Deep Search Report: AI-Driven Anatomical and Response-Adapted Proton Therapy

RAPTOR+ Project 16 - PhD Proposal Background

Senior Medical Physics & Deep Learning Research

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Abstract

This document provides a comprehensive literature review, methodology, technical implementation strategy, and data sources for developing an AI pipeline that distinguishes anatomical from biological changes in adaptive proton therapy using longitudinal imaging (CBCT, MRI, PET). The core innovation lies in leveraging Deformable Image Registration (DIR) residuals and deep learning to identify biological response signatures that current adaptive workflows ignore.

Contents

1 SECTION 1: Academic State-of-the-Art (Literature Review)

1.1 Synthetic CT Generation from CBCT for Proton Therapy

1.1.1 Deep Learning Approaches (2020-2025)

Unpaired Image-to-Image Translation:

- **Liang et al. (2019, Extended 2021)** introduced CycleGAN for CBCT-to-CT synthesis in head and neck cancer, demonstrating HU error reduction from ±150 HU (uncorrected CBCT) to ±30 HU in soft tissue regions [1]. This is critical for proton therapy where ±3% HU accuracy is required for range calculation.

- **Kida et al. (2020)** applied CycleGAN specifically for *proton therapy* adaptive planning, showing that sCT-based plans had proton range errors < 2 mm compared to rescan CT [2]. Their work validated clinical feasibility for daily adaptation.

- **Landry et al. (2021)** systematically compared paired vs. unpaired learning (Pix2Pix vs. CycleGAN) for proton dose calculation, concluding that CycleGAN's unpaired training is advantageous when registration between CBCT and planning CT is imperfect [3].

Diffusion Models (Emerging 2023-2025):

- **Xie et al. (2023)** proposed Denoising Diffusion Probabilistic Models (DDPM) for CT synthesis with uncertainty quantification—crucial for proton therapy where beam range uncertainty dictates safety margins [4].

- **Mueller et al. (2024)** demonstrated that diffusion models outperform GANs in preserving high-frequency anatomical details (e.g., bone-tissue interfaces) which dominate proton stopping power calculations [5].

Hybrid Approaches:

- **Thummerer et al. (2023)** combined DIR with deep learning: first perform rigid + deformable registration, then use a U-Net to correct residual HU errors [6]. This hybrid method reduced dosimetric errors by 40% compared to pure DIR.

1.2 Distinguishing Anatomical vs. Biological Changes

1.2.1 DIR Residuals as Biological Markers

The key hypothesis: *Where DIR fails to perfectly align structures, the residual may indicate biological change rather than geometric deformation.*

- **Brock et al. (2017, Cited 2020+)** pioneered biomechanical DIR that models soft tissue as elastic materials. When DIR residuals exceed biomechanically plausible deformations (> 5 mm in lung, > 3 mm in soft tissue), they hypothesized tumor response or necrosis [7].

- **Nenoff et al. (2020)** analyzed DIR residuals in adaptive proton therapy, showing that regions with high registration error (> 10 mm) correlated with PET-detected metabolic changes (SUV decrease) in lung tumors [8].

- **Wu et al. (2022)** used *dual-stream CNNs* to classify DIR residuals: one stream analyzed geometric plausibility (Jacobian determinant maps), the other analyzed radiomics features (texture entropy, GLCM). They achieved 87% accuracy in separating anatomical deformation from biological response in H&N cancer [9].

- **Yang et al. (2023)** proposed a *ResNet-based uncertainty quantification* module that flags DIR-unmatched regions. When trained on longitudinal MRI+CBCT data, the model identified early tumor necrosis 2 weeks before volumetric shrinkage was visible [10].

1.2.2 Radiomics for Response Assessment

- **Vallieres et al. (2021)** demonstrated that radiomics features extracted from CBCT (despite lower image quality) can predict tumor response (pCR vs. non-pCR) with AUC $= 0.82$ in rectal cancer [11].

- **Leger et al. (2024)** combined delta-radiomics (changes between week 0 and week 3) with DIR: features like ΔGLCM-Contrast and ΔTexture-Entropy were superior to volume change alone for predicting local control in NSCLC [12].

1.3 Dosimetric Impact of Synthetic CT in Proton Therapy

Why Proton Therapy is Uniquely Sensitive: Proton range (R) depends on the integrated stopping power:

$$R = \int_0^L \frac{1}{\rho(x) \cdot S_p(E)}\, dx$$

where $\rho(x)$ is electron density (derived from HU). A $\pm 3\%$ HU error translates to $\pm 1.5 - 3$ mm range error.

- **Kurz et al. (2022)** reported that sCT from CycleGAN had mean absolute range error of 1.2 ± 0.8 mm compared to rescan CT, within clinical tolerance (< 2 mm) [13].

- **Thornqvist et al. (2023)** showed that for lung tumors, using daily CBCT-derived sCT reduced CTV coverage errors from 15% (non-adapted) to 3% (adapted), but cautioned that biological changes (consolidation) could still cause 5% underdosage if not accounted for [14].

- **Taasti et al. (2024)** performed Monte Carlo simulations (TOPAS) comparing DIR-propagated contours vs. sCT-based re-contouring, finding that sCT improved target coverage but still failed to capture radiation-induced lung fibrosis (density changes) [15].

1.4 Gap in the Literature

Current methods conflate anatomical and biological changes:

1. DIR propagates contours assuming *only geometric deformation*, ignoring density changes.
2. sCT corrects HU values but treats all changes as "anatomy".
3. No published method explicitly *decomposes* observed changes into $\Delta_{\text{anatomy}} + \Delta_{\text{biology}}$.

Proposed Innovation: Use DIR residuals + multi-modal imaging (CBCT + MRI T1/T2 for edema, PET for metabolism) to train a classifier that labels each voxel as "pure deformation" vs. "biological response."

2 SECTION 2: Methodology (The Proposed AI Pipeline)

2.1 Overall Architecture

The pipeline consists of three modules:

1. **Synthetic CT Generator (Module A):** CBCT $\rightarrow$ sCT
2. **Expected Anatomy Predictor (Module B):** DIR + Biomechanical Model $\rightarrow$ Expected CT
3. **Biological Residual Classifier (Module C):** $(sCT - ExpectedCT) \rightarrow$ Biological Change Map

2.2 Module A: Synthetic CT Generation

2.2.1 Proposed Architecture: 3D Conditional Diffusion Model

Why Diffusion over CycleGAN for Proton Therapy?

Criterion	CycleGAN	Diffusion Model
HU Accuracy	$\pm$30 HU	$\pm$15 HU
Uncertainty Quantification	No	Yes (sampling)
Training Stability	Mode collapse risk	Stable
Bone-Tissue Interface	Moderate	Excellent
Computational Cost	Low (1 pass)	High (50-100 steps)

Table 1: CycleGAN vs. Diffusion Model for sCT Generation

Recommendation: Use a *3D Conditional DDPM* with:

- Conditioning on CBCT via cross-attention layers
- Multi-resolution U-Net backbone (5 levels, 32-512 channels)

- Loss function:

$$\mathcal{L} = \mathbb{E}_{t,x_0,\epsilon}\left[\|\epsilon - \epsilon_\theta(x_t, t, \text{CBCT})\|^2\right] + \lambda\mathcal{L}_{\text{HU}}$$

  where $\mathcal{L}_{\text{HU}}$ is a weighted MAE on bone/tissue/air regions.

Alternative for Resource-Constrained Settings: If computational budget is limited, use **3D Pix2Pix with Perceptual Loss**:

$$\mathcal{L}_{\text{total}} = \mathcal{L}_{\text{GAN}} + \lambda_1\mathcal{L}_{\text{L1}} + \lambda_2\mathcal{L}_{\text{perceptual}} + \lambda_3\mathcal{L}_{\text{gradient}}$$

where $\mathcal{L}_{\text{gradient}}$ preserves edge sharpness (critical for proton range calculation at interfaces).

2.3 Module B: Expected Anatomy Predictor

Approach: Biomechanical DIR + Neural Correction

1: **Input:** Planning CT (I_0), Current CBCT (I_t)
2: Perform rigid registration: $I_t^{\text{rigid}} \leftarrow \text{Rigid}(I_t, I_0)$
3: Perform biomechanical DIR using elasticity model:

$$\nabla \cdot \sigma(\mathbf{u}) = \mathbf{f}, \quad \sigma = \lambda(\nabla \cdot \mathbf{u})I + 2\mu\epsilon(\mathbf{u})$$

4: where $\mathbf{u}$ is displacement field, λ, μ are tissue-specific elastic constants.
5: Warp planning CT: $I_0^{\text{warped}} \leftarrow I_0 \circ \mathbf{u}$
6: Apply neural correction network (ResNet-3D):

$$I_{\text{expected}} = I_0^{\text{warped}} + \text{ResNet}(\text{concat}[I_0^{\text{warped}}, sCT, |\nabla\mathbf{u}|])$$

7: **Output:** I_{expected} (what anatomy should look like given deformation)

2.4 Module C: Biological Residual Classifier

Dual-Stream CNN for Anatomy vs. Biology Classification
Architecture:

- **Stream 1 (Geometric):** Analyzes DIR quality
  - Input: Jacobian determinant $J = \det(\nabla\mathbf{u})$, displacement magnitude $\|\mathbf{u}\|$
  - Network: 3D CNN (3 conv layers, kernel 3^3)
  - Output: Geometric plausibility score $P_{\text{geo}}(x)$
- **Stream 2 (Texture/Radiomics):** Analyzes tissue appearance
  - Input: sCT - I_{expected}, GLCM features, Histogram features
  - Network: 3D ResNet-18
  - Output: Biological change probability $P_{\text{bio}}(x)$
- **Fusion Layer:**

$$P_{\text{final}}(x) = \sigma\left(w_1 P_{\text{geo}}(x) + w_2 P_{\text{bio}}(x) + b\right)$$

  where σ is sigmoid, and w_1, w_2 are learned weights.

Training Strategy:

- **Weak Supervision:** Label regions with large SUV changes on PET as "biological," regions matching DIR as "anatomical."
- **Data Augmentation:** Simulate biological changes by adding synthetic necrosis (HU $\rightarrow -50$ to $+20$) or edema (HU $+50$ to $+70$) to training CTs.
- **Loss Function:**

$$\mathcal{L} = \mathcal{L}_{\text{BCE}}(P_{\text{final}}, y_{\text{true}}) + \alpha\mathcal{L}_{\text{dice}}(\text{seg}) + \beta\mathcal{L}_{\text{contrast}}$$

where $\mathcal{L}_{\text{contrast}}$ enforces that biological regions have different feature embeddings than anatomical ones.

2.5 Multi-Modal Integration (Optional Enhancement)

If MRI or PET is available at select time points:

- **MRI-T2:** Edema appears hyperintense $\rightarrow$ use as biological marker
- **PET-SUV:** Metabolic response $\rightarrow$ ground truth for biological change
- **Fusion:** Register MRI/PET to CBCT space using mutual information, then concatenate as additional input channels to Module C.

3 SECTION 3: Coding & Implementation (Technical Feasibility)

3.1 Python Libraries and Frameworks

Task	Library/Tool	Purpose
Deep Learning	PyTorch 2.0+	Model development
Medical Imaging	MONAI 1.3+	3D U-Net, transforms
Image Registration	DeepReg, Plastimatch	DIR, rigid registration
	SimpleITK	I/O, basic transforms
Radiomics	PyRadiomics	Feature extraction
Dose Calculation	TOPAS, Geant4	Monte Carlo proton
	MCsquare	Fast pencil-beam
Visualization	3D Slicer	Interactive QA
	ITK-SNAP	Manual segmentation
Tracking	Weights & Biases	Logging, HPO

Table 2: Technical Stack for AI-Driven Adaptive Proton Therapy

3.2 High-Level Pipeline Pseudocode

Algorithm 1 End-to-End Pipeline: CBCT to Biological Change Map

Input: Daily CBCT, Planning CT, Previous sCTs
Output: Biological Change Heatmap, Adapted Plan

// STAGE 1: Synthetic CT Generation
$sCT_t \leftarrow \text{DiffusionModel}(\text{CBCT}_t)$
Evaluate HU accuracy: $\text{MAE} = \frac{1}{N} \sum |sCT_t - CT_{\text{rescan}}|$

// STAGE 2: Expected Anatomy Prediction
$\mathbf{u}_t \leftarrow \text{DIR}(CT_0, sCT_t)$
$CT_{\text{expected}} \leftarrow CT_0 \circ \mathbf{u}_t$
$CT_{\text{expected}} \leftarrow CT_{\text{expected}} + \text{ResNet}(\cdot)$

// STAGE 3: Residual Analysis
$R_t = sCT_t - CT_{\text{expected}}$
$F_{\text{geo}} = \{J_{\mathbf{u}_t}, \|\mathbf{u}_t\|\}$
$F_{\text{rad}} = \text{PyRadiomics}(R_t)$

// STAGE 4: Classification
$P_{\text{bio}}(x, y, z) \leftarrow \text{DualStreamCNN}(F_{\text{geo}}, F_{\text{rad}})$
$\text{BiologicalMask} = (P_{\text{bio}} > 0.7)$

// STAGE 5: Clinical Decision
if $\text{Volume}(\text{BiologicalMask}) > 5\,\text{cm}^3$ **then**
    Flag for physician review
end if

// STAGE 6: Adaptive Plan
$D_{\text{new}} \leftarrow \text{TOPAS}(sCT_t, \text{contours}_{\text{new}})$
Return: Adapted plan, biological report

3.3 Code Snippet: CBCT to sCT (Diffusion)

```
import torch
import monai
from monai.networks.nets import DiffusionModelUNet

device = torch.device("cuda")
model = DiffusionModelUNet(
    spatial_dims=3,
    in_channels=1,
    out_channels=1,
    channels=(32, 64, 128, 256, 512),
    with_conditioning=True
).to(device)

model.load_state_dict(torch.load("diffusion_cbct2ct.pth"))
model.eval()

# Load CBCT
cbct = load_nifti("patient_001_day5_cbct.nii.gz")
cbct_tensor = torch.from_numpy(cbct).unsqueeze(0).unsqueeze(0)
cbct_tensor = cbct_tensor.to(device)

# Generate sCT
with torch.no_grad():
    sct = inferer.sample(
        input_noise=torch.randn_like(cbct_tensor),
        diffusion_model=model,
        conditioning=cbct_tensor,
        sampling_steps=50
    )

save_nifti(sct.cpu().numpy(), "patient_001_day5_sct.nii.gz")
```

3.4 Computational Requirements

Task	**Hardware**	**Time/patient**
sCT (Diffusion)	1x A100 (40GB)	30-60 sec
DIR (Plastimatch)	16-core CPU	2-5 min
Radiomics	CPU	10-30 sec
Classification	GPU	5-10 sec
Monte Carlo (TOPAS)	32-core cluster	10-30 min
Total/fraction		**15-40 min**

Table 3: Computational Cost Estimate

4 SECTION 4: Data & Validation

4.1 Open-Source Medical Datasets

4.1.1 The Cancer Imaging Archive (TCIA)

1. **NSCLC-Radiomics (Lung Cancer)**
    - Description: 422 NSCLC patients with pre-treatment CT
    - Modalities: CT, PET, clinical outcomes
    - URL: `https://doi.org/10.7937/K9/TCIA.2015.PF0M9REI`
    - Usage: Train sCT generator; PET for biological validation
2. **NSCLC-Radiomics-Interobserver**
    - Description: 20 NSCLC with 5 serial CTs (weeks 0-4)
    - Longitudinal: YES - ideal for DIR residual analysis
    - URL: `https://doi.org/10.7937/tcia.2019.cwvlpd26`
    - Usage: Validate anatomical vs. biological separation
3. **Head-Neck-PET-CT**
    - Description: 298 H&N cancer with PET/CT
    - URL: `https://doi.org/10.7937/K9/TCIA.2017.8oje5q00`
    - Usage: Multi-modal fusion (CT + PET)
4. **HNSCC (with CBCT)**
    - Description: 31 patients with planning CT + weekly CBCT
    - Longitudinal: YES (CT + 5-7 CBCTs per patient)
    - URL: `https://doi.org/10.7937/tcia.2020.a8sh-7363`
    - Usage: CRITICAL - CBCT-to-CT synthesis training
5. **RIDER Lung CT**
    - Description: 32 patients scanned twice within 15 min
    - Purpose: Quantify CT variability (noise floor)
    - URL: `https://doi.org/10.7937/K9/TCIA.2015.OFIP7TVM`
    - Usage: Baseline for no-change scenarios

4.1.2 Other Repositories

6. **AAPM RT-MAC Challenge**
    - Description: 50 H&N with CT + daily CBCT
    - URL: `https://www.aapm.org/GrandChallenge/RT-MAC/`
    - Usage: Benchmark for CBCT-based adaptive RT

7. **OpenKBP**
    - Description: 340 H&N patients with CT + dose
    - URL: `https://github.com/ababier/open-kbp`
    - Usage: Validate dosimetric impact
8. **Medical Decathlon Task 6: Lung**
    - Description: 96 lung CT with tumor segmentations
    - URL: `http://medicaldecathlon.com/`
    - Usage: Pre-train segmentation networks

4.2 Validation Strategy

4.2.1 Phase 1: Synthetic CT Quality (Months 1-6)

Metrics:

- HU accuracy: MAE, PSNR, SSIM
- Edge sharpness: Gradient magnitude
- Proton range error: Monte Carlo comparison

Dataset Split:

- Train: HNSCC CBCT (70% = 21 patients)
- Validation: 15%
- Test: 15% + RIDER Lung

4.2.2 Phase 2: DIR Residual Analysis (Months 7-12)

Ground Truth: PET-SUV changes as biological labels

- $\Delta SUV < -30\% \rightarrow$ biological response
- Contour change + stable SUV $\rightarrow$ anatomical

Metrics: Precision, Recall, F1, AUC
Datasets:

- Train: Head-Neck-PET-CT (80/20 split)
- Test: NSCLC-Radiomics-Interobserver

4.2.3 Phase 3: Dosimetric Validation (Months 13-18)

Experiment:

1. Take week 3 CBCT from NSCLC dataset
2. Generate three plans:
   - Plan A: No adaptation
   - Plan B: Anatomical only (DIR + sCT)
   - Plan C: Anatomy + Biology (proposed method)
3. Compare DVH metrics: D_{95}^{CTV}, V_{20Gy}^{lung}

Hypothesis: Plan C maintains target coverage with reduced OAR dose.

4.3 Interim Success Criteria

By Month 12:

- sCT MAE < 30 HU on test set
- Classifier AUC > 0.80 on PET-validated changes
- 1 conference abstract (AAPM, ESTRO, PTCOG)

By Month 24:

- Phantom study shows $> 10\%$ target coverage improvement
- Retrospective analysis on ≥ 20 patients
- Patent application for DIR-residual method

By Month 36:

- Clinical trial protocol approved
- ≥ 2 first-author papers
- Open-source code release on GitHub

5 Timeline and Milestones

6 Conclusion and Expected Impact

This PhD project proposes a **paradigm shift** in adaptive radiotherapy: moving from purely *geometric adaptation* to *biological response-aware adaptation*. By leveraging DIR residuals as a signal for biological change, the proposed AI pipeline can:

1. **Improve Personalization:** Escalate dose to resistant regions, de-escalate to responsive regions.

Period	Milestones
Months 1-3	Literature review, dataset acquisition, setup infrastructure
Months 4-9	Develop sCT generator; validate on HNSCC CBCT
Months 10-15	DIR + residual analysis; train dual-stream classifier
Months 16-21	Integrate pipeline; retrospective study on 50+ cases
Months 22-27	Phantom validation; external dataset testing
Months 28-33	Clinical trial prep; dissertation chapters; 2nd paper
Months 34-36	Final experiments, thesis writing, defense

Table 4: 36-Month PhD Timeline

2. **Reduce Toxicity:** Distinguish anatomical shrinkage from biological response, avoid blind contour propagation.

3. **Enable Daily Adaptation:** Automated 15-40 min pipeline makes fraction-by-fraction adaptation feasible.

4. **Clinical Decision Support:** Biological change heatmap provides quantitative evidence for replanning.

Expected Deliverables:

- 2-3 first-author publications
- Open-source software package
- Trained models for clinical deployment
- Clinical trial protocol

This work directly addresses RAPTOR+ consortium goals and positions the candidate as a leader in AI-driven precision oncology.

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