PAUL SCHERRER INSTITUT PSI

Ye Zhang, PhD :: tenure-track scientist :: Centre for Proton Therapy :: PSI

Pencil Beam Scanned proton therapy:

Challenges and Opportunities for the 4D treatments

About myself

since 2018/07 — Paul Scherrer Institut, **Tenure track scientist**

2016-2018 — Paul Scherrer Institut, **Postdoc** researcher

2014-2016 — Varian Medical Systems, Research **Scientist**

2010-2013 — ETH Zurich & Paul Scherrer Institut (Switzerland), **Ph.D** in Medical Physics

2008-2010 — KTH Royal Institute of Technology (Sweden), **M.Sc** in Medical Engineering

2004-2008 — Xi'an Jiaotong University (China), **B.Sc** in Biomedical Engineering

1986 — Born and grew up in Xi'an, China

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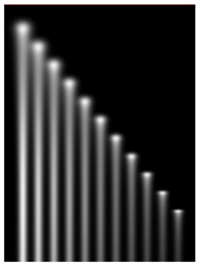
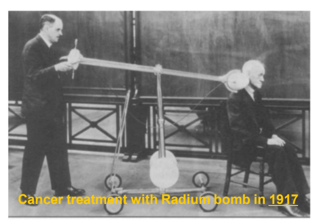


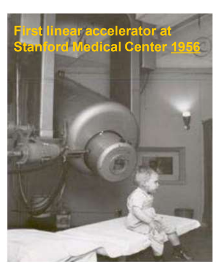
The principle of radiation therapy

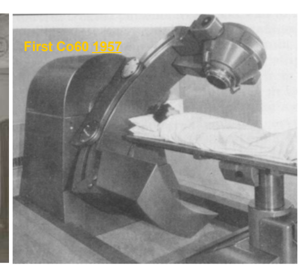
- Energy deposited by radiation (dose = J/kg or Gray) can sterilize cells through the production of free-radicals inside the cell.
- The higher the delivered dose to the whole tumour, the higher the probability of controlling it.

BUT…

- Normal tissues will also be damaged and sterilized by irradiation in a similar way.







The art of radiotherapy then, is to concentrate the dose in the tumour whilst sparing the surrounding normal tissues as much as possible.

Driven force for innovation in RT

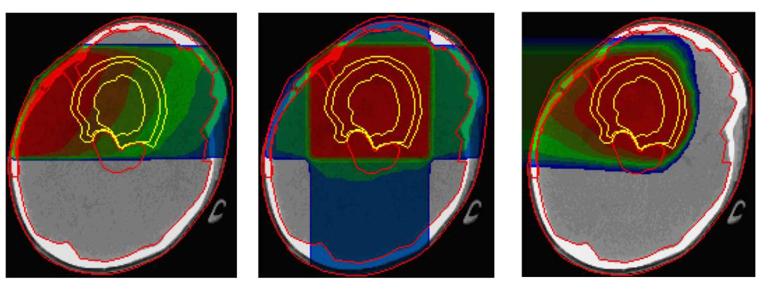
<dose is a surrogate for the biological effect>

Main goal of radiation therapy is to Put the dose to where the target is

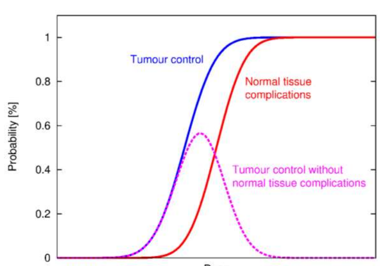
This means

- the right = necessary amount of dose
- in optimized = most efficient and best tolerable fractionation
- to the correct location = large enough, but as small and conformal as possible

TCP and NTCP



6M(e)V photon 1-field   6M(e)V photon 4-field   138MeV proton 1-field



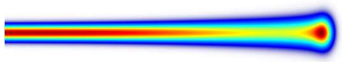
TCP Tumour control probability – generally a term used in modelling tumour radiation responses

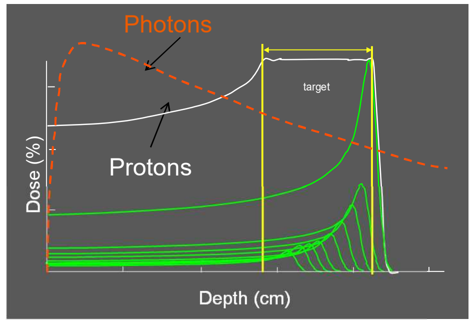
NTCP Normal-tissue complication probability – generally a term used in modelling normal-tissue radiation responses

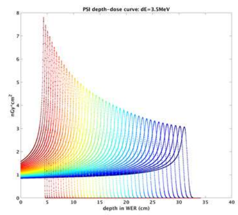
Optimization:
Maximize TCP and minimize NTCP

Physical advantages of proton therapy

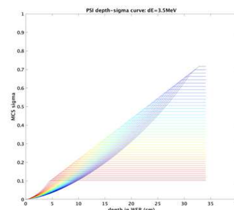
- dose conform to target
- dose reduced to OARs
- flexible for dose delivery
- less second neutrons



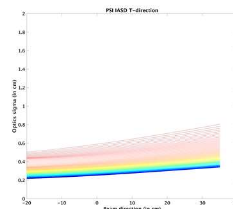




Proton depth-dose curve



Nuclear Coulomb scattering



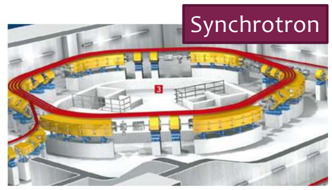
Initial beam optics

Beam delivery system for proton therapy

Cyclotron

For therapy application
- Energy: 75-245MeV
- Range: 5-35 cm in water

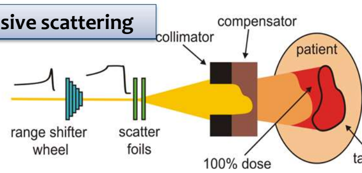
Synchrotron



Stable and continuous beam
High beam current
Intensity modulation
Single particle (proton)
Fixed energy

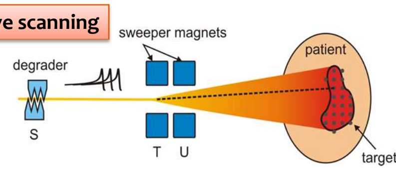
High energy
Any particle
Low radioactivity
Limited average intensity (ring filling)
Spill structure – discontinued beam
Noisy beam intensity

Passive scattering



- Delivery dose to the whole target ***simultaneously***

Active scanning

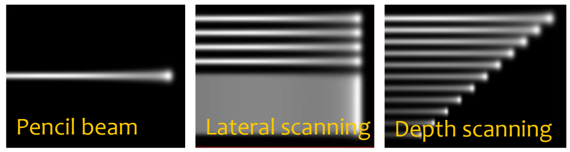


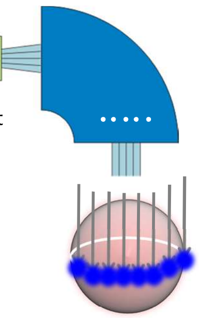
- Delivery dose to the whole target ***sequentially***

Lateral spread: *Active* scanning

- Charged particles can be directed by electro-magnetic fields
- Experimental set-up to demonstrate technical feasibility of scanning with protons (PSI, **1990**)
- For conformal scanning
  - Scanner magnets

  and / or
  - Patient table motion
- Similar developments also at GSI (Germany) and Japan





Delivery dose to the whole target ***sequentially***

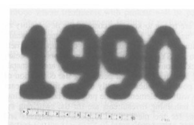
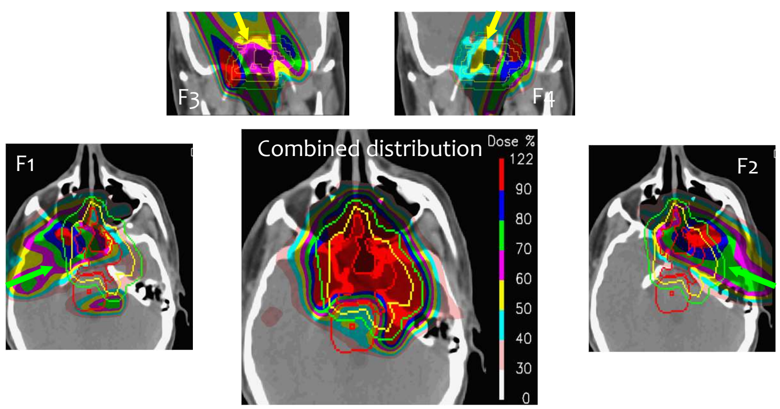


Fig. 4: X ray film irradiated with the 200 MeV proton beam using the spot scanning method.

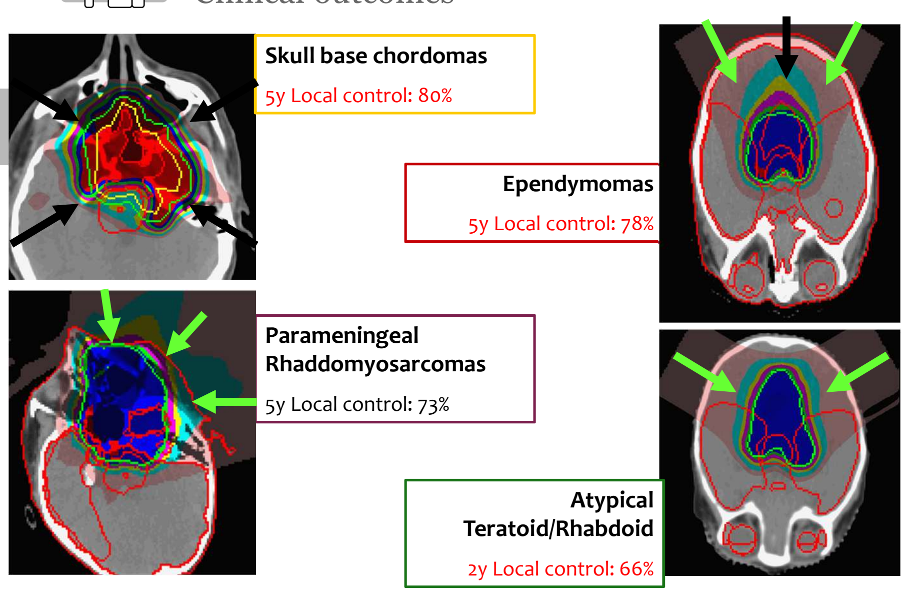
IMPT - Intensity Modulated Proton Therapy



Each individual field is highly in-homogenous (in dose) across the target volume (c.f. SFUD plans)

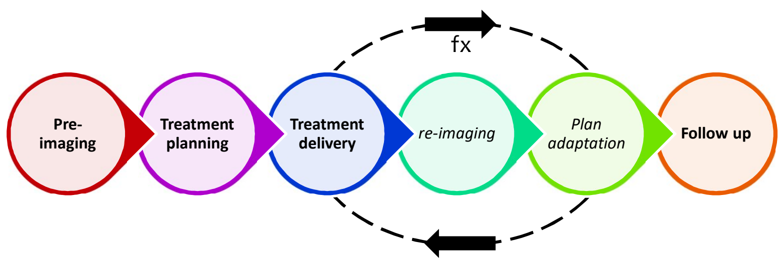
Proton Therapy in Paul Scherrer Institut

Clinical outcomes



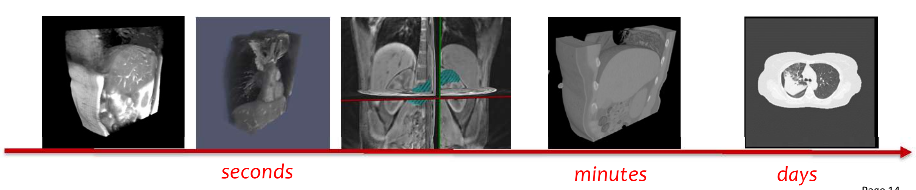
Challenges for PBS PT for mobile tumour treatment

Organ motion and 4D treatment

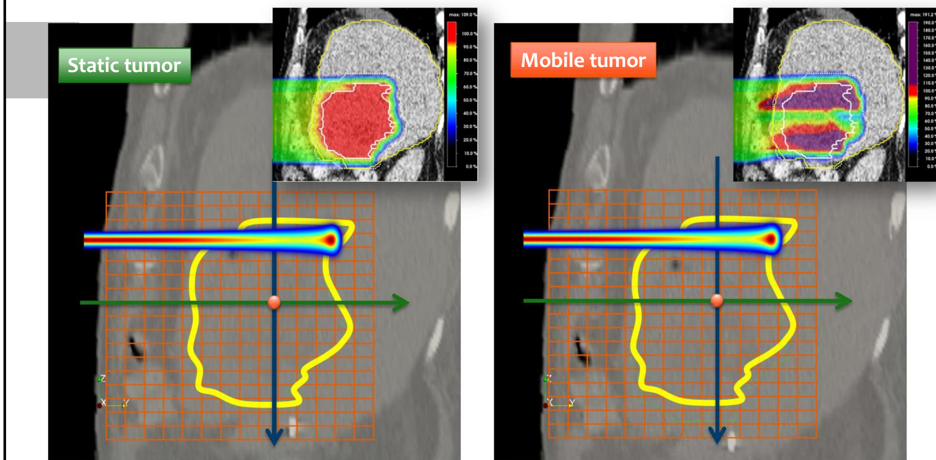


Generally, "motion" can be interpreted as any geometric _difference_ occurring between the phase of planning and the phase of dose delivery

- Intra-fractional: respiration, heart beating (deformable movement)
- *in between*: digesting movement, muscle relaxation (deformation, drift)
- Inter-fractional: anatomy variation (grows, shrink, shift)



Uncertainties for *intra*-fractional motion



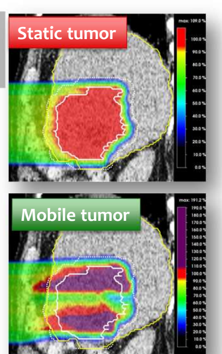
Effects of respiratory motion on dose uniformity with a charged particle scanning method

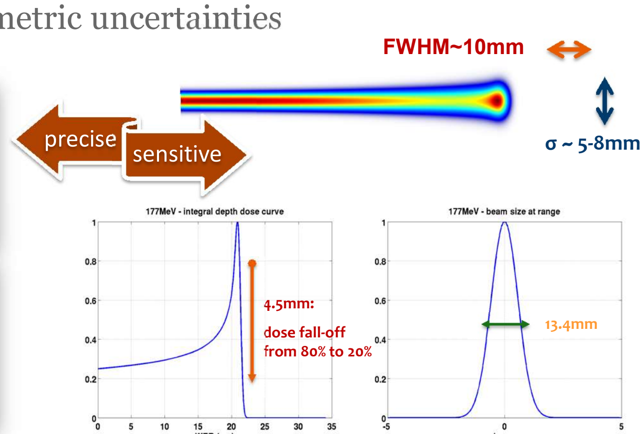
Mark H Phillips†, Eros Pedroni, Hans Blattmann, Terence Boehringer, Adolf Coray and Stefan Scheib
Paul Scherrer Institute, CH-5234 Villigen-PSI, Switzerland

Received 21 December 1990, in final form 25 July 1991

PMB 1992

Characteristics of the motion-induced dosimetric uncertainties





- lateral dose conformity — *Universal for any external RT*
- dose homogeneity — *only for scanning delivery due to lateral narrow beam profiles*
- distal dose conformity — *for particle therapy due to the sharp Bragg peak fall-off*

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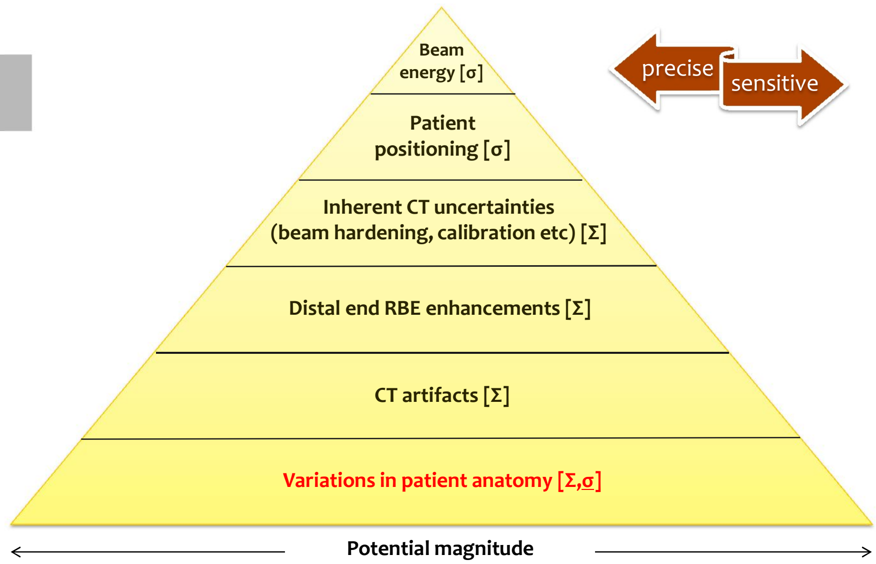
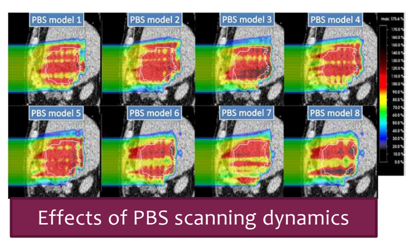
Challenges in PT – dealing with uncertainties

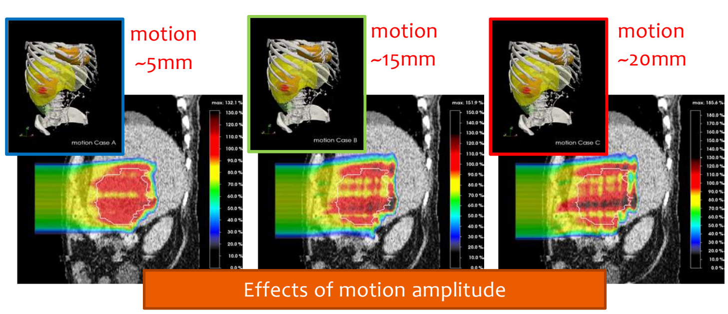


Courtesy of Prof. Dr. Tony Lomax

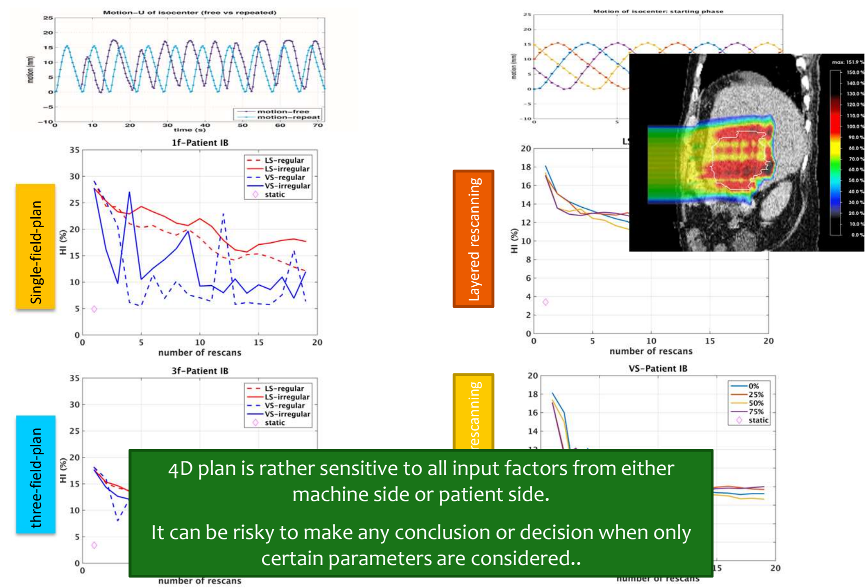
Interplay effects for 4D PBS proton treatments

- The **interplay effect** are significant, individualized and can be influenced by many 4D parameters
- **4D dose distribution** patterns is very difficult to predict without appropriate modelling the dynamics from both *moving organ* and *PBS-based dose delivery*





Sensitivity due to 4D input parameters



4D plan is rather sensitive to all input factors from either machine side or patient side.

It can be risky to make any conclusion or decision when only certain parameters are considered..

Overview of the 4D parameters

1. Patient geometry
2. Field direction
3. Field arrangement
4. PBS beam data
5. Spot distance
6. Energy layer distance
7. Prescribed dose
8. Fractionation scheme
9. 3D plan – density: AIP/mean/midV CT
10. 3D plan – geometry: CTV/gITV/rITV
11. Scanning path/direction

It is really a high dimension problem …

Motion pattern and variation

11. Period
12. Amplitude
13. Irregularity
14. Deformation

Beam delivery dynamics

15. Lateral position: Raster or spot
16. Dose rate: varied or constant
17. Energy switching time

18. Starting phase and combination for multi-fields

Motion mitigation approach

19. Rescan type and number
20. Combined with gating: GWs, surrogate
21. Combined with Tracking
22. 4D optimization

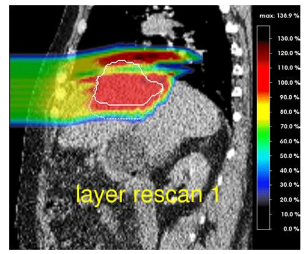
Anything would change timeline is matter for 4D result

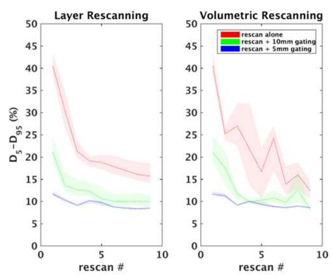
4D dose calculation – the approach for assessing motion effects and uncertainties

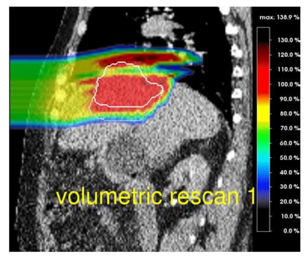
4DDC consists of two components:

- *time resolved PBS dose calculation*
- *4D patient model* – quantified by deformable motion fields

It can provide a systematical evaluation for understanding the 4D problems for individual patient under specific 4D scenarios

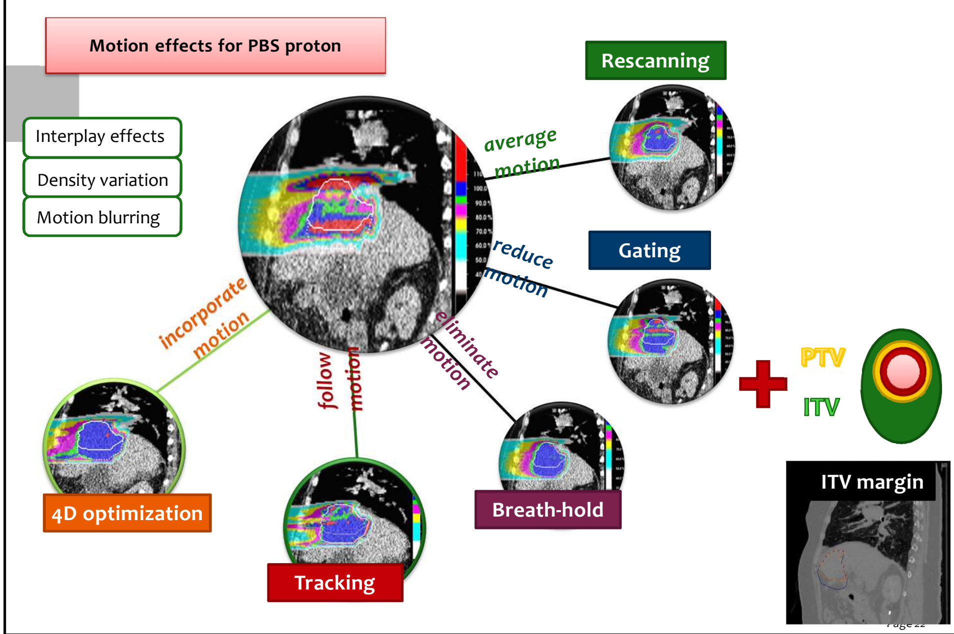






Zhang et al 2016 RO

Portfolio for motion mitigation strategies



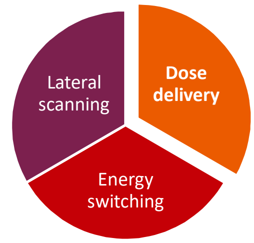
Breath-hold: request fast dose delivery

Technical challenges

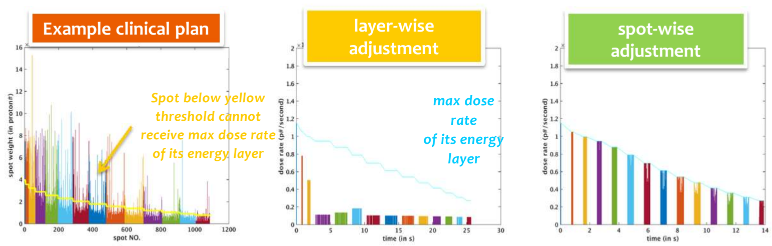
- Max. beam current for Cyclotron
- Energy dependent beamline transmission
- Max. acceptable beam current for beam diagnostic
- Achieve the minimal spot duration

Plan requirements

- high spot weight dynamics with each energy layer varies up to 10 times
- More low weight spots due to rescanning
- Capability to irradiate small weight spot

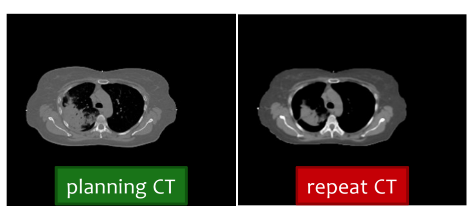


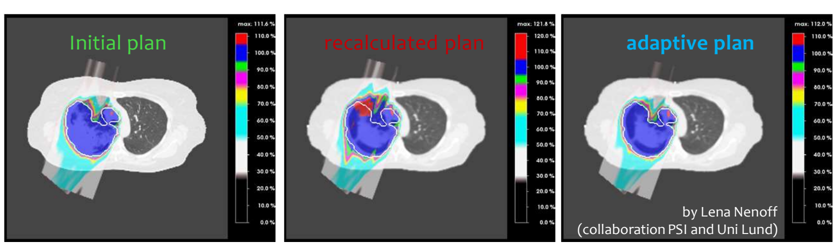
Reducing field delivery time by increasing proton beam current?



Zhang et al PTCOG 2017

Then… Handling the problem to inter-fractional motion -> online plan adaptation

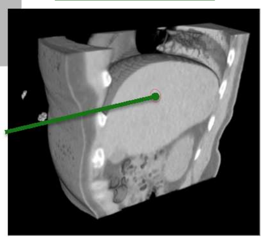




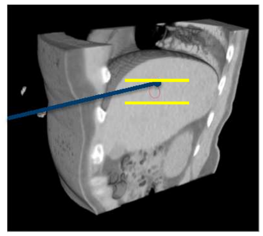
by Lena Nenoff
(collaboration PSI and Uni Lund)

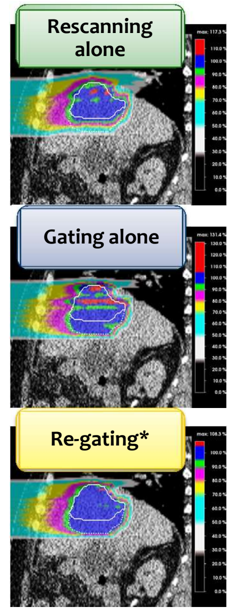
Re-gating: a practical approach

rescanning



gating





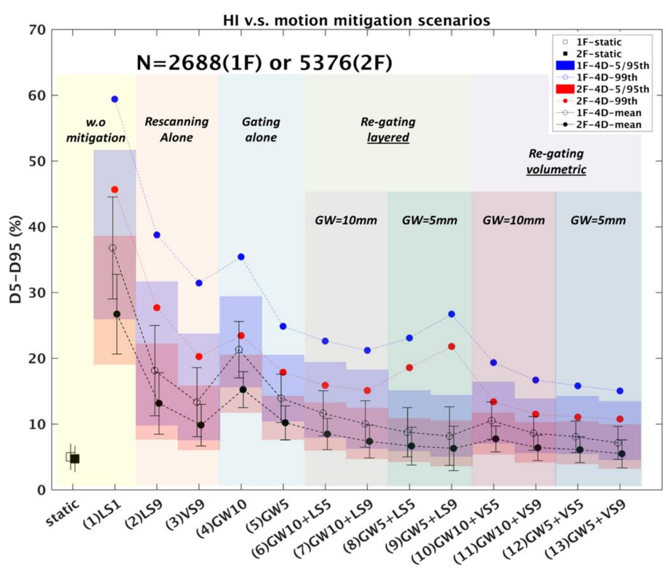
Rescanning

- easy to implement
- prolonged treatment duration
- extended irradiation volume
- appropriate ITV predefined
- scanning dynamic dependent
- need sufficient rescan number
- Statistical averaging is insufficient for **large** motion

Gating

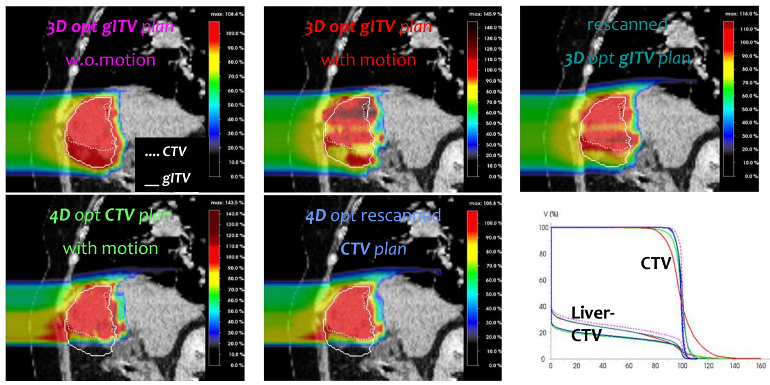
- not difficult to implement
- prolonged treatment duration
- Restricted target volume expansion
- need to tackle the residual motion (with rescanning)
- need online motion monitoring and correlation
- need to update gating window (baseline shift)

A comprehensive evaluation of re-gating



Zhang et al 2018 Radiotherapy & Oncology

4D optimization: making 4D plan motion robust by itself



Advantage

No prolonged delivery time

No extended ITV margin

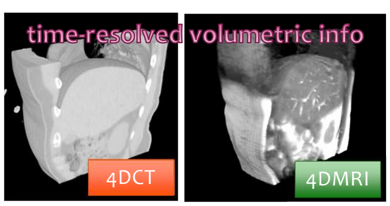
Disadvantage

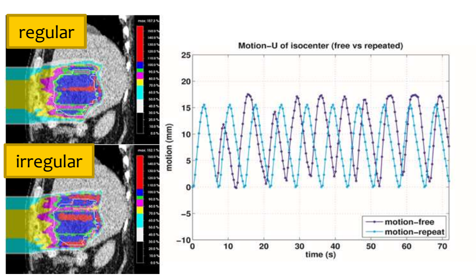
Sensitive to difference in motion for optimization and for delivery
(if motion used by 4D optimization was not reproducible for validation, optimized dose homogeneity would collapsed)

Graeff et al 2014 PMB
Bernatowicz et al 2017 PMB
Zhang et al ESTRO2018, AAPM2018
Engwall et al MP 2018

clinical beneficial → *technical feasible?* → *clinical applicable?*

How to obtain accurate and reliable motion?



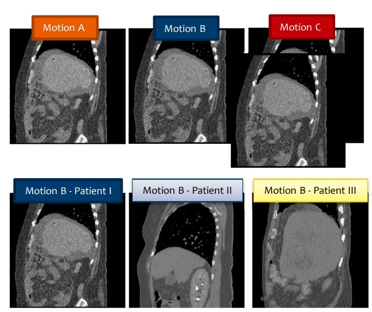


4D patient is "less reproducible" than a PBS proton machine. The caught motion is only a snapshot …

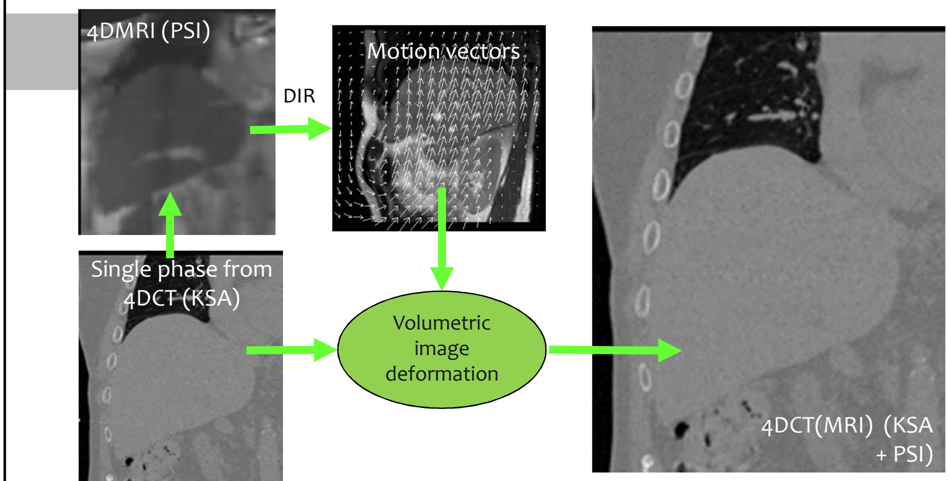
=> online image guidance is important for QA

Synthetic 4DCT-MRI

- Single patient geometry modulated by different deformable motions
- Different patient geometries modulated by the "same" motion
- Single patient geometry modulated by regular or irregular motion patterns



The synthetic 4DCT-MR approach



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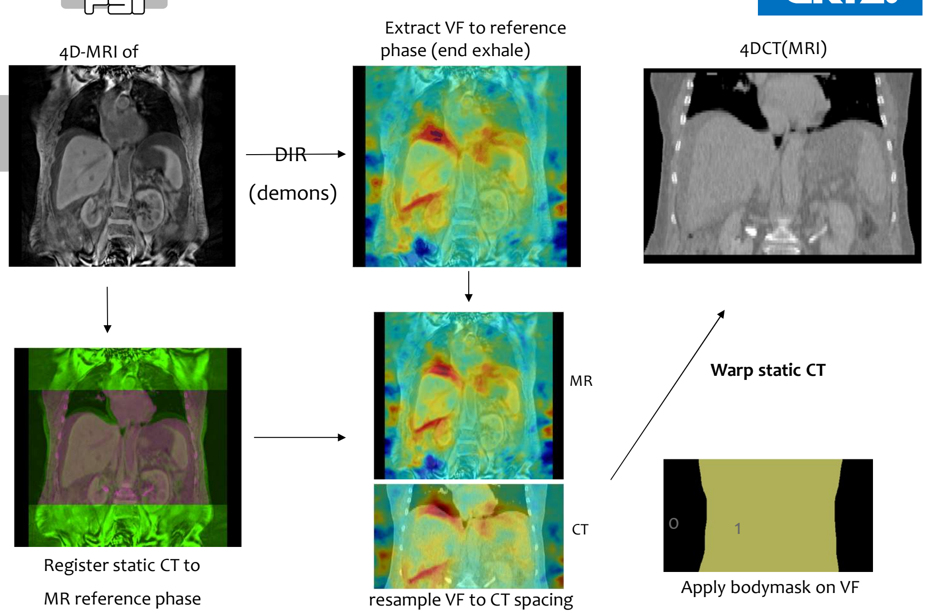
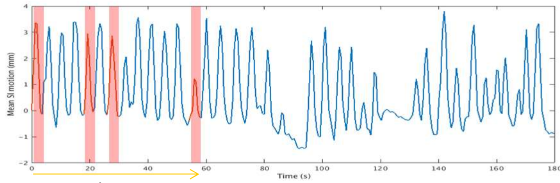


→ 5 4DCT(MRI) for this patient

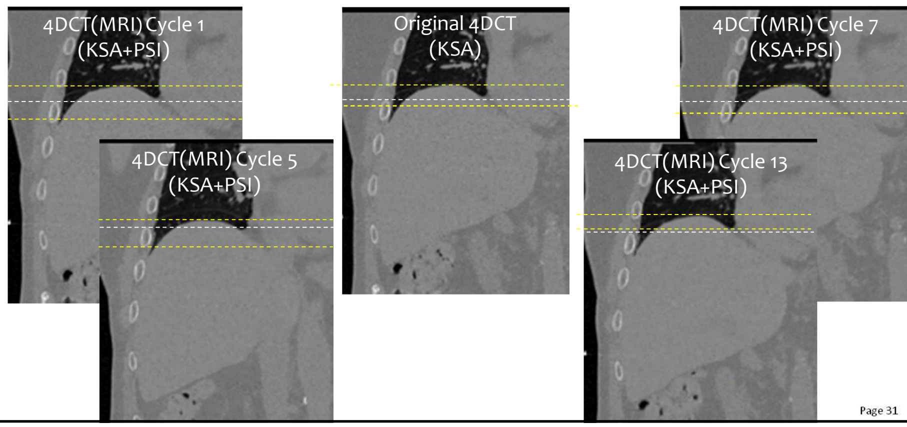
K. Dolde et al 2018 PMB

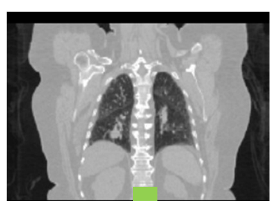
The usually neglected motion variability



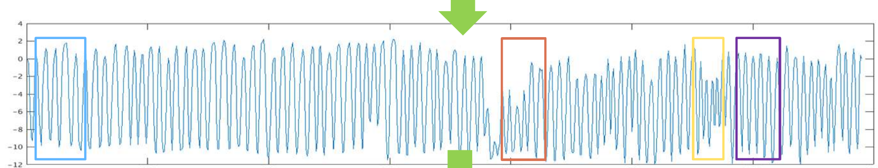
~10 minutes

36 Breathing cycles for 1st KSA patient extracted from 4DMRI acquired at PSI

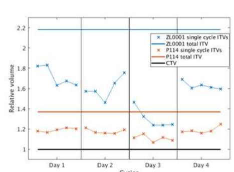


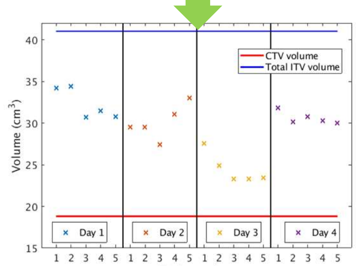


Single phase of lung cancer 4D CT from open source database



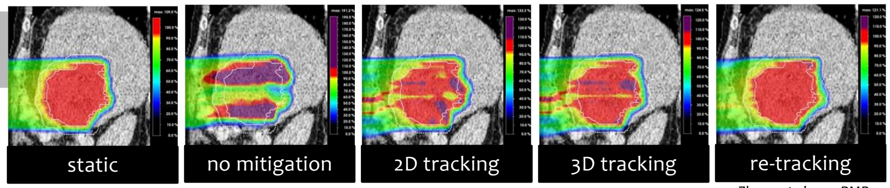
4D MRI in lung of volunteer





ITV volumes calculated from different cycles

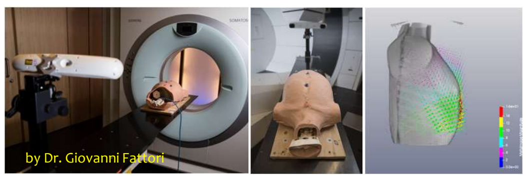
Beam tracking: following tumour as its current situation



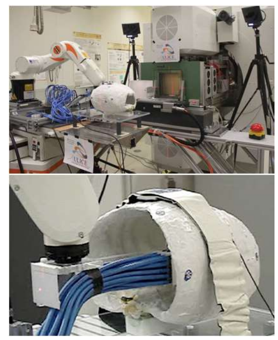
Zhang et al 2014 PMB

clinical beneficial → **technical feasible** → ***clinical applicable?***

- Real-time motion monitoring without "too much additional" imaging dose
- Low latency (~50ms) measurements with high accuracy (<1mm)
- Fast energy adaptation with good beam quality
- Capable to adapt treatment field according to real-time updates



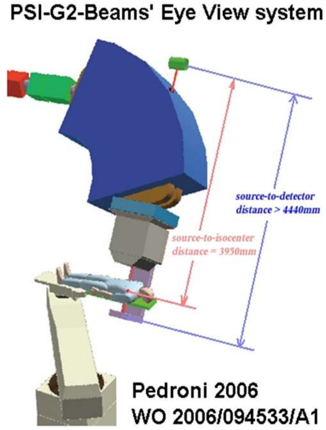
by Dr. Giovanni Fattori



Steidl et al 2012 PMB (project from GSI)

Importance to have online image guidance

PSI-G2-Beams' Eye View system



Pedroni 2006
WO 2006/094533/A1

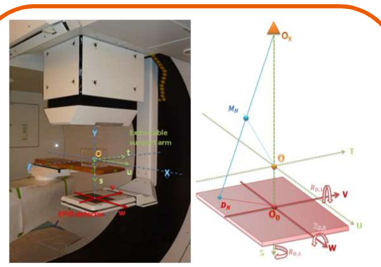
Why IGPT is needed?

scanned proton is sensitive to small motion and density variation	respiratory motion is varied and irregular

How to use IGPT?

Know where is the dose delivered to (4D dose reconstruction)	Online motion compensation (image guided beam gating or tracking)

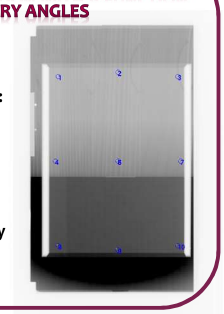
Geometry calibration of on-board BEV imaging system

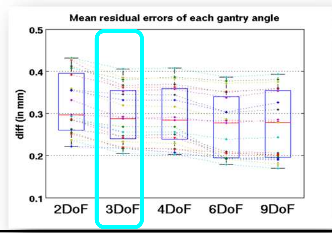


- To derive geometry parameter in reality
  - To calculate exact DRR images
  - To derive the magnification factor

GEOMETRY CALIBRATION WITH A FUNCTION OF GANTRY ANGLES

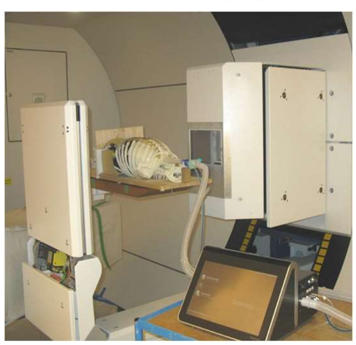
- Physical phantom
- Mathematical model: projected marker
- Minimize difference: detected w.r.t expected positions
- Deduce the geometry correction vector using extrinsic 2D/3D registration

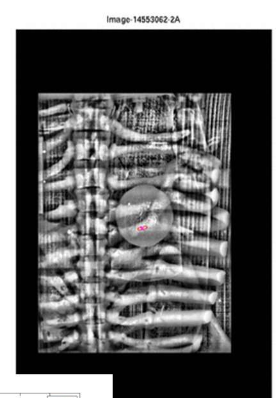




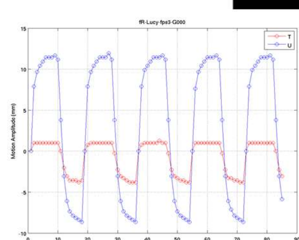
- 3DOF translation correction of the imager is sufficient
- max. mean error can be reduced within 0.4mm for all gantry angles, due to the large SAD/SID ratio.

On-line 2D motion tracking using the BEV imaging system



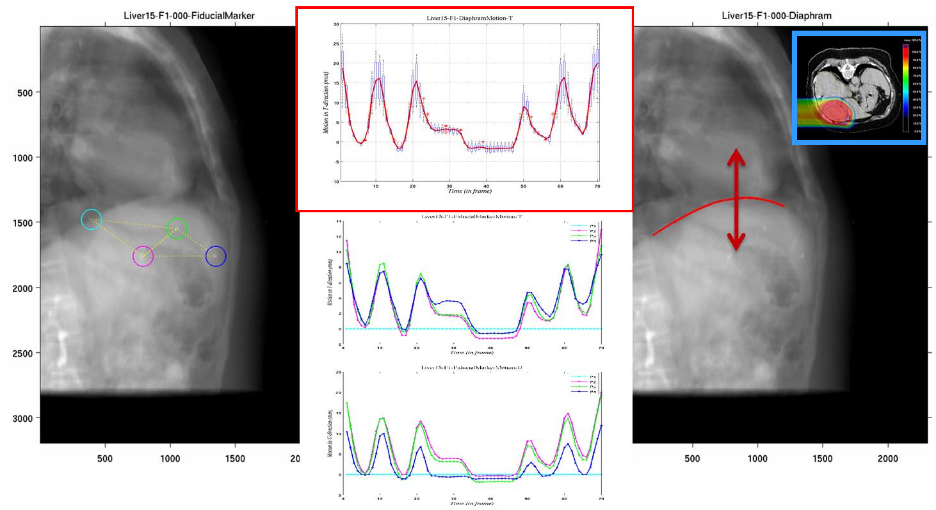


BEV imaging system is capable to online track the internal 2D motion from the same direction of therapeutic beam (maximally resolve lateral motion)

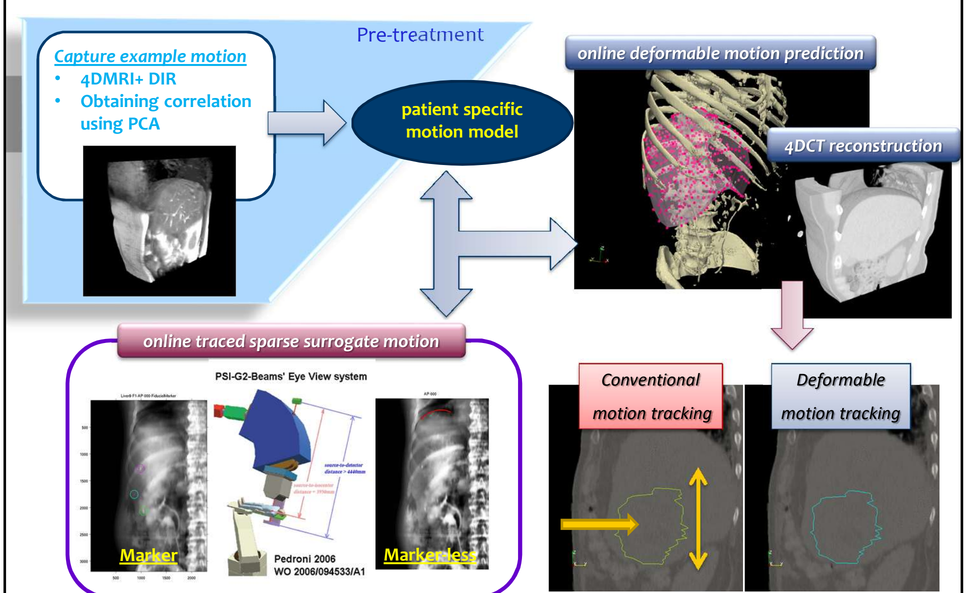


- Imaging Frequency: 3 Hz
- Breathing Cycle:6s
- Fiducial Marker
  - type: Visicoil Gold
  - length:1cm
  - diameter: 1.1mm
- Detection error <0.5mm
- Detection efficiency > 95%

On-line surrogate motion tracking (BEV-DRRs)



Bridging the gap of *online* and *offline* information



Zhang et al 2013 PMB

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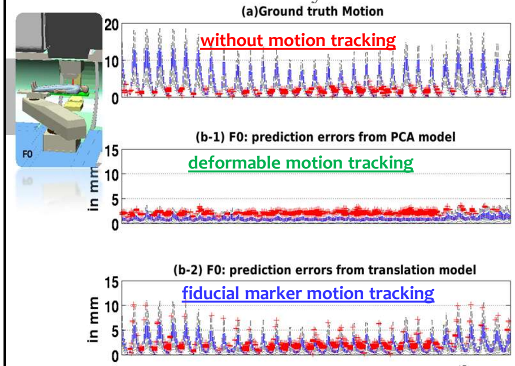
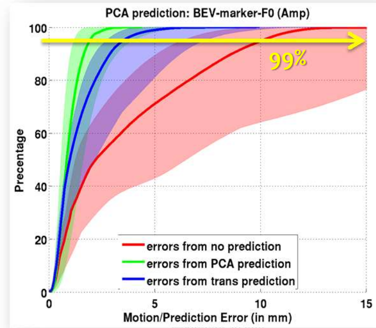
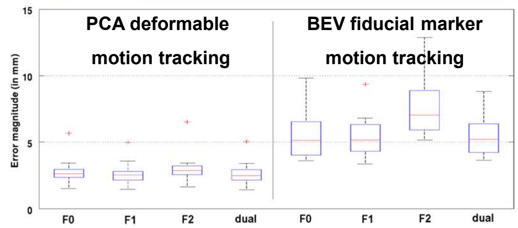
Online deformable motion reconstruction – spatial accuracy





Enable the possibility of online deriving

- spatial motion differences
- lost motion component in imaging direction
- density variation
- Tackle the trade-off between real time and volumetric imaging

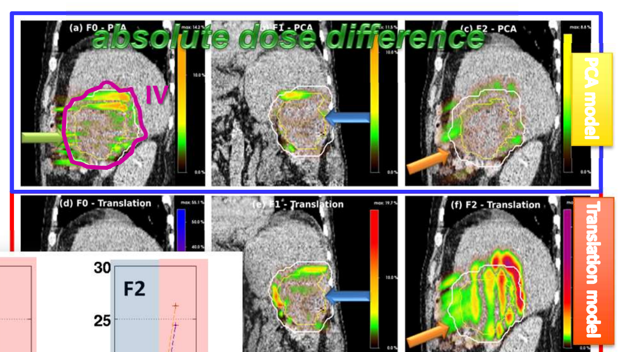


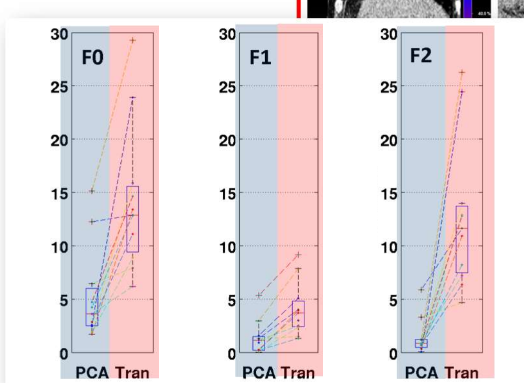
- Zhang Y *et al* 2013 *Phys.Med.Biol.* 58 8612-45

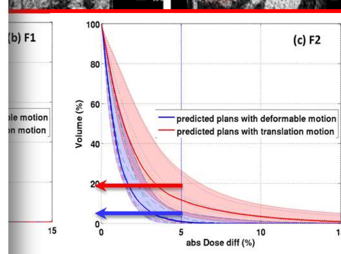
Retrospective 4D dose reconstruction

Accuracy of estimated motions ~= similarity of their 4DDC

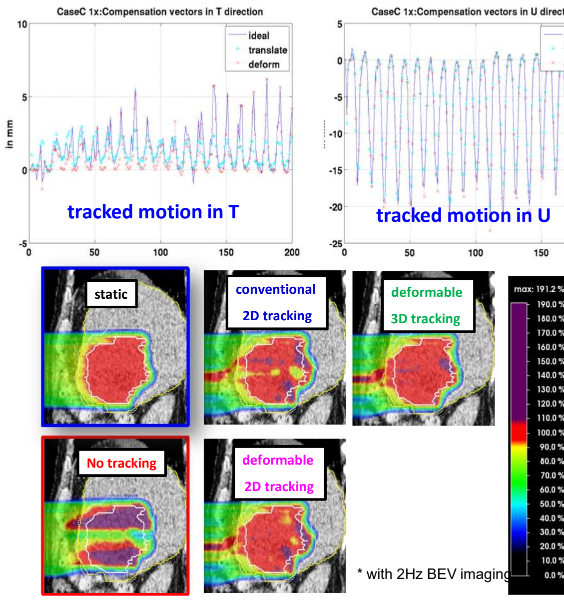
- 4D plans considering either *ground truth motions* or *predicted motions*
- absolute dose difference
- Dose Different Volume Histograms (DDVH) in Irradiation Volume (IV)
- $V_{dosediff=5\%}$







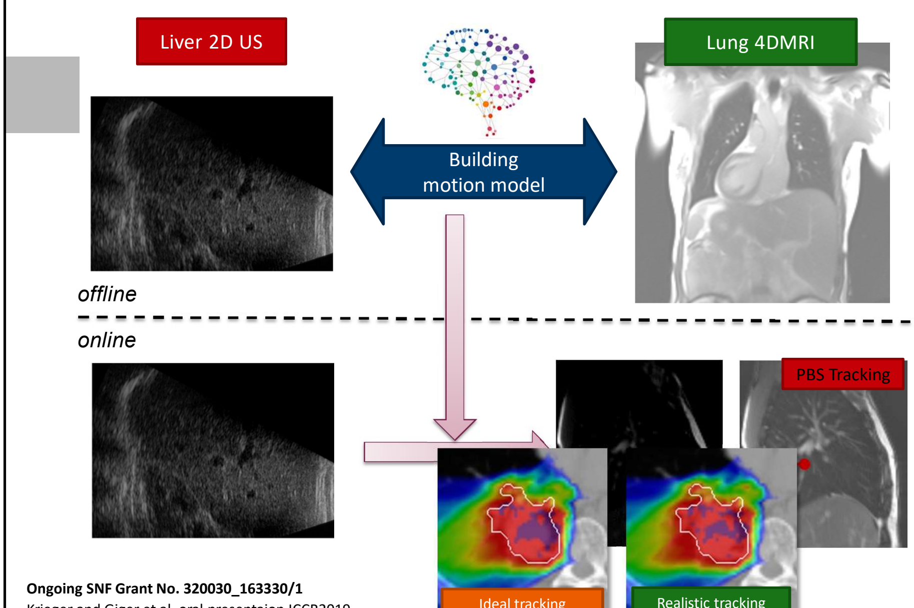
Online image guided beam tracking



- Beam (Bragg peak) specific **lateral motion compensation vectors** derived from online prediction deformable motion fields
- Beam specific **range compensation value** derived from the reconstructed CT

Beam tracking only cannot fully restore the dose homogeneity of the static plan, due to extensive organ rotation and deformation

Model-based IGPT to lung scenarios …

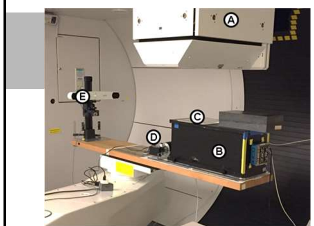


Ongoing SNF Grant No. 320030_163330/1

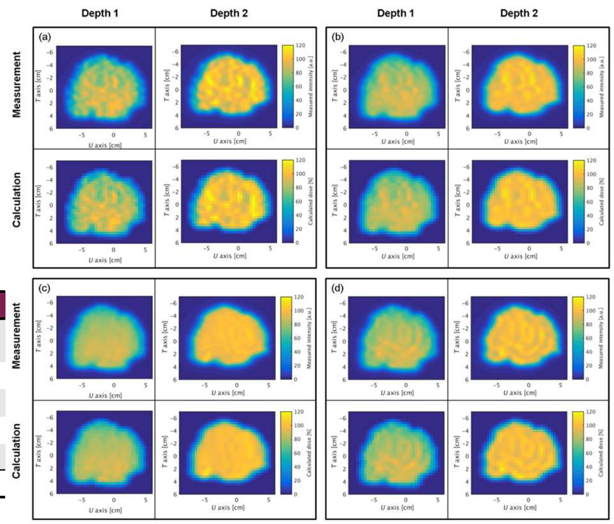
Krieger and Giger et al, oral presentaion ICCR2019

PAUL SCHERRER INSTITUT

Uncertainties – experimental validation for 4DDC



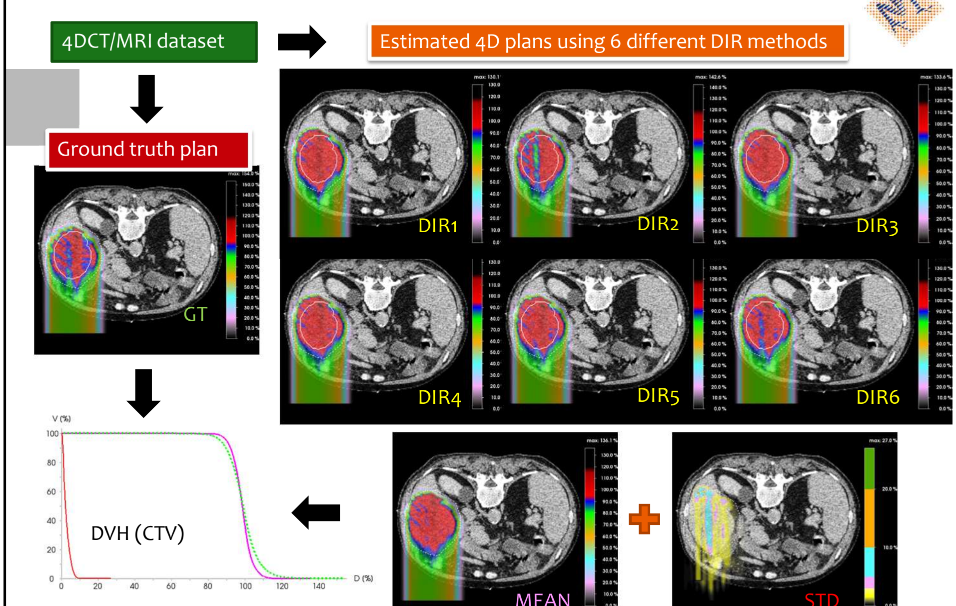
	Depth 1	Depth 2	Mean
NoMotion	99.91%	97.20%	98.56%
NR, 3.7s	98.23%	97.87%	98.05%
LR, 3.7s	99.98%	99.32%	99.65%
VR, 3.7s	99.98%	99.52%	99.75&
VR, 4.4s	99.98%	98.81%	99.40%
Mean	99.62%	98.54%	**99.08%**



Krieger et al PMB 2018

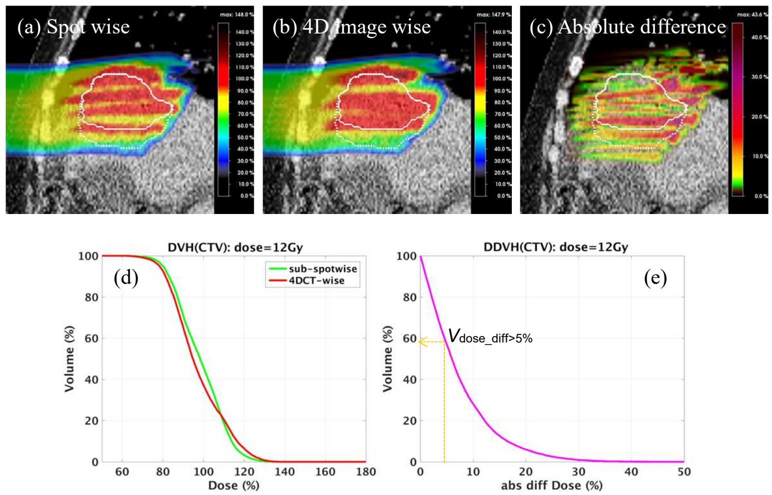
PAUL SCHERRER INSTITUT

Uncertainties – deformable registration



Ribeiro et al RO 2018 (PSI and UMCG)

Uncertainties – temporal resolution for 4DDC



Zhang et al PMB 2019

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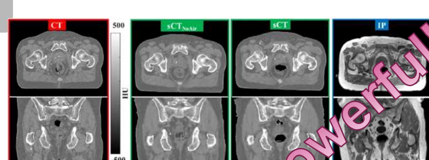
Outlooks

Machine learning in PT?

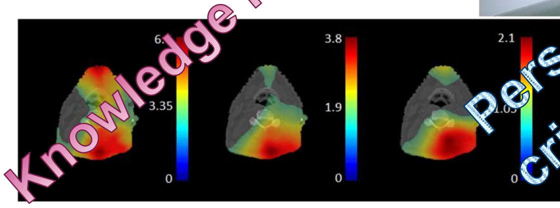
Online MR guided PT?

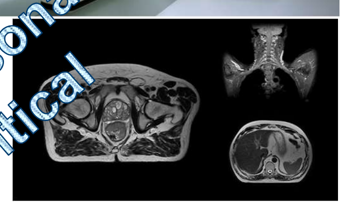


Matteo Maspero et al 2018 Phys. Med. Biol. 63 185001

Knowledge is powerful!

Personalization is critical





Vasant Kearney et al 2018 Phys. Med. Biol. 63 185017

Outlooks

FLASH

34 Gy

31 Gy

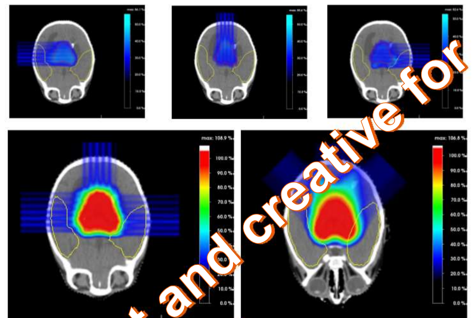
28 Gy

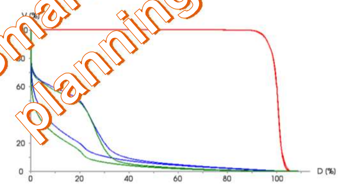
Vozenin et al
clin cancer res 2018

HYPLflash-PT induces a transient radiation-induced hypoxia that protects only the normoxic tissues

Explore and exploit biology

Grid/micro beam therapy

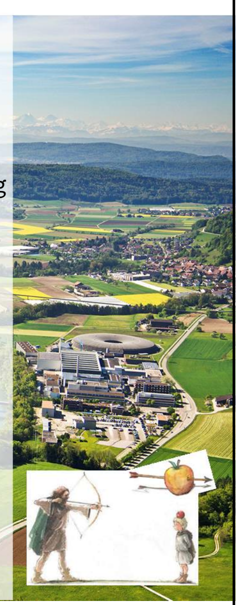




Smart and creative for planning

Summary for PBS 4D treatments

- **4DDC** is an important risk analysis tool for patient specific motion mitigation selection
- Motion is a problem, but could be partially dealt with using simple (gating, breath-hold, re-scanning) or more challenging techniques (tracking, re-tracking, 4D optimization)
- **Online image guidance** is important for treatment QA, and **Motion model** is useful for combining online and offline information
- **Beam tracking** and **4D optimization** will ameliorate 4D PBS treatments in future
- There are many upcoming opportunities/trends for improving the current solutions



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