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Investigating the Robustness of Long Short-Term Memory Deep Neural Networks for Tumor Motion Tracking at External Surrogates Radiotherapy

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ABSTRACT

Introduction: At radiotherapy, tumor motion is clinically tracked in real-time using external surrogates. To achieve this. A reliable correlation model is used to predict tumor coordinates based on the motion of external markers. In this work, a deep neural networks model is introduced for tumor motion tracking.

Material and Methods: A motion database of 20 patients treated with the CyberKnife Synchrony System has been used to train and evaluate the model. The proposed model is based on Long-Short Term Memory neural network developed in a Python software package. The network consists of two layers, each with 40 neurons, and a fully connected layer with a linear activation function.

Results: In this study, three-dimensional RMSE which is a common approach for calculating the model error is utilized. The obtained 3D RMSE of the proposed model is compared with the performance accuracy of the CyberKnife modeler. The results show a significant 15.3% reduction in three-dimensional error, indicating that our developed model has a lower error compared to the CyberKnife modeler.

Conclusion: In this study, a model based on deep Long-Short Term Memory neural network is used for tumor tracking using a motion database of real patients. The reason for using this model is its robustness to remember information for a long period and its high predictive ability, which makes it promising for future clinical implementation. Unlike previously used models, this model can retain useful information from past time series and use it for training, allowing the model to outperform other models.

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Introduction

Cancer is characterized by the uncontrolled proliferation of atypical cells, which have the potential to infiltrate adjacent tissues. The principal therapeutic strategies for this disease include surgical intervention, chemotherapy, and radiotherapy[1-4]. Radiotherapy now plays a more significant role in cancer treatment than other modalities due to advancements ranging from the introduction of new therapeutic beams to improved tumor cell eradication. The main aim of radiation therapy is to deliver the maximum dose to the tumor volume while minimizing the dose received by healthy tissue at the same time [5-7]. Achieving this goal is challenging when the tumor is located in the thoracic region and moves primarily due to respiration. It is difficult to target the tumor in this situation due to the difficulties in locking the beam therapy on the tumor. One strategy is to irradiate the entire moving area, including the tumor volume, defined as the Planning Target Volume (PTV). In this method, the normal nearby tissues receive remarkably high doses that may cause serious side effects. Several solutions have been proposed to address tumor targeting challenges in external radiotherapy [5-8] including patient's breath hold, motion-gated radiotherapy [9-10], and real-time tumor tracking radiotherapy . Since breath-hold techniques require patient cooperation and tumor coordinates vary with each breath-hold, this method cannot be considered a precise solution for tumor motion management. In gated radiation therapy, the beam is irradiated only in a specific part of the breathing interval mainly at the end of exhalation [9,10]. In real-time tumor tracking radiotherapy, the radiation is continuous and the therapeutic beam is dynamic and synchronized with the tumor's movement. Both gated radiation therapy and real-time tumor-tracking radiation therapy methods require accurate information on tumor location. Several strategies have been introduced to detect tumor location information as a function of time such as Fluoroscopy [11] and using external surrogates. The first method provides tumor coordinates as a video stream; however, the additional imaging dose received by the patient is significant [11]. Recently,

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external surrogates-based radiotherapy has been widely adopted for estimating tumor motion based on the movement of external markers placed on the patient's thoracic surface. To do this, a consistent correlation model is required which is trained and constructed at pre-treatment and then predicts internal tumor motion from external markers motion. Several correlation models have been developed for real-time tumor tracking, ranging from linear to non-linear mathematical strategies [11-17]. Some efforts illustrate the performance of several correlation models in a competitive fashion [15-18]. Among them, each method has its unique performance accuracy with specific uncertainty errors. Therefore, reaching an accurate model is still a requirement to be implemented clinically with smaller uncertainty errors.

In this work, a deep learning correlation model has been proposed based on a Long-Short Term Memory (LSTM) neural network developed by a Python software package [20-30]. To achieve this, a real patient database from CyberKnife [29-30] Synchrony System treatments at Georgetown University Hospital has been used. This database includes external motion data extracted from infrared markers located on the patient skin and internal tumor motion data detected by a stereoscopic X-ray system in the treatment room.

Long Short-Term Memory (LSTM) networks, introduced by Hochreiter and Schmidhuber in 1997, represent an enhanced variant of recurrent neural networks (RNNs) developed to address several inherent limitations of conventional RNNs. Retaining information from previous inputs plays a crucial role in sequence-learning tasks and must therefore be incorporated into the model’s architecture.LSTMs were specifically designed to mitigate the vanishing gradient problem encountered during long-term training. Due to their internal memory cells, LSTMs are capable of preserving error signals and sustaining gradient propagation, which ultimately leads to improved performance compared to standard RNNs by alleviating the gradient vanishing issue.

Machine learning algorithms, particularly LSTM, are employed due to their ability to process information through multiple layers, extract meaningful features from raw input, and effectively maintain long-term dependencies for accurate time series prediction. Unlike standard recurrent neural networks, LSTM possesses long-term memory and operates in a looped structure. It selectively retains essential information by discarding less relevant data, allowing it to focus on critical pate inputs.

The final results compare the targeting error of the proposed LSTM model with that of the Cyberknife model. As a result, the LSTM model can track tumor motion accurately, with a targeting error 15.3% smaller than the Cyberkife model, making it a strong candidate for clinical implementation.

Materials and Methods

Cyberknife Synchrony system and tumor motion database

The data set analyzed in this research includes the movement data of 86 patients treated at Georgetown University Hospital in the United States [12-15]. This database contains data on patients treated with real-time tumor motion compensation using the Synchrony respiratory tracking module, which is integrated into the Cyberknife system. The Cyberknife system tracks tumors by first acquiring information about their size, shape, and precise position using advanced imaging technologies. This system enables an optimal radiation delivery strategy, resulting in a safe and accurate treatment. During treatment, external markers attached to the patient's vest are tracked using a synchronized infrared camera, capturing chest and abdominal motion data as an external dataset. In contrast, internal tumor motion data is obtained by tracking the tumor using a stereoscopic X-ray imaging system. The paired external and internal motion databases are used to determine the parameters of the LSTM model, which is constructed before actual treatment. The process is shown in Fig. 1. During treatment, the accuracy of the model's performance is consistently monitored. Moreover, the model is updated every few minutes using newly acquired data points from the patient's thoracic surface and tumor motion in an order of a few minutes. It should be noted that the relevant data are logged and stored in ASCII format. The primary goal of the model update stage is to ensure that if the model fails to function correctly, irradiation is halted to protect healthy tissue from excessive radiation exposure.

The objective of this study is to develop an LSTM-based model capable of tracking and predicting tumor position with maximal accuracy and minimal error.

Among the population database, a group of patients is extracted randomly including patients with normal and abnormal breathing motions as depicted at table 1.

The range of motion for external markers is reported at table 1, while tumor motion refers to the entire motion dataset. They are computed as the peak-to-peak motion in three dimensions for the external markers and the implanted clips as tumor motion.

LSTM as a correlation model

A series of adaptive models is employed in this strategy to forecast the tumor's location. In this approach, during the pre-treatment stage, an adaptive model is created utilizing data received from the simultaneous movement of the chest and the tumor. Following the construction of the model, only information about the movement of the chest is sent to the model, and the model estimates the position of the tumor based on previous training. Further details are as follows.

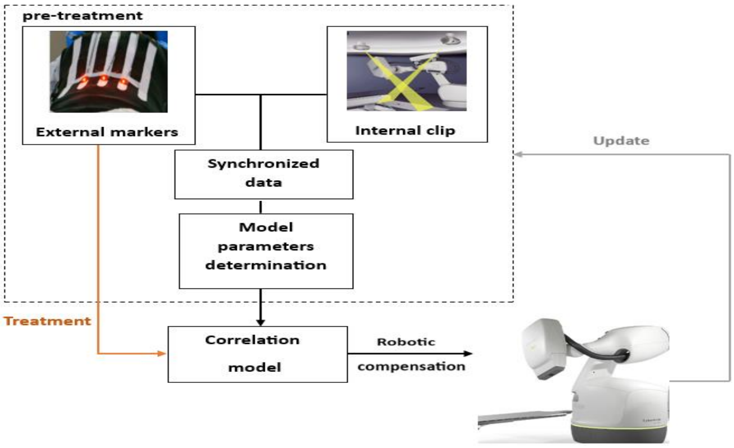

Figure 1. Workflow of tumor motion compensation with Cyberknife Synchrony (model construction: black color, model performance: orange color, model update: gray color)

Table 1. Features of the Cases Selected for This Study. (LLL: Left Lower Lobe, RLL: Right Low Lobe, RUL: Right Upper Lobe)

Case	Site	External Motion (mm)	Tumor Motion SI(mm)	Tumor Motion LR(mm)	Tumor Motion AP(mm)	Synchrony Error mean(mm)	Synchrony Error STD(mm)	Imaging Intervals Mean[s]	Imaging Intervals STD[s]	Treatment Time[min]
1	LLL	96.9	70.50	75.7	31.9	11.3	12.6	41.0	59.2	97.8
2	RLL	14.8	28.4	11.8	24.3	7.9	12.9	57.2	33.8	38.1
3	LLL	20.3	45.9	12.9	7.8	7.5	5.7	53.2	44.1	93.1
4	LLL	20.2	54.1	9.2	4.6	6.4	7.7	65.2	42.4	93.5
5	LEFT LUNG	95.9	23.4	24.5	37.2	6.2	10.5	67.5	29.6	27.0
6	LEFT LUNG ARTERY	8.6	9.1	33.5	20.1	5.9	11.7	63.7	62.1	87.1
7	LEFT LUNG	27.0	55.8	25.8	40.7	5.5	6.1	71.9	59.8	105.4
8	RIGHT LUNG	29.2	17.3	4.4	6.2	5.4	7.3	61.7	25.6	38.5
9	LLL	23.6	32.4	14.5	16.8	5.1	4.9	61.2	50.8	85.7
10	RUL	12.2	24.7	18.9	21.2	5.0	3.6	75.1	54.2	118.8
11	RLL	3.4	31.1	5.0	3.8	3.2	3.2	66.9	33.1	78.0
12	LLL	4.4	11.6	6.1	10.2	2.7	1.1	81.7	32.1	68.1
13	PANCERAS	3.3	15.8	15.9	12.0	2.2	2.3	55.0	33.0	90.1
14	RIGHT HILUM	1.4	18.2	12.4	7.7	1.8	1.9	73.7	38.2	61.4
15	LLL	2.7	23.8	3.1	1.8	1.7	1.2	65.1	32.0	68.3
16	CHESTWALL	1.9	2.6	3.2	7.7	1.4	0.9	63.6	31.7	59.4
17	LIVER	5.5	18.7	3.3	7.8	1.2	0.7	65.4	29.1	41.9
18	RUL	5.8	4.0	1.8	6.4	1.2	0.7	97.6	44.1	70.0
19	LEFT SPLENIC BED	6.0	2.0	3.5	4.3	0.9	0.4	81.7	32.8	61.3
20	LEFT FLANK	1.6	3.0	2.2	2.4	0.5	0.3	58.1	26.0	69.7

The correlation model based on LSTM is proposed and assessed in this research [31-32]. The tumor motion data consist of a sequence of data points collected over time intervals and it has time series properties, so the dense neural network-based models are not efficient in processing this data. As a result, recurrent neural networks are used, which can recognize patterns and learn from consecutive data sets. RNNs are one of the networks that have memory and the ability to retain data, but they cannot store information in the long term, while LSTM can learn order dependence and handle the vanishing gradient problem. LSTM networks contain memory blocks. They are a type of RNN in which the block structure has been modified by adding an input cell denoted as C. This cell allows them to adjust which of the past long sequences of information and how much they affect the block. Since patients' respiratory cycles vary during external radiotherapy, a model should be developed to track the tumor despite these differences and predict its position with the least amount of error.

For model development, artificial intelligence and deep learning-based neural networks offer a robust solution. LSTM networks, a type of standard RNN with both long- and short-term memory, are capable of analyzing not only individual data points, such as images, but also entire data sequences, including audio and video. This capability makes LSTM particularly suitable for data processing and predictive tasks. Each

LSTM unit consists of a memory cell, an input gate, an output gate, a forget gate, and an output activation function. By selectively controlling the flow of relevant information from the current state, LSTM networks can preserve significant long-term dependencies, enabling accurate predictions for both present and future time steps. These gating mechanisms effectively address the long-term memory limitations inherent in conventional RNNs.[31-32].

In this study, the LSTM network is utilized to create a time series adaptive model to achieve successful tracking. Initially, the coordinates supplied by the external markers are gathered using the available data sets and stored in a file as a matrix so that it can be fed into the network. Moreover, there is a separate file containing the coordinates provided by the internal marker placed in the tumor, which shows the location of the tumor, is also created, and a portion of it is given to the network as an output. Due to the presence of a non-linear relationship between the movement of external markers and the internal tumor motion, the correlation model should be capable and accurate enough to correctly track the tumor.

To estimate the tumor's location, at first, a model is created during the training phase, and then it predicts tumor coordinates with the information of the external markers' coordinates. To build and train the model, the presented data should be defined as input and output so that the model can learn the mathematical correlation by comparing the coordinates of the external markers and the actual location of the tumor (internal marker), in a synchronized mode. The data is defined in such a way that the model can guess the data of the next column by reviewing several previous columns that are determined based on the information available from the external-internal motion database. The data is firstly normalized between -1 and 1 before being used as the input and output of the network to have the same scale and improve the accuracy of the model performance. It should be noted that to improve the model parameters determination and hence its performance, the training dataset is multiplied using mathematical interpolation strategies. This method increases the size of the dataset with the help of the interpolation method and with a factor of 1000. After determining the model parameters, LSTM is applied during the treatment to infer tumor trajectory as a function of time. The image data points obtained during the treatment by stereoscopic X-ray imager, are utilized to evaluate the model performance accurately. Moreover, this dataset is also used to update the parameters of the correlation model after receiving each new arrival data point. In this way, the model is rebuilt using the most recent imaging data points synchronized with external data obtained at the same time.

In this study, a long short-term neural network with two LSTM layers and 40 neurons at each layer and the Adam Optimization Algorithm is designed for the training process. In the network output, a fully connected layer known (a dense layer) is employed with a linear activation function to forecast the three values of X, Y, and Z associated with tumor coordinates. It should be noted that the number of training data points is different and varies for each patient on a case-by-case basis.

Mean Square Error (MSE), as a key model parameter, is directly influenced by the number of error terms. The number of training iterations is set to 30 epochs as the optimal value that minimizes computational time. The model is then constructed utilizing external motion data as input and internal tumor motion data as output, in the matrix form.

On average, 12% of the total data points are used for network training, while the remaining data is reserved for testing. It should be noted that the amount of training and testing data varies depending on the information available from each patient on a case-by-case basis. To predict the location of the tumor at any moment during the treatment, the most recent external data points are used as the model input. Table 2 summarizes the properties of the developed network.

Table 2. Summary of Information About The LSTM, Constructed for One Patient as an Example (Total trainable parameters are 21563 with 84.23 KB capacity).

Layer (type)	Output shape	The number of parameters
LSTM_1 (LSTM)	(None, 11, 40)	8480
LSTM_2 (LSTM)	(None,40)	12960
Dense (Dense)	(None, 3)	123

The first column lists the model layers, including two LSTM layers and one Dense layer. In the second column of table 2, the output shape is presented. The batch size, time steps, and the number of features were 1, 11, and 12 respectively. Batch size specifies the number of samples in each batch during training and testing, time steps show the value in a sequence, and the feature illustrates the dimensions for showing data in a time step which here includes 9 rows related to data obtained from external markers plus 3 rows related to internal marker information.

Results

In this study, the model was designed using the Python programming language, and the results were reported. Several libraries, including TensorFlow, NumPy, and Pandas were utilized to construct the network. The Root Mean Square Error (RMSE) is a commonly used metric for evaluating model accuracy in predicting tumor location during patient breathing. The RMSE, which is equivalent to the standard deviation of residuals, mathematically quantifies the average difference between the values anticipated by the statistical model and the actual values. Low RMSE values indicate that the model fits the data well and predicts tumor motion more accurately. It can be stated that RMSE is an important measure in the development of forecasting models while its value indicates how effectively a model works. In this work, the three-dimensional RMSE was calculated alongside the RMSE for each spatial direction separately, as presented in Equation 1.

$$RMSE = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(X_i - X)^2} \quad (1)$$

Where Xi represents the value predicted by the model, X is the actual value and n is the sample size. In Equation 1, the squared differences between actual and predicted values are summed, divided by the total number of samples(n), and then squred-rooted to compute RMSE.

Table 3 presents the RMSE values for model performance in the X, Y, and Z spatial directions across all patient datasets.

Table 3. The RMSE of LSTM model performance for all patients (In three X, Y, and Z directions)

Patient number	RMSE on X (mm)	RMSE on Y (mm)	RMSE on Z (mm)
1	2.34	1.82	1.68
2	1.44	0.41	1.2
3	0.49	0.43	0.80
4	0.76	0.33	1.53
5	5.54	0.40	0.47
6	1.54	1.42	1.04
7	1.23	1.03	1.34
8	4.40	0.55	0.28
9	0.86	0.63	1.37
10	0.30	0.46	1.42
11	2.55	5.74	5.28
12	11.45	8.24	2.16
13	2.90	0.77	1.21
14	9	3.59	7.53
15	3.71	2.69	3.06
16	1.94	0.43	1.08
17	4.56	1.43	1.02
18	5.17	1.62	1.03
19	6.79	0.69	1.03
20	13.77	6.36	2.95

Table 4. The Average Errors of the LSTM Model in comparison with CyberKnife Model on X, Y, and Z Directions and 3 Dimensionally

Utilized model	Average RMSE on X (mm)	Average RMSE on Y (mm)	Average RMSE on Z (mm)	Average 3D RMSE (mm)
LSTM model	4.03	1.95	1.87	5.07
CyberKnife Modeler	4.16	2.96	2.30	5.99

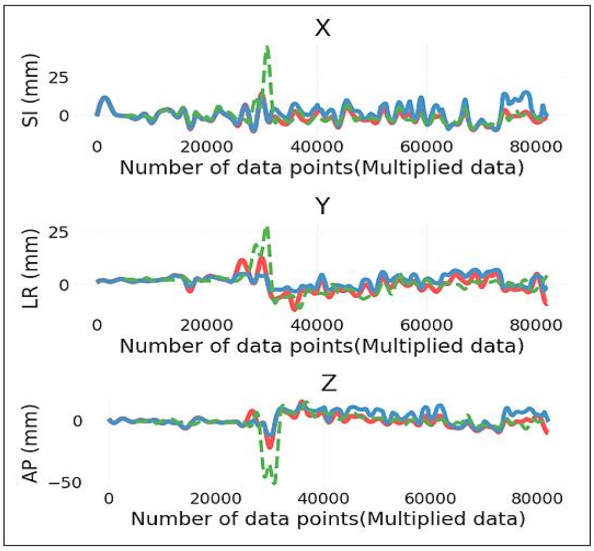

Figure 2. A view of tumor tracking by the LSTM model versus the Cyberknife model for one patient (Red, Blue, and Green colors represent imaging, LSTM, and CyberKnife model outputs.(SI: Superior-Inferior, LR: Left-Right, AP: Anterior-Posterior)

Moreover, the calculated RMSE of the proposed model was compared with the performance accuracy of the CyberKnife modeler at table 4. The final results indicate that the LSTM model exhibits lower errors compared to the CyberKnife model in tumor tracking. According to a quantitative assessment, the LSTM model achieves a significant error reduction of 3.1%, 34.1%, and 18.7% in the X, Y, and Z directions, respectively. It should be noted that the three-dimensional error reduction has a 15.3% improvement versus the CyberKnife Synchrony Modeler. Figure 2 illustrates the motion amplitude of tumor displacements for one patient in the X, Y, and Z directions, representing Superior-Inferior (SI), Left-Right (LR), and Anterior-Posterior (AP), respectively. In this figure, the horizontal axis represents the number of data points, which are expanded using the interpolation algorithm and saved as a log file in the external-internal motion database. As observed in this figure, the LSTM model traces tumor motion more accurately than the Cyberknife model.

As mentioned, numerous studies have been conducted in the field of tumor tracking, introducing various models, including state models, fuzzy systems, and artificial neural networks (ANN). However, a comparison between the results of these studies and the LSTM model demonstrates the superior accuracy of LSTM in tumor tracking. Therefore, this study proposes the use of LSTM for tumor tracking due to its superior predictive capabilities. Based on the findings of previous studies and the reported error rates, the fuzzy model had previously shown improved performance. In the present study, as shown at the table 5, the proposed LSTM model not only outperformed the model used in the CyberKnife system but also demonstrated better performance compared to the three major models introduced in earlier research.

Table 5. 3D RMSE Reduction Percentage for Four Prominent Predictive Models in Tumor Tracking

Prediction models	3D RMSE Reduction (%)
State model	0.6%
ANN	8.7%
Fuzzy system	10.8%
LSTM	15.3%

Discussion

Recently, external surrogate radiotherapy is one of the clinical strategies for treating tumors located in the thorax region of the patient's body, which moves mainly due to respiration. In this way, tumor motion is managed, additional imaging dose is controlled, and the delivered dose to nearby normal tissues is significantly reduced to decrease the risk of serious radiation-induced side effects.

In this study, an LSTM model is developed as a consistent correlation model used in external surrogates radiotherapy for real-time tumor motion tracking. The LSTM neural network is based on Long-Short Term Memory and is increasingly used in various fields, ranging from medicine to industry.

The proposed model is implemented using a real database of a group of patients treated with the CyberKnife Synchrony System. This database consists of external motion data from infrared markers located on the patient's chest and internal motion data representing thorax tumors. The model is first constructed by determining its parameters using training data points at the pre-treatment step. Then, the LSTM model is ready to track the tumor in real-time during the treatment by using only external markers as input. Moreover, its performance accuracy is tested after each one to five minutes during the treatment by taking real X-ray images to extract the tumor coordinates.

The RMSE of LSTM model's performance is calculated for 20 patients. This error shows the distance between the tumor location predicted by the developed LSTM model and the actual tumor coordinate extracted practically using a stereoscopic X-ray imager in three X, Y, and Z directions. Moreover, the RMSE of the LSTM model is compared with the performance accuracy of the CyberKnife modeler. As seen in this table, the average error of our model is lower than the Cyberkinfe modeler, while the maximum error reduction happened in the Y direction with a 34.1% improvement. With the same strategy, the average 3D RMSE is calculated and the LSTM model provides better performance accuracy with a 15.3% improvement in error reduction.

The aim of this study is to measure the output of the model on real patient data. Since the available information from patients treated at Georgetown Hospital in the United States was limited, in this study, for the initial investigation with the available information, the comparison was made for this group of 20 patients. According to the promising results obtained from this study, it is possible to further validate this model in future studies and by obtaining a larger dataset and demonstrating its improved performance with a larger number of data points.

The LSTM model in Recurrent Neural Networks (RNNs) is designed to better manage non-linear temporal dependencies compared to traditional methods such as Moving Average (MA) and other models, including standard RNNs. Traditional models are typically suited for data with short-term dependencies. However, when long-term dependencies are present, these models tend to forget previous information. Furthermore, these traditional models rely on linear relationships. In contrast, the LSTM model addresses these shortcomings due to its unique cell structure, long-term memory, adaptive learning gates, and its ability to model non-linear relationships, making it a highly popular model for time series prediction. As evident from the results of this study, the use of the LSTM model in the field of tracking has led to improved performance accuracy and error reduction. Reducing Root Mean Square Error (RMSE) in predictions related to radiotherapy can have a significant impact on improving patient outcomes. Additionally, more accurate tracking of the dose received by healthy tissue also reduces the risk of side effects. More precise predictions of tumor changes or patient responses to treatment facilitate better treatment planning, and models with lower RMSE can better identify the likelihood of side effects, thereby recommending preventive measures.

Using LSTM for more accurate predictions of radiation dose and side effects can enhance treatment efficacy. As seen at table 5, a reduction in RMSE directly leads to improved patient outcomes as prediction accuracy increases, and treatment decisions become more optimized. Among the four predictive models evaluated in this work, the LSTM model demonstrated superior performance compared to the state-space model, the artificial neural network, and the fuzzy model. Its advantage was particularly evident in reducing prediction error, highlighting the model's capacity to effectively capture temporal dependencies and complex patterns in tumor tracking data. Unlike more traditional approaches, which rely on predefined rules or simpler architectures, the LSTM benefits from an internal memory structure that allows it to retain and utilize past information more effectively. This enables the model to perform more robustly in dynamic and nonlinear contexts.

In future studies, to enhance accuracy and generalizability, combining LSTM with other deep learning models is suggested: LSTM + GRU: Combining these two architectures can retain the benefits of both. GRU is simpler and faster, while LSTM handles longer-term dependencies more effectively. LSTM + CNN: Combining CNN for extracting spatial features from medical images and LSTM for modeling temporal dependencies can be particularly useful in applications such as radiation dose analysis. Testing on multi-center datasets is a crucial step to ensure the robustness and generalizability of the proposed models. Future steps should include model optimization, reduction of computational complexity, and integration with existing radiotherapy systems for the practical implementation of these techniques.

Conclusion

In radiotherapy of moving tumors, the information about tumor coordinates in real-time is highly important to improve targeting accuracy and tumor localization during therapeutic beam irradiation. In this study, a machine learning-based model entitled LSTM was developed in Python to track moving tumors located in the thorax region of the patient body. After comparing the performance of the LSTM model in different patients to the Cyberknife modeler, it can be concluded that the LSTM model has superior performance accuracy with lower uncertainty error. Moreover, LSTM offers greater simplicity, making it suitable for real-time applications. For future studies, before giving the input to the network, another pre-processing on the motion dataset can be applied by deleting outliers to yield error reduction with shorter deviations. Moreover, the GRU-LSTM hybrid model , CNN-LSTM can be considered as future work to improve the proposed model.

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