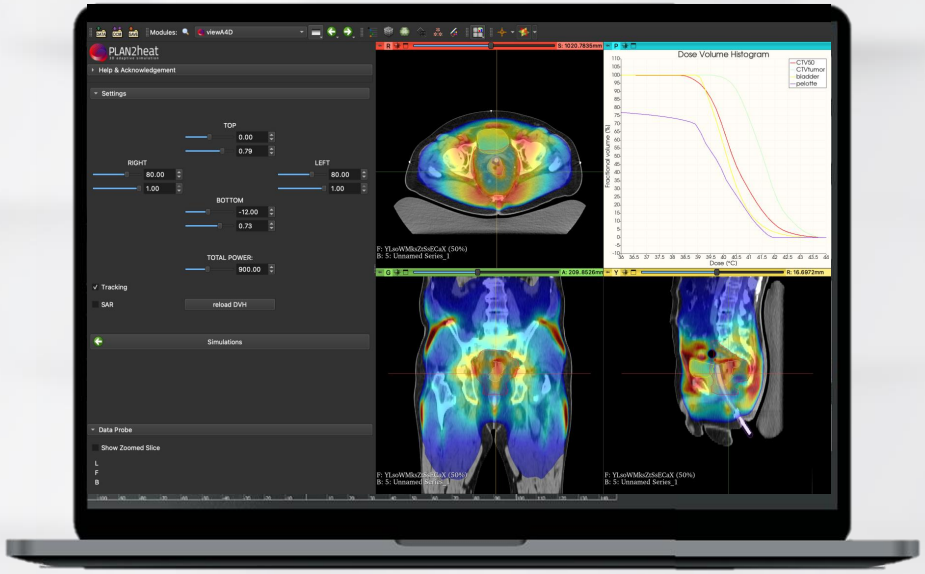
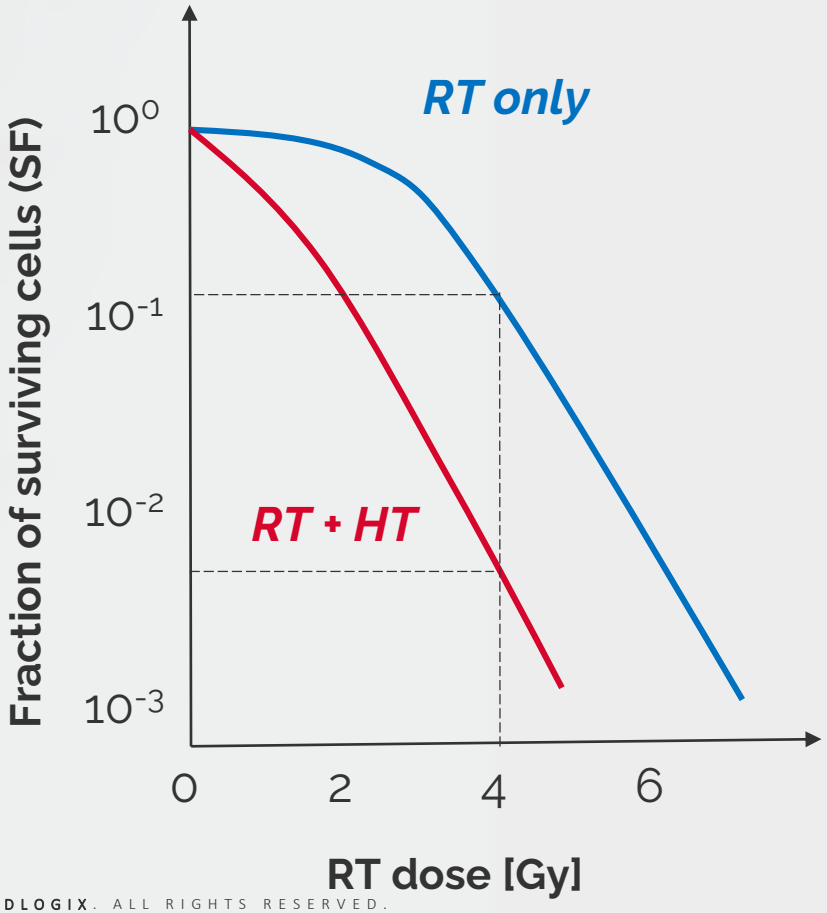
PLAN2heat
3D adaptive simulation

RayStation

COMBINED THERMO-RADIOTHERAPY OPTIMIZATION

ALBA
precision hyperthermia





Amsterdam UMC
University Medical Centers

HYPERTHERMIA RADIO-BIOLOGICAL RATIONALE

Hyperthermia (HT), heating tumors in the range 41-43°C, is a powerful radio and chemosensitizer. The effectiveness of HT as well as its safety, in combination with radiotherapy and chemotherapy, has already been proven in phase III clinical trials [1,3], particularly in patients with very large or very advanced stages of cancer and recurrent tumors. HT enhances the effect of radiotherapy on the tumor, without additional toxicity for nearby healthy tissue, by multiple synergistic mechanisms.

INHIBITION OF DNA DAMAGE REPAIR:
HT enhances the effectiveness of radiotherapy by inhibiting the repair of DNA damage. [2,4,5,6]

REOXYGENATION:
HT increases tissue perfusion resulting in reoxygenation, thereby reducing hypoxia and increasing radiosensitivity. [2,6,7]
With regard to chemotherapy, hyperthermia targets its action within the heated tumor region without aggravating systemic toxicity. [8]
Local hyperthermia has also been shown to be capable of inducing systemic anti- tumor immune responses. [1]

DIRECT CELL KILLING:
HT selectively kills radioresistant hypoxic tumor cells. [2]

1. *Datta, N. R. et al., 2015. Local hyperthermia combined with radiotherapy and-/or chemotherapy: Recent advances and promises for the future. Cancer Treatment Reviews, 1*
2. *Crezee, H. et al., 2015. Thermoradiotherapy planning: Integration in routine clinical practice. International Journal of Hyperthermia,*
3. *Issels, R. D. et al., 2018. Effect of Neoadjuvant Chemotherapy Plus Regional Hyperthermia on Long-term Outcomes Among Patients With Localized High-Risk Soft Tissue Sarcoma. JAMA Oncology,*
4. *Krawczyk, P. M. et al., 2011. Mild hyperthermia inhibits homologous recombination, induces BRCA2 degradation, and sensitizes cancer cells to poly (ADP-ribose) polymerase-1 inhibition. Proceedings of the National Academy of Sciences,*
5. *Oei, A. L. et al., 2015. Effects of hyperthermia on DNA repair pathways: one treatment to inhibit them all. Radiation Oncology,*
6. *Franken, N. A. P. et al., 2013. Cell survival and radiosensitisation: Modulation of the linear and quadratic parameters of the LQ model. International Journal of Oncology,*
7. *Vujaskovic, Z. & Song, C. W., 2004. Physiological mechanisms underlying heat-induced radiosensitization. International Journal of Hyperthermia, 3,*
8. *Issels, R. D., 2008. Hyperthermia adds to chemotherapy. European Journal of Cancer, 11,*

TREATMENT PLANNING FACILITATES CLINICAL DECISION MAKING FOR HYPERTHEMIA TREATMENTS

KOK ET AL., INTERNATIONAL JOURNAL OF HYPERTHERMIA, 2021

International Journal of Hyperthermia

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ihyt20

Treatment planning facilitates clinical decision making for hyperthermia treatments

H. P. Kok, J. van der Zee, F. Navarro Guirado, A. Bakker, N. R. Datta, S. Abdel-Rahman, M. Schmidt, P. Wust & J. Crezee

To cite this article: H. P. Kok, J. van der Zee, F. Navarro Guirado, A. Bakker, N. R. Datta, S. Abdel-Rahman, M. Schmidt, P. Wust & J. Crezee (2021) Treatment planning facilitates clinical decision making for hyperthermia treatments, International Journal of Hyperthermia, 38:1, 532-551, DOI: 10.1080/02656736.2021.1903583

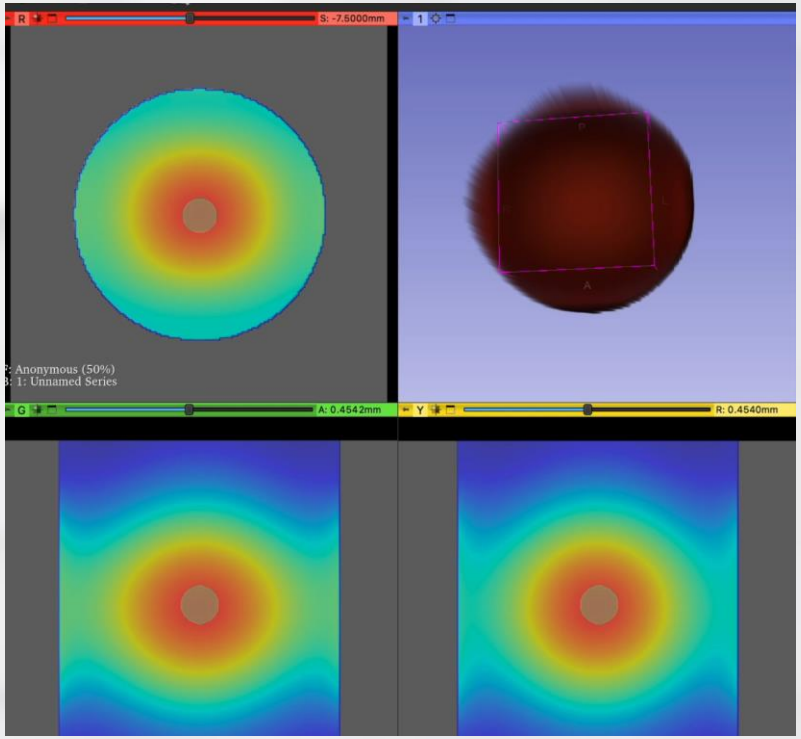
BASIC HTP CAN FACILITATE CLINICAL DECISION MAKING AND IMPROVING TREATMENT QUALITY

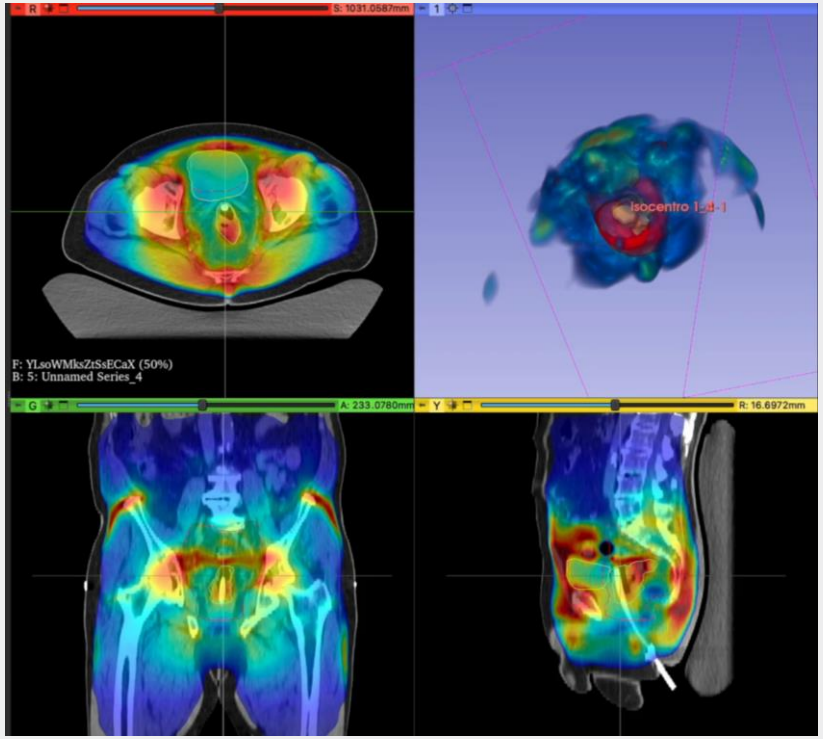
TREATMENT QUALITY STRONGLY DEPENDS ON THE ACHIEVED TUMOR TEMPERATURES AND TREATMENT PLANNING

HYPERTHERMIA TREATMENT PLANNING (HTP) CAN BE APPLIED IN CLINICAL DECISION MAKING BOTH FOR **SUPERFICIAL AND LOCOREGIONAL HYPERTHERMIA TREATMENTS**

PLAN2heat
3D adaptive simulation

WHY HYPERTHERMIA TPS?





PLAN2heat
3D adaptive simulation

PATIENT REPRESENTATION

ALBA
precision hyperthermia
ON4000D

ALBA4D
precision hyperthermia

DATA MANAGEMENT SYSTEM AND INTEGRATION INTO RT WORKFLOW

CT/MRI

Oncology Information System

- **Aria** (Varian)
- **Mosaiq** (Elekta)
- **RayCare** (RaySearch)

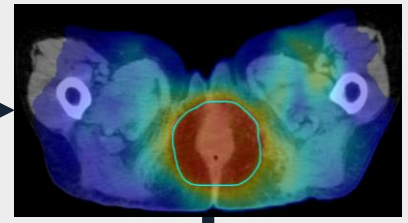
HT & RT CTs

RT TPS

RT PLAN

LINAC

RT DOSE



Equivalent Radiation Dose

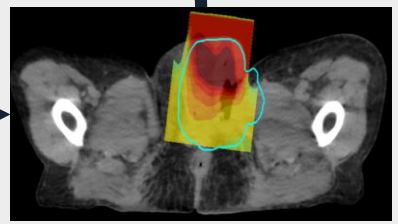
CT and RT STRUCT

HT TPS

PLAN2heat 3D adaptive simulation

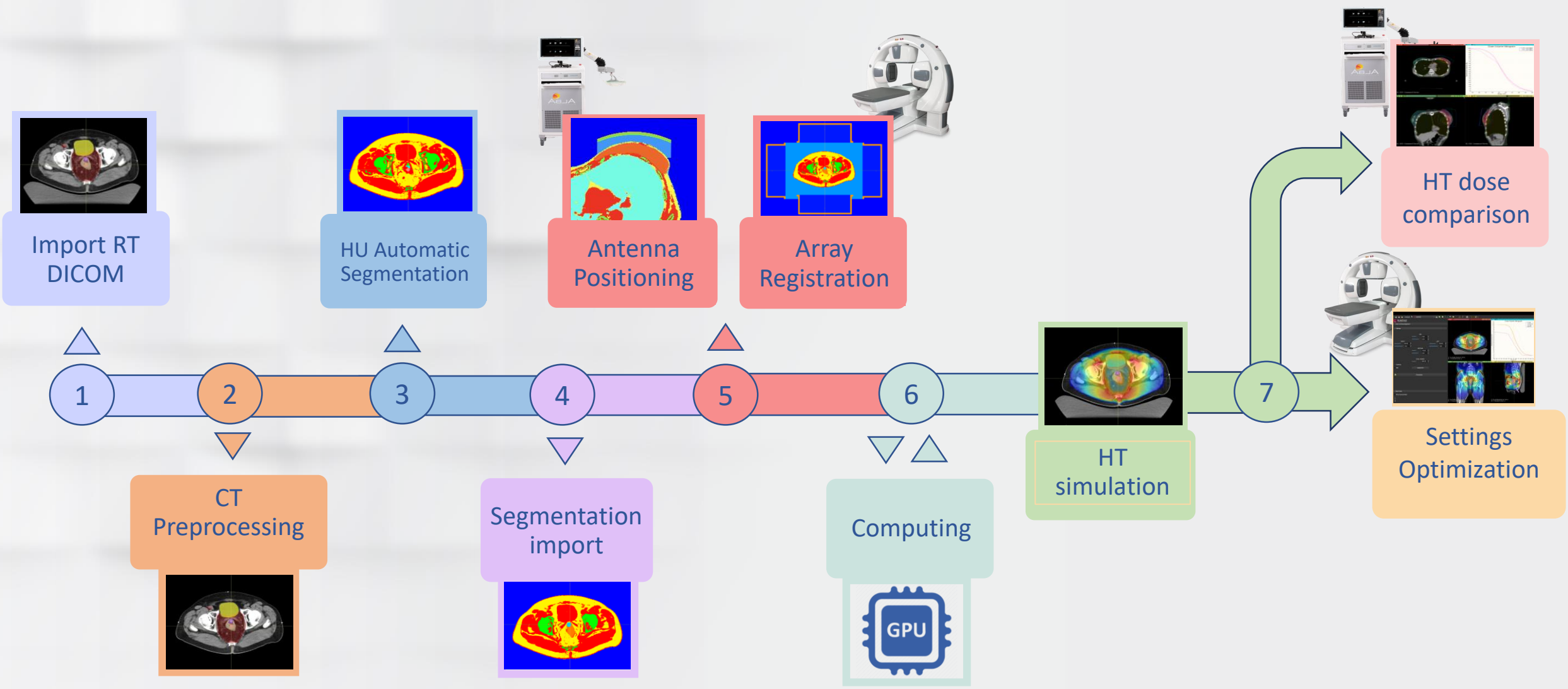
HT PLAN

HT DOSE

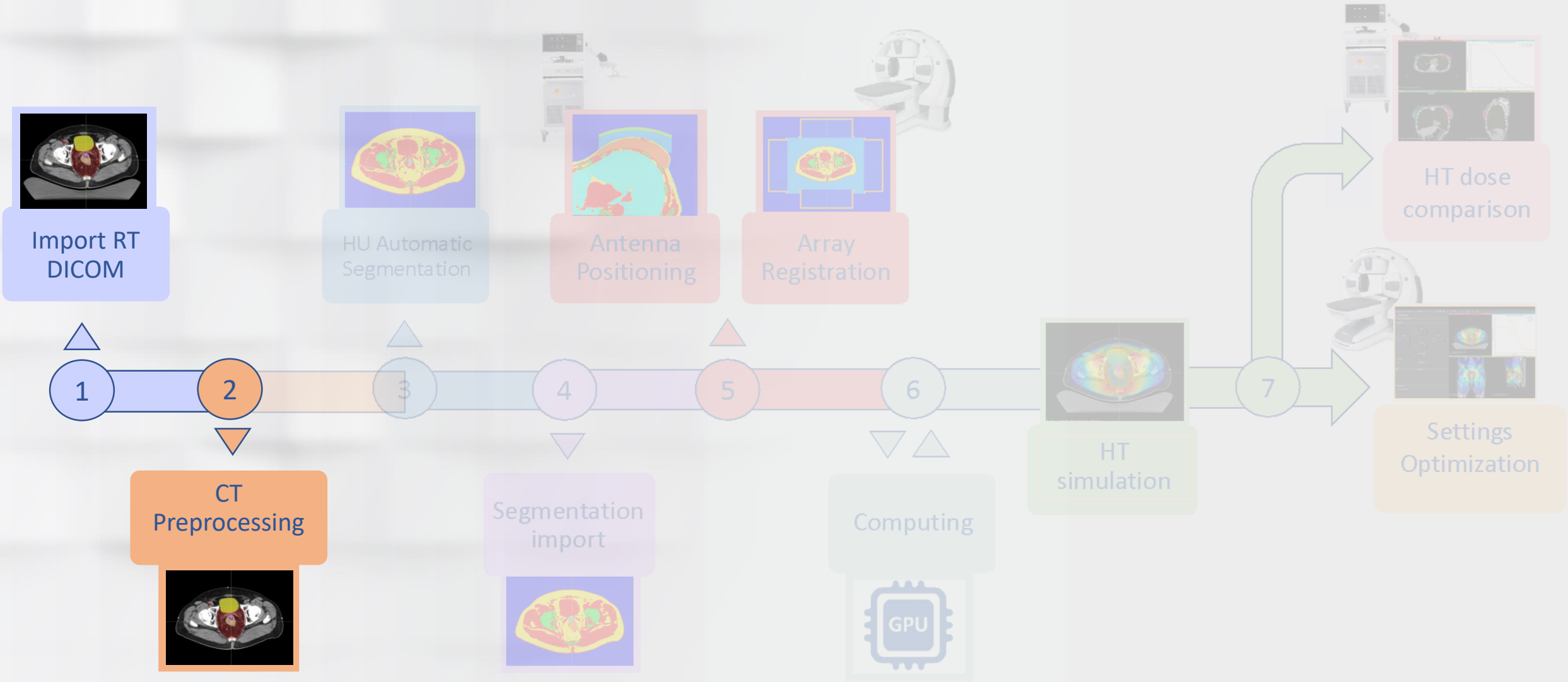


PLAN2heat
3D adaptive simulation

ALBA HTPS - PLAN2HEAT WORKFLOW



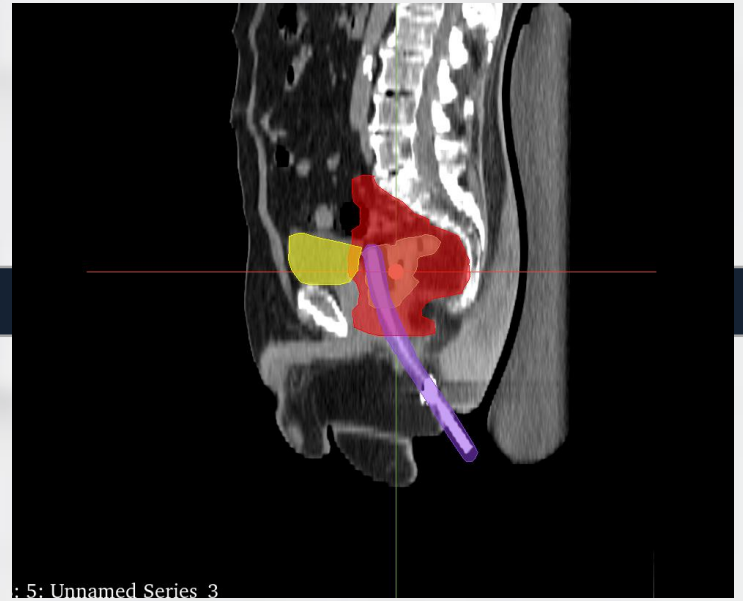
ALBA HTPS - PLAN2HEAT WORKFLOW

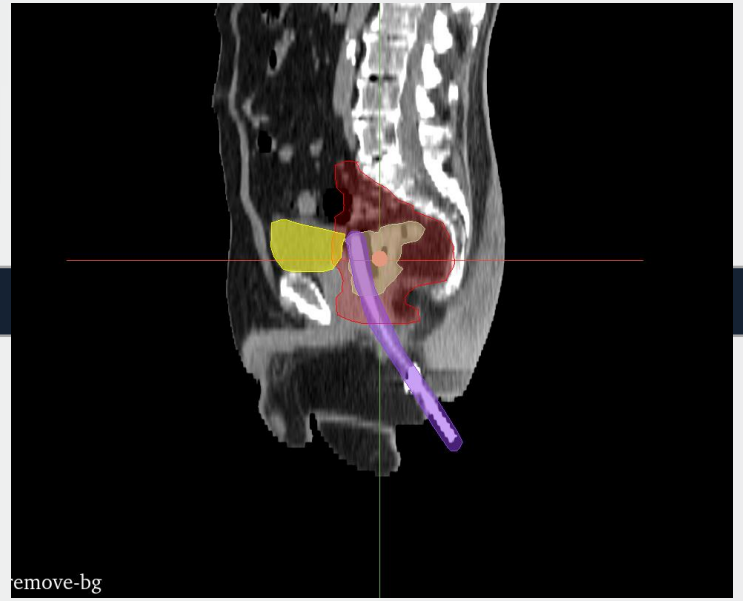


ALBA HTPS - PLAN2HEAT
IMAGE PREPROCESSING

PRE-PROCESSING
Background and Bolus removal

2

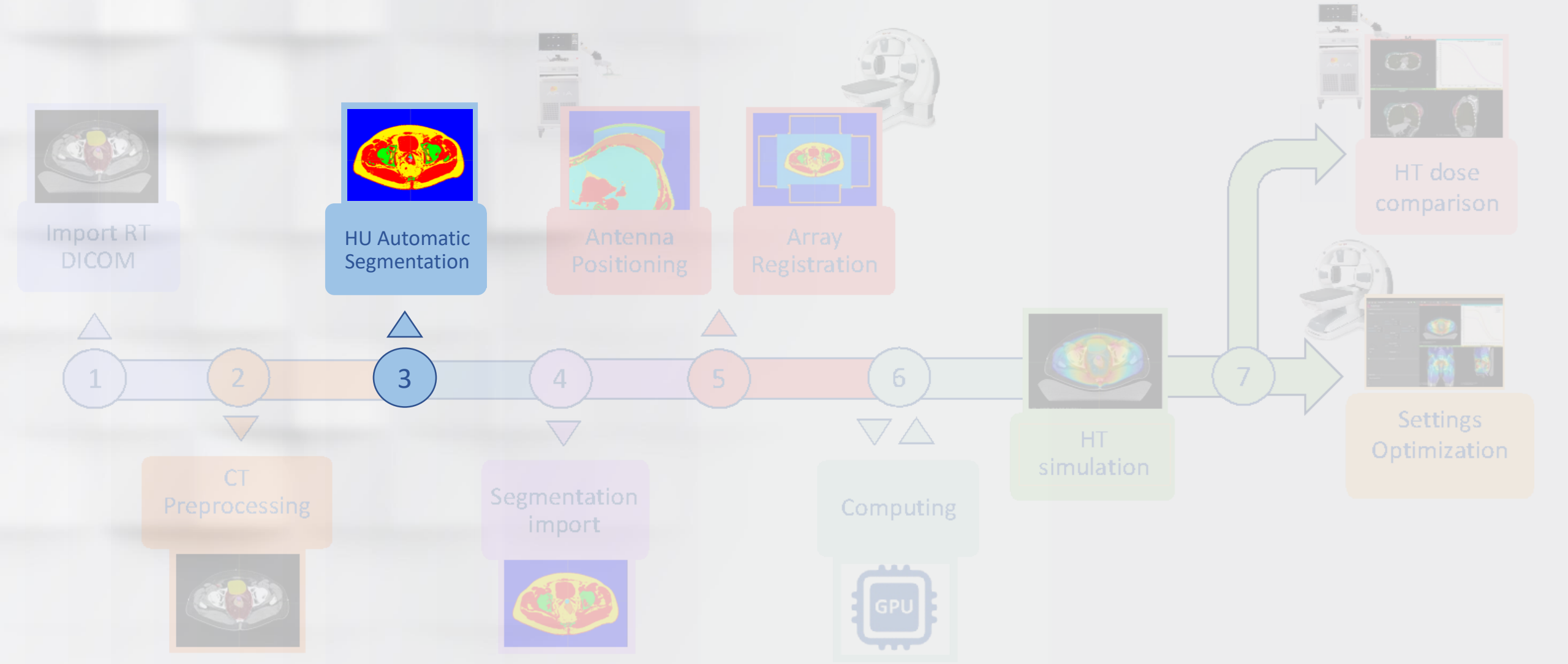




1

3

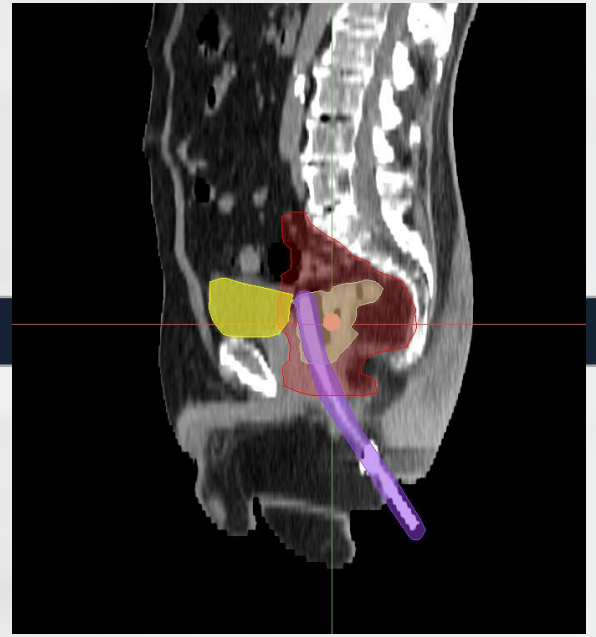
ALBA HTPS - PLAN2HEAT WORKFLOW

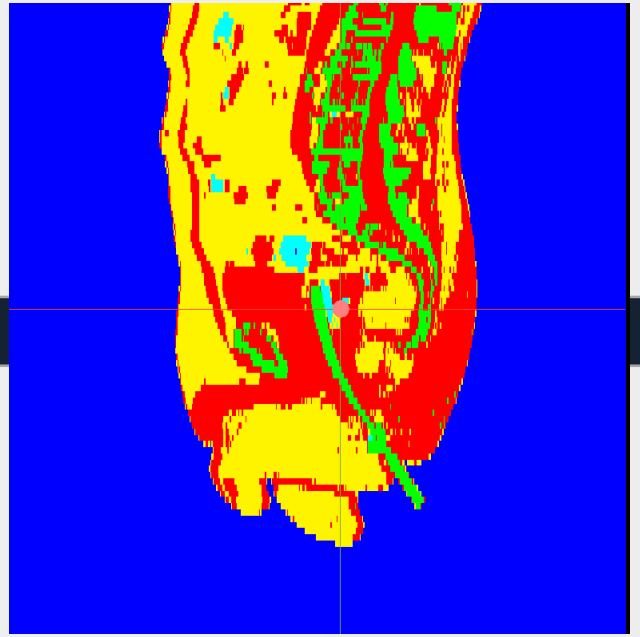


ALBA HTPS – PLAN2HEAT
HU AUTOMATIC SEGMENTATION

LARGE TISSUES SEGMENTATION
For dielectric properties assignment

3





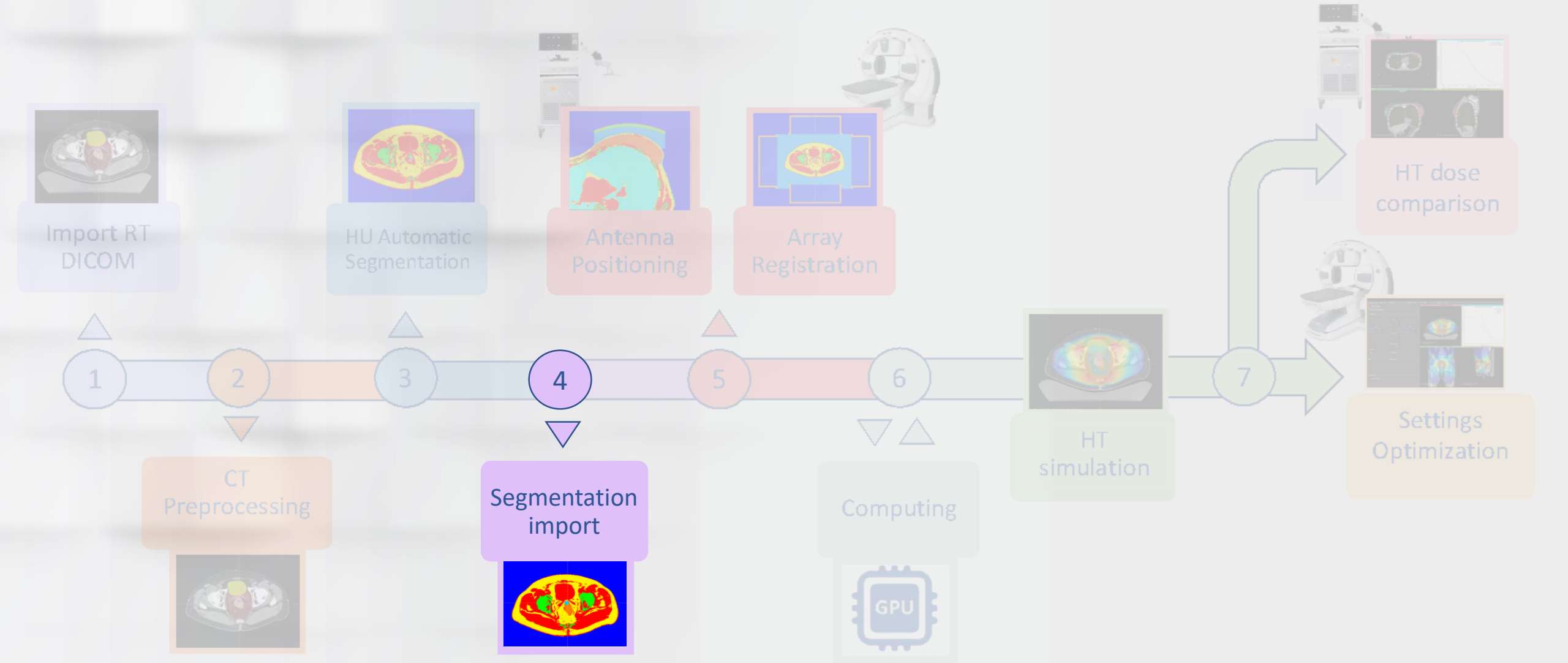
- Bone
- Muscle
- Inner air
- Fat

2

4

PLAN2heat
3D adaptive simulation

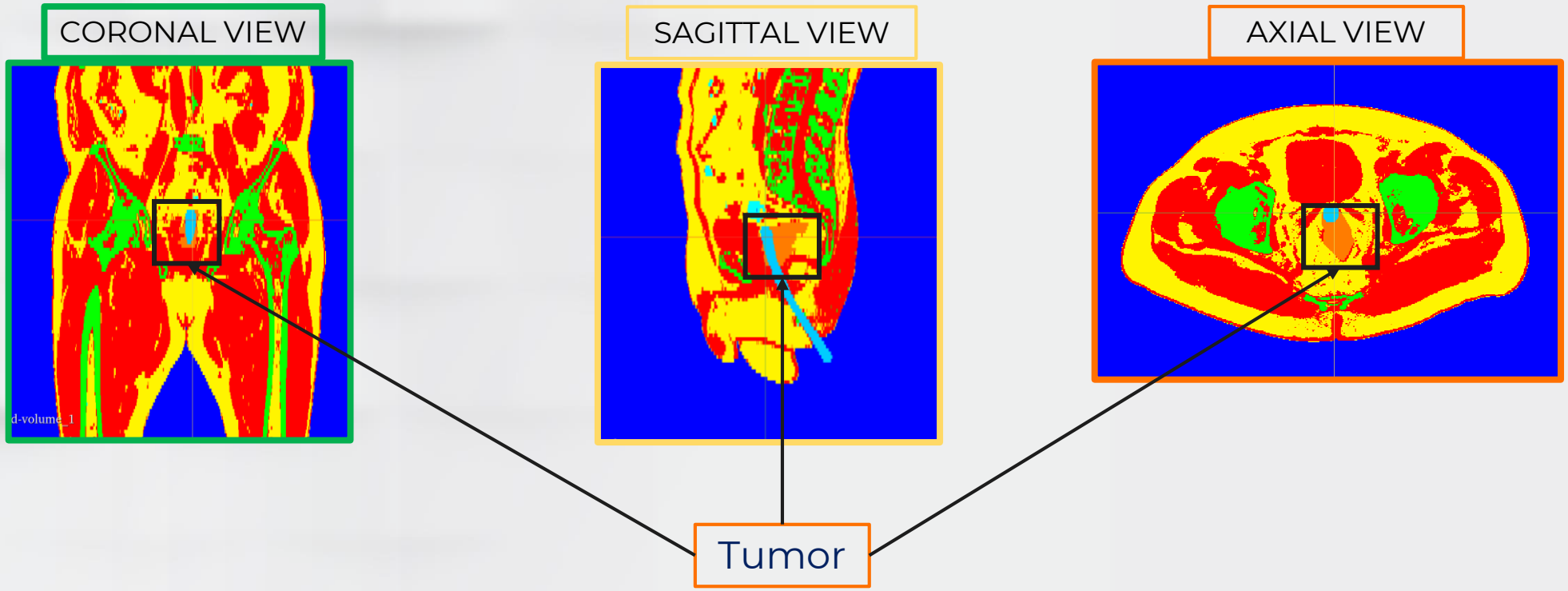
ALBA HTPS - PLAN2HEAT
WORKFLOW



ALBA HTPS - PLAN2HEAT
IMPORT STRUCTURES

4

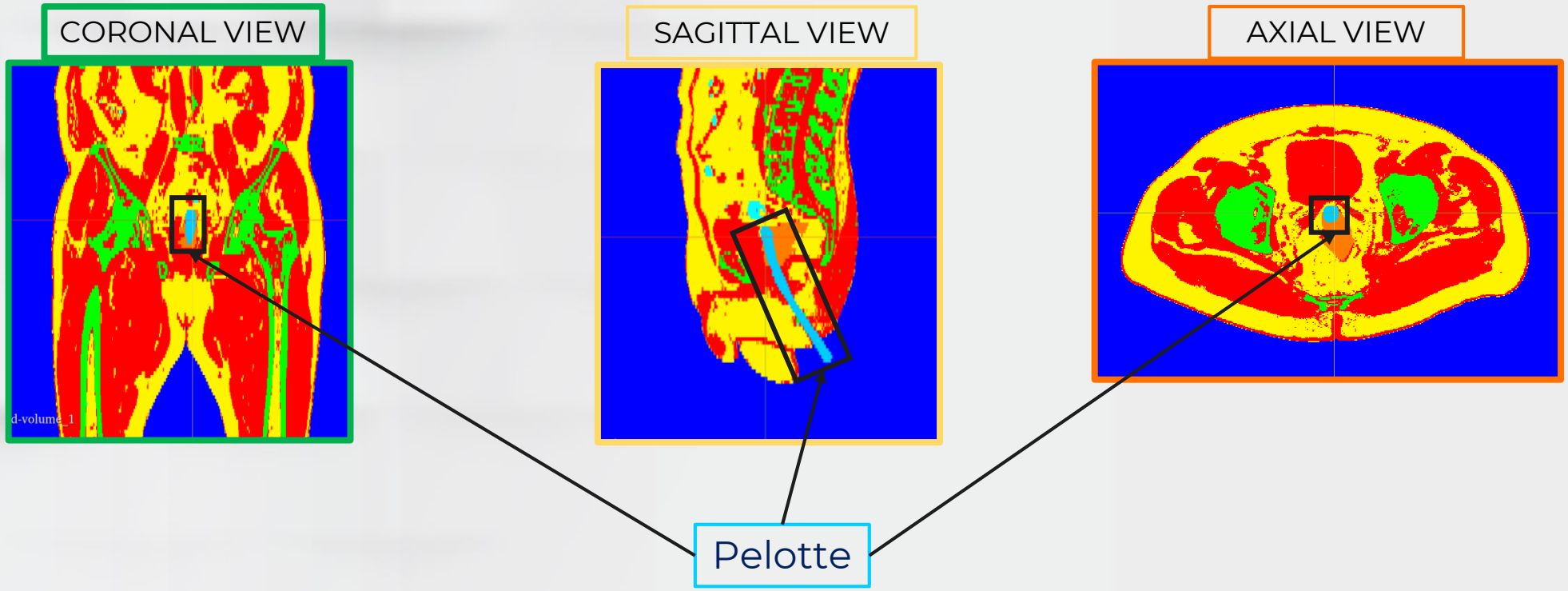
Overlay any structure with known dielectric properties
on the base segmentation



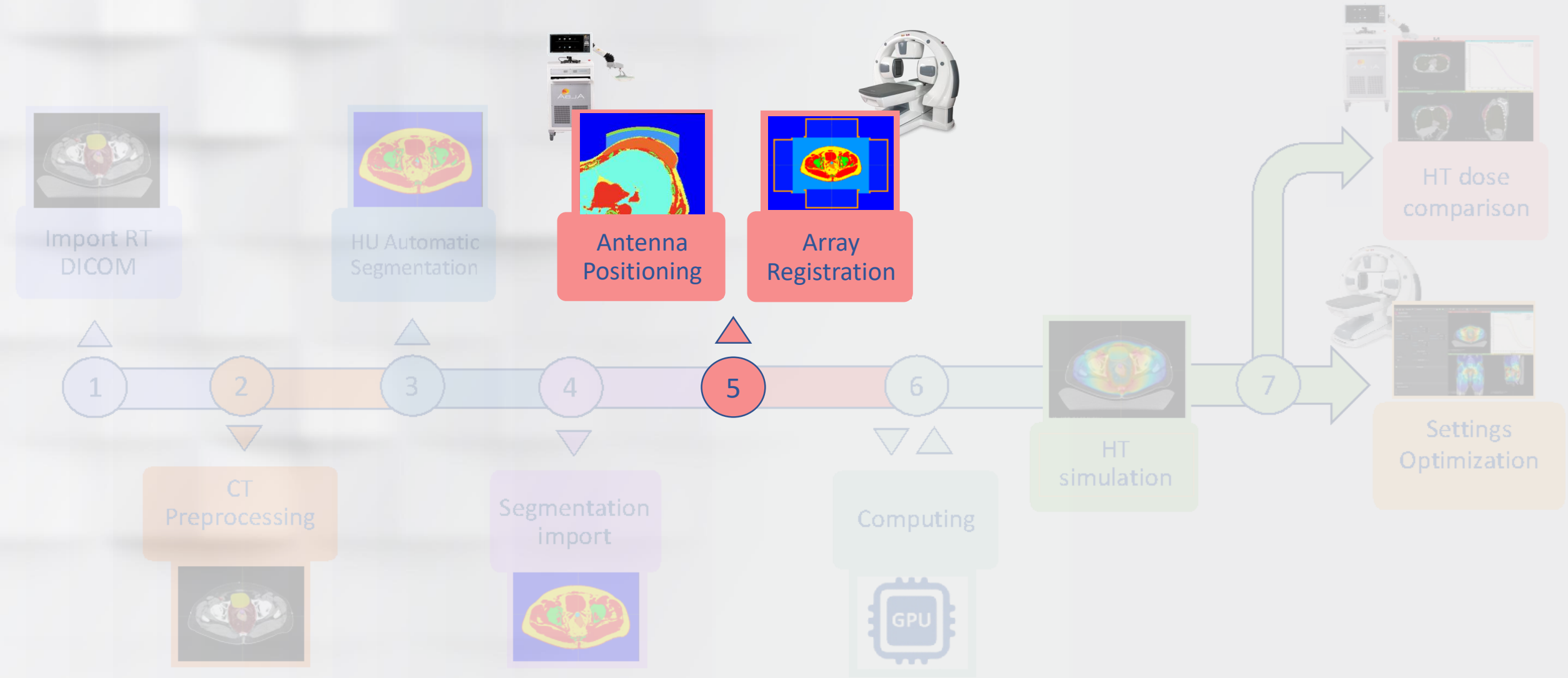
ALBA HTPS - PLAN2HEAT
IMPORT STRUCTURES

4

Overlay any structure with known dielectric properties
on the base segmentation



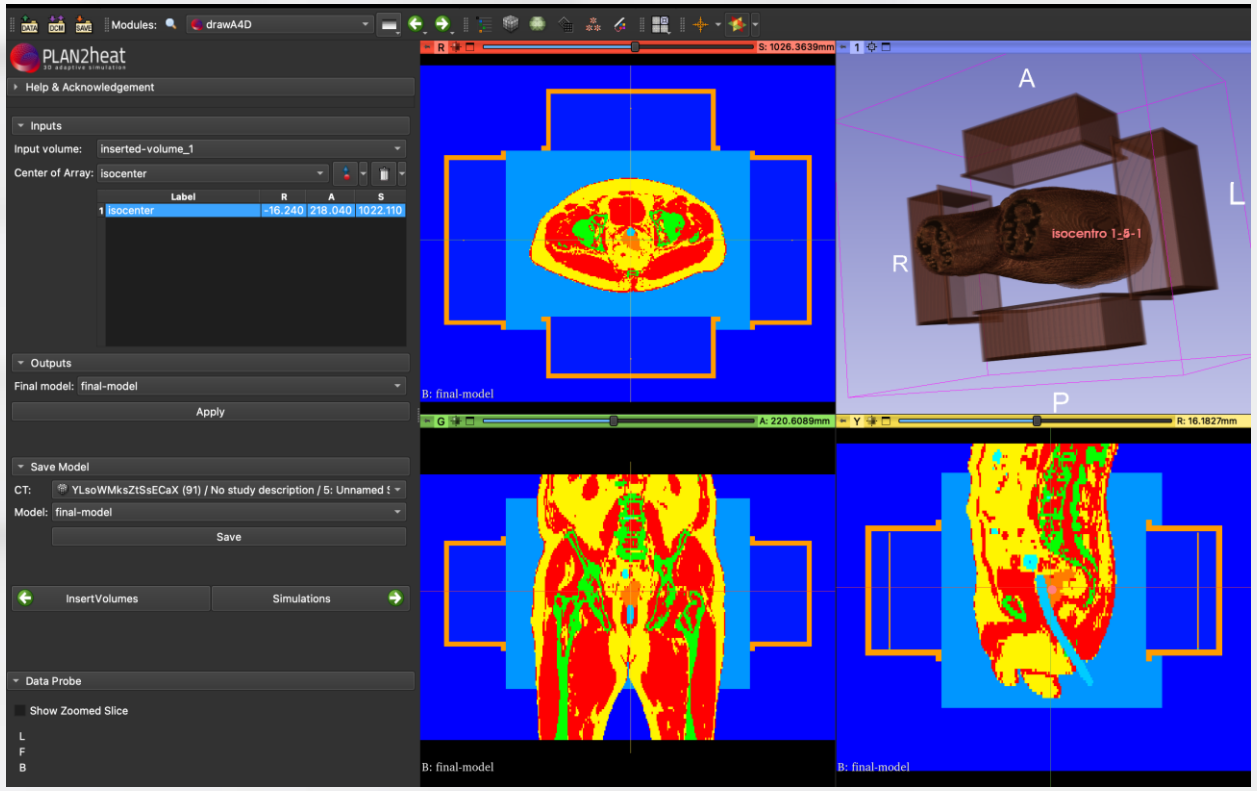
ALBA HTPS - PLAN2HEAT
WORKFLOW



ALBA HTPS - PLAN2HEAT
ARRAY REGISTRATION

4

Patient positioning through one single point



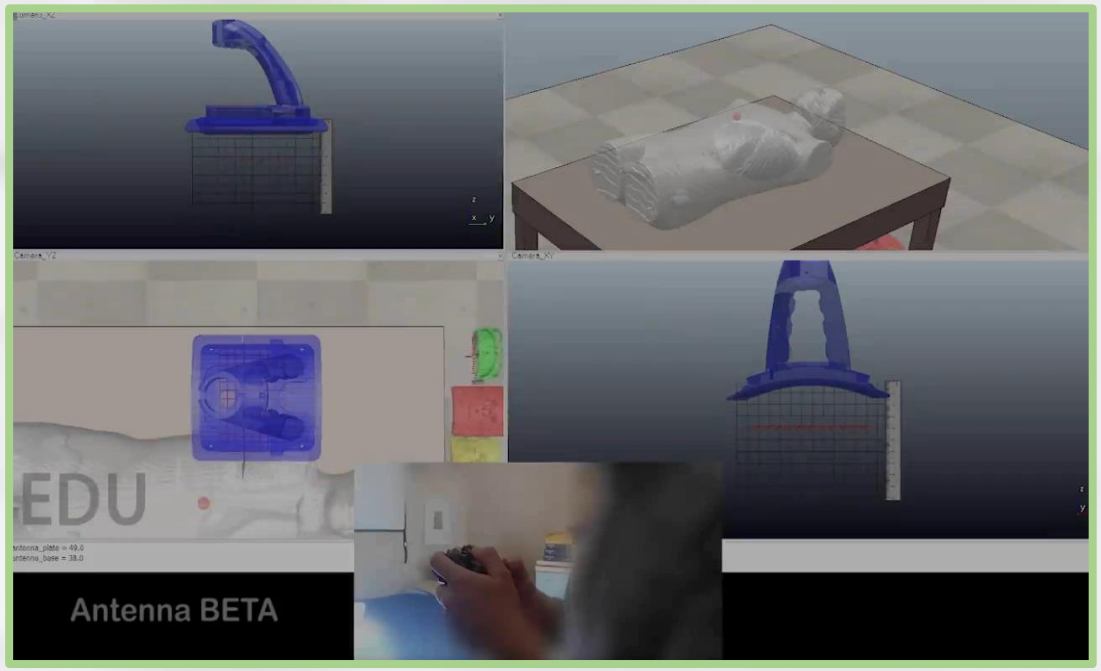
X : PATIENT CENTER

Y : PATIENT CENTER

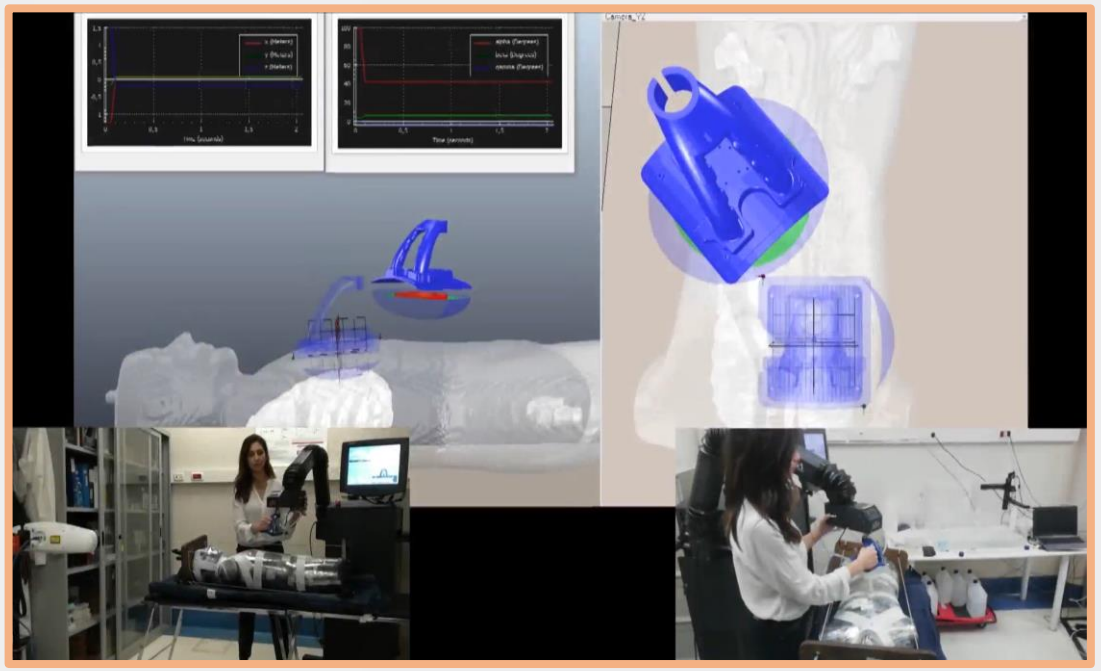
Z : TUMOR CENTER

ALBA HTPS - PLAN2HEAT
ANTENNA AND PATIENT REGISTRATION: TWO OPTIONS

PLANNING IN **VIRTUAL ROOM**



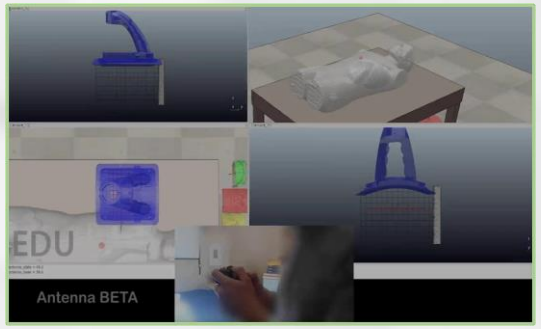
OPTICAL TRACKING IN THE **TREATMENT ROOM**



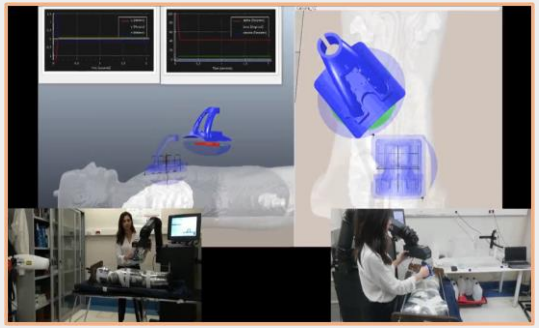
PLAN2heat
3D adaptive simulation

ALBA HTPS - PLAN2HEAT
ANTENNA POSITIONING

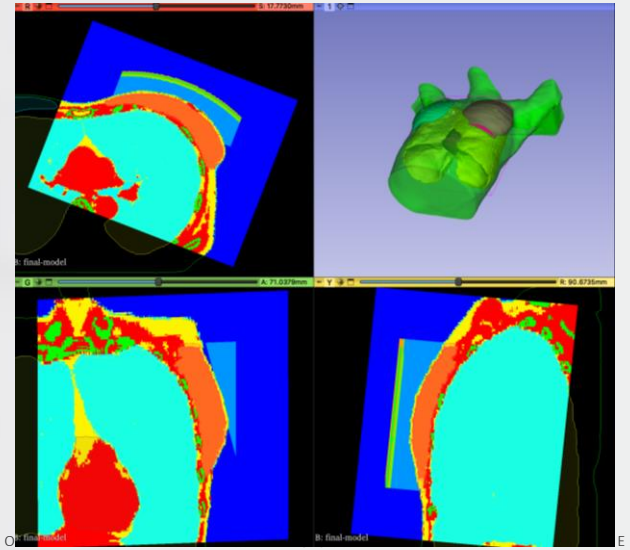
VIRTUAL PLANNING



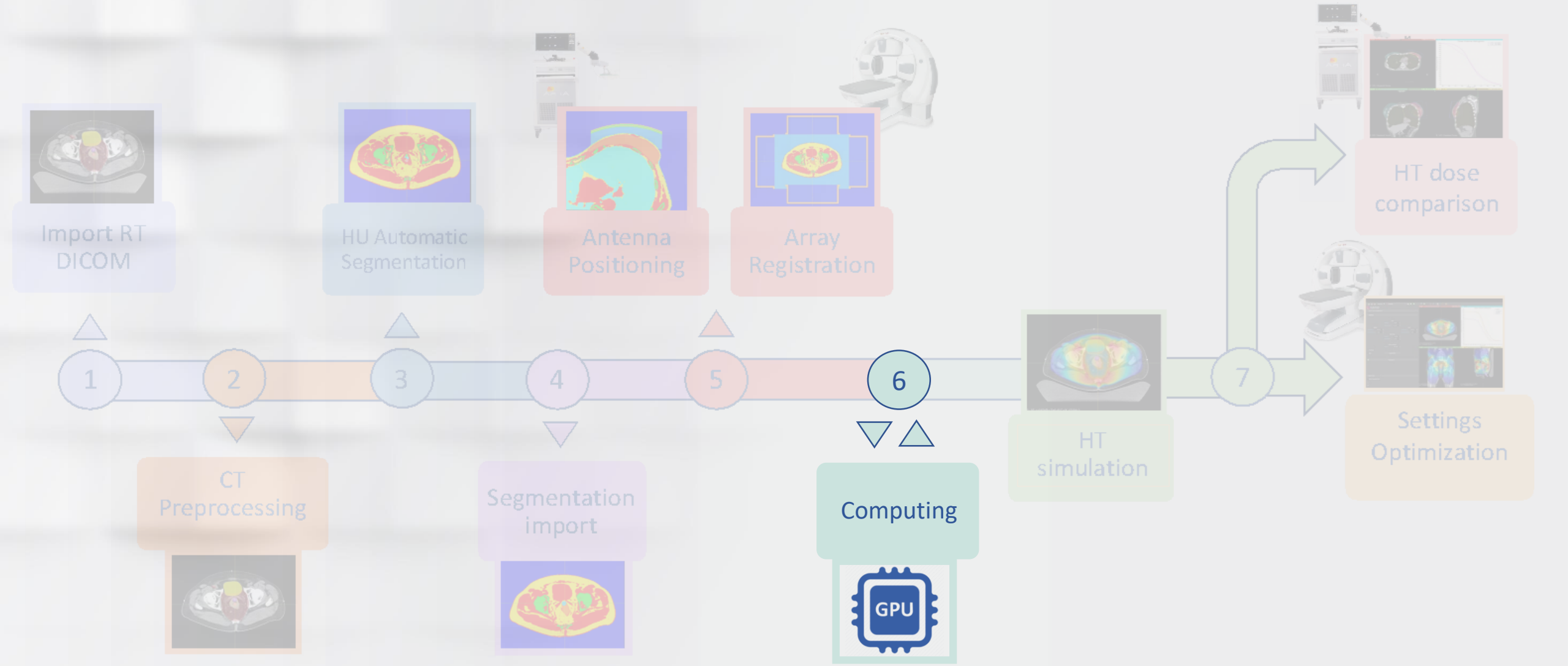
TREATMENT ROOM FEEDBACK



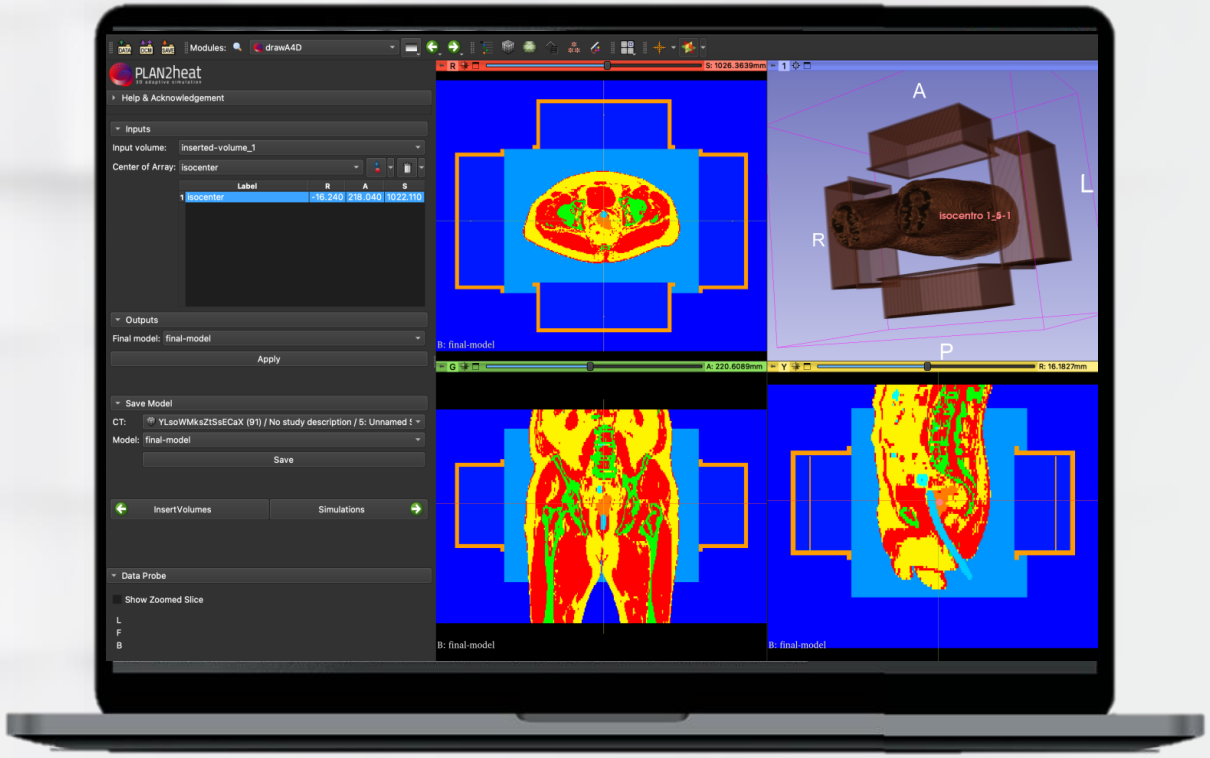
SIMULATION MODEL

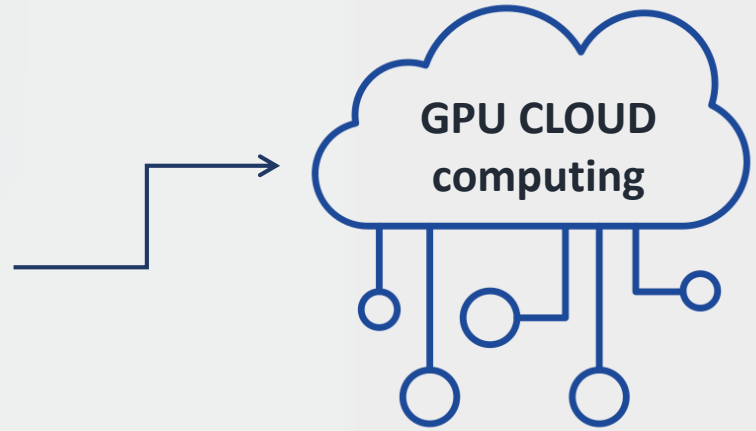


ALBA HTPS - PLAN2HEAT WORKFLOW



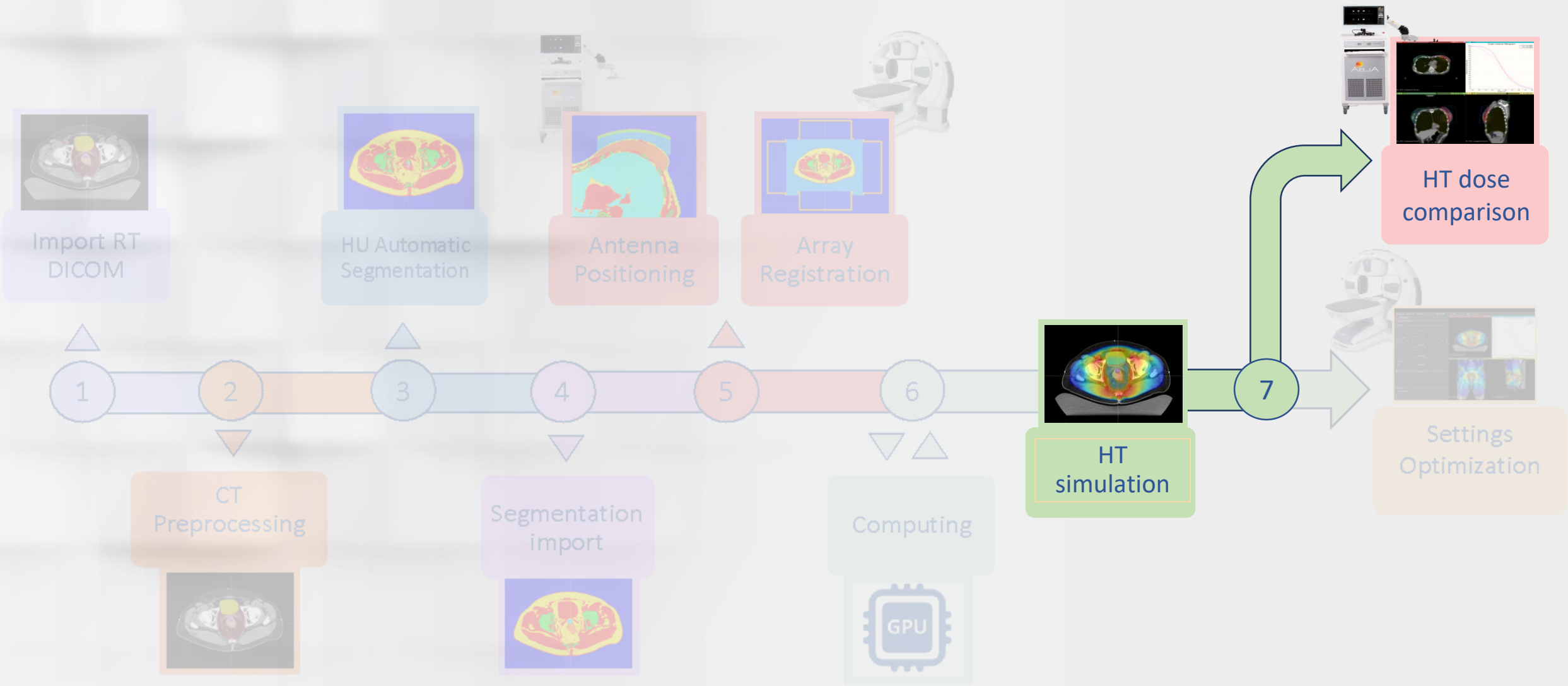
ALBA HTPS - PLAN2HEAT COMPUTING





Launching simulation

ALBA HTPS - PLAN2HEAT WORKFLOW

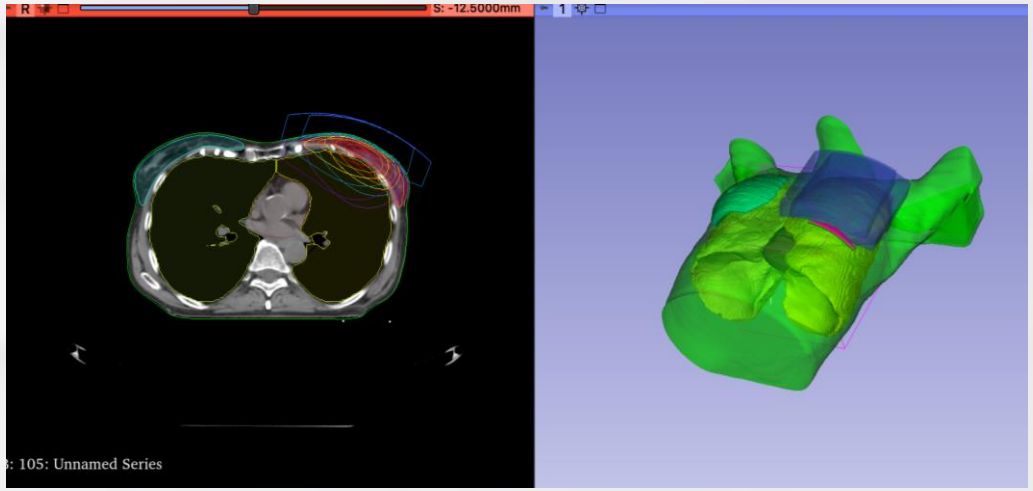


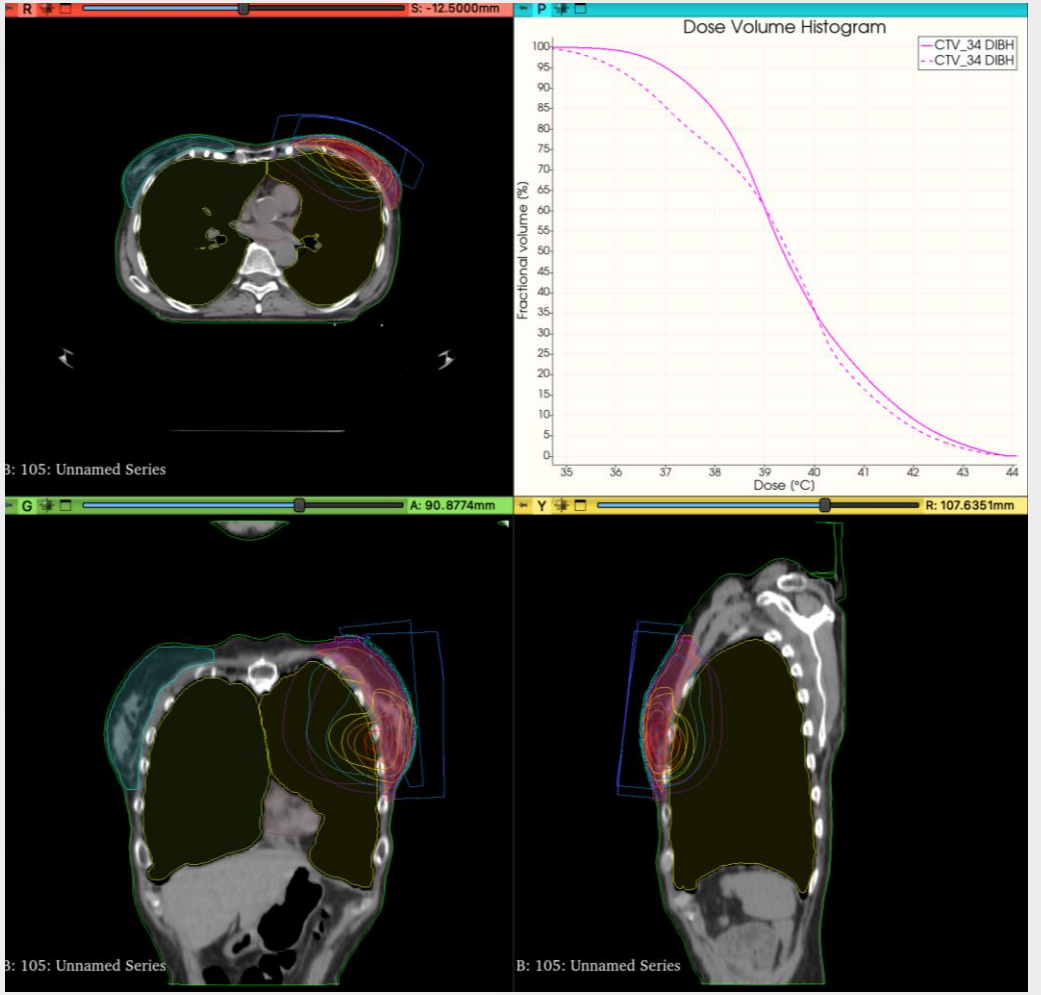
PLAN2heat
3D adaptive simulation

ALBA HTPS - PLAN2HEAT
ANTENNA POSITIONING

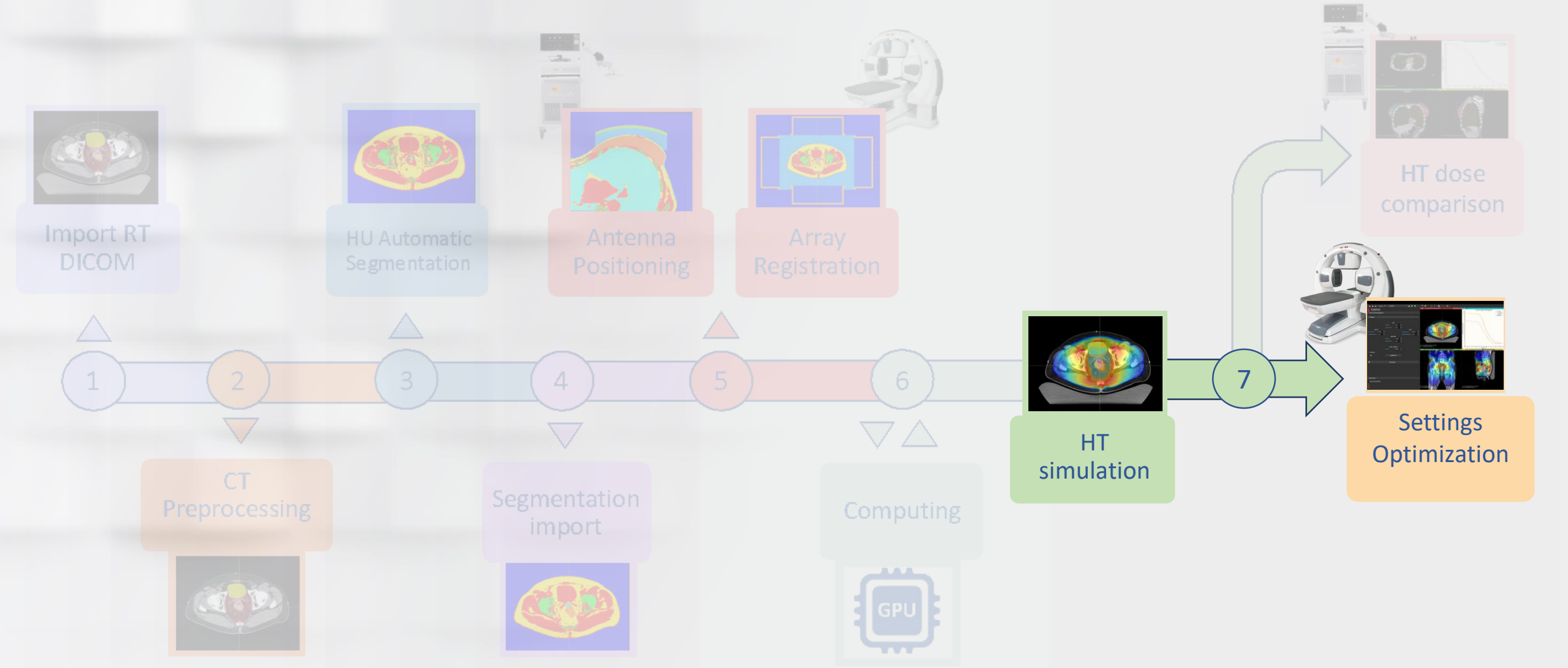
7

- Compare **ANTENNAS**
- Compare **POSITIONS**





ALBA HTPS - PLAN2HEAT WORKFLOW



PLAN2heat
3D adaptive simulation

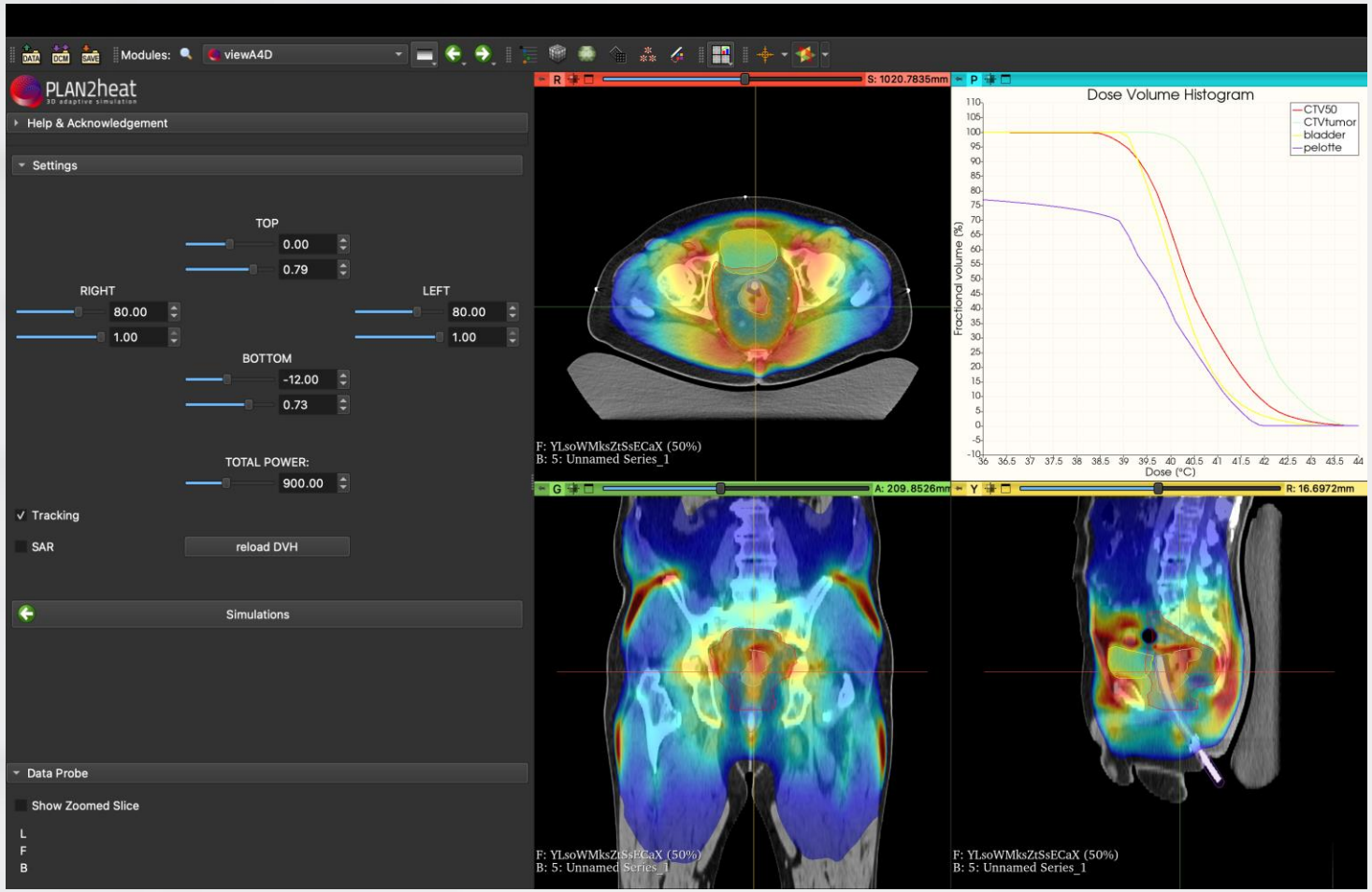
ALBA HTPS - PLAN2HEAT
PHASE ARRAY OPTIMIZATION

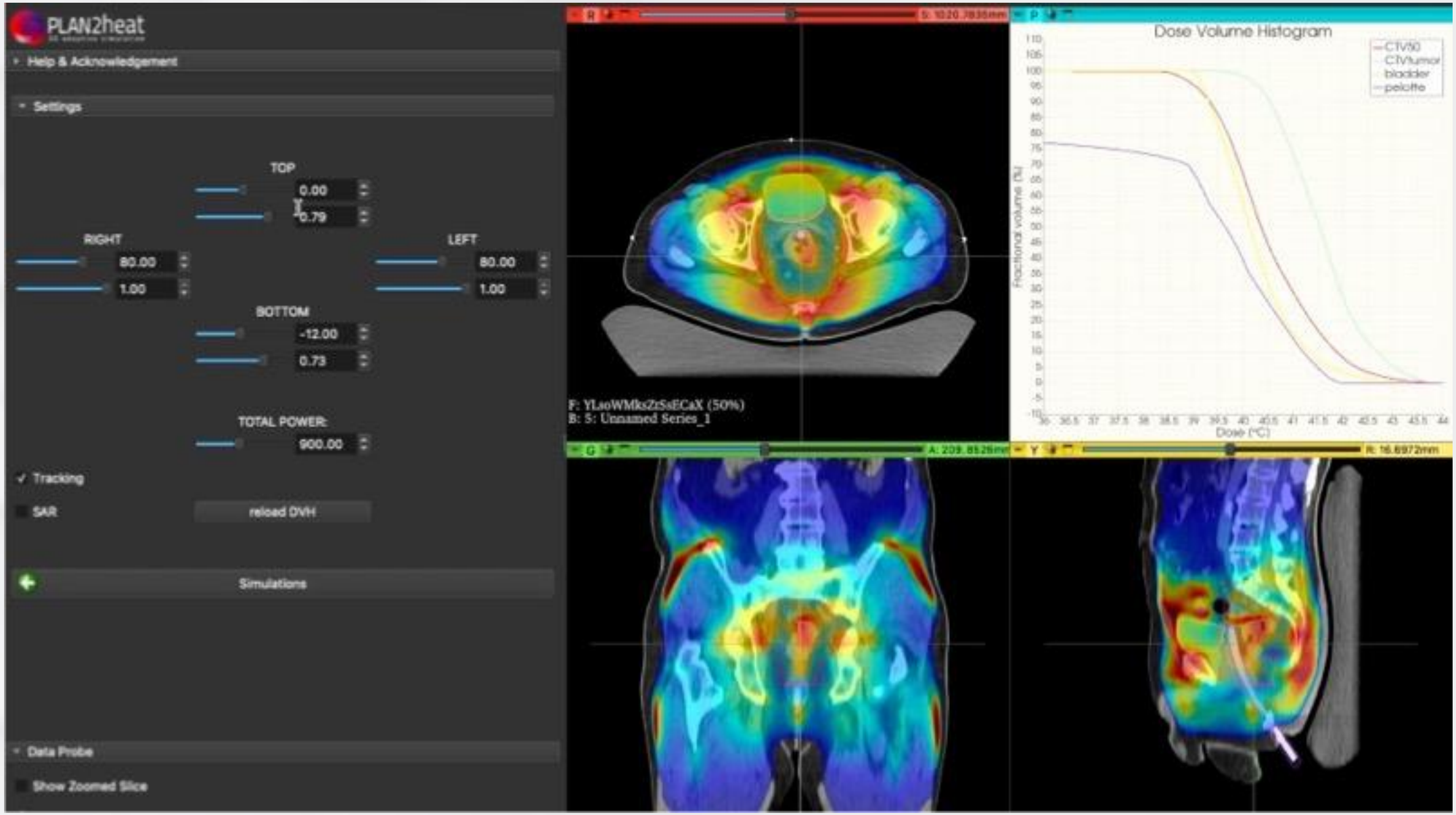
7

Optimize treatment settings

- **CONTROLS:**
- Phase
- Power Ratio
- Total Power

- **OUTPUT:**
- Temperature
- SAR





Thermoradiotherapy optimization in RayStation

RaySearch Laboratories

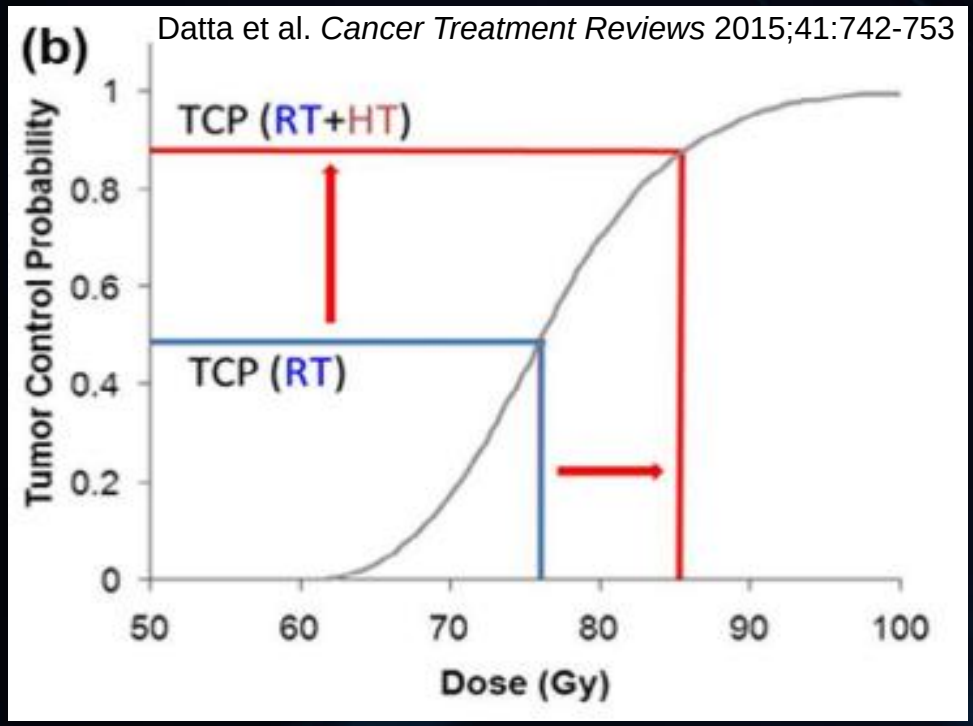
jakob.oden@raysearchlabs.com

Thermoradiotherapy

- Thermoradiotherapy…
  - …increases the effective dose through tumor heating
  - …potentially increases tumor control probability (TCP)

- RT and HT treatment plans are optimized individually
  - Thermal radiosensitization not fully taken advantage of
  - Ongoing research evaluates the total effect using equivalent radiation dose in 2 Gy fractions ($EQD2_{RT+HT}$)

Datta et al. *Cancer Treatment Reviews* 2015;41:742-753

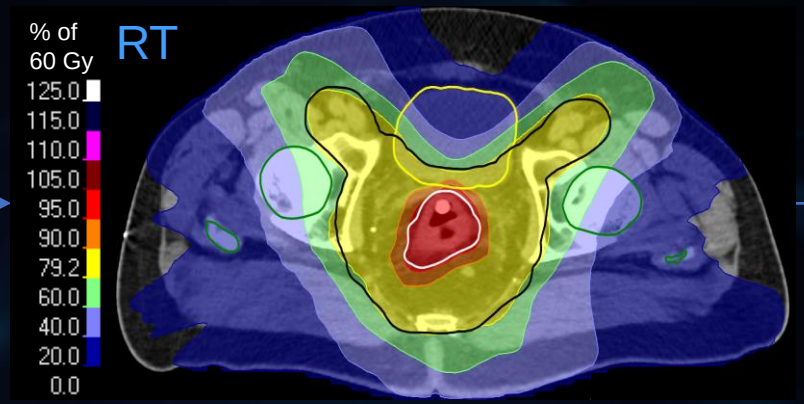


$EQD2_{RT+HT}$ evaluation

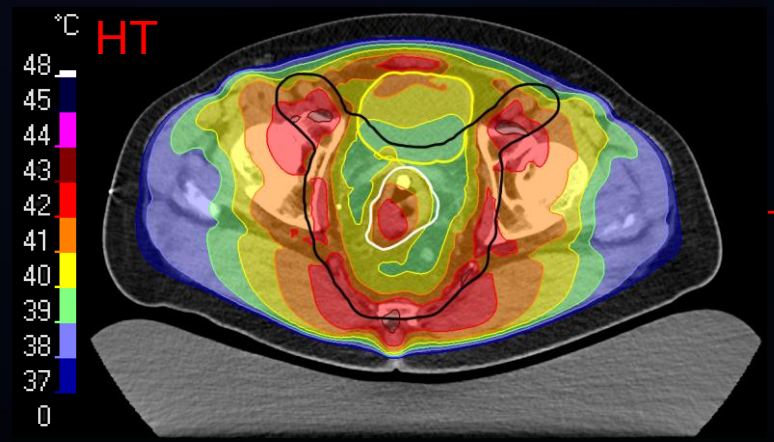
EQD2 with temperature dependent α, β and thermal cell kill

$$EQD2_{RT+HT} = \frac{\sum_{i=1}^{n} \alpha(T_i, t_{int,i}) \cdot d_i + \beta(T_i, t_{int,i}) \cdot d_i^2 + c(T_i)}{\alpha_{37} + 2 \cdot \beta_{37}}$$

RT optimization



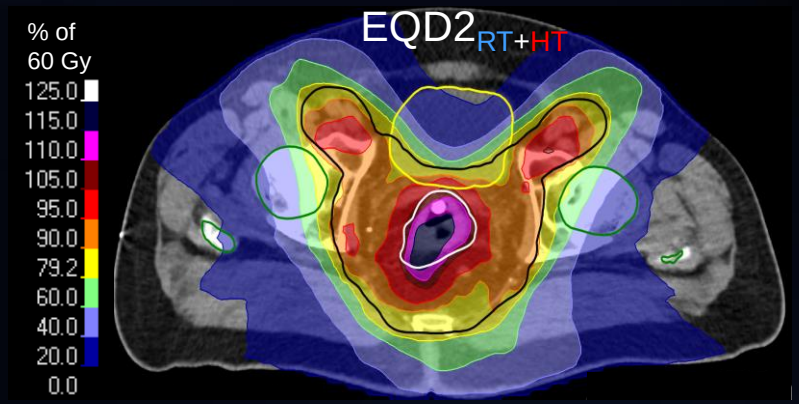
HT optimization



EQD2 evaluation

Thermal radio-sensitization

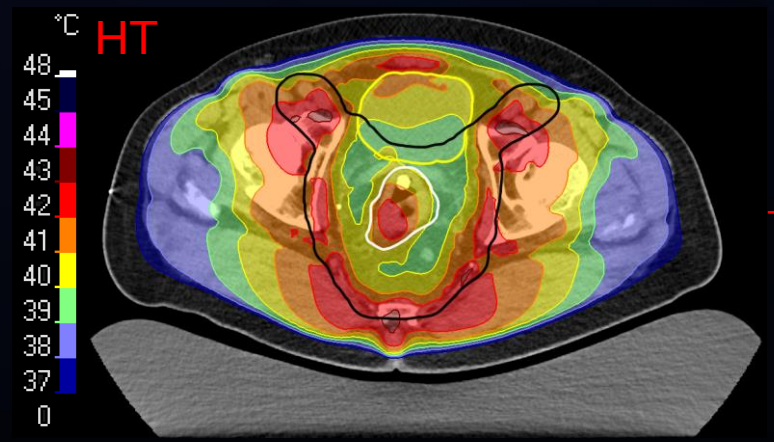
Mapped to CT_{RT}



$EQD2_{RT+HT}$ evaluation → $EQD2_{RT+HT}$ optimization

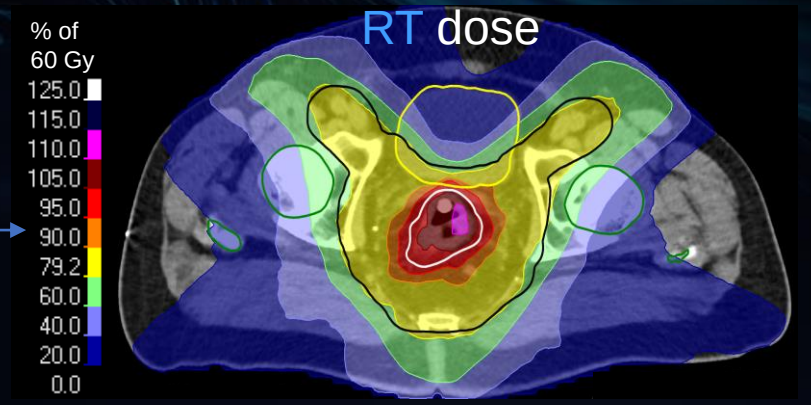
RT optimization

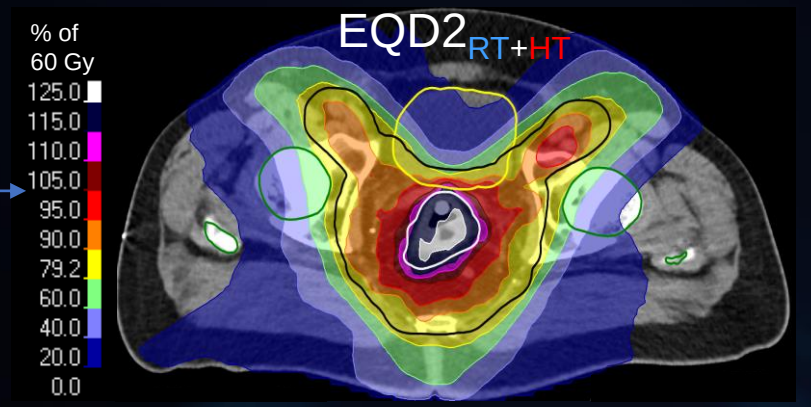
HT optimization



Mapped to CT_{RT}

Thermal radio-sensitization





$EQD2_{RT+HT}$ optimization tool in RayStation

1. Import CT_{HT}, CT_{RT} & temperature distribution into RayStation

2. Map temperature distribution CT_{HT} → CT_{RT}

3. RT plan generation
   - Calculate thermal radiosensitization parameters on voxel level
   - $EQD2_{RT+HT}$ optimization w/wo dose objectives

4. Treatment evaluation
   - Temperature, dose, $EQD2_{RT+HT}$, NTCP, TCP…

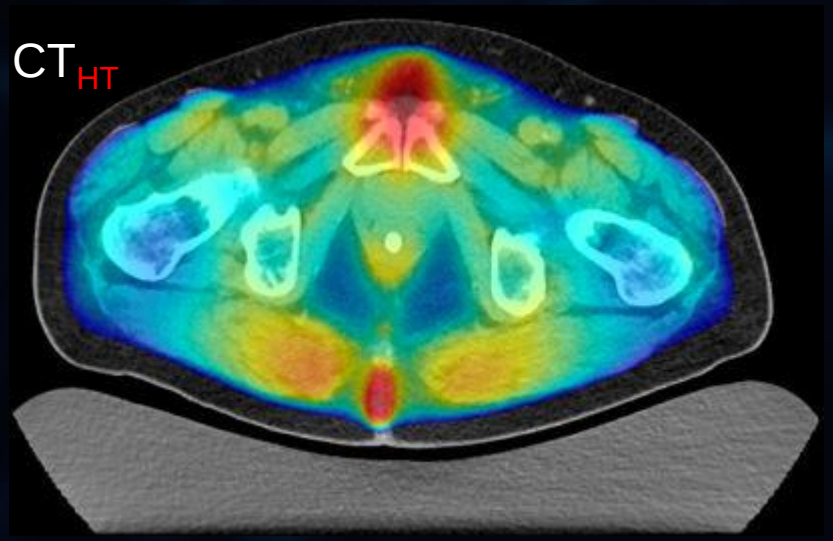
$EQD2_{RT+HT}$ = Equivalent radiation dose in 2 Gy fractions for thermoradiotherapy treatment

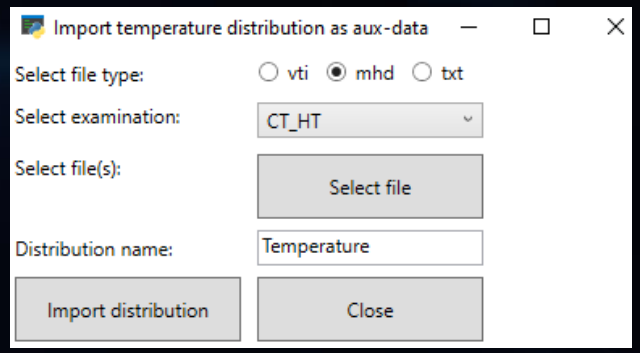
1. CT & temperature distribution import into RayStation

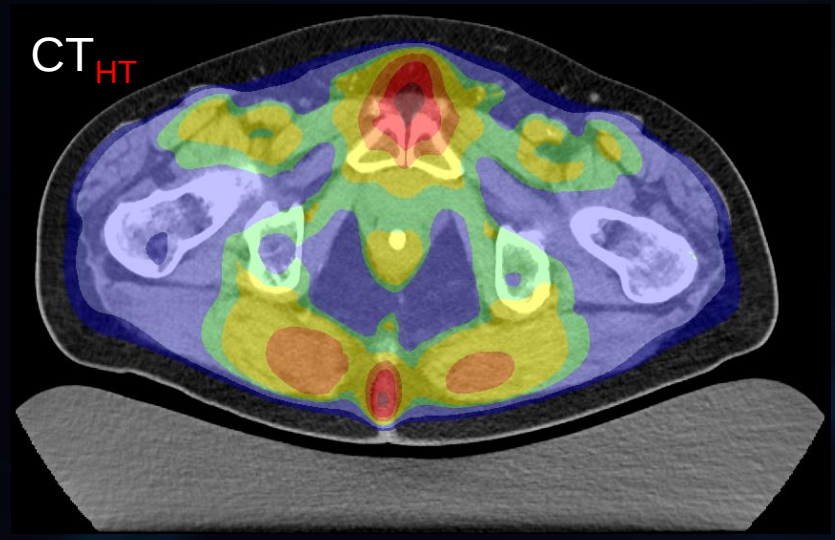
DICOM and Python scripting

PLAN2heat
3D adaptive simulation

RayStation 12A



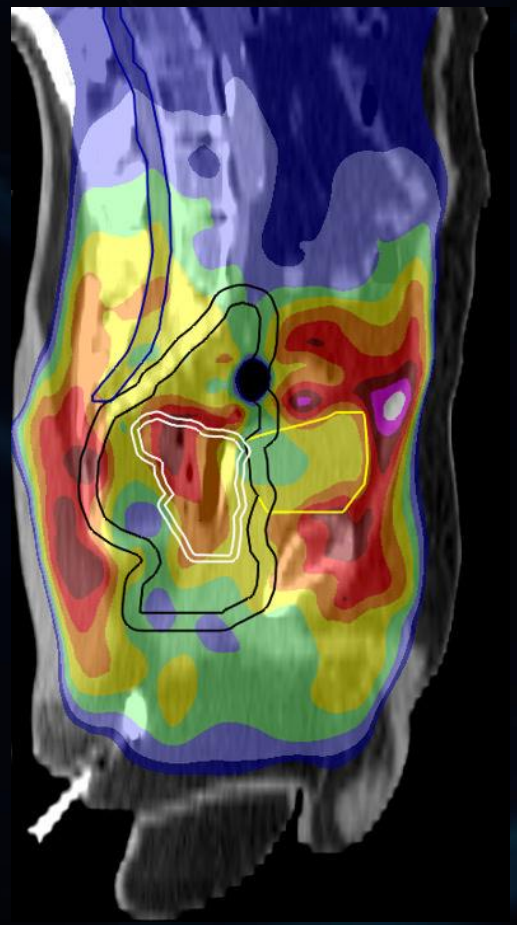




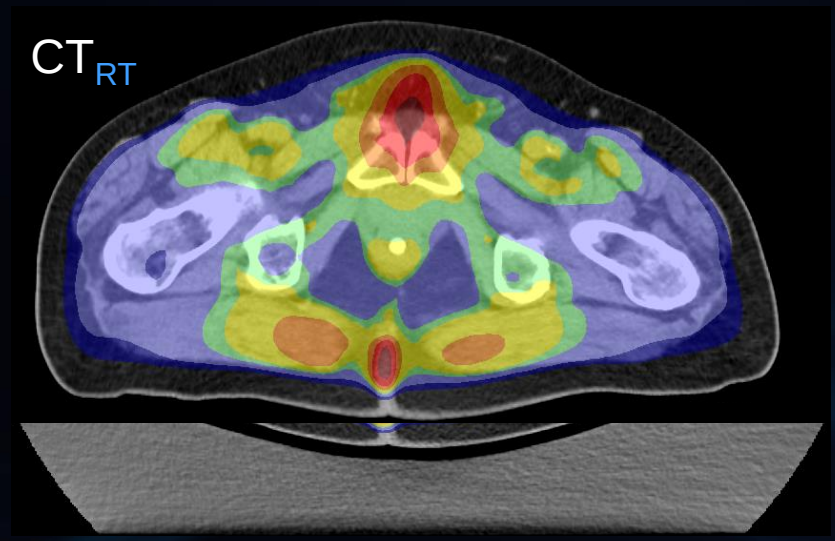
2. Map temperature distribution

CT_{HT} → CT_{RT}

- Deformable image registration (DIR)
  - Hybrid algorithm ‘ANCONDA’
  - Biomechanical algorithm ‘MORFEUS’
- Mapping temperature CT_{HT} → CT_{RT}
- ROI segmentation on CT_{RT}
  - Manual
  - Mapped using DIR
  - Deep Learning auto segmentation

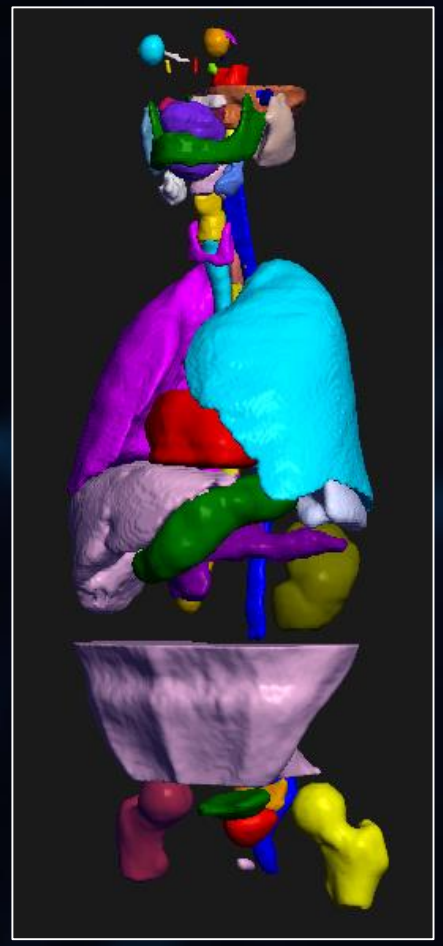


RayStation 12A



DL segmentation in RayStation using 3D U-Net CNN

Available to all users from RayStation 12A



H&N/Brain

Eye
Lens
Pituitary
Nasolacrimal duct
Lacrimal gland
Oral cavity
Tongue base
Nasopharynx
Oropharynx
Glottic larynx
Supraglottic larynx
Superior esophagus
Brainstem
Spinal cord
Cochlea
Posterior fossa
Mandible
TM joint
Parotid gland
Submandibular gland
Optical nerve
Chiasm
Brain
Lips
PCMs
Hippocampus
Lymph nodes neck I – VII

Thorax/Breast

Lungs
Heart
Esophagus
Spinal canal
Stomach
LAD
Breast
Trachea
Thyroid gland
Humeral heads
Lymph nodes breast 1 – 4, IMN, Pect
Brachial plexus
Carina
Bronchus
Great vessels
Lymph nodes thoracic 1 – 8
Chest wall

Abdomen

Liver
Kidney
Spleen
Pancreas
LumbSacPlex
Ureter
Bowel small / large

Pelvis

Bladder
Rectum / Anal Canal
Femoral heads
Prostate
Seminal vesicles
Penile bulb
Bowel Space
Pelvic lymph nodes
Sigmoid
Cervix-Uterus
Ovaries
Vagina
Genitals

- Existing models
- Research/Development
- Future

3. RT plan generation

Proof-of-concept – 3 VMAT plans for the rectum case

1) RT_{only}
   - Uniform dose of 50 and 60 Gy to PTV_{nodes} & PTV_{tumor}, respectively
   - $EQD2_{RT}$ objectives for OARs (α/β=3 Gy)
2) $RTHT_{OAR}$
   - As (1), but $EQD2_{RT+HT}$ objectives for normal tissues
3) $RTHT_{OAR+tumor}$
   - As (2), but uniform $EQD2_{RT+HT}$ of 75 Gy to PTV_{tumor} (α/β=10 Gy)

Thermal radiosensitization

Equivalent radiation dose in 2 Gy fractions (EQD2)

- $EQD2_{RT+HT}$ with dose d_i, temperature T_i and time interval $t_{int,\,i}$ between RT and HT for fraction i

$$EQD2_{RT} = D \cdot \frac{\alpha/\beta + d}{\alpha/\beta + 2} \quad \Rightarrow \quad EQD2_{RT+HT} = \frac{\sum_{i=1}^{n} \alpha(T_i, t_{int,\,i}) \cdot d_i + \beta(T_i, t_{int,\,i}) \cdot d_i^2 + c(T_i)}{\alpha_{37} + 2 \cdot \beta_{37}}$$

Thermal cell kill

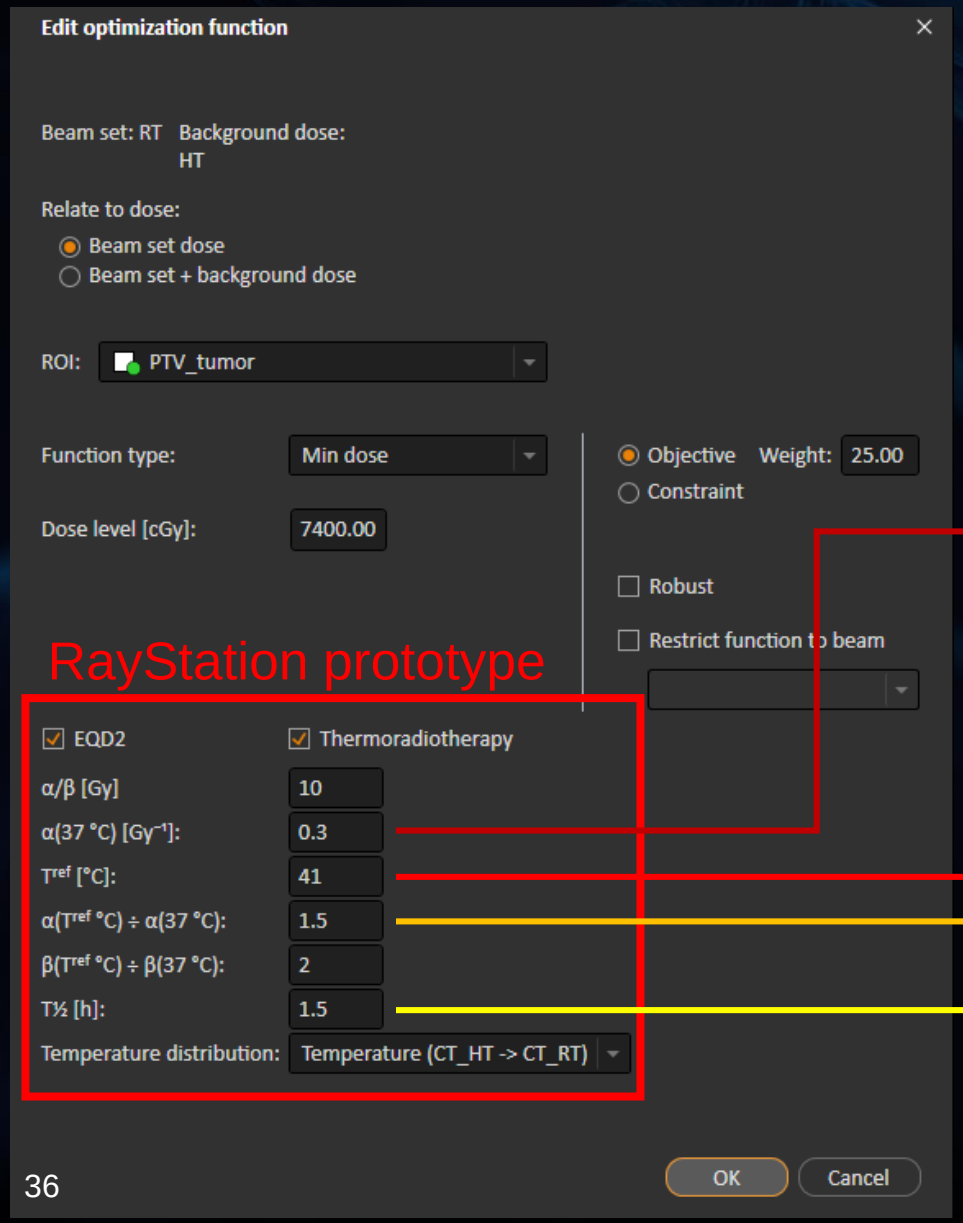
General EQD2 with temperature dependent α and β

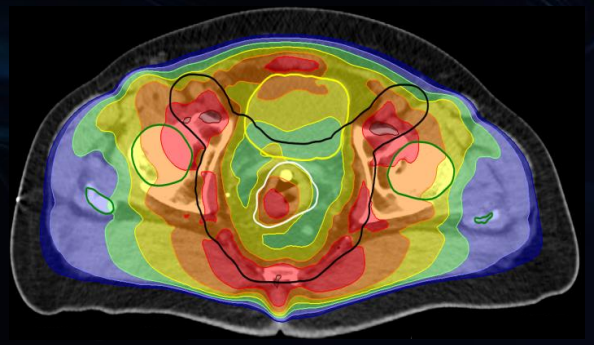
$$\alpha(T, t_{int}) = \begin{cases} \alpha_{37}, & T \le 37°C \\ \alpha_{37} \cdot \exp\left[\frac{T-37}{T_{ref}-37} \cdot \ln\left(\frac{\alpha_{T_{ref}}}{\alpha_{37}}\right) \cdot \exp\left(\frac{-\ln(2) \cdot |t_{int}|}{T_{1/2}}\right)\right], & T > 37°C \end{cases}$$

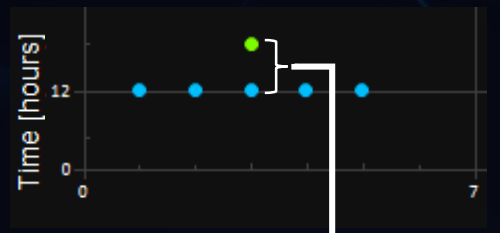
$$\beta(T, t_{int}) = \begin{cases} \beta_{37}, & T \le 37°C \\ \beta_{37} \cdot \exp\left[\frac{T-37}{T_{ref}-37} \cdot \ln\left(\frac{\beta_{T_{ref}}}{\beta_{37}}\right) \cdot \exp\left(\frac{-\ln(2) \cdot |t_{int}|}{T_{1/2}}\right)\right], & T > 37°C \end{cases}$$

- Exponential *increase* with temperature $T > 37°C$
- Exponential *decreasing* exponent with $t_{int} > 0$ h

RTHT optimization functions







$$\alpha(T, t_{int}) = \begin{cases} \alpha_{37}, & T \le 37°C \\ \alpha_{37} \cdot \exp\left[\dfrac{T-37}{T_{ref}-37} \cdot \ln\left(\dfrac{\alpha_{T_{ref}}}{\alpha_{37}}\right) \cdot \exp\left(\dfrac{-\ln(2) \cdot |t_{int}|}{T_{1/2}}\right)\right], & T > 37°C \end{cases}$$

RTHT optimization functions

(3) $RTHT_{OAR+tumor}$

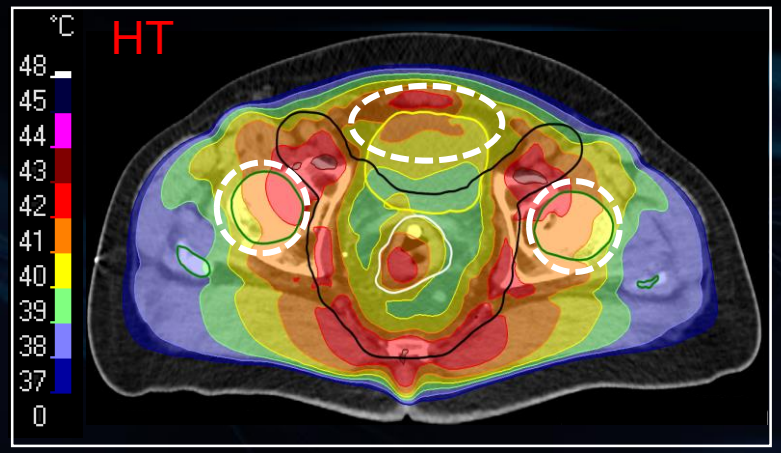
Thermoradiotherapy parameters

Temperature distribution:	**Temperature (CT_HT -> CT_RT)**
Thermal cytotoxicity:	**True**
α(37) [Gy⁻¹]:	**0.3**
α(41) ÷ α(37):	**1.5**
β(41) ÷ β(37):	**2**
T½ [h]:	**1.5**

Function	Constraint	Dose	ROI	Description	Robust	Weight	Value	EUD [cGy]	α/β [Gy]	Thermoradiotherapy
Physical composite objective							0.0890			
Min dose		Beam set	PTV_tumor	Min dose 7400.00 cGy		25.00	0.0212		10	★
Max dose		Beam set	PTV_tumor	Max dose 7600.00 cGy		50.00	0.0099		10	★
Min dose		Beam set	f_PTV_RT_rim	Min dose 4850.00 cGy		75.00	0.0087			
Max dose		Beam set	f_PTV_RT_rim	Max dose 5050.00 cGy		25.00	0.0023			
Max dose		Beam set	Ring_PTVtumor	Max dose 5500.00 cGy		100.00	0.0269			
Max dose		Beam set	Ring_PTV_RT	Max dose 4500.00 cGy		10.00	0.0020			
Dose fall-off		Beam set	External	Dose fall-off [H]6000.00 cGy [L]2500.00 cGy, Low dose distance 1.00 cm		1.00	0.0051		3	★
Dose fall-off		Beam set	External	Dose fall-off [H]6000.00 cGy [L]600.00 cGy, Low dose distance 6.00 cm		1.00	0.0038		3	★
Max EUD		Beam set	Femoral_heads	Max EUD 1200.00 cGy, Parameter A 1		1.00	4.0971E-4	1254.31	3	★
Max dose		Beam set	Femoral_heads	Max dose 4000.00 cGy		1.00	0.0022		3	★
Max EUD		Beam set	f_bladder	Max EUD 2000.00 cGy, Parameter A 1		5.00	9.5944E-4	2061.95	3	★
Max dose		Beam set	f_bladder_rim	Max dose 5000.00 cGy		1.00	0.0049		3	★
Max dose		Beam set	Spinal_cord	Max dose 4200.00 cGy		1.00	5.9554E-4		2	★

4. Plan evaluation

Dose and $EQD2_{RT+HT}$ distributions



(1) RT_{only} (2) $RTHT_{OAR}$ (3) $RTHT_{OAR+tumor}$

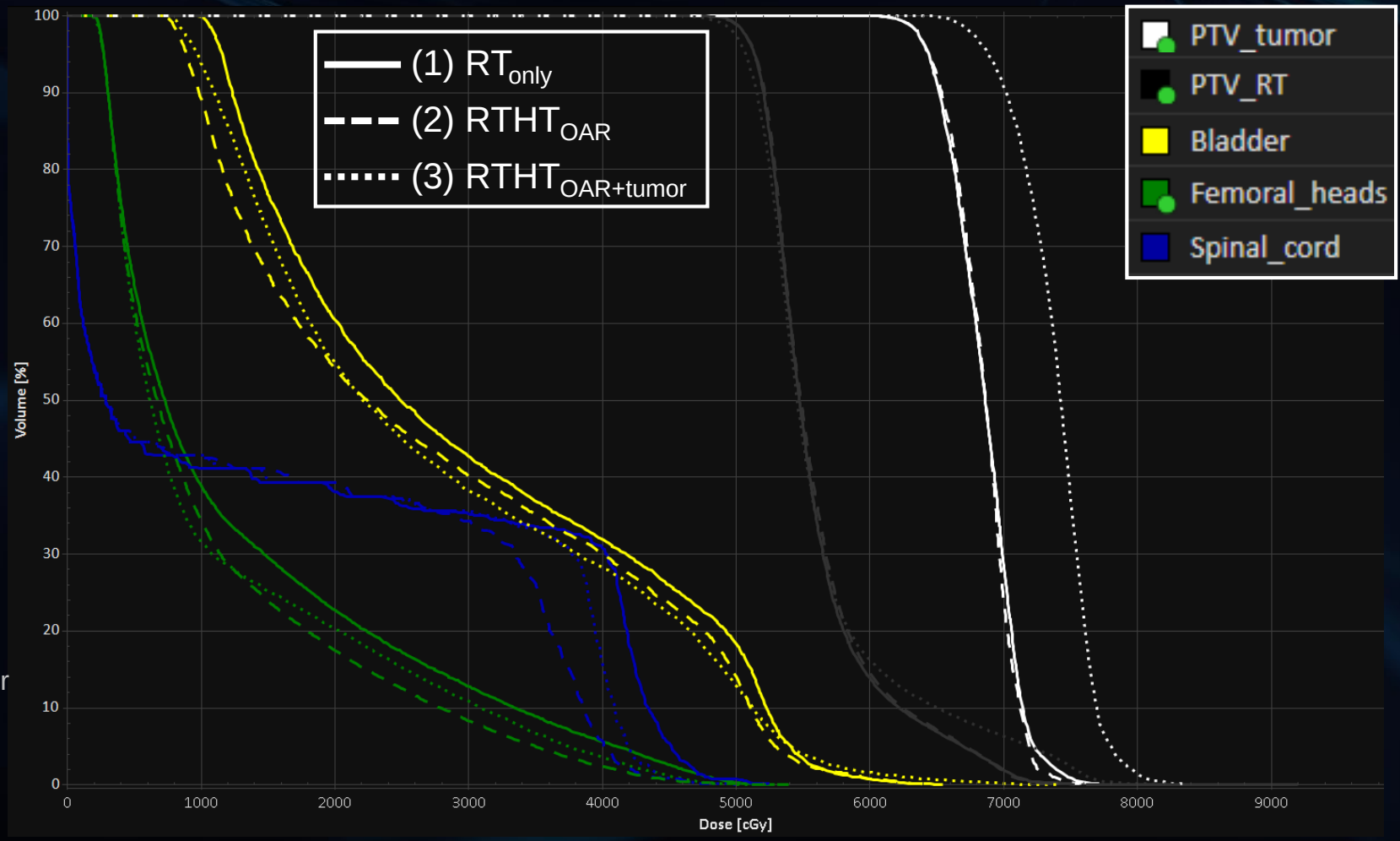
RT dose

$EQD2_{RT+HT}$

4. Plan evaluation

$EQD2_{RT+HT}$-volume histograms

- PTV $EQD2_{RT+HT}$ similar for…
  …(1) RT_{only} and (2) $RTHT_{OAR}$
- Higher PTV_{tumor} $EQD2_{RT+HT}$ for…
  …(3) $RTHT_{OAR+tumor}$
- Lowest $EQD2_{RT+HT}$ to OARs for…
  …(2) $RTHT_{OAR}$ and (3) $RTHT_{OAR+tumor}$



Conclusions

- Novel thermoradiotherapy planning tool…
  - …allow $EQD2_{RT+HT}$ optimization & evaluation
  - …improve the overall $EQD2_{RT+HT}$ distribution, potentially leading to improved treatment outcome
- The tool can be utilized in individualized…
  - …pre-treatment planning & adaptive re-planning
- Future work includes…
  - …further clinical exploration within the HYPERBOOST project (https://www.hyperboost.eu)
  - …robust evaluation & optimization accounting for temperature uncertainties

Thank you for the attention!

Questions?

RaySearch Laboratories

MEDLOGIX medical solutions

Jakob Ödén
jakob.oden@raysearchlabs.com

Brando Pavoni
brando.pavoni@medlogix.eu