

Investigation the Efficacy of Fuzzy Logic Implementation at Image-Guided Radiotherapy

Abstract

At image-guided radiotherapy, technique, different imaging, and monitoring systems are utilized for (i) organs border detection and tumor delineation during the treatment planning process and (ii) patient setup and tumor localization at pretreatment step and (iii) real-time tumor motion tracking for dynamic thorax tumors during the treatment. In this study, the effect of fuzzy logic is quantitatively investigated at different steps of image-guided radiotherapy. Fuzzy logic-based models and algorithms have been implemented at three steps, and the obtained results are compared with commonly available strategies. Required data are (i) real patients treated with Synchrony Cyberknife system at Georgetown University Hospital for real-time tumor motion prediction, (ii) computed tomography images taken from real patients for geometrical setup, and also (iii) tomography images of an anthropomorphic phantom for tumor delineation process. In real-time tumor tracking, the targeting error averages of the fuzzy correlation model in comparison with the Cyberknife modeler are 4.57 mm and 8.97 mm, respectively, for a given patient that shows remarkable error reduction. In the case of patient geometrical setup, the fuzzy logic-based algorithm has better influence in comparing with the artificial neural network, while the setup error averages is reduced from 1.47 to 0.4432 mm using the fuzzy logic-based method, for a given patient. Finally, the obtained results show that the fuzzy logic based image processing algorithm exhibits much better performance for edge detection compared to four conventional operators. This study is an effort to show that fuzzy logic based algorithms are also highly applicable at image-guided radiotherapy as one of the important treatment modalities for tumor delineation, patient setup error reduction, and intrafractional motion error compensation due to their inherent properties.

Keywords: Fuzzy logic, image-guided radiotherapy, margins, patient positioning, tracking

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Introduction

Apart from surgery or chemotherapy, radiotherapy is a curative method that is commonly used to treat cancers by means of ionizing radiation.^[1,2] In radiotherapy, the degree of treatment success depends on delivering a uniform prescribed dose onto tumor volume while minimizing complication probability of normal tissues around the tumor during irradiation.^[3,4] For this aim, tumor delineation must be done accurately during the treatment planning process. Moreover, the exact information of tumor position and surrounding normal tissues is also necessary to enhance targeting accuracy^[5] and yield proper patient positioning, to minimize inter-fractional

error between the treatment sessions.^[6-9] Since tumors located in the thorax and abdominal region of the patient's body move mainly due to breathing (known as intra-fractional motion), target localization uncertainty error is increased, and 3D homogenous dose conformation will not be achieved.^[10-12] Accordingly, some over and/or under dosage will occur on tumor volume that results in a gap between the actual and prescribed doses.^[13]

In order to address these issues, image-guided radiotherapy (IGRT) is introduced to enhance the treatment quality using (1) tomography images data for exact tumor delineation and (2) in-room stereoscopic X-ray images for patient positioning and real-time tumor tracking.^[14] By implementing IGRT, Planning Tumor Volume (PTV) that must be irradiated as the target is decreased significantly by

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restricting the treatment fields during radiotherapy, and therefore normal nearby tissues will be better protected against the additional high dose, in comparison with conventional radiotherapy.^[14-16]

In IGRT, many nonlinear parameters with different weights and a high degree of variability are extracted from an extensive images database provided at different steps of the treatment process ranging from tumor definition to therapeutic beam delivery. Several conventional mathematical approaches are available to utilize this database and give the associated outputs with specific uncertain errors. However, a fuzzy logic concept that is highly applicable at artificial intelligence; will be optimal for making a proper decision with less error at each treatment step considering the effect of all factors with nonequal weights.^[17] The fuzzy Logic idea was introduced by Lotfi A. Zadeh in 1965.^[18-22] It works on the basis of *IF-THEN* rules that are more close to a human-like way of thinking, and this idea is the most important sign of fuzzy logic to generate a solution for many applications compared to the proposed mathematical methods. Due to this property of fuzzy logic, for a large variety of problems with imperfect database and even qualitative problems where analytical solutions do not work well, fuzzy logic is highly recommended. In fact, fuzzy logic-based systems replace two-valued logic systems with a sense of gradual truth in order to finally yield superior results compared to conventional mathematical-based systems.

It should be noted that patient anatomical changes, patient geometrical setup, and breathing phenomena are highly variable.^[23,24] Furthermore, the breathing phenomenon varies in different patients on a case-by-case basis. In this highly nonlinear situation, the robustness of fuzzy logic in (1) data classification, (2) breathing motion prediction, (3) diagnostic tasks at organ border detection, and (4) functions fitting makes it a promising approach for improving the treatment error reduction. It is worth mentioning that the results obtained from fuzzy logic-based algorithms in this study are compared with commonly available methods used practically.

We formerly developed some nonlinear prediction models for real-time tumor tracking at external surrogates radiotherapy,^[23-26] but our main focus in this work is investigating the efficacy of fuzzy logic implementation at three main steps of IGRT considering also to fuzzy limitations and possible sensitivities, due to lack of research work in this strategy as overall.

In our study, fuzzy logic is implemented at two nondeterministic models as (1) fuzzy inference system (FIS) and Adaptive Neuro-FIS (ANFIS). ANFIS, which is the combination of fuzzy logic abilities and an adaptive neural network is used for simulating patient setup correction and also edge detection process.^[27,28] In contrast, real-time tumor motion tracking is performed by FIS. The robustness

and drawbacks of ANFIS performance at IGRT have been investigated as independent work in our recent studies.^[25]

Three different databases are utilized in this work to assess the effect of fuzzy logic on IGRT treatment quality enhancement as (1) tomography images provided by anthropomorphic 4DXCAT phantom for edge detection calculations, (2) computed tomography (CT) data of real patients with defining external markers located on patient body surface for simulating patient setup before the treatment and (3) motion data of real patients treated with Cyberknife Synchrony system for real-time tumor motion tracking during the treatment.^[29-33] The latter case includes internal tumor motion data synchronized with corresponding external rib cage and abdominal motion data as a function of time.^[31,32]

In this work, fuzzy logic is proposed to increase treatment precision by: (1) modifying of edge detection process used for target definition and by (2) improving patient positioning and (3) real-time tumor motion tracking. However, fuzzy logic-based algorithms can be over-trained while configuring for parameter determination. Moreover, the response of these algorithms is more sensitive in some cases in comparison with conventional methods.

Methods

Fuzzy logic at image Guided radiotherapy

IGRT accomplishes the radiation treatment process in three main steps: (1) image-guided target definition and (2) image-guided patient geometrical setup and (3) image-guided tumor tracking in case of dynamics tumors located at thorax region.^[15] As resulted images as a key component of IGRT, plays an important role to reduce the errors associated with each section. The required images for tumor delineation can be taken by a large variety of modalities ranging from high-resolution anatomical image as regular CT or Cone-Beam CT to functional images as Positron Emission Tomography.^[34] Concerning two latter steps, sample data from stereotactic in-room X-ray imaging in combination with optical and/or laser-based surface body monitoring are utilized for patient setup and tumor tracing. At all three steps, the extracted database should be mathematically analyzed by experts to make proper decisions with the least uncertainty errors for tumor definition and then target bombarding by therapeutic beam irradiation. In the following, a brief description has been brought about each step of IGRT and how fuzzy logic-based algorithms can be implemented to enhance treatment accuracy.

Tumor motion tracking

Consecutive breathing cycles cause intra-fraction motion of organs and tumors located at thorax region of the patient body. This motion is nonrigid and is a combination of translation, rotation and/or deformation of the tumor and surrounding organs. One of the main goals of the IGRT

strategy, is to obtain the exact information of tumor position in real-time mode during the treatment.^[32] This information can be significantly helpful to improve the imaged-based dose delivery. Using this information, the target is better localized, and hence normal tissues will be saved against high dose at the same time. Several strategies were proposed to extract tumor position information over the time such as fluoroscopic imaging^[35] or using external surrogates.^[24]

In external surrogates radiotherapy, tumor moving information is correlated with rib cage or abdominal motion using a consistent correlation model.^[23,25,36,37] Therefore, the output of the correlation model is an estimation of tumor position information using only external motion data as input. External data including thorax surface motion is obtained by means of a vest including three infra-red markers (and has worn by patients) and an optical or laser-based monitoring system for markers monitoring. Internal data including tumor motion is achieved by implanting fiducial marker inside or near tumor volume and its detecting using stereoscopic X-ray imaging system. In order to obtain the external motion dataset, patients were asked to wear a vest with three infra-red markers. Furthermore, a fiducial as the internal marker is implanted inside tumor volume to enhance the contrast at stereoscopic X-ray images.

Firstly, the model should be configured using training data at the beginning of each treatment fraction. Training data is gathered at pretreatment step and includes external motion data paired with synchronized internal tumor motion data. After model configuration, it is ready to estimate tumor displacement during the treatment using moving data of external markers as input file. Since, each correlation model has uncertainty error in finding a consistent correspondence between external markers motion with tumor motion, the main goal is to obtain a proper model with the lowest uncertainly errors. In this part, fuzzy logic-based correlation model will be optimal for tumor motion tracking.

The external motion data will be arranged as a matrix with 9 columns. Columns of input matrix represent $x(t)$, $y(t)$, and $z(t)$ position of three external markers where the output matrix illustrates the tumor position at one spatial direction. Therefore, three fuzzy logic-based models with the same parameters are working as parallel to estimate tumor position information, three dimensionally.

Correlation model based on fuzzy logic

Fuzzy logic-based correlation model was developed in MatLab (The MathWorks Inc., Natick, MA). It should be noted that our fuzzy model is able to be updated during the treatment step by means of X-ray imaging system for detecting new positions of internal tumor. New arrival data during update step is accumulated to previous training data, and the model is re-built by means of total training data.

When an external motion data point is given as model input during the treatment, the FIS acts as five following

steps: (1) fuzzifying input data, (2) inducing the *if-then* rules, (3) applying implication method, (4) aggregating the output, and (5) defuzzifying step.^[25,38] The fuzzy correlation model is then applied to tune robotic linear accelerator according to the estimated tumor position.

Fuzzy-based clustering algorithm

When external-internal database is collected from related devices (optical monitoring system and stereotactic X-ray imaging system), the extracted data must be initially sub-divided into several groups in order to simplify the data processing in lesser computational run time. In our program, data clustering is the premier step at construction of the FISs as the correlation model. Different data clustering algorithms have their unique properties in grouping the dataset due to their robustness and drawbacks.^[24,39] In fuzzy logic-based correlation model data clustering algorithm is responsible for membership function generation required for next step of inference system.^[25] Membership functions represent the degree of participation for each input/output database. It should be noted that the fuzzy logic can play an important role in data grouping. In the current study, since the main focus is on fuzzy logic applications, a fuzzy-based clustering algorithm was considered in configuration of final correlation model utilized for tumor motion tracking.^[40]

Among different clustering algorithms, Fuzzy C-Means (FCM) was chosen for grouping of our external-internal database. In FCM clustering algorithm, each data point in the dataset belongs to each cluster with a specific degree of membership which is determined by the distance of given data point to cluster centers. In this way, higher membership degree represents a data point that is closer to the cluster center, and vice versa.^[41,42]

Figure 1 represents the performance of our FIS in input and output generation by implementing rule set. In this case, nine inputs representing 3D motions of three external markers (at x , y , and z directions) are correlated with 3D motion of one implanted internal marker with x , y , and z outputs. The internal-external data were clustered into three groups, and therefore three rules connected with and operator were implemented. This figure shows Gaussian membership functions of input number 7 (upper panel) and output number 1 (middle panel) and given rule number 2 (lower panel).

Patient setup uncertainty error

In external beam radiotherapy, after personalized treatment planning, patient positioning and its immobilization verification must be implemented to localize the target against treatment beam at each irradiation fraction. However, uncertainties in the patient geometrical setup, known as inter-fractional motion error (random and systematic) disturb proper prescribed dose distribution onto tumor volume. Patient positioning with nonnegligible

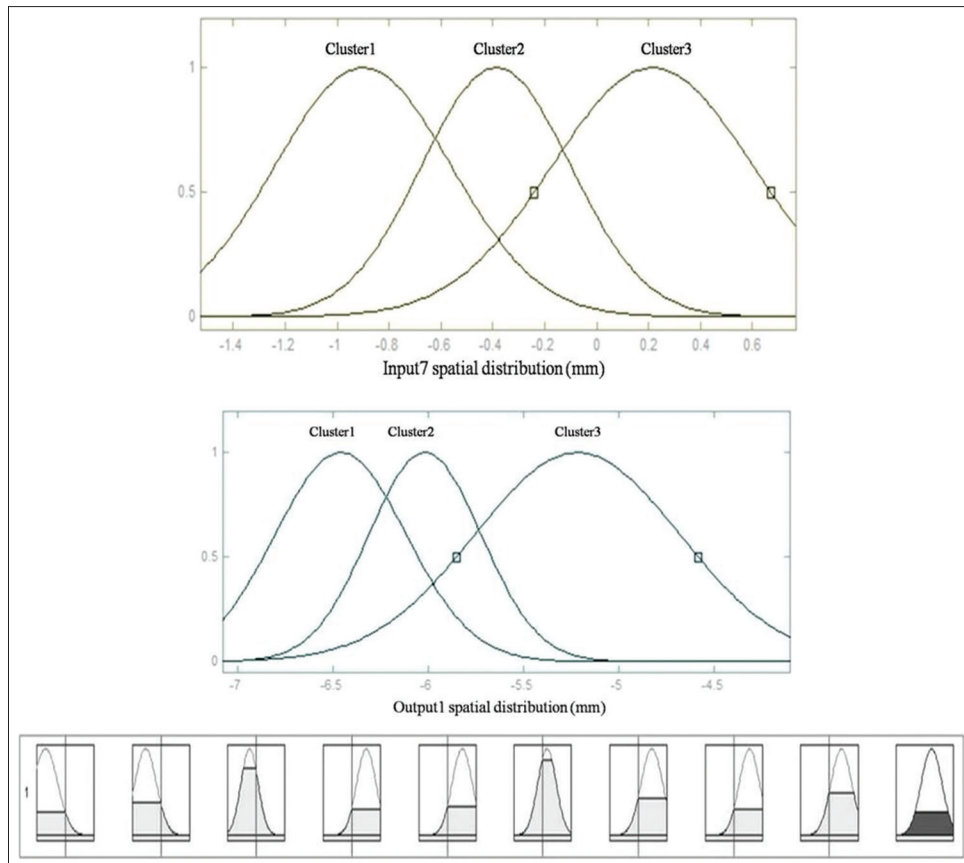


Figure 1: A typical membership function generated by input training data (upper), a typical membership function generated by output training data (middle), a typical rule from 3 rule set in conjunction with AND operator at antecedent (gray) and consequent (black) parts of fuzzy inference system (lower)

uncertainty error may shift a high dose onto surrounding normal tissues, which causes serious side effects.

Several strategies were proposed to improve patient setup and target localization. Some of these efforts have been commercially available,^[7,8] and the most applicable methods are skin fiducials with optical tracking system, laser-based surface body depiction and in-room X-ray imaging techniques.^[43,44] Among mentioned techniques, optical tracking system in combination with external markers is a reliable method for patient re-positioning and verification of irradiation setup to quantify the amplitude of operator dependence target displacement. Then, the detected misalignment is automatically corrected by means of servo-controlled patient couch. The parameters of patient setup correction can be predicted by developing a consistent correlation between 3D external motion of markers located on the chest and abdomen skin and given reference point emerged from the personalized treatment planning process.

In this section, similar to the fuzzy-based correlation model for real-time tumor tracking, another fuzzy logic-based model as adaptive neuro FIS is proposed to align target volume against beam trajectory by finding out mismatched error of patient setup. In fact, the output of developed model representing misalignment of patient setup participates in only a part of patient setup step.

ANFIS was chosen due to its robustness to combine the abilities of the fuzzy inference section with the numeric potentials of an adaptive neural network system.

All possible roto-translation parameters that vary in the range of ± 45 mm translation and ± 9 degree rotation were considered for training our nondeterministic model. After model configuration, in given unknown random position of external markers, ANFIS is able to predict the amount and direction of patient displacement with the least error. The predicted spatial roto-translation is used to improve patient setup by means of the controllable motorized treatment unit.

Fuzzy logic based edge detection of organs

In radiotherapy, Treatment Planning System (TPS) is one of the main step of treatment process that gives detailed information including target delineations and surrounding normal tissues as requirements for beam irradiation system. Therefore, the accuracy of tumor definition by TPS is a crucial issue at radiotherapy process. This issue will be highly significant at hadron therapy where imprecise target definition might cause severe damages to the healthy tissues mainly on the distal part of tumor position due to different energy deposition profile of hadrons versus photons. Moreover, some over and/or under dosage will happen onto tumor volume which are significantly different

from prescribed dose distribution. Several efforts have been done on edge detection and tumor definition.^[45-47]

To extract the edges of the desired organ from CT data, some algorithms such as Laplacian, Roberts, and Sobel operators are commonly utilized. Since, some information of CT images taken from real patient contains ambiguities due to hardware devices limitation of imaging system (e.g., motion artifact of breathing phenomena) a lack of edge detection accuracy is sensed. In this study, a neuro-fuzzy based operator is introduced to extract the edges of desired organs or tumor volume using gray-scale information between two neighbor organs that must be separated. Since the gray level is a concept of fuzzy logic, the proposed idea is optimal for performing border extraction even better than conventional mathematical methods.

Several research studies were performed recently by means of neural networks and fuzzy logic systems on edge detection issues.

In this study, ANFIS is proposed to do edge detection by combining the abilities of neural network at model training and fuzzy logic at model performance. In ANFIS, the membership function parameters of FIS are tuned only using the back-propagation algorithm or in combination with a least-squares approach.

For edge detection, ANFIS scans all pixels of a given image by a local 3×3 mask matrix including 9 arrays. Before edge detection, ANFIS is configured and trained by finding out all possible relationships between each typical pixel and its eight closest neighbor pixels.

During ANFIS edge detection by 3×3 mask, eight closest neighbors act as input, and the middle pixel is resulted as output. In this way, ANFIS is able to correctly detect the locations of the edge pixels of the image taking into account input pixels data.

Results

In order to investigate the performance of fuzzy logic-based correlation model for tumor motion tracking, three patients treated by means of the Synchrony[®] respiratory tracking system (Accuray Inc., Sunnyvale, CA) between 2005 and 2007, were chosen randomly. This database is available by the Georgetown University Medical Center. Moreover, for evaluating and testing the proposed ANFIS model for patient setup, three external markers located on body surface of two real patients using their CT data were utilized and processed by means of AMIDE (A Medical Image Data Examiner, V. 1.15) software package. Finally, in order to evaluate the performance of ANFIS edge detection algorithm, some thoracic images extracted from anthropomorphic 4DXCAT phantom (developed by Prof. William Paul Segars) were utilized, and two tumors with 15 mm and 20 mm diameters were defined in liver and lung organs of the phantom to mimic real condition.

Among three patients treated with Cyberknife Synchrony system, one of them with Left Lower Lung tumor was chosen. The number of training data for fuzzy model configuration at pretreatment step is 18 synchronized external-internal motion data points, and total number of X-ray imaging during the treatment for model testing and update is 38. Three clusters were utilized for membership functions generation, and hence three if-then rules were implemented.

Figure 2 represents tumor motion tracking in Anterior-Posterior direction by fuzzy-based correlation model regarding with Cyberknife model at specific period of time from 11.0 till 14.5 min. Black dots in this plot illustrate real position of tumor in AP direction detected by means of stereotactic X-ray imaging system during a given time of period. X-ray imaging points act as benchmark data, demonstrating how well the motion is estimated. As seen in this figure, fuzzy model output, that is tumor position information three dimensionally, is crossing through all four imaging points, as well. However, Cyberknife model output is significantly far away from two premier imaging data points at the corresponding moments. In other word, the proposed fuzzy logic-based model is more accurate at tumor motion estimation against Cyberknife modeler performance.

For simulating patient setup, correction using ANFIS output, another correlation model based on Artificial Neural Network (ANN) was considered, as an available commonly used approach, to be compared with ANFIS. To this aim, Root Mean Square Error (RMSE) was calculated among bed couched by ANFIS and also by ANN model in contrast with real position of treatment couch as ground truth data. Figure 3 Shows calculated RMSE at only 9 irradiation fractions among 30 fractions over the course of radiotherapy for better visualization. As seen in this figure, both ANFIS and ANN models highly improve re-positioning of treatment bed as well, where ANFIS model is more robust in performing patient geometrical setup than ANN with less uncertainty error.

To investigate the edge detection for organ definition by means of image processing algorithms based on ANFIS, two tomography images taken from anthropomorphic XCAT phantom were selected. As illustrated in following images, edges detected by ANFIS processing algorithm visually have detailed information further than other common methods. Since tumor located at lung region has enough contrast with surrounding tissues, all edge detection methods could recognize tumor margin. However, in some regions (depicted by dashed rectangle), where contrast difference between two similar nearby organs is not significant, ANFIS could better perform edge detection compared to other conventional Canny, Sobel, and Prewitt-based approaches.

Discussion

In recent few years, different features of conventional radiotherapy were significantly evolved by applying imaging techniques. The main outcome of image-guided

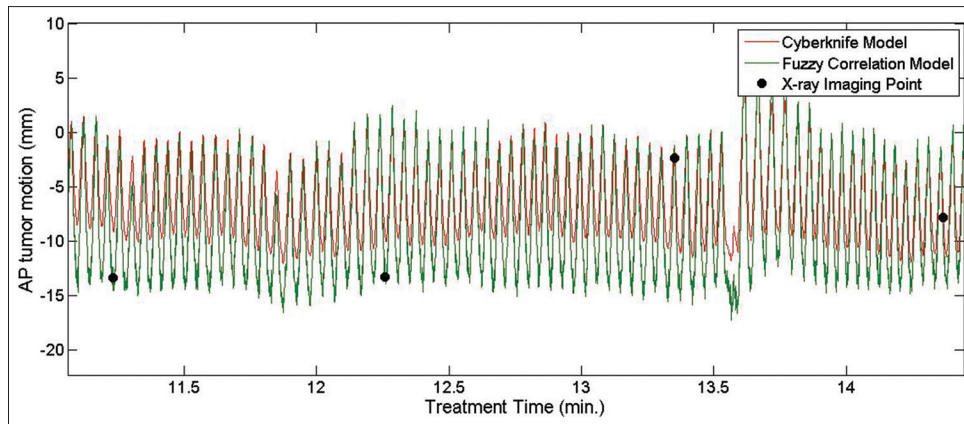


Figure 2: Tumor motion prediction by means of fuzzy correlation model (green line) regarding with Cyberknife modeler (red line) versus imaging points (black dots)

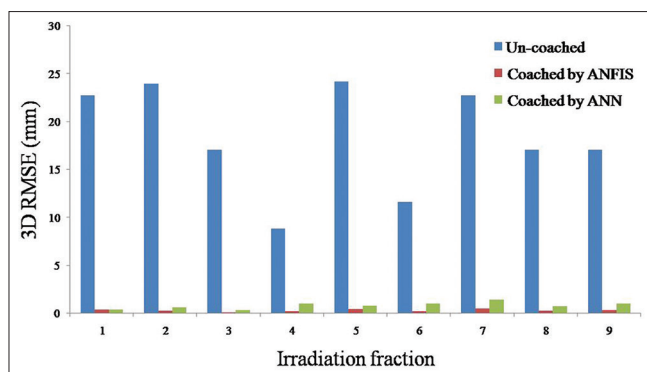


Figure 3: 3D Root Mean Square Error versus irradiation fraction between Adaptive Neuro-Fuzzy Inference System and Artificial Neural Network based coached against un-coached position of motorized treatment unit

radiotherapy versus conventional conformal radiotherapy is the implementation of smaller radiation fields onto tumor volume, due to the more precise target localization. This point will be highly beneficial for tumors that move mainly due to respiration and yields better protection of healthy tissues nearby tumor cells. IGRT enhances treatment quality by improving edge detection for tumor delineation and surrounding healthy sparing during TPS, patient positioning and also tumor motion targeting if tumor moves due to respiration or abdominal changes. Target delineation is associated with tomography images data. Tumor targeting accuracy will be increased using imaging devices incorporated with treatment machines for inter-fraction patient positioning and time-resolved stereoscopic X-ray imaging systems for intra-fraction tumor motion prediction during the treatment. When imaging database was acquired, selecting a proper data processing and analysis can remarkably reduce the errors associated with each step. In this study, the robustness of nondeterministic fuzzy logic-based algorithms was taken into account at three mentioned steps of IGRT. Since the uncertainties of daily patient setup (as inter-fraction motion error) and breathing cycles (as intra-fraction motion error) are inherently high, fuzzy logic-based algorithms are promising to minimize the errors.

Based on the achievements in this work, fuzzy logic proved to be better than Cyberknife modeler while tumor motion tracking. The average 3D RMSE of fuzzy correlation model output at a total treatment time of given patient was 4.57 mm, while this value is 8.97 mm using Cyberknife modeler. It should be noted that the simplicity factor of fuzzy logic-based algorithm was advantageous to highly decrease the computational time of tumor motion tracking. This ability makes it robust for clinical application in which the run time is important, and tumor prediction must be performed as real time. However, some concern may raise due to over-training issue, while fuzzy-based models are configuring using training data points. Moreover, fuzzy-based correlation model seemed to be more sensitive than other modelers at some cases while it starts to trace tumor motion.

Moreover, in patient geometrical setup, fuzzy logic-based correlation algorithm can be effective in different aspects, depending on the reference point predefined at treatment planning process. A successful patient setup increases the reproducibility of target localization regarding with normal tissues and therefore reduces treatment uncertainties. In this study, the fuzzy-based algorithm was utilized for target alignment to therapeutic beam irradiation, and its performance was compared with ANN. Final analyzed results represent that although both models performed couching successfully (against un-couched situations), but fuzzy logic-based algorithm performed better than ANN, while the average 3D RMSE is 0.4432 mm and 1.476 mm implementing ANFIS and ANN, respectively, for given patient with 30 irradiation fraction. It is worth mentioning that the robustness of fuzzy algorithm depends on the training data. In this work, training database includes more than 16000 data points at all possible roto-translation conditions of treatment unit position considering both symmetric and asymmetric modes.

At final step, the fuzzy logic concept was considered for edge detection of tumor and surrounding organs. An ANFIS edge detector was proposed based on the fact that the neuro-fuzzy system is very suitable tool for dealing with uncertainties during image processing,

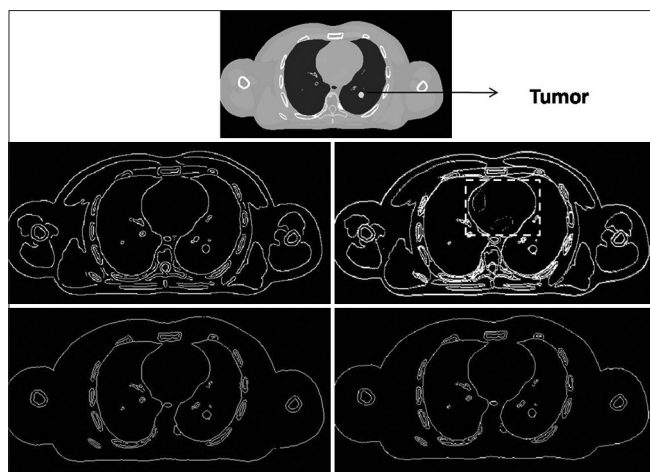


Figure 4: Original Computed Tomography image (top) edges detected by Adaptive Neuro-Fuzzy Inference System algorithm (upper right), Canny (upper left), Sobel (lower right), Prewitt (lower left)

and useful information extracting. The obtained results showed that the proposed ANFIS edge detector exhibits much better performance compared to the conventional operators used clinically by implementing Canny, Sobel and Prewitt strategies [Figure 4]. Apart from using fuzzy-based edge detection algorithm at therapy process, it will be highly applicable at lesion detection using fused functional-anatomical images at diagnostic process. Therefore, at IGRT treatment strategy, fuzzy logic-based algorithms allows safe dose utilization and improves patient treatment with accurate border detection during TPS and minimizing inter and intra-fractional motion errors at pretreatment and during the treatment steps, respectively.

Conclusion

A successful image-guided radiotherapy delivers high prescribed dose to planning target volume and keep surrounding normal organs safe against high dose by using tomography and X ray images information for tumor delineation, patient setup, and real time motion tracking as three main steps. Several algorithms have been proposed to perform these steps ranging from linear to nonlinear mathematical approaches using images information as feeders. Since the variability degree among extracted information from intera-and intra-fraction motions are remarkable for each patient and also on case by case basis, the robustness of fuzzy logic-based algorithms seems to enhance performance accuracy of each step. In this study fuzzy logic was implemented on the algorithms of all three steps, and the results were compared with common available strategies which are used practically. Finally, it's worth mentioning that using nondeterministic fuzzy logic at different steps of IGRT reduces treatment margins, minimizes patient setup uncertainties and improves real-time tumor motion tracking, significantly. It should be noted that the use of fuzzy logic concept can

be considered at Adaptive radiotherapy while re-treatment planning process is needed by means of tomography data, as future study. Moreover, various common deep learning algorithms can be implemented for inter- and intra-fraction motion data analysis and medical image processing and segmentation, as comparative study.

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Conflicts of interest

There are no conflicts of interest.

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