Predicting 3-D Deformation Field Maps (DFM) based on Volumetric Cine MRI (VC-MRI) and Artificial Neural Networks for On-board 4D Target Tracking

by

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Thesis submitted in partial fulfillment of
the requirements for the degree of
Master of Science in the Department of
Medical Physics in the Graduate School
of Duke University

2019
ABSTRACT

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Abstract

Accurate and precise organ and tumor localization, before and during radiation therapy, is critical for treatment planning and delivery. Localization precision is most significant in stereotactic body radiation therapy (SBRT), which aims to aggressively target tumors by delivering high fractional dose with tight planning target volumes (PTV) margin. Inter-fraction uncertainties from therapy-responding anatomical change and or patient positioning errors can be mitigated with adaptive on-board imaging. On the other hand, intra-fraction uncertainties from respiratory movement must be minimized by using real-time imaging. Real-time imaging enables more advanced treatment delivery techniques such as respiratory-gating and target tracking. Currently, target tracking is limited to 2D using either x-ray projection images or MR cine images. No real-time 3-dimensional (3D) target tracking exists due to the lack of imaging and prediction techniques to predict the real-time 3D location of the target. Advancing to real-time 3D target tracking can provide plane-to-plane information of the target motion and greatly improve the tracking accuracy. The purpose of this thesis is to investigate the feasibility of real-time 3D target tracking by developing real-time 3D deformation field map (DFM) predictions using volumetric cine MRI (VC-MRI) and adaptive boosting and multi-layer perceptron neural network (ADMLP-NN).
On-board VC-MRI is considered as the deformation of a prior 4D-MRI phase, MRI\textsubscript{prior}, obtained during patient simulation. The DFM that best estimates VC-MRI is constructed from a weighted linear combination of three major respiratory deformation modes extracted from the principal component analysis (PCA) of DFMs between MRI\textsubscript{prior} and its remaining phases. PCA weighting coefficients are solved by the data fidelity constraint using on-board 2D cine MRI. The optimized PCA weighting coefficients are tracked and used to train an ADMLP-NN to estimate future coefficients from previous ones. ADMLP-NN uses several identical multi-layer perceptron neural networks with an adaptive boosting decision algorithm to avoid local minimums. Predicted PCA weighting coefficients are used to build 3D DFMs to generate predicted VC-MRI images, which predict the real-time 3D locations of the target for tracking.

This method was evaluated using a 4D computerized extended-cardiac torso (XCAT) simulation of lung cancer patients. Motion was simulated in the anterior-posterior and superior-inferior direction based on patient-specific real-position management (RPM) curves. Predicted PCA weighting coefficient accuracy was evaluated against true coefficients obtained during VC-MRI estimation using normalized cross-correlation (NCC) and normalized root-mean-squared error (NRMSE). Predicted VC-MRIs was evaluated against ground-truth VC-MRIs using Volume Percent Difference (VPD), Volume Dice Coefficient (VDC), and Center of Mass Shift (COMS) of the target. Effects of the breathing pattern changes and ADMLP-NN parameter
variations (number of input neurons, number of hidden neurons, number of MLP-NN, cost function threshold, prediction step-size) on VC-MRI prediction were evaluated.

The NCC between predicted and actual PCA weighting coefficients for the 1\textsuperscript{st}/2\textsuperscript{nd} principal components for a regular breathing pattern with no breathing amplitude change from the prior to on-board imaging was 0.99/0.88 and 0.99/0.63 in the SI and AP directions, respectively. The corresponding NRMSE was 0.05/0.14 and 0.04/0.24, respectively. The average VPD, VDC, and COMS for the predicted target was 17.54 ± 3.81\%, 0.92 ± 0.02, and 1.07 ± 0.40 mm respectively, across all predicted time-steps. Prediction accuracy decreased when the breathing amplitude increased from prior 4D MRI to on-board 2D cine and remained the same or improved when the breathing amplitude decreased. VC-MRI prediction accuracy was relatively robust against the number of neurons and MLP-NNs. Prediction accuracy decreased with too small or too large cost function thresholds. Additionally, prediction accuracy decreased with increasing prediction step-size. Overall, the feasibility and robustness of using ADMLP-NN to predict deformation field maps 120 ms ahead for VC-MRI predictions for on-board target localization during radiotherapy treatments was demonstrated.
Dedication

This work is dedicated to my loving parents, sister, my cousin. To my parents, Jimmy Pham and Loan Cao, thank you for your unconditional love and support through my ups and downs. To my sister, Jennifer Pham, thank you for your kindness and honesty. To my cousin, Andy, thank you for being my friend and my brother. All my achievements are not possible without any of you. Thank you.
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1. Introduction

Respiratory target motion during radiation therapy results in intra-fraction target localization uncertainties. Lung tumors can move as much as 3 cm in the cranio-caudal direction [1]. Stereotactic body radiation therapy (SBRT) is becoming an emerging and effective treatment to treat non-small cell lung cancer (NSCLC) patients with promising early outcomes [2-6]. SBRT uses tight planning target volume margins (Lung: 3-5 mm) and high fractionated dose (Lung: 10-34 Gy/fx) to aggressively treat targets and avoid nearby critical structures [7]. As a result, SBRT treatment times are longer than conventional treatments and target localization, prior to and during treatment, is crucial for preventing tumor under-dosing and nearby healthy tissue over-dosing.

Several methods have been developed to minimize intra-fraction target localization uncertainty. One method is to train patients to hold their breaths to prevent the target from moving [8]. However, this method is not applicable to patients who cannot hold their breaths consistently. As a result, free breathing treatment methods have been implemented, which uses planning target volumes (PTVs) to encapsulate the target’s range of motion [9]. PTV ensures the target receives the prescribed dose but delivers higher dose to nearby normal tissues compared to the breath-hold treatments.

Alternatively, respiratory gated treatments have been used to exclusively irradiate targets in the beam eyes view (BEV) [10,11]. Gated treatments utilize real-time imaging systems to track the tumor’s motion and signal to the treatment system when the target is in or out of the BEV. Gating is effective in focusing the treatment beam solely on the target. However, the treatment time is extended dramatically. On the other hand, real-time target tracking radiotherapy traces the target for the full duration of the treatment to continuously maintain and treat the tumor in the BEV [12]. Target tracking treatment is much faster to deliver than gated treatments due to its high duty cycle. It
also maintains a small target treatment volume to avoid excessive dose to the healthy tissues.

Target tracking demands the radiation beam be synchronized with the target motion. Implementation of target tracking requires the incorporation of system latency in the treatment process, which is the finite time between detection of a new target location and synchronization of the radiation beam to compensate for the detected target motion. Latency due to motion tracking, beam shaping calculation, and MLC movement leads to delivered dose geometric uncertainties. Two methods to minimize latency errors are target motion prediction and latency error quantification into the treatment planning process [13]. Error quantification requires to redefine dose calculations to incorporate geometric errors via probability density functions (PDF). On the other hand, prediction methods can be used to predict tumor position from prior positions, allowing the treatment system to adjust ahead of time.

The general workflow of target tracking with prediction algorithm includes four mains steps: 1) determine current tumor position, 2) predict tumor’s next position based on current position, 3) systematically adjust treatment beam’s shape and orientation to anticipate tumor motion, 4) adapt dosimetry to the changing configuration of the tumor and treatment beam. In this study, we focus on the first two steps: determine current and predict future tumor positions.

The current real-time tumor position is accomplished via real-time imaging systems. One method of real-time imaging is Calypso markers, which are electromagnetic arrays implanted into the target. Markers emit radiofrequency signals and are tracked by a detector to generate a continuous 1D signal of position with sub-millimeter levels of accuracy [14]. Alternatively, on-board kV/MV or MRI [15] cine slices can be used for real-time imaging. However, information is limited as no volumetric data is available, which is crucial for complete target localization.
Real-time volumetric imaging or tracking does not exist but is continuing to be developed with imaging modalities such as computed tomography (CT) or magnetic resonance imaging (MRI). CT is limited by long scanning time, high imaging dose and poor soft tissue contrast. Previous work has been done using patient prior images and deformation models for cone-beam CT (CBCT) fluoroscopy that would provide real-time volumetric imaging at a reduced dose [16-20]. However, soft tissue contrast is still inadequate. Thus, volumetric-cine MRI (VC-MRI) is being developed for real-time volumetric MR imaging. Like CBCT fluoroscopy, VC-MRI is based on prior images and motion models. Additionally, VC-MRI uses real-time on-board 2D MR cine slices for optimization and validation. In comparison to 4D-CBCT, VC-MRI does not utilize ionizing radiation and provides strong soft tissue contrast [21].

Once the current position of the tumor is determined, prediction algorithms can be used to predict future positions. Previous studies considering latency attempted to predict 100 ms ahead to account for detection and communication delay [22].

Several methods have been used to predict future respiratory signals from previous ones. Of these, autoregressive integrating moving average model (ARIMA) is a linear filtering method that assumes a linear relationship between prior and future respiratory signals [23]. In contrast, artificial neural networks (ANN), in particular, multi-layer perceptron neural networks (MLP-NN) have been developed to be effective in predicting both linear and non-linear respiratory signals [24, 25].

This thesis aims to use VC-MRI for real-time imaging and adaptive boosting and multi-layer perceptron neural network (ADMLP-NN) for VC-MRI prediction and real-time 3D target tracking. ADMLP-NN has been shown to be effective in predicting future RPM signal positions from previous ones [26]. Deformation field map (DFM) weighting coefficients from VC-MRI estimations are extracted and used to train an ADMLP-NN to predict future weighting coefficients. Predicted weighting coefficients are used to construct predicted DFMs and ultimately predicted VC-MRIIs. The VC-MRI estimation
and prediction are simulated using a 4D computerized extended-cardiac torso (XCAT) simulation of lung cancer patients. Motion was simulated in the anterior-posterior (AP) and superior-inferior (SI) direction based on patient-specific real-position management (RPM) curve. Effects of breathing amplitude change and ADMLP-NN parameter variation were assessed. The predictions accuracy is evaluated based on predicted DFM weighting coefficients and resulting predicted VC-MRIs.
2. Methods and Materials

2.1 VC-MRI estimation

VC-MRI, at any time instant, is assumed to be the deformation of a prior 4D-MRI phase, MRI\textsubscript{prior}, obtained during patient simulation. On-board VC-MRI estimation is expressed as a function of the prior phase, MRI\textsubscript{prior}, and deformation field map (DFM), D, as shown in Equation 1.

\[
V_{CMRI}(i, j, k) = \text{MRI}_{\text{prior}}(i + D_x(i, j, k), j + D_y(i, j, k), k + D_z(i, j, k))
\]

(1)

\(D_x, D_y,\) and \(D_z\) are the deformation fields along the three Cartesian coordinates. The end-of-expiration (EOE) phase is selected to be MRI\textsubscript{prior} as it is the most stable with minimal motion artifacts. The deformation field D in Equation 1 consists of a large number of variables, which makes D optimization inefficient and prone to local optimal value traps. Principal component analysis (PCA)-based motion modeling is used to reduce the number of variables in the deformation field D.

2.2 PCA motion model

PCA analysis is used to extract patient respiratory motion modes from a prior 4D-MRI obtained during patient simulation. Assuming the 4D-MRI has N phases, the prior (EOE) phase is deformed to the remaining \(N - 1\) phases using MIM (MIM Maestro, Cleveland) deformable image registration to generate \(N - 1\) DFMs. PCA analysis is applied to the series of DFMs, \(\{D_0^i\}, i = 1, 2, \ldots, N-1\), to extract principal modes, \(\{\tilde{D}_0^i\}\), which are orthogonal eigenvectors of the covariance matrix of \(\{D_0^i\}\). The importance of the principal motion modes is determined by the magnitude of its corresponding eigenvalue. The DFM, D, for VC-MRI estimation is represented by a linear combination of the first three PCA principal modes as they are maximally decorrelated and provide
ample body and tumor respiratory motion information. On-board DFM, D, used for Equation 1 is modeled as follows in Equation 2.

\[ D = D_{ave} + \sum_{j=1}^{3} w_j D_0^j \]  

(2)

\( D_{ave} \) is the average of the DFMs \( \{D_0^j\} \). \( w_j \) (j = 1,2,3) are the PCA weighting coefficients corresponding to each principal motion mode, \( D_0^j \).

PCA weighting coefficients, \( w_j \), are solved for by matching on-board 2D cine MR images with its corresponding VC-MRI slice via the data fidelity constraint in Equation 3.

\[ S \ast VCMRI(D, MRI_{prior}) = 2D\text{Cine}_{slice} \]  

(3)

\( S \) is an operator that extracts the corresponding 2D slice from the estimated VC-MRI image. On-board sagittal cine MR at the location corresponding to the central slice of the lesion in prior phase, MRI_{prior}, is selected to be 2D\text{Cine}_{slice}. For the purposes of target tracking, the data fidelity constraint is optimized using the region of interest (ROI) surrounding the tumor region in the 2D\text{Cine}_{slice}.

The data fidelity constraint is satisfied by minimizing the following objective function in Equation 4:

\[ f(w) = \left\| S \ast VCMRI(D = D_{ave} + \sum_{j=1}^{3} w_j D_0^j, MRI_{prior}) - 2D\text{Cine}_{slice} \right\|^2 \]  

(4)

A gradient descent method is used to find PCA weighting coefficients, \( w_j \), that minimize \( f(w) \). Once the optimal value of \( w_j \) is found, the DFM, D, is generated via Equation 2 and the VC-MRI is estimated via Equation 1.
2.3 VC-MRI Prediction

VC-MRIs are predicted ahead of time using adaptive boosting and multi-layer perceptron neural networks (ADMLP-NN). VC-MRI prediction is based on predicting PCA weighting coefficients, $w_j^{pred}$, to generate predicted DFMs, $D^{pred}$, that will be used to construct predicted VC-MRIs. In contrast to VC-MRI estimation, predicted DFMs are constructed from the first two principal motion modes rather than three. Thus, Equation 2 is adapted for predicted DFMs:

$$D^{pred} = D_{ave} + \sum_{j=1}^{2} w_j^{pred} D_0^j$$  \hspace{1cm} (5)

The predicted VC-MRIs are constructed with Equation 1 using the predicted DFM, $D^{pred}$, and the prior phase, MRI$_{prior}$.

2.4 Predicting PCA weighting coefficients using ADMLP-NN

ADMLP-NN is composed of $T$ identical multi-layer perceptron neural networks (MLP-NN), which are used as weak predictors to compose a strong predictor. A flow chart of PCA weighting coefficient prediction and evaluation using ADMLP-NN is shown in Figure 2. Additionally, the flow chart of ADMLP-NN is shown in Figure 3.
Figure 1: Flow chart of PCA weighting coefficient prediction and evaluation using ADMLP-NN

Figure 2: ADMLP-NN Flow chart
MLP-NNs are configured to estimate future PCA weighting coefficients from previous coefficients. Adaptive boosting (Adaboost) is applied to sequentially adjust weightings of each MLP-NN based on its sample prediction error. Adaboost reduces the risk of predicting local minima and over-fitting from MLP-NN.

During VC-MRI estimation of the RPM signal, the first two PCA weighting coefficients, $w_j$ (j = 1,2), are tracked to generate PCA weighting coefficient curves. A PCA weighting coefficient curve for the 1st principal component in the superior-inferior (SI) direction is shown in Figure 3.

![Figure 3: 1st SI PCA weighting coefficient curve](image)
2.4.1 MLP-NN algorithm

For MLP-NN training, PCA weighting coefficients curves are divided into two components separated at time K as shown in Figure 4 for the PCA weighting coefficient curve shown in Figure 3.

![Figure 4: Time-series diagram of 1st SI principal PCA weighting coefficient curve](image)

The coefficients prior to time K, is referred to as the training signal, $S(0, \ldots, K)$, and is used to train and determine the weights ($w$'s) and biases ($b$'s) of each MLP-NN. The coefficients after time K are referred to as the testing signal, $S(K+1, \ldots, L)$, and is used to evaluate ADMLP-NN PCA weighting coefficient and VC-MRI prediction.

Prior to training, the PCA weighting coefficient curves are normalized in the range of [-1,1] to reduce training time. Additionally, the training signal is smoothed
using a Savitzky-Golay finite impulse response smoothing filter (S-G filter) to reduce
signal noise and improve prediction results.

The architecture of an MLP-NN is shown in Figure 5.

Figure 5: MLP-NN architecture
MLP-NN consists of 3 layers: input, hidden, and output. The input, hidden, and output
layer consists of H, N, and one neuron, respectively.

For each MLP-NN, the training algorithm requires, from the training signal,
training data sets, q, which are pairs of data points consisting of a training input (for
prediction) and a training output (for validation). The signal between time, t = 0 and t =
H-1, represents a training input used to predict a training output at time, t = H-1+M. The
variable H represents the number of input neurons or data points used to predict the
training output. M is the prediction step-size that represents how far ahead in time a
prediction is made. The training process continues for the next training data set (training input: \( t = 1 \rightarrow H \); training output: \( t = H+1 \)) and repeats until the final training data set. In a training signal with \( K \) points, there are \( K-H-M+1 \) training data sets.

The output, \( y_1^\varepsilon(q) \), of layer, \( \varepsilon \), of neuron, \( l \), of a training MLP-NN from a training set \( q \) is determined from the following equation:

\[
y_1^\varepsilon(q) = f^\varepsilon \left( \sum_{j=1}^{n} w_{ji}^\varepsilon y_j^{\varepsilon-1}(q) + b_i^\varepsilon \right), \quad \varepsilon = 2,3 \tag{6}
\]

\( \varepsilon = 1 \) is the input, \( \varepsilon = 2 \) is the hidden, and \( \varepsilon = 3 \) is the output layer. \( l \) and \( j \) are the neuron number of the current and fore-layer, where there are \( H \) neurons in the input layer, \( N \) neurons in the hidden layer, and one neuron in the output layer. The output of the input layer is simply the training input. \( f^\varepsilon \) is the activation function of the layer \( \varepsilon \). The activation function for the hidden layer (\( \varepsilon = 2 \)) is a log-sig function:

\[
f^2(x) = \frac{1}{1 + e^{-x}} \quad \tag{7}
\]

The activation function for the output layer (\( \varepsilon = 3 \)) is a linear function:

\[
f^3(x) = x \quad \tag{8}
\]

\( w_{ji}^\varepsilon \) and \( b_i^\varepsilon \) act as weights and biases to the inputs of the activation functions.

Initially, the weights and biases in each MLP-NN are set randomly to compute an output, \( y_1^3 \). Afterwards, the network training performance is evaluated based on a cost function:
\[ e(w, b) = \frac{1}{2} \sum_{q=1}^{K-H-M+1} \left( y_1^2(q) - S(q) \right)^T \left( y_1^2(q) - S(q) \right), \quad (9) \]

where \( S(q) \) is the training output. The cost function is minimized by updating weights and biases through an iterative back-propagation training method. Weights and biases are optimized via the Levenberg-Marquardt (LM) algorithm until either the pre-set maximum iteration number or cost function threshold value, \( G \), is reached.

### 2.4.2 Adaptive boosting algorithm

Adaptive boosting modifies the MLP-NN prediction algorithm by using a combination of several MLP-NNs with different weighting factors. After the first MLP-NN's weights and biases are optimized, each training data set, \( q \), is assigned an initial uniform probability distribution:

\[ D_1(q) = \frac{1}{K-H-M+1}, \quad q = 1, \ldots, K-H-M+1 \quad (10) \]

Next, the normalized absolute error of each \( q \) was calculated:

\[ \Theta_t(q) = \left| \frac{S'_t(q) - S(q)}{\max |S'_t(q) - S(q)|} \right| \quad (11) \]

\( S'_t(q) \) is the optimized predicted output of the \( t \)th MLP-NN. Using Equations 10 and 11, the total distribution, \( \xi_t \), of the \( t \)th MLP-NN is determined:

\[ \xi_t = \sum_{q=1}^{K-H-M+1} \left( D_t(q) \times \Theta_t(q) \right) \quad (12) \]

Furthermore, each MLP-NN was assigned an adaptive boosting weight, \( \alpha_t \), associated with its total distribution:
\[
\alpha_t = \frac{\xi_t}{1 - \xi_t} \quad \text{(13)}
\]

Probability distributions for each MLP-NN, after the first one, is sequentially updated according to the normalized error between the predicted signals and true signals of subsequent MLP-NNs:

\[
D_{t+1}(q) = D_t(q) \times \alpha_t^{1-\Theta_t(q)} \quad \text{(14)}
\]

The probability distribution is normalized as follows:

\[
D_{t+1}(q) = \frac{D_{t+1}(q)}{\sum_{c=1}^{t+1} D_c(q)} \quad \text{(15)}
\]

Once all adaptive boosting weights, \( \alpha_T \), they are normalized:

\[
\alpha_T = \frac{\alpha_T}{\sum_{t=1}^{T} \alpha_T} \quad \text{(16)}
\]

The final predicted output, \( S' \), of the ADMLP-NN is the weighted sum of all MLP-NN predictions:

\[
S' = \sum_{t=1}^{T} (\alpha_t \times S'_t) \quad \text{(17)}
\]

After each MLP-NN’s weights, biases, and associated adaptive boosting weighting are determined, the ADMLP-NN is trained. The testing PCA weighting coefficient signals, denoted by \( S(K+1, ... , K+L) \) is used to validate the goodness of the trained ADMLP-NN’s PCA weighting coefficient and VC-MRI prediction. The signal between \( t = K+1 \) and \( t = K+H \) are imported to the trained ADMLP-NN to predict the first target position, \( S'(K+H+M) \) at time, \( t = K+H+M \). Points are continually imported to
predict the next target position. The variable $L$ is the number of points predicted, $P$, plus the number of initial points imported to predict the first target position.

$$L = P + H + M - 1 \quad (18)$$

### 2.5 Simulation using RPM signal and XCAT phantom

XCAT, a digital anthropomorphic phantom, was used to simulate a 4D extended cardiac torso for the prior 4D MRI set, on-board ground-truth VC-MRIs, and 2D cine MRIs. XCAT uses human anatomy data from the National Library of Medicine and nonuniform rational B-spline surfaces to model 4D detailed human anatomical structures and images [27].

A 30 mm diameter spherical tumor with uniform intensity was simulated in the middle of the lung. Both the body and tumor were simulated to move in the anterior-posterior (AP) direction and superior-inferior (SI) direction, where the AP motion was defined by a diaphragm curve and SI motion was defined by a chest curve. The diaphragm and chest curves were based on patient respiratory breathing patterns obtained by a real-time position management (RPM) system, where an infrared camera tracks the motion of reflective markers placed on top of a patients’ abdomen [28].

Five different two-minute long RPM signals were used to assess the effects of breathing patterns on VC-MRI estimation and prediction as shown in Figure 6, highlighting characteristics of baseline drift, frequency change, and chaotic motion. RPM 1 in Figure 6 reflects a regular breathing pattern. Figure 6 displays the relative amplitude of the RPM signal, where peaks represent end-of-inhalation (EOI) and troughs represent end-of-exhalation (EOE). The maximum peak-to-peak amplitudes of the diaphragm and chest curve were set to 3 and 2 cm, respectively.
A 10-phase 4D MRI was simulated as the prior 4D MRI from one cycle from the RPM signal. The MRI volume of each phase was composed of $256 \times 256 \times 100$ voxels, with each voxel measuring $1.875 \times 1.875 \times 3$ mm. XCAT was used in activity mode to produce MRI-like images. Organ and tissue intensities were assigned using values derived from fast imaging employing steady-state (FIESTA)/TrueFISP MR images [29].

On-board 2D-cines MR slices were extracted from simulated on-board VC-MRIs, which were used as the “ground-truth” VC-MRIs. On-board 2D-cines and VC-MRIs were generated for the entire RPM signal with a frequency of 8.33 Hz (~8 frames/s). For 2 minutes of RPM signal, 1001 cine frames were generated, each with a resolution of $1.875 \times 1.875$ mm and a slice thickness of 3 mm.

To evaluate the effects of potential patient breathing pattern change from simulation to treatment, three on-board patient scenarios were simulated:

1) Scenario 1: No breathing pattern change.
2) Scenario 2: For both body and tumor volume, the peak-to-peak amplitude of the diaphragm curve and chest wall curve decreased to 2 cm and 1.2 cm respectively.

3) Scenario 3: For both body and tumor, the peak-to-peak amplitude of the diaphragm curve and chest wall curve increased to 4 cm and 2.8 cm, respectively.

2.6 ADMLP-NN Parameters

Unless otherwise specified, the default parameters of the ADMLP-NN was set, for K+L = 1001 PCA weighting coefficient data points, to:

<table>
<thead>
<tr>
<th>ADMLP-NN Parameter</th>
<th>Default</th>
<th>Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of MLP-NNs (T)</td>
<td>10</td>
<td>2, 5, 8, 12</td>
</tr>
<tr>
<td>Number of input neurons (H)</td>
<td>5 (.6s)</td>
<td>3, 7, 9, 11</td>
</tr>
<tr>
<td>Number of hidden neurons (N)</td>
<td>3</td>
<td>1, 2, 4, 5</td>
</tr>
<tr>
<td>Cost function threshold (G)</td>
<td>0.05</td>
<td>0, 0.1, 0.15, 0.2</td>
</tr>
<tr>
<td>Prediction step-size (M)</td>
<td>1 (.12s)</td>
<td>2, 3, 4, 5</td>
</tr>
<tr>
<td>Number of points predicted (P)</td>
<td>250 (30s)</td>
<td>Constant</td>
</tr>
<tr>
<td>Number of training points (K)</td>
<td>746</td>
<td>Varies accordingly</td>
</tr>
</tbody>
</table>

ADMLP-NN was further optimized by fine-tuning and independently evaluating the parameters, T, H, N, G, and M, at different values as shown in Table 1. The number of predicted points, P, remains constant to assess the parameter variation effects on
prediction. Furthermore, to keep the total number of points used, K+L, constant for varying ADMLP-NN parameters, K (the number of training points) is incremented or decremented accordingly.

2.7 Evaluation metrics

2.7.1 PCA weighting coefficient prediction evaluation metrics

The predicted 1st and 2nd principle PCA weighting coefficient, \( w_{j}^{pred} \), in the SI and AP direction is evaluated against the estimated (true) weighting coefficients, \( w_{j} \), at every time-step predicted via normalized cross-correlation (NCC) (Equation 19) and normalized root-mean-square-error (NRMSE) (Equation 20)

\[
NCC_j = \frac{\sum_{t=K+H+M}^{K+L} w_{j}^{pred}(t) w_{j}(t)}{\sqrt{\sum_{t=K+H+M}^{K+L} (w_{j}^{pred}(t))^2 (w_{j}(t))^2}} \quad j = 1,2 \quad (19)
\]

\[
NRMSE_j = \sqrt{\frac{1}{L-H-M+1} \sum_{t=K+H+M}^{K+L} (w_{j}^{pred}(t) - w_{j}(t))^2} \quad j = 1,2 \quad (20)
\]

The lateral component is not evaluated as there was no motion simulated in the lateral direction.

2.7.2 VC-MRI prediction evaluation metrics

Predicted VC-MRIs are constructed from all PCA weighting coefficient sets predicted from \( t = K+H+M \) to \( t = K+L \) using Equations 1 and 5. The predicted VC-MRI tumor is evaluated against the ground-truth VC-MRI tumor. Results were reported as an average across the time-steps with corresponding standard deviations. Tumors were contoured by an in-house MATLAB (MathWorks, Natick, MA) code based on threshold
voxel values and preset ROIs. Volume percentage different (VPD) (Equation 21), volume dice coefficient (VDC) (Equation 22), and center-of-mass-shift (COMS) (Equation 23) was used to assess the accuracy of the predicted tumor volume.

\[
VPD = \frac{|V \cup V_0 - V \cap V_0|}{V_0} \quad (21)
\]

\[
VDC = \frac{2|V \cap V_0|}{|V| + |V_0|} \quad (22)
\]

V is the volume of the tumor contoured in the predicted image and \(V_0\) is the volume of the tumor contoured in the ground-truth image.

\[
COMS = \sqrt{\Delta x^2 + \Delta y^2 + \Delta z^2} \quad (23)
\]

\(\Delta x, \Delta y,\) and \(\Delta z\) are the center-of-mass distances from \(V\) to \(V_0\).

Additionally, estimated VC-MRIs were constructed using Equations 1 and 2 between \(t = K+H+M\) to \(t = K+L\) and evaluated against the ground-truth VC-MRIs similarly as the predicted VC-MRIs.
3. Results

3.1 PCA weighting coefficient estimation

Figure 7-9 shows the complete estimated/true curve for RPM 1 Scenario 1-3 used for ADMLP-NN training and prediction validation, respectively.

![Figure 7: RPM 1 Scenario 1 estimated PCA weighting curve](image)
Figure 8: RPM 1 Scenario 2 estimated PCA weighting curve
3.2 PCA weighting coefficient prediction

Figure 10 shows the default ADMLP-NN predicted signal of PCA weighting coefficients (red) plotted with the estimated/true signal (blue) for RPM 1 Scenario 1’s first two principal components. Figure 11 shows the same prediction, but with ADMLP-NN (M = 4).
Figure 10: Default ADMLP-NN predicted PCA weighting coefficient signal (red) and estimated/true signal (blue) for RPM 1 Scenario 1.
Figure 11: ADMLP-NN (M = 4) predicted PCA weighting coefficient signal (red) and estimated/true signal (blue) for RPM 1 Scenario 1.

Figure 12 shows the ADMLP-NN (N = 2) predicted signal of PCA weighting coefficients (red) plotted with the estimated/true signal (blue) for RPM 2 Scenario 2’s first two principal components.
Figure 12: ADMLP-NN (N = 2) predicted PCA weighting coefficient signal (red) and estimated/true signal (blue) for RPM 2 Scenario 2.

Figure 13 shows the ADMLP-NN (G = 0) predicted signal of PCA weighting coefficients (red) plotted with the estimated/true signal (blue) for RPM 3 Scenario 3’s first two principal components.
Figure 13: ADMLP-NN (G = 0) predicted PCA weighting coefficient signal (red) and estimated/true signal (blue) for RPM 3 Scenario 3.

Figure 14 shows the ADMLP-NN (T = 8) predicted signal of PCA weighting coefficients (red) plotted with the estimated/true signal (blue) for RPM 4 Scenario 1’s first two principal components.
Figure 14: ADMLP-NN (T = 8) predicted PCA weighting coefficient signal (red) and estimated/true signal (blue) for RPM 4 Scenario 1.

Figure 15 shows the ADMLP-NN (H = 3) predicted signal of PCA weighting coefficients (red) plotted with the estimated/true signal (blue) for RPM 5 Scenario 1’s first two principal components.
Figure 15: ADMLP-NN (H = 3) predicted PCA weighting coefficient signal (red) and estimated/true signal (blue) for RPM 5 Scenario 1.

3.3 PCA weighting coefficient prediction NCC and NRMSE

Figure 16 and 17 shows the NCC and NRMSE of RPM 1-5’s predicted PCA weighting coefficient curves for different scenarios as a function of input neurons, respectively.
Figure 16: RPM 1-5’s predicted PCA weighting coefficient curves’ NCC for different scenarios as a function of input neurons.

• RPM 5 1st Principal Component
• RPM 5 2nd Principal Component

• RPM 1 1st Principal Component
• RPM 1 2nd Principal Component

• RPM 2 1st Principal Component
• RPM 2 2nd Principal Component
Figure 17: RPM 1-5’s predicted PCA weighting coefficient curves’ NRMSE for different scenarios as a function of input neurons

Figure 18 and 19 shows the NCC and NRMSE of RPM 1-5’s predicted PCA weighting coefficient curves for different scenarios as a function of hidden neurons, respectively.
Figure 18: RPM 1-5’s predicted PCA weighting coefficient curves’ NCC for different scenarios as a function of hidden neurons
Figure 19: RPM 1-5’s predicted PCA weighting coefficient curves’ NRMSE for different scenarios as a function of hidden neurons

Figure 20 and 21 shows the NCC and NRMSE of RPM 1-5’s predicted PCA weighting coefficient curves for different scenarios as a function of cost function threshold, respectively.
Figure 20: RPM 1-5’s predicted PCA weighting coefficient curves’ NCC for different scenarios as a function of cost function threshold.
Figure 21: RPM 1-5’s predicted PCA weighting coefficient curves’ NRMSE for different scenarios as a function of cost function threshold

Figure 22 and 23 shows the NCC and NRMSE of RPM 1-5’s predicted PCA weighting coefficient curves for different scenarios as a function of MLP-NNs, respectively.
Figure 22: RPM 1-5’s predicted PCA weighting coefficient curves’ NCC for different scenarios as a function of MLP-NNs
Figure 23: RPM 1-5’s predicted PCA weighting coefficient curves’ NRMSE for different scenarios as a function of MLP-NNs

Figure 24 and 25 shows the NCC and NRMSE of RPM 1-5’s predicted PCA weighting coefficient curves for different scenarios as a function of prediction step-size, respectively.
Figure 24: RPM 1-5’s predicted PCA weighting coefficient curves’ NCC for different scenarios as a function of prediction step-size
Figure 25: RPM 1-5’s predicted PCA weighting coefficient curves’ NRMSE for different scenarios as a function of prediction step-size

3.3 VC-MRI estimation and prediction

Figures 26 displays the prior MRI at the EOE phase, ground-truth VC-MRI, estimated VC-MRI, and default ADMLP-NN predicted VC-MRI for RPM 1 Scenario 1.
Figure 26: RPM 1 Scenario 1 - Prior MRI at end-of-expiration (EOE), ground-truth VC-MRI, estimated VC-MRI, and predicted VC-MRI

The estimated VC-MRI’s VPD, VDC, and COMS for RPM 1-5 in Scenarios 1, 2, and 3 are shown in Table 2, 3, and 4, respectively.

Table 2: VPD, VDC, and COMS for RPM 1-5 Scenario 1 estimated VC-MRIs

<table>
<thead>
<tr>
<th>Scenario 1</th>
<th>VPD (%)</th>
<th>VDC</th>
<th>COMS (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPM 1</td>
<td>15.95 ± 3.58</td>
<td>0.93 ± 0.02</td>
<td>0.83 ± 0.29</td>
</tr>
<tr>
<td>RPM 2</td>
<td>15.64 ± 2.36</td>
<td>0.93 ± 0.01</td>
<td>0.72 ± 0.22</td>
</tr>
<tr>
<td>RPM 3</td>
<td>15.66 ± 2.84</td>
<td>0.93 ± 0.01</td>
<td>0.68 ± 0.26</td>
</tr>
<tr>
<td>RPM 4</td>
<td>14.95 ± 2.23</td>
<td>0.93 ± 0.01</td>
<td>0.57 ± 0.27</td>
</tr>
<tr>
<td>RPM 5</td>
<td>13.83 ± 2.50</td>
<td>0.94 ± 0.01</td>
<td>0.54 ± 0.21</td>
</tr>
</tbody>
</table>
Table 3: VPD, VDC, and COMS for RPM 1-5 Scenario 2 estimated VC-MRIs

<table>
<thead>
<tr>
<th>Scenario 2</th>
<th>VPD (%)</th>
<th>VDC</th>
<th>COMS (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPM 1</td>
<td>14.78 ± 3.34</td>
<td>0.93 ± 0.02</td>
<td>0.75 ± 0.27</td>
</tr>
<tr>
<td>RPM 2</td>
<td>15.23 ± 2.33</td>
<td>0.93 ± 0.01</td>
<td>0.77 ± 0.22</td>
</tr>
<tr>
<td>RPM 3</td>
<td>15.31 ± 2.85</td>
<td>0.93 ± 0.01</td>
<td>0.66 ± 0.24</td>
</tr>
<tr>
<td>RPM 4</td>
<td>15.03 ± 1.96</td>
<td>0.93 ± 0.01</td>
<td>0.61 ± 0.33</td>
</tr>
<tr>
<td>RPM 5</td>
<td>13.76 ± 2.289</td>
<td>0.94 ± 0.01</td>
<td>0.65 ± 0.16</td>
</tr>
</tbody>
</table>

Table 4: VPD, VDC, and COMS for RPM 1-5 Scenario 3 estimated VC-MRIs

<table>
<thead>
<tr>
<th>Scenario 3</th>
<th>VPD (%)</th>
<th>VDC</th>
<th>COMS (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPM 1</td>
<td>17.60 ± 5.71</td>
<td>0.92 ± 0.03</td>
<td>1.00 ± 0.53</td>
</tr>
<tr>
<td>RPM 2</td>
<td>15.90 ± 2.60</td>
<td>0.93 ± 0.01</td>
<td>0.71 ± 0.28</td>
</tr>
<tr>
<td>RPM 3</td>
<td>17.97 ± 5.70</td>
<td>0.92 ± 0.02</td>
<td>0.85 ± 0.47</td>
</tr>
<tr>
<td>RPM 4</td>
<td>15.33 ± 2.20</td>
<td>0.93 ± 0.01</td>
<td>0.79 ± 0.28</td>
</tr>
<tr>
<td>RPM 5</td>
<td>14.32 ± 3.17</td>
<td>0.93 ± 0.01</td>
<td>0.57 ± 0.21</td>
</tr>
</tbody>
</table>

Figures 27-29 displays the VPD, VDC, COMS and its standard deviation (STD) for RPM 1-5’s estimated and predicted VC-MRIs for different scenarios as a function of input neurons, respectively. The blue solid and dashed line represents the VC-MRI estimation result and standard deviation.
Figure 27: RPM 1-5's estimated and predicted VC-MRI VPD for different scenarios as a function of input neurons
Figure 28: RPM 1-5’s estimated and predicted VC-MRI VDC for different scenarios as a function of input neurons
Figure 29: RPM 1-5’s estimated and predicted VC-MRI COMS for different scenarios as a function of input neurons.

Figures 30-32 displays the VPD, VDC, COMS and its standard deviation (STD) for RPM 1-5’s estimated and predicted VC-MRIs for different scenarios as a function of hidden neurons, respectively.
Figure 30: RPM 1-5’s estimated and predicted VC-MRI VPD for different scenarios as a function of hidden neurons
Figure 31: RPM 1-5's estimated and predicted VC-MRI VDC for different scenarios as a function of hidden neurons
Figure 32: RPM 1-5’s estimated and predicted VC-MRI COMS for different scenarios as a function of hidden neurons

Figures 33-35 displays the VPD, VDC, COMS and its standard deviation (STD) for RPM 1-5’s estimated and predicted VC-MRIs for different scenarios as a function of cost function threshold, respectively.
Figure 33: RPM 1-5's estimated and predicted VC-MRI VPD for different scenarios as a function of cost function threshold
Figure 34: RPM 1-5’s estimated and predicted VC-MRI VDC for different scenarios as a function of cost function threshold
Figure 35: RPM 1-5’s estimated and predicted VC-MRI COMS for different scenarios as a function of cost function threshold

Figures 36-38 display the VPD, VDC, COMS and its standard deviation (STD) for RPM 1-5’s estimated and predicted VC-MRIs for different scenarios as a function of MLP-NN, respectively.
Figure 36: RPM 1-5's estimated and predicted VC-MRI VPD for different scenarios as a function of MLP-NNs
Figure 37: RPM 1-5’s estimated and predicted VC-MRI VDC for different scenarios as a function of MLP-NNs
Figure 38: RPM 1-5’s estimated and predicted VC-MRI COMS for different scenarios as a function of MLP-NNs.

Figures 39-41 display the VPD, VDC, COMS and its standard deviation (STD) for RPM 1-5’s estimated and predicted VC-MRIs for different scenarios as a function of cost function threshold, respectively.
Figure 39: RPM 1-5’s estimated and predicted VC-MRI VPD for different scenarios as a function of prediction step-size
Figure 40: RPM 1-5’s estimated and predicted VC-MRI VDC for different scenarios as a function of prediction step-size
Figure 41: RPM 1-5’s estimated and predicted VC-MRI COMS for different scenarios as a function of prediction step-size
4. Discussion

ADMLP-NN’s feasibility and robustness for PCA weighting coefficient prediction were assessed. In Figures 16 and 17, the NCC and NRMSE between the predicted and estimated/true PCA weighting curve as a function of input neurons showed that ADMLP-NN PCA weighting coefficient prediction was relatively robust against the number of input neurons. The 1st principal component was more robust than the 2nd, which is reflective of the more cyclic and less noisy pattern seen in the 1st PCA weighting curve in Figures 10-15. The SI weight curve tended to score better than the AP weighting curve as there was a larger range of motion in the SI direction than AP. RPM breathing amplitude/scenario variations would result in similar PCA weighting curve peak-to-peak amplitude change as seen in Figures 7-9 for RPM 1 Scenario 1-3. Among breathing scenarios, no scenario prediction was better than the other when considering all 5 RPM curves. Experimentally, the optimal number of input neurons that best satisfied all RPM curves under different breathing scenarios for PCA weighting coefficient prediction was $H = 7$.

The VC-MRI prediction accuracy (VPD, VDC, and COMS) as a function of input neurons was assessed in Figures 27-29, which showed similar trends as PCA weighting coefficient prediction of robustness against input neuron. VPD and VDC shared the same trends as COMS, indicating target volume accuracy is crucial in target positioning accuracy. Like PCA weighting coefficient prediction, the optimal number of input
neurons that best satisfied all RPM curves under different breathing scenarios for VC-MRI prediction was \( H = 7 \). Strong PCA weighting coefficient prediction resulted in more accurate VC-MRI predictions. If the number of input neurons was too small, the PCA weighting curve could not fill well; therefore, increasing the number of input neuron would add more features that could initially improve the prediction performance. However, if the number of input neurons was more than the optimal value (\( H=7 \)), the performance of the network would degrade due to overfitting and local minimum problems. Overall, ADMLP-NN was stronger at predicting PCA weighting curves with cyclic patterns.

Scenario 3’s VC-MRI prediction accuracy and margin of uncertainty were poorer than Scenario 1 and 2. This is not due to the limitations of ADMLP-NN prediction as NCC and NRMSE showed predictions between breathing scenarios to be indistinguishable. The discrepancy between VC-MRI scenario prediction is due to the absolute difference between estimated and predicted PCA curves. NCC and NRMSE for different scenarios were similar; however, after unnormalizing the coefficients for VC-MRI construction, the error for Scenario 3 scaled more than the other scenarios, and as a result Scenario 3’s VC-MRIs accuracy worsened. This highlights the sensitivity of PCA motion mode scaling.

In Figures 18 and 19, the NCC and NRMSE between the predicted and estimated/true PCA weighting curve as a function of hidden neurons showed that
ADMLP-NN PCA weighting coefficient prediction was relatively robust after $N = 4$ or more hidden neurons was used. VC-MRI prediction accuracy as a function of hidden neurons in Figures 30-32 agrees and matches the NCC and NRMSE trend.

The cost function threshold, $G$, reflects the accuracy requirement for the cost function in Equation 9. In Figures 20 and 21, the NCC and NRMSE between the predicted and estimated/true PCA weighting curve as a function of cost function threshold showed that the prediction accuracy would initially improve with increasing cost function threshold. However, as the cost function threshold continued to increase, the prediction accuracy had minimal improvement and after $G = 0.2$ became dramatically worse for some RPM curves. VC-MRI prediction accuracy as a function of cost function threshold in Figures 33-35 showed the same cost function threshold trend. The optimal cost function threshold was experimentally determined to be $G = 0.05$.

In Figures 22 and 23, the NCC and NRMSE between the predicted and estimated/true PCA weighting curve as a function of MLP-NNs showed that the prediction accuracy was relatively robust after $T = 5$ MLP-NNs or more were used. VC-MRI prediction accuracy as a function of MLP-NNs in Figures 36-38 showed the most optimal number of MLP-NNs to be $T = 10$. Using too few MLP-NNs had poorer accuracy and much larger uncertainties as the adaptive boosting algorithm weighted sum in Equation 17 had fewer weak predictors (MLP-NNs) to make a strong predictor with less uncertainty.
In Figures 24 and 25, the NCC and NRMSE between the predicted and estimated/true PCA weighting curve as a function of prediction step-size showed that the prediction accuracy decreased with increasing prediction step-size. VC-MRI prediction accuracy in Figures 39-41 showed the same degradation with increasing prediction step-size. Relative to 120 ms (M =1) prediction step-size, the VPD/ VDC/ COMS could degrade as much as 10%/ 0.05/ 3mm for prediction step-size of 600 ms (M = 5). This is understood by comparing Figures 10 and 11s’ predicted PCA weighting curve, where both predictions were made with the same parameter, except Figure 11 shows ADMLP-NN prediction with a prediction step-size of M = 4. Increasing the prediction step-size results in a noisier predicted PCA weighting curve, which degrades VC-MRI prediction accuracy. Previous studies have shown that 100 ms predictions may be enough to compensate for system latency effects, thus choosing the lowest prediction step-size, M = 1 (120 ms) with the most accurate results would be optimal.

VC-MRI enables real-time volumetric MR imaging for high precision target localization during treatment. VC-MRI spatial resolution can be approximately 1 mm in-plane and 1 to 3mm plane-to-plane depending on the quality of the prior image set. Currently, VC-MRI reconstruction takes approximately two minutes, but can potentially be accelerated to high temporal resolutions of 3 to 5 frames/second via graphics card and parallel processing. Furthermore, ADMLP-NN PCA weighting coefficient prediction can improve VC-MRI optimization speed by initializing PCA weighting coefficients at the
predicted value, which would be near the optimal value that satisfies the data fidelity constraint. Ultimately, real-time volumetric localization by VC-MRI would allow for margin reduction and dose escalation in SBRT treatments.

Clinical design of this work would begin with a patient obtaining a 4D MRI during patient simulation. The 4D MRI will be used to generate a motion model for DFM and VC-MRI construction. PTV and critical structures contours can be drawn on the 4D MRI for treatment planning. VC-MRI as a function of DFMs allows contours to deform with the target. Thus, VC-MRI target tracking does not need target relocalization, which can lessen system latency and improve target localization accuracy. On treatment day, patients can obtain an additional fast 4D MRI (still under development) to check that the motion model generated from the simulation is still adequate. If the motion model is adequate, then the patient can lie on the table to be imaged with 2D cines for several minutes. The on-board 2D cines will be used for VC-MRI estimation; then a neural network will be trained, based on the estimated VC-MRIs, to predict future VC-MRIs. Once the network is fully trained, a few preliminary images comparing on-board and predicted images can be taken to assess the prediction accuracy. With satisfactory prediction accuracy, the patient can be treated via target tracking with on-board VC-MRIs. If the prior 4D MRI motion model does not match with the on-treatment day fast 4D MRI, then a motion model may be potentially made from the fast 4D MRI. Prediction is prone to errors caused by sporadic unexpected
events like patient coughing. This can be potentially alleviated by implementing a hybrid technique of gating and target tracking, where gating is used when breathing becomes irregular and unpredictable.

This thesis work was carried out using simulation studies to investigate the feasibility of the proposed technique. Future work will be designed to conduct patient studies to further evaluate the methods comprehensively. Additionally, respiratory signals used in the study were based on RPM signals only, which could be different from the actual respiration motion of internal organs. Therefore, another direction of future work would be to evaluate ADMLP-NN VC-MRI prediction based on internal respiratory motion data.
5. Conclusion

It is feasible to predict PCA weighting coefficients using ADMLP-NN to construct predicted deformation field maps, which can be used to generate predicted VC-MRIs for real time 3D target tracking. Overall, ADMLP-NN prediction was relatively robust against the number of input neurons used. Using more hidden neurons and MLP-NNs in ADMLP-NN would improve VC-MRI prediction accuracy and minimize its uncertainty. VC-MRI prediction accuracy was sensitive to ADMLP-NN cost function threshold as too small thresholds would overfit the prediction, and too large thresholds would underfit it. Increasing the prediction step size led to degradation of the prediction accuracy. Simulation studies showed that VC-MRIs can be accurately predicted 120-ms ahead of time, which can compensate for the treatment system latencies to achieve accurate target tracking.
References


