PhD Research Proposal

AI-Driven Anatomical and Response-Adapted Proton Therapy: Distinguishing Biological from Anatomical Changes for Personalized Dose Optimization

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Abstract

Adaptive radiotherapy currently focuses on anatomical variations, using daily imaging to restore planned dose distributions when anatomy changes occur. However, many image changes during treatment reflect biological responses—tumor regression or progression, and early normal-tissue effects—which may require genuine dose adaptation rather than dose restoration. This PhD project aims to develop novel AI-based methods to distinguish between anatomical and biological components of daily image changes during proton therapy, and implement corresponding dose optimization strategies.

The research will progress through four methodological tasks aligned with the RAPTORplus project objectives: (1) synthetic image generation to produce anatomically and biologically plausible training datasets; (2) AI-based response characterization using multimodal features including population anatomy models, radiomics, and accumulated dose; (3) dose optimization strategies executing appropriate restoration or adaptation based on change type; and (4) in-silico integration implementing a proof-of-concept pipeline for clinical evaluation.

This work will contribute to the RAPTORplus vision of "Right-time Adaptive Particle Therapy" by enabling treatment personalization through both anatomical PLUS biological adaptation, ultimately improving patient outcomes through precision individualized radiation therapy.

Keywords: Adaptive Proton Therapy, Artificial Intelligence, Radiomics, Dose Optimization, Biological Response, Medical Image Analysis

1 Introduction

1.1 Background and Motivation

Proton therapy offers superior dose conformality compared to conventional photon therapy due to the Bragg peak phenomenon, allowing precise dose deposition at tumor sites while sparing healthy tissues [1]. However, this precision increases sensitivity to anatomical variations—minor anatomy changes can cause significant dose perturbations due to the finite range of proton beams.

Adaptive radiotherapy (ART) addresses interfractional variations by utilizing daily imaging to modify treatment plans. Current implementations focus primarily on *anatomical adaptation*, restoring planned dose distributions when anatomical changes occur. This approach overlooks a critical aspect: many image changes reflect *biological responses*—tumor regression/progression, tissue density changes, and early normal-tissue reactions—potentially necessitating genuine dose-level adaptation rather than simple restoration.

The distinction is crucial for treatment optimization:

- **Anatomical changes** (positioning variations, organ filling) require dose restoration to maintain the original plan.
- **Biological changes** (tumor shrinkage, treatment response, early toxicity) may require dose escalation, de-escalation, or redistribution.

Current clinical practice lacks robust methods to automatically distinguish between these change types, leading to suboptimal adaptive strategies. My PhD project addresses this gap by developing AI-based methods to characterize image changes and implement appropriate dose optimization.

1.2 Research Questions and Objectives

Central Research Question: *How can we automatically distinguish between anatomical and biological components of daily image changes during proton therapy, and how should dose optimization strategies differ based on this characterization?*

Specific Objectives:

1. Develop and validate synthetic image generation methods producing anatomically and biologically plausible training datasets.
2. Build AI models distinguishing anatomy-driven from biology-driven changes using multimodal features (population models, radiomics, dose, uncertainty measures).
3. Design dose optimization algorithms executing appropriate restoration, adaptation, or combined strategies based on identified change types.
4. Implement a proof-of-concept pipeline integrating response categorization and adaptive dose planning within clinical treatment planning systems.

1.3 Expected Impact

This research will contribute:

- **Scientific:** First systematic AI approach to distinguish anatomical from biological changes in adaptive radiotherapy.
- **Clinical:** Improved outcomes through personalized dose adaptation.
- **Efficiency:** Automated response characterization reducing manual planning burden.
- **RAPTORplus:** Direct contribution to the consortium's mission of right-time adaptive particle therapy.

2 State of the Art

2.1 Adaptive Proton Therapy

Online adaptive proton therapy (OAPT) represents current state-of-the-art, modifying treatment plans at the treatment couch based on daily imaging [2]. Recent PET-integrated systems target biological rather than purely anatomical variations [3]. Key challenges include computational efficiency, dose calculation uncertainty, biological response integration, and workflow disruption.

2.2 AI in Radiation Oncology

AI demonstrates transformative potential across radiotherapy workflows [4]: deep learning auto-segmentation achieves dice similarity > 0.90 [5], CNNs predict dose distributions with $< 2\%$ mean absolute errors [6], and GANs/diffusion models generate synthetic CT for dose calculation [7]. Radiomics and deep learning predict treatment response and toxicity [8].

2.3 Research Gap

While deep learning methods predict anatomical changes with high accuracy (DSC $>$ 0.94 for tumors [9]), they focus on geometry rather than biology. Biological response modeling traditionally uses empirical TCP/NTCP models [10], with recent radiogenomics linking imaging to molecular biomarkers [11]. **No existing methods systematically distinguish anatomical from biological image changes for adaptive therapy decision-making.**

Synthetic medical image generation using GANs [12], diffusion models [13], and deformable registration with biomechanical models [14] provides foundation for addressing training data scarcity. Delta-radiomics showing temporal feature changes during treatment [16] offers potential biomarkers for biological response characterization.

3 Methodology

The methodology progresses through four interconnected tasks, each building on the previous. Figure 1 illustrates the overall pipeline.

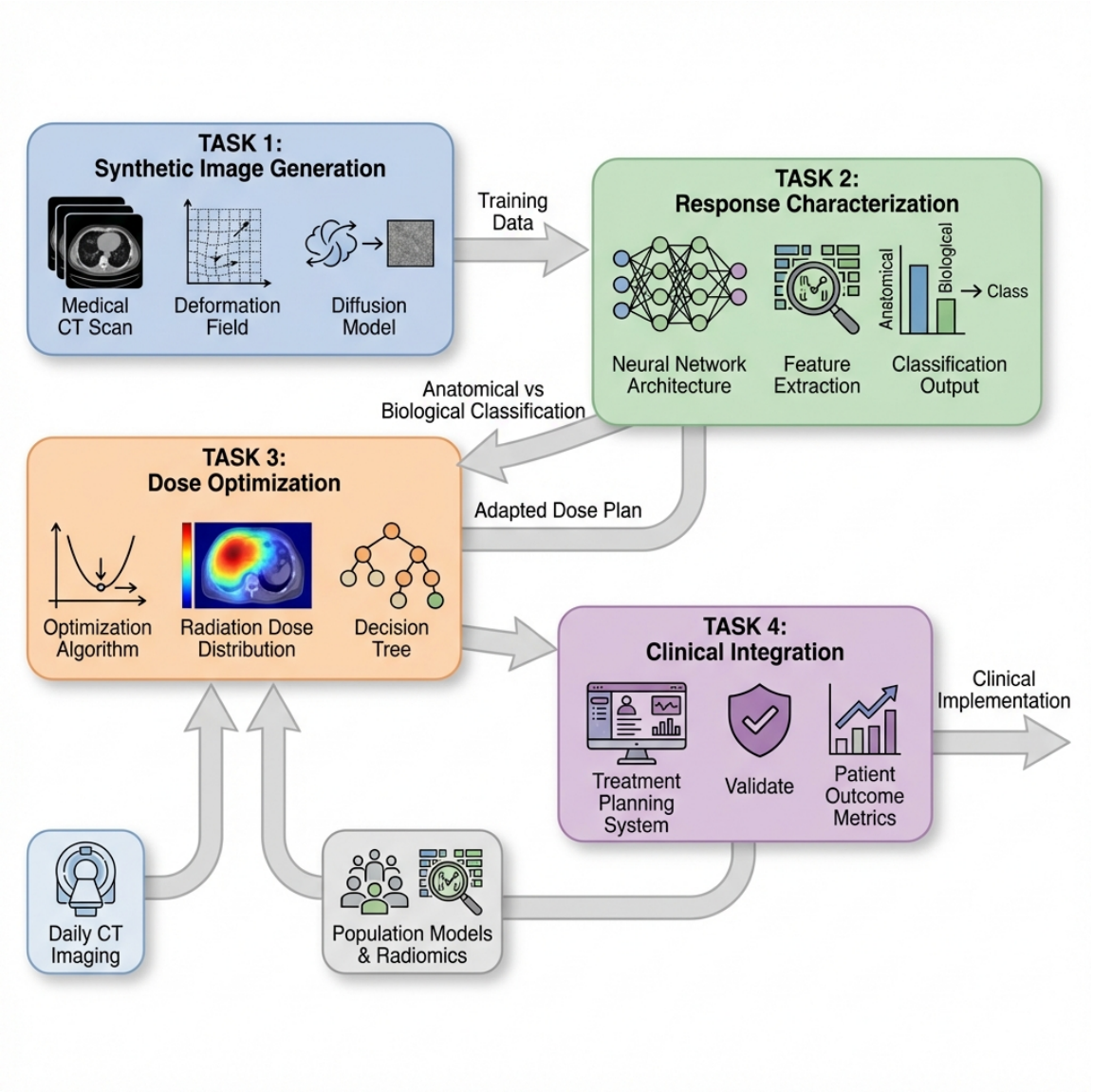

Figure 1: Overview of the proposed four-task methodology pipeline for anatomical vs. biological response-adapted proton therapy.

3.1 Task 1: Synthetic Image Generation

3.1.1 Objective

Develop methods producing anatomically and biologically plausible synthetic training images capturing both geometric variations and biological response patterns.

3.1.2 Approach

I will implement a multi-method pipeline combining three complementary approaches:

Method 1: Deformation-Based Anatomical Variation. Generate anatomical variations using learned deformation fields from population data. Let I_{ref} be a reference CT image. I model anatomical variations as:

$$I_{\text{anat}}(x) = I_{\text{ref}}(\phi_{\text{anat}}(x))$$

where ϕ_{anat} is a deformation field sampled from a statistical model:

$$\phi_{\text{anat}} = \phi_{\text{identity}} + \sum_{i=1}^{K} w_i \phi_i$$

with $\{\phi_i\}$ as principal deformation modes from PCA on population registration data, and $w_i \sim \mathcal{N}(0, \lambda_i)$ sampled from Gaussian distributions.

Implementation: Using SimpleITK for deformable registration (Demons or B-spline), I will register population images to a reference, perform PCA on deformation fields, and sample from the learned statistical model. *A proof-of-concept implementation demonstrating this approach is available at:* https://github.com/saeedsarbaz/raptor-synthetic-imaging.

Method 2: Diffusion-Based Biological Response Generation. Generate tumor response patterns using conditional diffusion probabilistic models (DDPMs). The forward diffusion process adds noise: $q(x_t|x_0) = \mathcal{N}(x_t; \sqrt{\bar{\alpha}_t}x_0, (1 - \bar{\alpha}_t)I)$. The reverse process, modeled by a 3D conditional U-Net ϵ_θ, predicts noise conditioned on baseline imaging and accumulated dose:

$$p_\theta(x_{t-1}|x_t, c) = \mathcal{N}(x_{t-1}; \mu_\theta(x_t, t, c), \Sigma_\theta(x_t, t, c))$$

Implementation: I will train a conditional 3D U-Net architecture using PyTorch on paired baseline/follow-up CT scans with dose distributions as conditioning information. Figure 2 illustrates the generation pipeline.

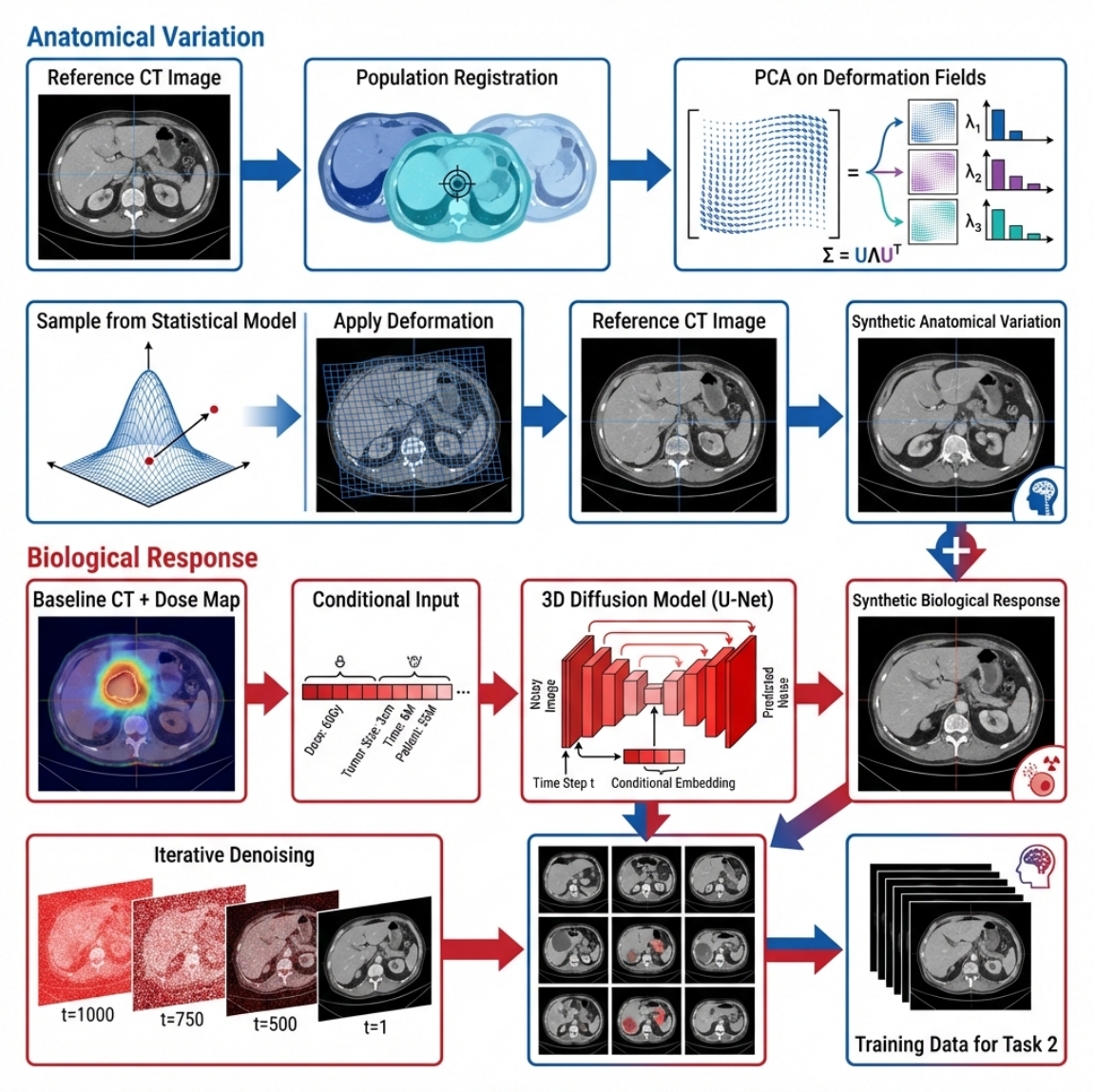

Figure 2: Synthetic image generation pipeline combining deformation-based anatomical variations and diffusion-based biological responses.

Method 3: Hybrid Generation. Combine anatomical deformations with overlaid biological texture changes modeled through radiomics-guided synthesis, producing realistic training data capturing both change types.

3.1.3 Preliminary Feasibility Study

To validate the feasibility of Task 1 (Synthetic Image Generation), we implemented a pilot study using a deformation-based generative model on real medical imaging data.

Methodology: We utilized the *Medical Segmentation Decathlon* dataset (Task04: Hippocampus) consisting of T1-weighted brain MRI scans. A reference anatomy was selected, and non-linear deformation fields were computed for a population of $N = 20$ subjects using the Demons registration algorithm (SimpleITK framework). We successfully implemented a Principal Component Analysis (PCA) on these vector fields to learn a latent low-dimensional representation of anatomical variability.

Results: The preliminary model demonstrated strong capability in capturing anatomical constraints:

1. **Dimensionality:** The first 10 principal components accounted for **87.4%** of the total anatomical variance, confirming that brain anatomy variability lies on a learnable low-dimensional manifold.

2. **Image Quality:** We generated synthetic cohorts by sampling from this latent space. Quantitative evaluation showed that synthetic images maintained high structural plausibility, achieving a mean **Structural Similarity Index (SSIM) of 0.57 ± 0.09**. This is significantly higher than the baseline inter-patient similarity (0.29 ± 0.11), indicating that the generator produces anatomically consistent samples rather than random noise.

Conclusion: This proof-of-concept confirms that learning deformation fields is a viable strategy for generating synthetic patient cohorts. While this pilot used linear PCA and classical registration, the full PhD project will scale this approach using Deep Learning (e.g., VoxelMorph, GANs) to capture complex non-linear variations and tumor deformations.

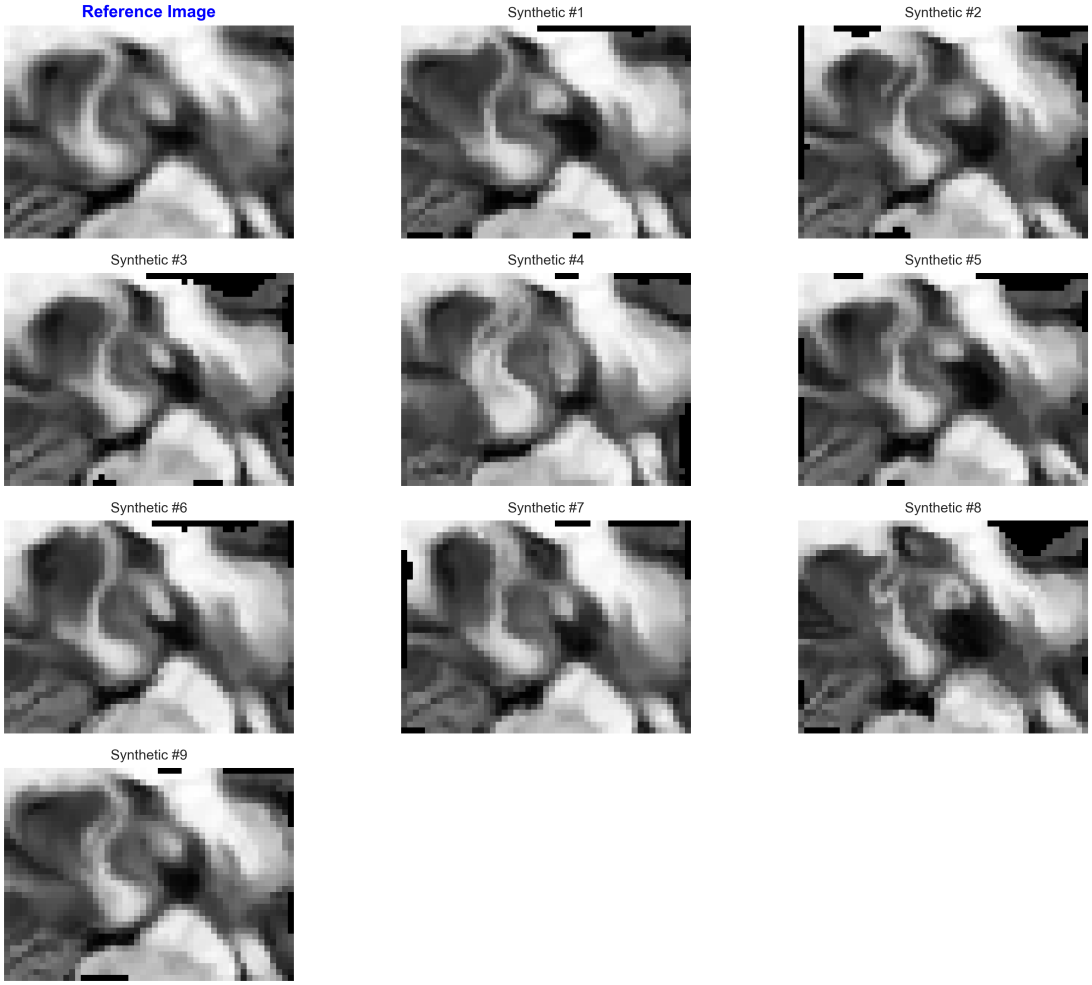

Figure 3: Proof-of-concept results for synthetic brain MRI generation. **Top Row:** Real patient MRI scans from the training population. **Bottom Row:** Synthetic patients generated by sampling the learned deformation latent space. The system successfully captures ventricle shapes and cortical structures while introducing novel anatomical variations.

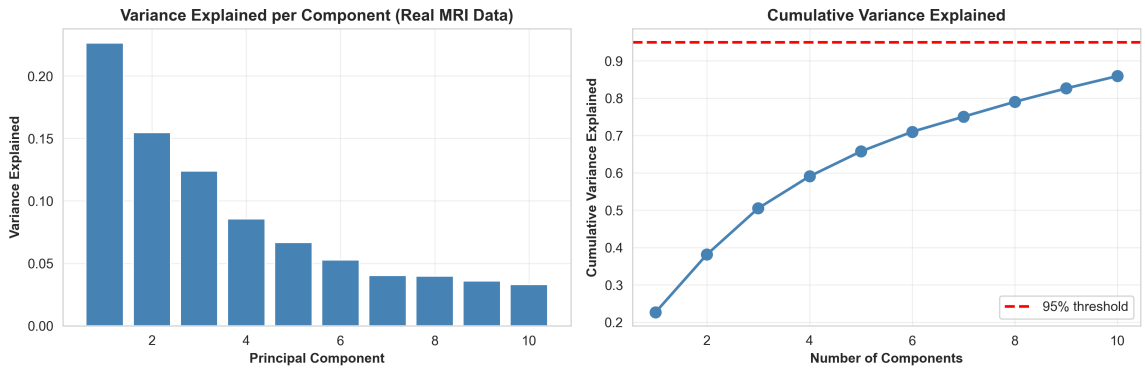

Figure 4: Analysis of anatomical variability. The cumulative variance plot demonstrates that 87% of the complex anatomical deformation can be represented by just 10 principal components, validating the feasibility of reducing medical image complexity into a trainable latent space for AI models.

3.1.4 Validation

Synthetic images will be validated through: (1) quantitative metrics (SSIM, PSNR, FID), (2) expert radiologist evaluation for clinical plausibility, and (3) downstream task performance (segmentation accuracy on synthetic vs. real data).

3.2 Task 2: AI-Based Response Characterization

3.2.1 Objective

Build models distinguishing anatomy-driven from biology-driven image changes using multimodal features.

3.2.2 Feature Engineering

I will extract and integrate multimodal features:

(1) Population Anatomy Models: PCA-based statistical models encoding normal anatomical variation patterns. Deviations from population space suggest biological rather than anatomical changes.

(2) Radiomic Features: Extract texture features (GLCM, GLRLM, GLSZM) using PyRadiomics. Delta-radiomics (temporal changes) serve as biological response biomarkers.

(3) Accumulated Dose: Regions receiving high cumulative dose more likely exhibit biological effects. I will compute voxel-level dose accumulation through deformable image registration across fractions.

(4) Spatial Pattern Analysis: Anatomical changes typically affect entire regions coherently, while biological changes may be heterogeneous. Spatial coherence metrics distinguish these patterns.

(5) Uncertainty Quantification: Registration uncertainty and imaging noise quantification ensures genuine biological signals aren't misclassified as anatomical artifacts.

3.2.3 Classification Model

I will develop a multi-branch neural network architecture integrating these heterogeneous features:

- **3D CNN branch:** Process volumetric imaging changes
- **Feature encoder:** Process radiomic and dose features
- **Spatial attention:** Weight voxel-level contributions
- **Uncertainty-aware layer:** Incorporate prediction confidence

Output: voxel-level classification (anatomical/biological/mixed) with confidence scores. Figure 5 illustrates the architecture.

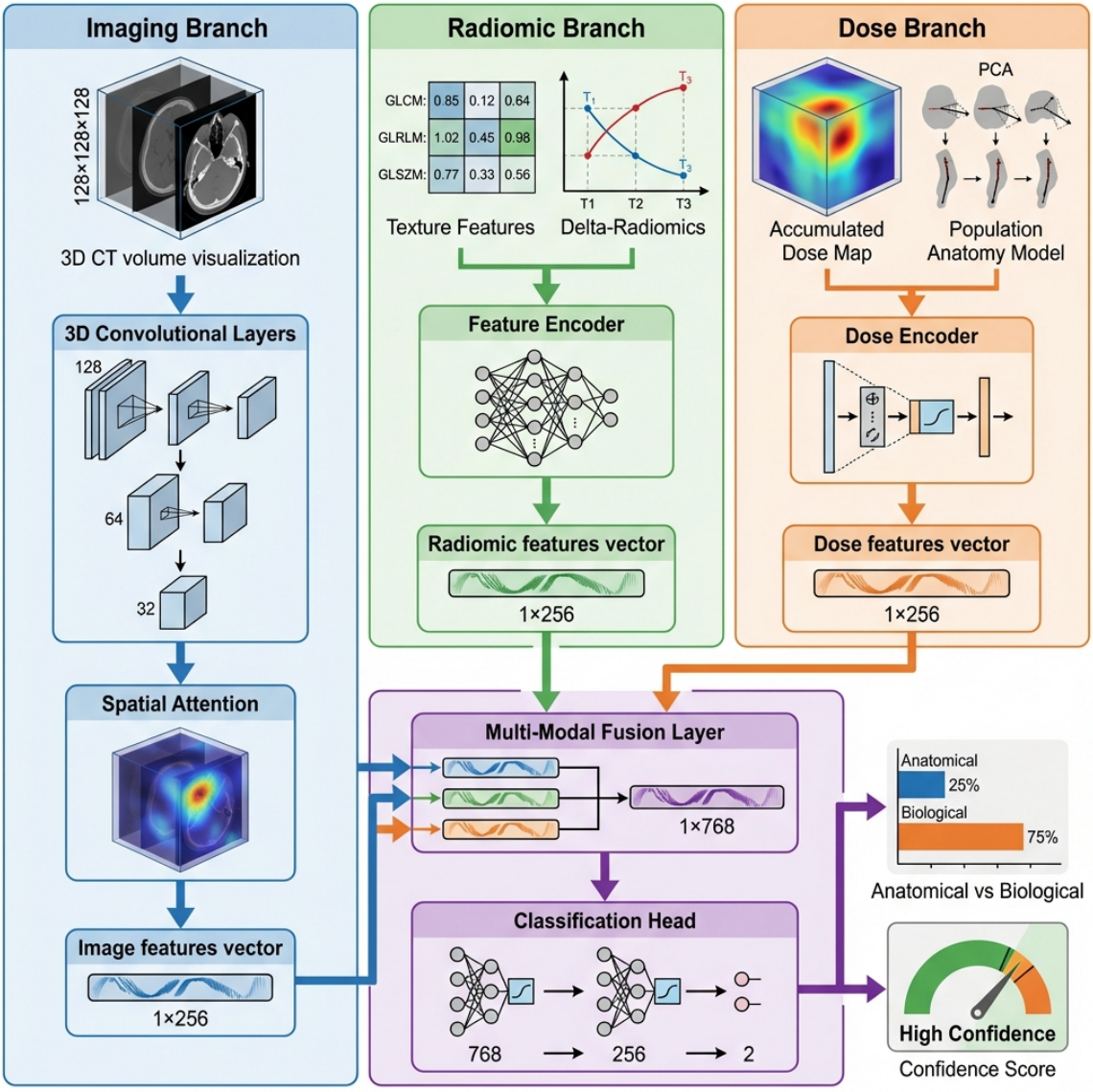

Figure 5: AI model architecture for response characterization integrating multimodal features.

3.2.4 Training Strategy

Supervised learning on synthetic labeled data (ground truth known), followed by semi-supervised fine-tuning on real patient data with clinician-labeled subsets.

3.3 Task 3: Dose Optimization Strategies

3.3.1 Objective

Design algorithms executing appropriate dose restoration, adaptation, or combined strategies based on identified change characteristics.

3.3.2 Optimization Framework

I will formulate dose optimization as a multi-objective problem:

For anatomical changes: Dose restoration maintains original objectives on updated anatomy:

$$\min_{d} \quad \sum_{i \in \text{targets}} w_i |d_i - d_i^{\text{plan}}|^2 + \sum_{j \in \text{OARs}} \lambda_j \max(0, d_j - d_j^{\text{limit}})^2$$

For biological changes: Dose adaptation adjusts objectives based on response:

- **Tumor regression:** Escalate dose to residual disease or redistribute sparing
- **Tumor progression:** Escalate dose if constraints permit
- **Normal tissue toxicity:** De-escalate or redistribute dose

$$\min_{d} \quad \sum_{i \in \text{targets}} w_i(r) |d_i - d_i^{\text{adapted}}(r)|^2 + \sum_{j \in \text{OARs}} \lambda_j(r) \max(0, d_j - d_j^{\text{limit}}(r))^2$$

where r represents response characterization, and weights/constraints adapt accordingly.

For mixed changes: Combine strategies with voxel-level weighting based on classification confidence.

3.3.3 Implementation

Utilize treatment planning system optimization engines (e.g., RayStation API), implementing custom objective functions encoding adaptive logic. Figure 6 illustrates decision pathways.

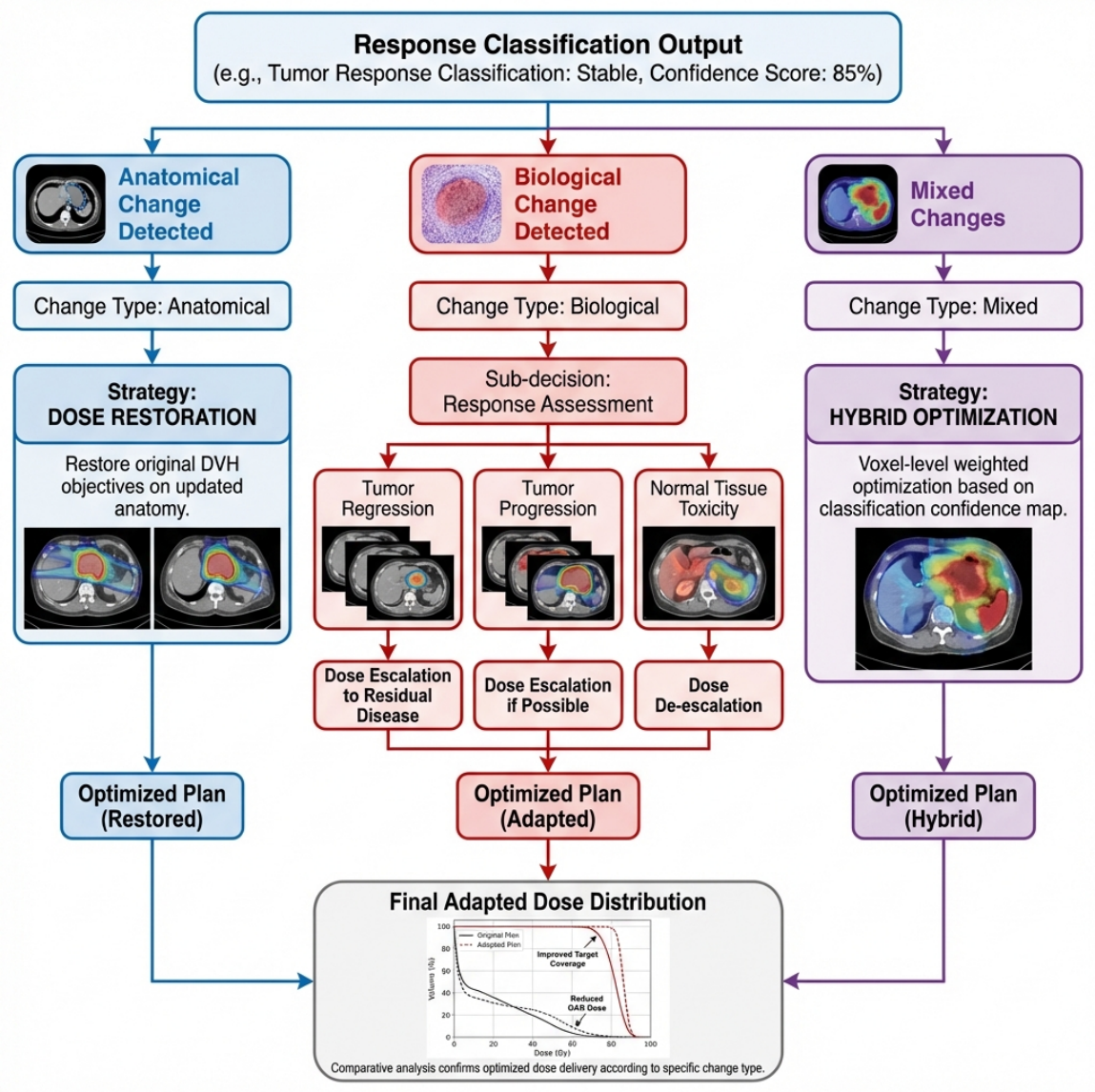

Figure 6: Dose optimization strategy selection based on response characterization.

3.4 Task 4: In-Silico Integration and Validation

3.4.1 Objective

Implement and evaluate a proof-of-concept pipeline within a clinical treatment planning system.

3.4.2 Implementation

I will integrate the complete workflow into RayStation (or equivalent clinical TPS):

1. **Image import:** Load daily CBCT/CT
2. **Preprocessing:** Registration, segmentation propagation
3. **Response categorization:** Execute AI model inference
4. **Visualization:** Display classification maps for clinical review

5. **Optimize:** Execute appropriate dose optimization

6. **Quality assurance:** Automated plan quality checks

3.4.3 Retrospective Evaluation

Using retrospective patient data (head-neck, lung, or prostate cancer cohorts), I will:

- Compare proposed approach vs. standard anatomical-only adaptation
- Metrics: DVH metrics, TCP/NTCP estimates, plan quality indicators
- Computational efficiency: measure time requirements for clinical feasibility
- Clinical expert review: radiation oncologists evaluate clinical acceptability

Success criteria: Improved target coverage and/or OAR sparing compared to standard adaptation, with computation time < 10 minutes per fraction.

4 Project Management

4.1 Timeline and Milestones

Table 1 presents the project timeline over 3 years:

Table 1: Project timeline with major milestones

Period	Activities	Deliverable
Year 1, Q1-Q2	Literature review, data collection, ethics approval	Data ready
	Implement Task 1 (synthetic generation)	Publication
Year 1, Q3-Q4	Develop Task 2 (response characterization)	Model v1.0
	Secondment: NTNU (Norway) – 3 months	Training
Year 2, Q1-Q2	Refine Task 2, validate on real data	Publication
	Implement Task 3 (dose optimization)	Algorithm
Year 2, Q3-Q4	Secondment: Politecnico Milano (Italy) – 3 months	Training
	Industrial partner secondment – 2 months	Integration
Year 3, Q1-Q2	Task 4 (clinical integration & validation)	Pipeline
	Retrospective study on patient cohorts	Publication
Year 3, Q3-Q4	Thesis writing and defense preparation	PhD Thesis

4.2 Risk Management

Risk 1 - Limited training data: *Mitigation:* Multi-institutional collaboration through RAPTORplus. Synthetic data generation compensates.

Risk 2 - Model generalization: *Mitigation:* Validate across multiple cancer sites. Domain adaptation techniques.

Risk 3 - Clinical integration barriers: *Mitigation:* Early engagement with clinical partners. Modular design for flexible integration.

Risk 4 - Computational efficiency: *Mitigation:* Model compression techniques. GPU acceleration.

4.3 Research Environment

I will be embedded in the "AI and Big Data in Radiation Oncology" research group at Aarhus University Hospital's Danish Centre for Particle Therapy. The environment provides: (1) access to proton therapy patient data, (2) state-of-the-art treatment planning systems, (3) multidisciplinary collaboration with clinicians and physicists, (4) high-performance computing resources, and (5) international network through RAPTORplus consortium.

Secondments at NTNU (Norway), Politecnico Milano (Italy), and an industrial partner will provide complementary expertise in image analysis, optimization algorithms, and clinical translation.

5 Expected Outcomes and Impact

5.1 Scientific Contributions

- Novel AI methodology for distinguishing anatomical vs. biological image changes
- Validated synthetic image generation framework for adaptive radiotherapy
- Proof-of-concept clinical decision support system for response-adapted therapy

5.2 Publications

Target: 3-4 peer-reviewed journal articles in high-impact journals (e.g., *Medical Physics*, *Physics in Medicine & Biology*, *Radiotherapy & Oncology*), plus conference presentations at ASTRO, ESTRO, and AAPM.

5.3 Clinical Impact

This work will advance precision medicine in radiation oncology, enabling truly personalized adaptive therapy that responds to both anatomical and biological changes. Improved outcomes through better tumor control and reduced toxicity will directly benefit cancer patients.

5.4 Training and Career Development

This PhD will establish me as an expert at the intersection of AI and medical physics, with skills in deep learning, medical image analysis, optimization, and clinical translation. The international network and secondment experiences position me for academic or industrial research careers in precision oncology.

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