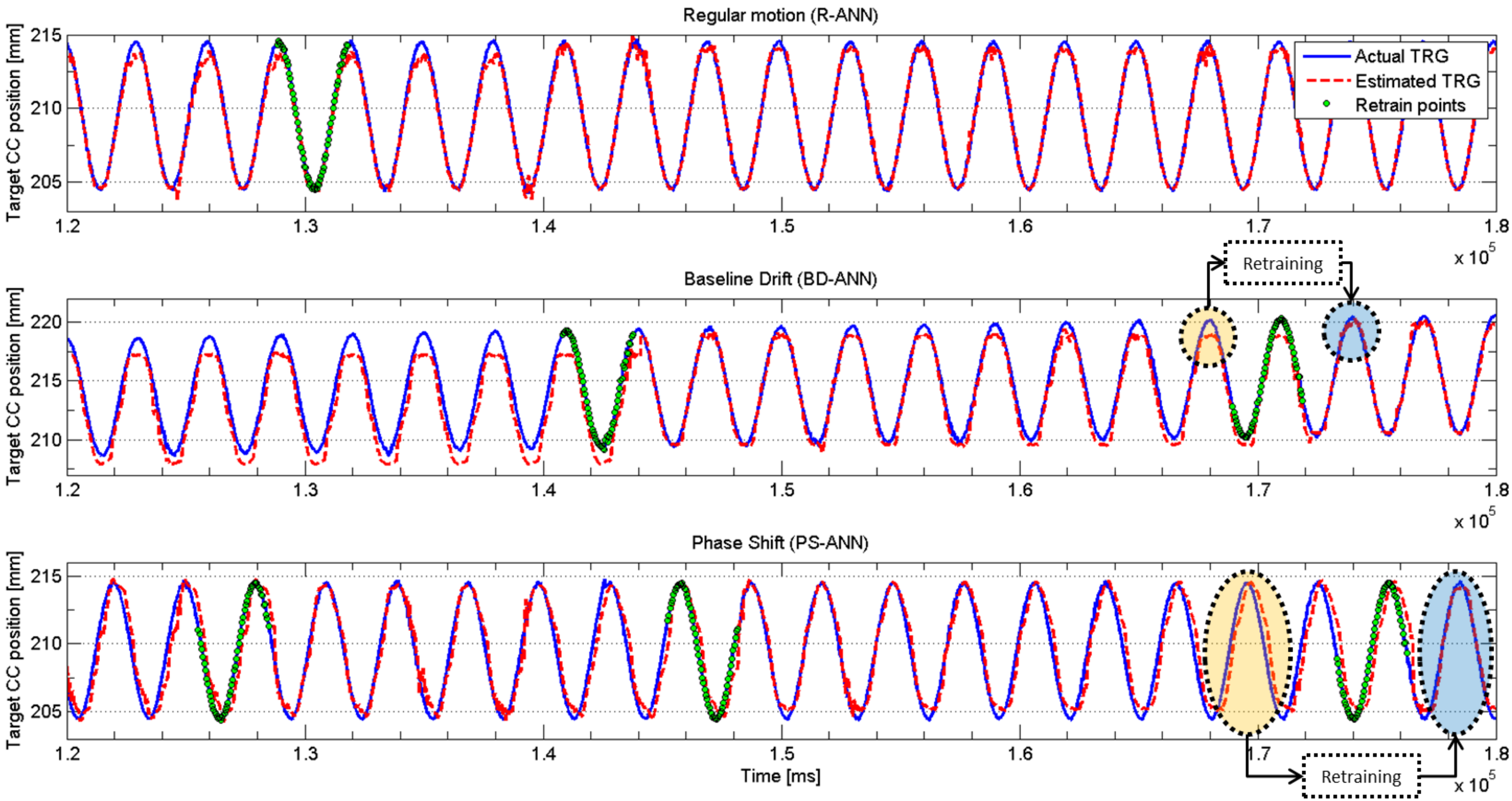


Figure 6: Interpolation and time prediction accuracy. Left panel: reference, time-compensated and non-compensated signals overlay (top), time-compensated and non-compensated delta wrt reference (bottom) for two breathing cycles; Right panel: Error distribution for compensated wrt non-compensated (top), non-compensated (middle) and compensated (bottom) wrt reference.

(Fattori *et al*, Techn Cancer Res Treat, 2013)

Performance of correlation models

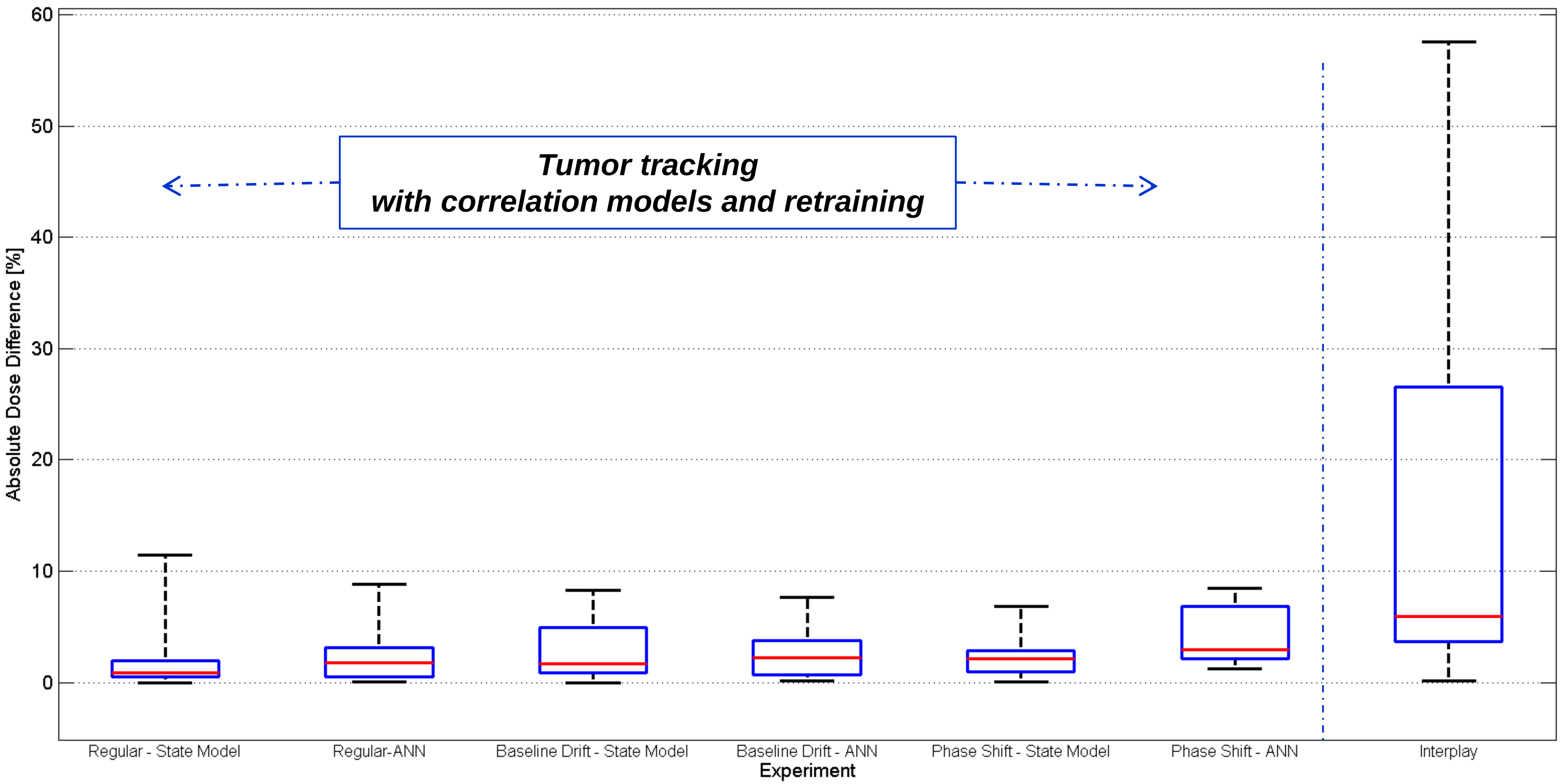


Overall dosimetric results

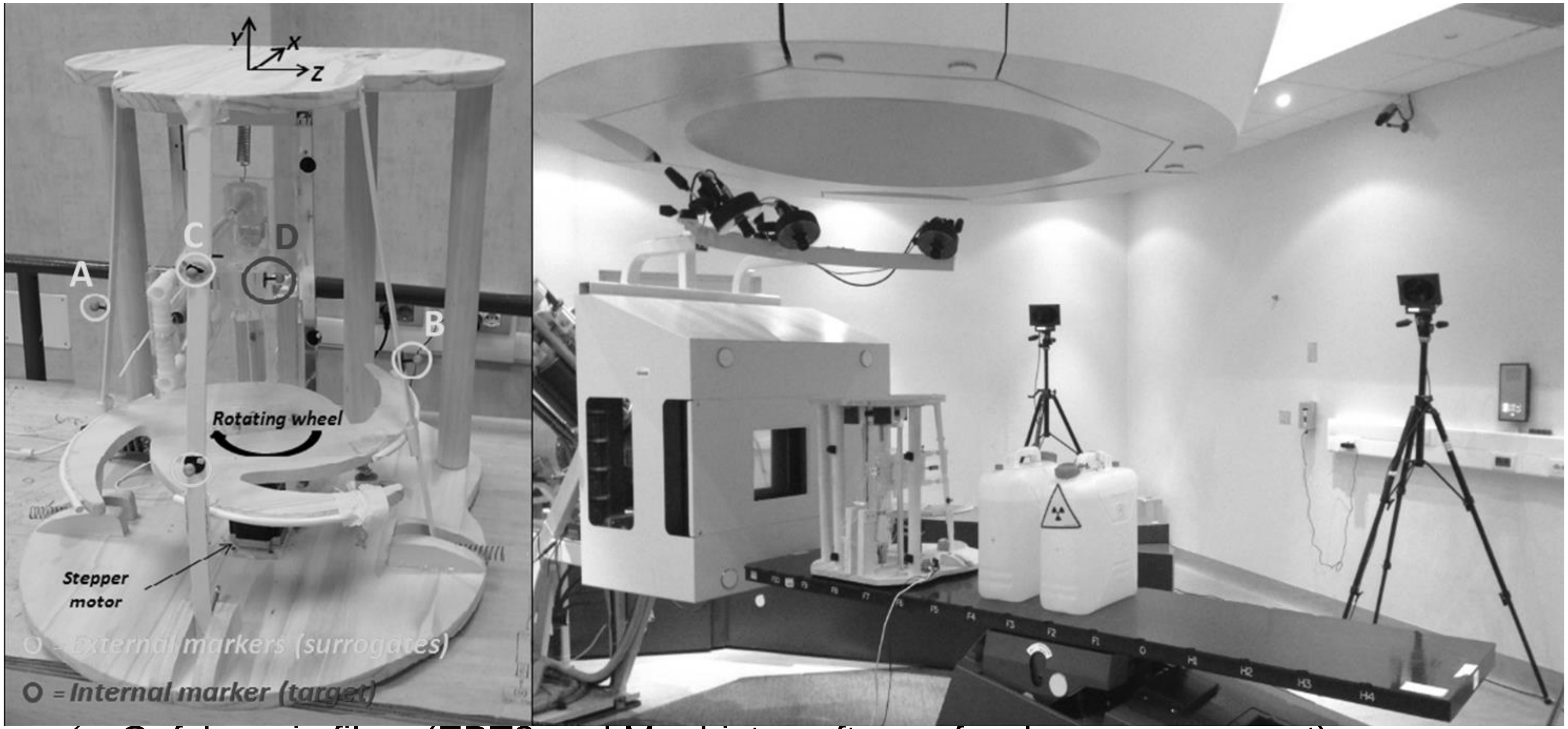
Dose differences w.r.t. static irradiation

- ✓ Static irradiation = beam fixed, static target
  → Measurement of nominal delivered dose
- ✓ '*Interplay*' = beam fixed, taget moving
  → Measurement of «motion blurred» dose

(Seregni *et al*, PMB, 2013)



Experimental set-up (CNAO, June 2013)



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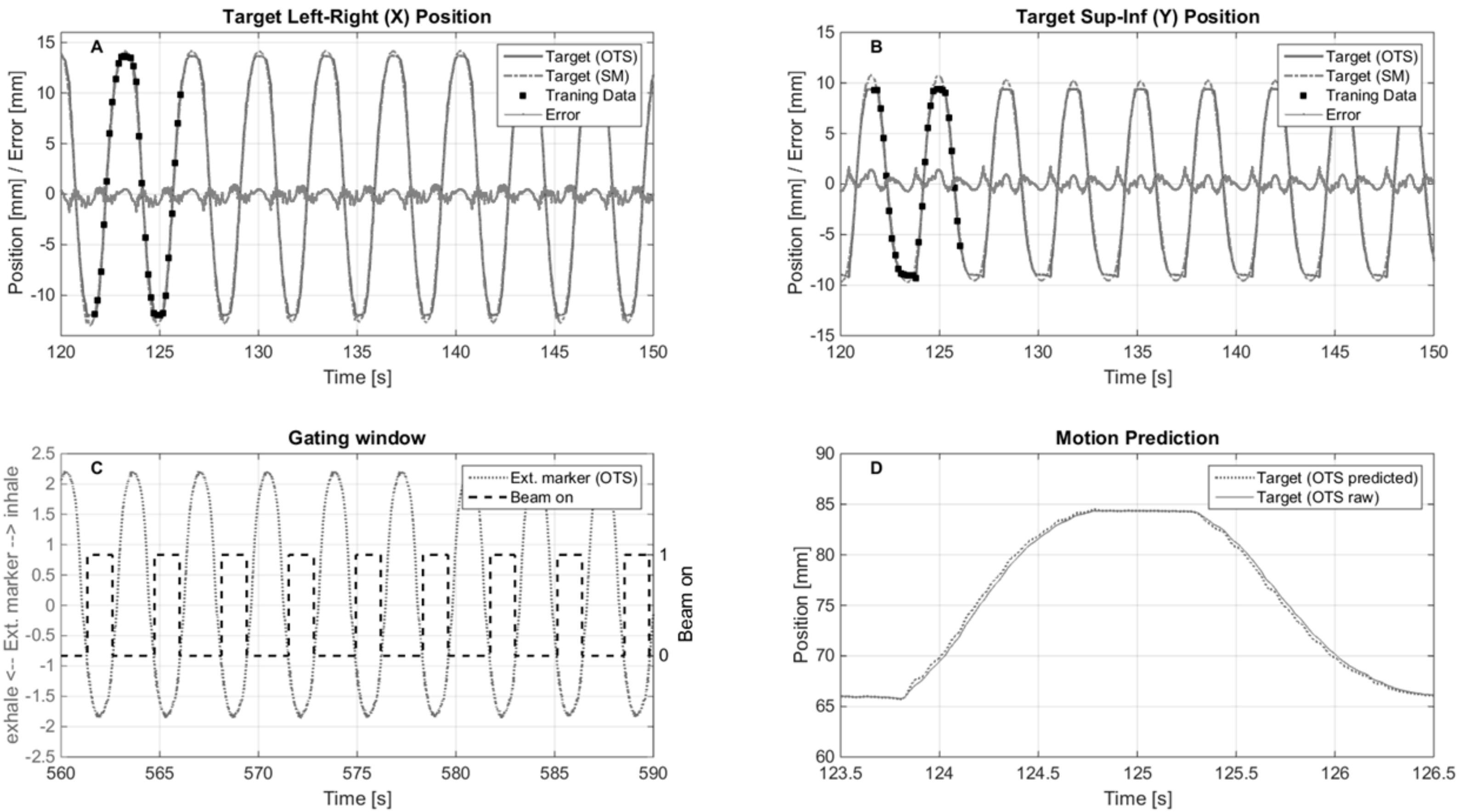
-
-
-
  - ✓ Gafchromic films (EBT3 and Mephisto software for dose assessment)
  - ✓ Measurement area 60x60 mm^2

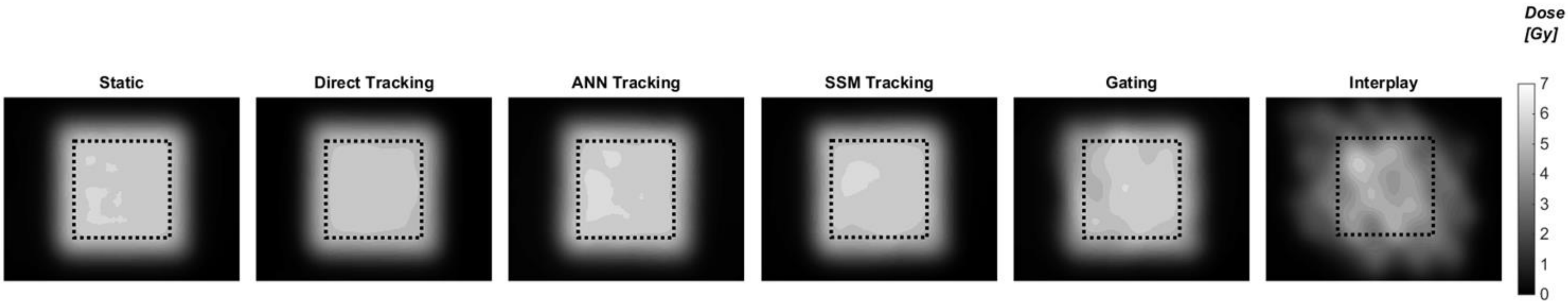
Performance of correlation models (for tracking and gating)

- ✓ Estimated tracking traces (ANN and SSM)
- ✓ 20.6 msec motion prediction for communication delay compensation



Overall dosimetric results

Dose differences w.r.t. static irradiation



	Experiment	Static	Direct Tracking	ANN Tracking	SSM Tracking	Gating	Uncompensated (interplay)
Dose (nominal 6 Gy)	Min : Max	4.70 : 5.95	4.68 : 5.48	4.78 : 6.03	4.38 : 5.98	4.15 : 6.08	1.89 : 5.51
	Median	5.49	5.48	5.57	5.52	5.62	4.08
Inhomogeneity index	ΔIC	--	-0.10	0	+0.10	+0.20	+1.65
Conformity index	ΔCI	--	-0.01	0	0	-0.13	-0.93

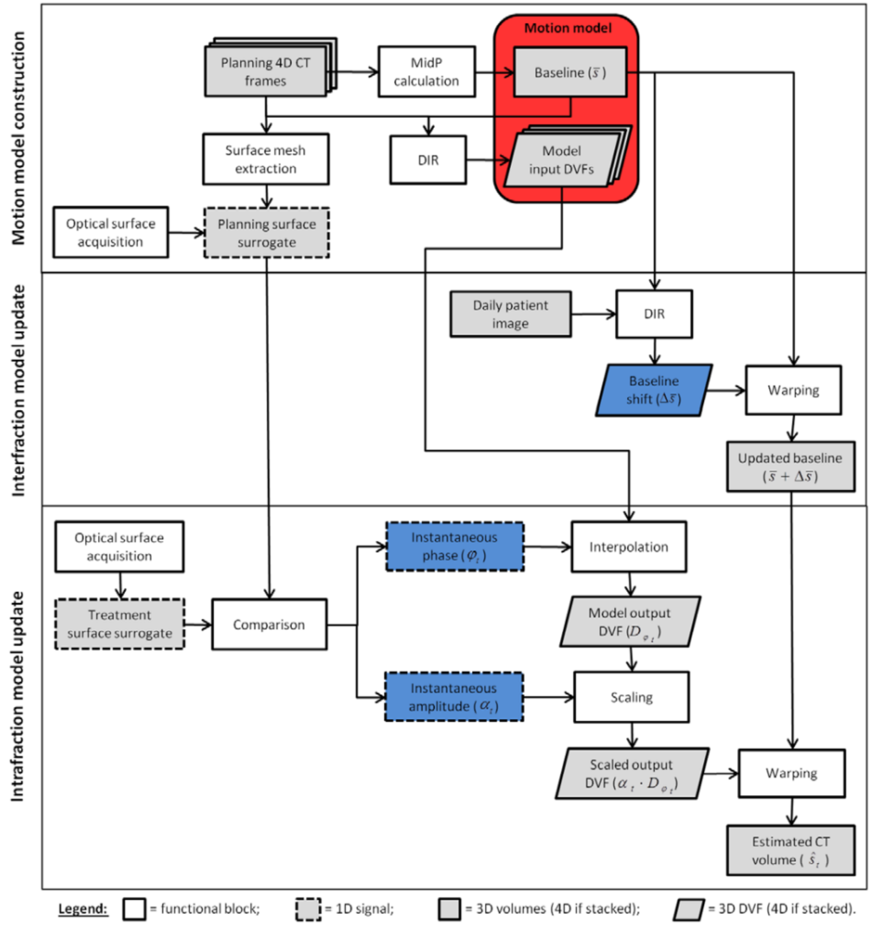
(Fattori *et al*, NIMA-D, *2016*)

Motion modeling beyond tumor tracking

- ✓ Global motion models for adaptive strategies
- ✓ Estimation of anatomical changes due to breathing irregularities

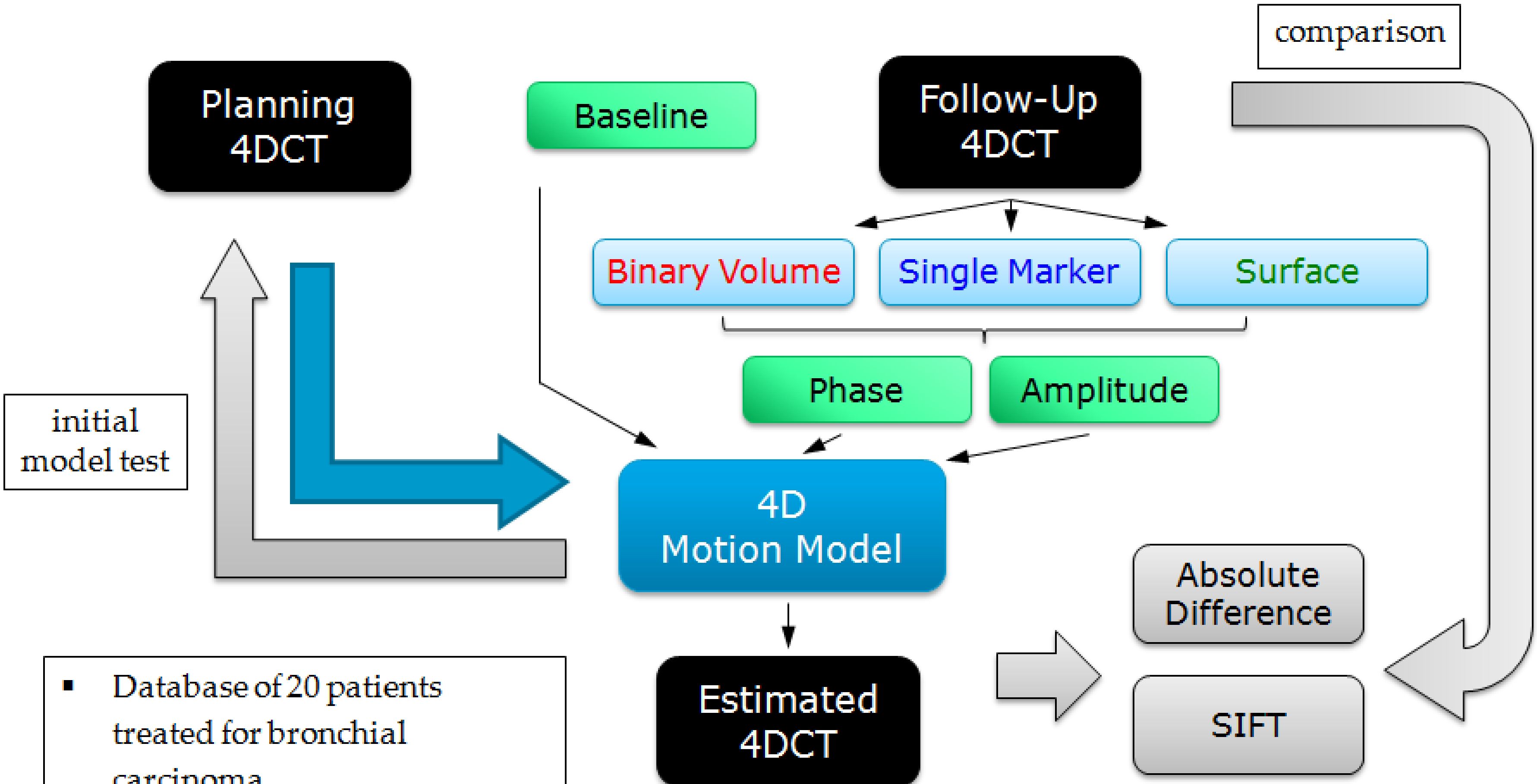
Global modelling: 4DCT-of-the-“day”

- ✓ *4D Motion Modeling* was introduced[1,2,3] to predict CT volumes corresponding to arbitrary respiratory phases
- ✓ Respiratory surrogates are used to estimate CT volumes by means deformable image registration



[1]Vandemeulebroucke *et al.*, *Med Image Comput Comput Assist Interv*, 2009
[2]Fassi *et al.*, *Int J Radiat Oncol Biol Phys*, 2014
[3]Fassi *et al.*, *PMB*, 2015

Workflow and patient data



- Database of 20 patients treated for bronchial carcinoma
- Two 4DCT sets within 30 days

(Woelfelschneider J.,Fassi A., Seregni M., ... Baroni G., Bert C. Med Phys, *in press*)

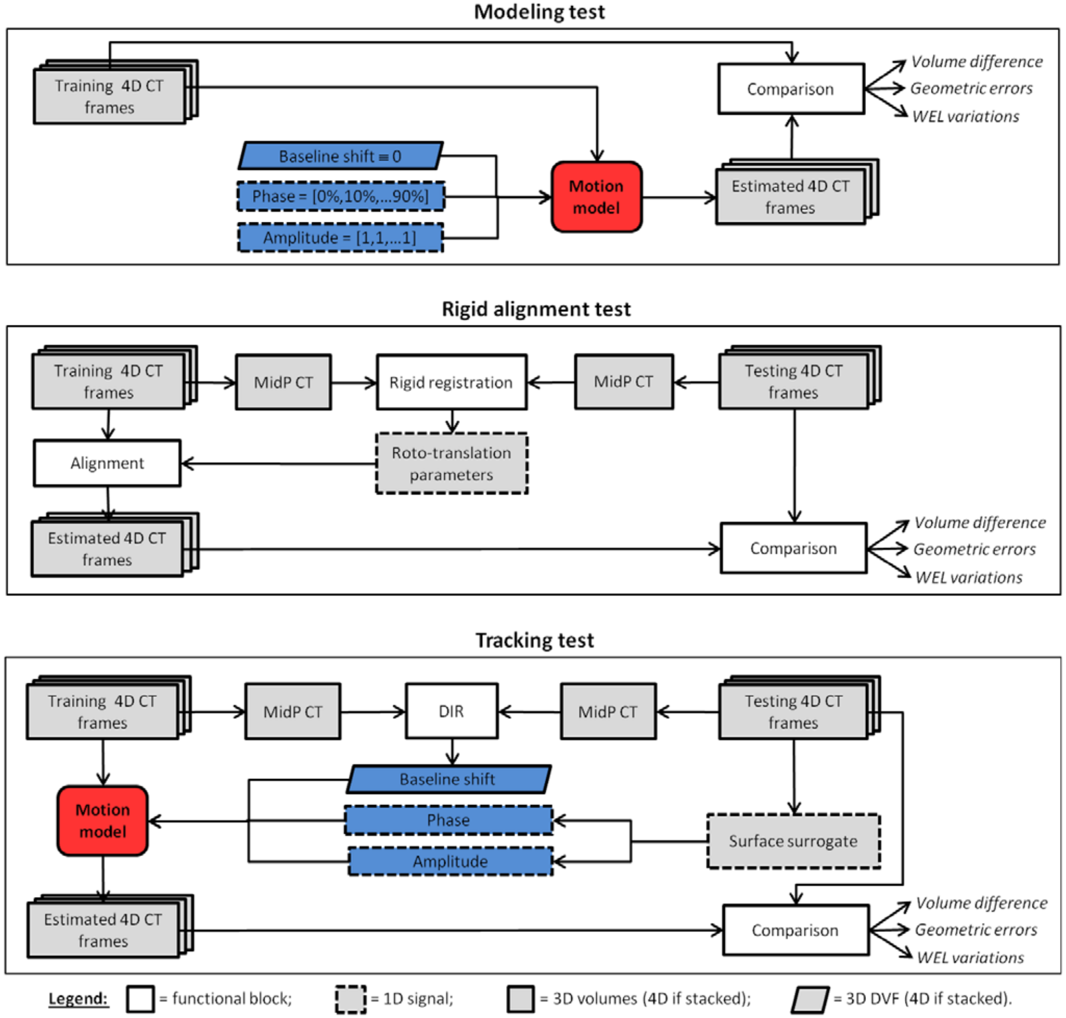
Global modelling: 4DCT-of-the-“day”

- ✓ 7 patients database with repeated 4D CT (1day-18 days time interval)
- ✓ Outcomes: HU differences, COM differences, WEL variations

Model testing (reference)

Worst case (rigid registration)

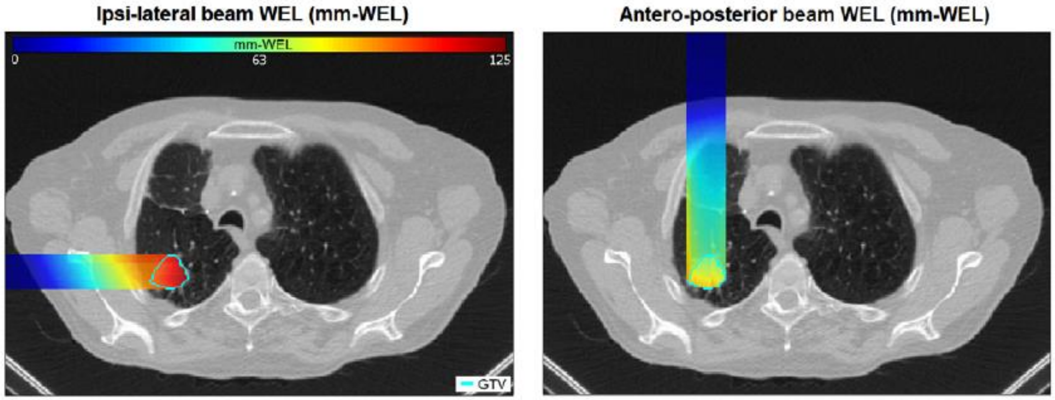
Surrogate driven warping (DIR model)



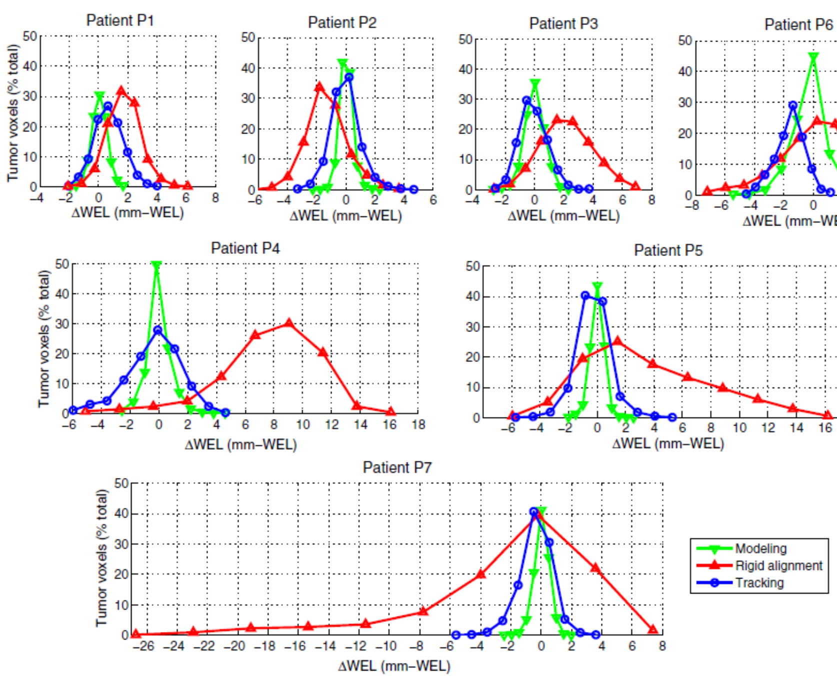
(Fassi *et al.*, *PMB*, 2015)

Global modelling: 4DCT-of-the-“day”

✓ WEL variations in GTV voxels and computational cost for ROI



according to Jaekel *et al.*, *Med Phys*, 2001



Fassi *et al.*, *PMB*, 2015

	Absolute ΔWEL (mm-WEL)					
	Ipsi-lateral beam			Antero-posterior beam		
Patient	Modeling	Tracking	Rigid	Modeling	Tracking	Rigid
P1	0.42 ± 0.06	1.00 ± 0.23	1.73 ± 0.15	0.61 ± 0.24	0.95 ± 0.60	1.04 ± 0.25
P2	0.30 ± 0.05	0.67 ± 0.10	1.67 ± 0.39	0.65 ± 0.22	1.30 ± 0.53	2.71 ± 0.32
P3	0.49 ± 0.15	0.72 ± 0.22	2.33 ± 0.10	0.72 ± 0.28	1.03 ± 0.60	2.65 ± 0.39
P4	0.56 ± 0.42	1.36 ± 0.92	7.95 ± 0.56	0.74 ± 0.53	1.40 ± 0.32	4.49 ± 0.43
P5	0.38 ± 0.10	0.85 ± 0.16	4.31 ± 0.42	0.81 ± 0.39	1.64 ± 1.03	3.90 ± 0.63
P6	0.70 ± 0.67	1.55 ± 0.72	1.86 ± 0.64	0.80 ± 0.80	1.89 ± 0.83	2.43 ± 0.59
P7	0.37 ± 0.03	0.79 ± 0.14	3.90 ± 0.11	0.31 ± 0.06	0.48 ± 0.13	9.39 ± 0.42
Median ± IQR	0.41 ± 0.20	0.90 ± 0.43	2.33 ± 2.21	0.70 ± 0.45	1.33 ± 0.81	3.03 ± 1.94

	Computational time (s)	
Patient	Ipsi-lateral beam	Antero-posterior beam
P1	0.46 ± 0.03	0.48 ± 0.03
P2	0.64 ± 0.05	0.75 ± 0.05
P3	0.39 ± 0.02	0.60 ± 0.04
P4	0.38 ± 0.02	0.34 ± 0.02
P5	0.40 ± 0.04	0.46 ± 0.04
P6	0.17 ± 0.01	0.15 ± 0.02
P7	0.56 ± 0.04	0.48 ± 0.02
Median ± IQR	0.42 ± 0.18	0.48 ± 0.22

Wrap-up

- ✓ Tumor tracking is a reality in X-ray radiotherapy and relies on external-internal correlation based on the integration between intermittent X-ray imaging and optical tracking technologies

- ✓ The feasibility of the same strategy has been demonstrated technically in active scanning particle therapy (of course alternative approaches exist)

- ✓ On-line global motion modeling driven by external surrogates may represent a way to enrich tumor position estimation with information on range uncertainties due to variable breathing patterns

- ✓ Artifacts-free and reliable 4DCT imaging and deformable image deformation methods are needed

- ✓ Particle therapy of mobile targets is a reality on the “safe path” (gating, rescanning)

- ✓ Need to assess the clinical advantages vs. technical effort of the “tracking path”

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