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Development and validation of a prototypal neural networks-based tumor tracking method

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Abstract— **In radiotherapy, intra-fractional organ motion introduces uncertainties in target localization, leading to unacceptable inaccuracy in dose delivery. Especially in highly selective treatments, such as those delivered with particles beams instead of photons, organ motion may results in severe side effects and/or limited tumor control. Tumor tracking is a motion mitigation strategy that allows an almost continuous dose delivery while the beam is dynamically steered to match the position of the moving target in real-time. Currently, tumor tracking is applied clinically only in the CyberKnife system for photon radiotherapy, whereas neither clinical solutions nor dedicated methodologies are available for particle therapy. Consequently, the aim of the proposed study is to develop a neural networks-based prototypal tracking algorithm intended for particle therapy. We developed a method that exploits three independent neural networks to estimate the internal target position as a function of external surrogate signals. This method was tested on data relative to 20 patients treated with CyberKnife, whose performance was used as benchmark. Results show that the developed algorithm allows targeting error reduction with respect to the CyberKnife system, thus proving the potential value of artificial neural networks for the implementation of tumor tracking methodologies.**

I. Introduction

A recent technique for radiotherapy, known as hadrontherapy, consist in the irradiation of tumor lesions through accelerated charged particles, such as protons and carbon ions. Compared with photon radiotherapy, hadrontherapy features two main advantages [1]. The first one is that the maximum relative dose is delivered at a precise depth (Bragg peak), which depends on tissue density and on beam energy. As a consequence, hadrontherapy allows the delivery of a high dose even to deep seated tumors while decreasing, at the same time, the damage to healthy tissues placed proximal and distal to the target.

The second advantage is the increased relative biological effectiveness (RBE) with respect to photons beams, which allows more efficient tumor control. However, these advantages can be fully exploited only if the treatment is delivered with very high accuracy, otherwise it may cause severe side effects and an inefficient tumor control.

It may be challenging to achieve the desired accuracy when treating lesions affected by intra-fractional organ motion, that is the movement due to physiological processes such as respiration and heart beat [2]. Different motion mitigation strategies have been developed for image-guided interventions [3] and, in particular, for radiotherapy. Among these strategies there are breath hold [4] and respiratory gating [5]. Another possible approach to motion mitigation is tumor tracking [6]-[7], a technique where a moveable beam is dynamically steered in order to follow in real-time the target motion along its trajectory. For this purpose, continuous information about the target position is required but real-time direct tumor localization (through fluoroscopy or frequent radiographic acquisitions) is not applicable due to constraints in imaging dose. Therefore, a possible solution is estimating internal target position form external surrogate signals.

Currently this kind of solution has achieved successful clinical application only in photon radiotherapy, where the robotic treatment device called CyberKnife (Accuray Inc, Sunnyvale, CA) is available [8]. This system, equipped with the Synchrony Respiratory Tracking System (RTS) module, uses three parallel polynomial internal/external correlation models to infer the internal tumor position as a function of the position of three external markers [8]-[9]. The system periodically acquires stereoscopic X-ray images, where the tumor is localized, in order to build the correspondence model at the beginning of the session and to check and update it during irradiation.

Today, neither clinical applications nor dedicated methodologies for tumor tracking are reported in hadrontherapy, even if studies conducted at the GSI Helmholtzzentrum für Schwerionenforschung proved its technical feasibility for treatments delivered with active scanning systems [10].

For this reason, our work aims at the development and validation of a prototypal tumor tracking method for hadrontherapy. Since a comparative study demonstrated that more complex strategies than a polynomial model are required to improve accuracy in tumor tracking [11], the proposed method will be based on external surrogate signal processing by means of artificial neural networks (ANNs). ANNs has already been proposed for the spatial and temporal prediction of the tumor position relying on external surrogate [12]. Further studies [13]-[14] investigated their performance, proving that nonlinear activation functions allows to reproduce highly complex patterns in the input

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data and that the higher is the frequency of adaptation of the inter-synaptic weights, the better is the prediction accuracy. In this study we retrospectively tested the developed method on 20 treatments delivered by means of Synchrony RTS.

II. Materials and Methods

The proposed study was conducted exploiting a database relative to treatments delivered by CyberKnife at the Georgetown University Medical Center (Washington, DC). This database contains 130 patients who received stereotactic body radiotherapy with real-time compensation of tumor motion by means of the Synchrony RTS. For each patient, a set of log files reports the following information:

- The 3D position of three optical markers attached to a tight fitting vest and acquired with an infrared localization system at frequency of an approximately 25 Hz. These signals, which are recorded during the entire duration of the session, will be referred to as external signals and will be processed with ANNs to estimate the internal target position.
- The 3D position of the tumor that is acquired with intermittent stereoscopic X-ray imaging. These data, which will be referred to as internal signal, are acquired by the Synchrony system both before irradiation, to build the internal/external correlation model, and during the treatment, to check and update it.
  A status index distinguishes images acquired before irradiation from those acquired during irradiation as control.
  In the proposed work, these data will be exploited for neural networks initial training, tracking error quantification and, when necessary, for ANNs retraining.

Both the internal and the external signals share a common temporal basis, so that it is possible to identify, for each acquired image, the simultaneous position of the three external markers.

Among the available population, 20 patients were selected and divided into two groups [11]. The first one, referred to as worst group, contains the 10 fractions where the largest average tracking error is observed from the analysis of log files. The second one, called control group, is formed by 10 patient randomly selected among the remaining population.

The prototypal tumor tracking method that we developed processes the external signals using three distinct neural networks, one for each external marker, implemented in C/C++. In this way, three independent estimations of the internal target position are calculated and then averaged to obtain a unique output.

We selected a feed-forward double-layer architecture, featuring 3 inputs, a hidden layer of 10 units and an output layer of 3 units. Hyperbolic tangent transfer function is applied to both the hidden and the output layer.

Neural networks' training is performed with a back-propagation algorithm based on gradient descent (learning rate set to 0.07) and featuring the following termination criteria:

- 100 maximum iterations
- Root mean square error (between simulated output and ground truth tumor position) < 0.01 mm

Both the ANNs architecture and the training termination criteria were selected in order to achieve a compromise between tracking accuracy and computational time, but also to avoid overfitting, which may result in poor performance when simulating data that are not included in the training set. The flowchart of the proposed tumor tracking algorithm is shown in Fig. 1.

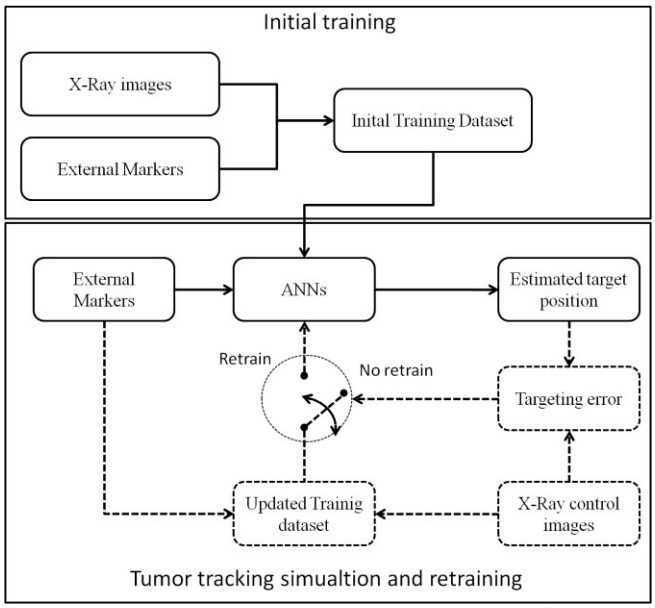

Fig. 1. Flowchart of the proposed tracking algorithm. Dotted lines refer to the retrain procedure.

The first stage of the developed algorithm consists of the following preliminary steps:

1) Data loading: all the samples of the internal and external signals stored in the log files are loaded into two distinct variables.
2) Initial training set collection: images used by Synchrony to build the correlation model are identified using their status index. Then, thanks to the common temporal basis, the simultaneous position of the three external markers is determined for each image. However, since the number of available samples for the internal signal is limited by the constraints due to imaging dose, the algorithm includes spline interpolation at this stage in order to obtain a training dataset containing 500 distinct examples.
3) Initial ANNs training: once the training dataset is collected, each network is trained according to the previously described method.

As this first stage is completed, the algorithm proceeds with a second stage, whose objective is to simulate tumor tracking. Its main steps are now described:

4) Internal signal estimation: the external signals are given as input, sample by sample and starting from the first one available, to the trained ANNs. In this way, for each of these samples, the corresponding internal target position is estimated.

5) Tracking error calculation: for every sample of the external signals, the algorithm checks if a control image is available at the same time point. When it is available, the ground truth tumor position is known, so it is possible to calculate the targeting error. For this purpose, the following figure E_i is computed for each network:

$$\boldsymbol{S_i} = [S_{x,i}\ S_{y,i}\ S_{z,i}];\ \boldsymbol{P} = [P_x\ P_y\ P_z];\ \forall\, i = 1\ldots3$$

$$E_i = max\left(|S_{x,i} - P_x|, |S_{y,i} - P_y|, |S_{z,i} - P_z|\right)$$

where $\boldsymbol{S}_i$ is the target position estimated by the i-th network and $\boldsymbol{P}$ is the ground truth target position.
Then, the training set is update with a *first in first out* approach, i.e. by including the most recent input/output data and discarding the oldest one.

6) Neural networks retraining: the figure E_i is used to determine if the ANNs have to be retrained or not. We defined two threshold values (α and β) both expressed in millimetres and referred to as *retrain* and *rebuild* threshold, respectively. The values of these thresholds are user-defined but β is intended to be larger than (or equal to) α: we set α = 1 mm and β = 2 mm in our implementation.
According to the value of E_i, the algorithm proceeds as follows:
   - If $E_i \leq \alpha$, the i-th network is not retrained.
   - If $\alpha < E_i \leq \beta$, the i-th network is retrained starting from current inter-synaptic weights.
   - If $E_i > \beta$, then the i-th network is retrained starting from randomly initialized inter-synaptic weights. In these cases, a significant variation in the internal/external correspondence model is expected due to the large measured tumor tracking errors. Hence current inter-synaptic weights are discarded in order to have a quicker adaptation to the new condition.

At the end of the simulation, all the estimated target positions are recorded in a log file that is exported in MatLab (The MathWorks Inc., Natick, MA) for offline analysis.

III. Results

We quantified the performance of the ANN-based tumor tracking algorithm by calculating, for each control image, the 3D targeting error (TE), which is the distance between the estimate and the ground truth target position. Overall median value, interquartile range and 95th percentile were calculated for both the control and worst group and are reported in Table I.
Cumulative probability distribution functions (PDFs) are reported in Fig. 2.

TABLE I
3D TARGETING ERRORS STATISTICAL PARAMETERS

Group	Parameters	ANNs	Synchrony
Control	Median [mm]	0,98	1,27
	Interquartile range [mm]	1,29	1,39
	95th percentile [mm]	3,72	4,22
Worst	Median [mm]	3,58	4,28
	Interquartile range [mm]	4,81	5,94
	95th percentile [mm]	14,37	21,27

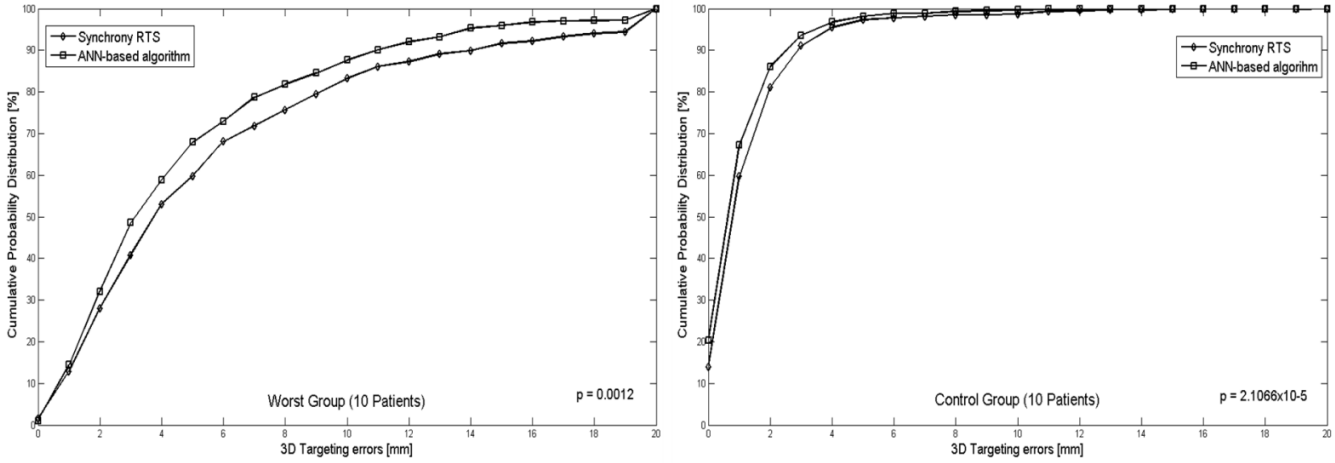

Fig. 2. Cumulative PDFs of 3DTEs for worst (left panel) and control (right panel) groups.

Finally, non parametric statistical analysis (Wilcoxon rank sum test) was applied, obtaining *p-values* of 2.1066×10^{-5} for the control group and 0.0012 for the worst group.

IV. Discussion

The results that we presented show a statistically significant tracking error reduction for the proposed ANNs-based method with respect to the Synchrony RTS, proving the potential value of the developed algorithm. With respect to the work presented by Murphy *et al.* [15], our results are obtained on signal relative to the entire duration of the considered CyberKnife treatments, that is between 27 and 118 minutes in the 20 selected cases. In addition, the proposed algorithm estimates the target position in 3D. However, we do not include either signal preprocessing or temporal prediction, since the goal of this study was to test the ability of the ANNs to accurately correlate the internal target position to external surrogate signals, using the performance of the Synchrony system as a benchmark.

We chose to implement three parallel neural networks instead of a single one with 9 inputs (3 coordinates for each marker). This approach replicates what is implemented in the Synchrony RTS, featuring an independent polynomial model for each of the external markers [8]. This strategy also gives more flexibility to the retraining procedure, since each network can be treated independently from the others, thus providing a way to parallelize the retraining process. Alternative solutions to the simple average of the 3 independent target position estimations are feasible and would potentially increase the method robustness. For example, independent estimation could be averaged using as weights the current tracking errors measured for each network.

We have to point out that our results are limited only to time points where a control image is acquired. In the 20 selected patients, the average control imaging interval is 66.3 seconds. Therefore, tracking errors for both the developed algorithm and the Synchrony RTS can be calculated only at very low frequency. For this reason the proposed method requires further validation on data where the ground truth tumor position is available at higher frequency. In order to meet this requirement, we are currently developing a moving phantom for respiratory motion simulation. This device will be composed by two main components: the first one will simulate the external body surface motion whereas the second moving element will reproduce internal tumor motion. By placing markers on both this components and tracking their motion with an optical localization system, we will be able to estimate the tumor position with the developed algorithm and, at the same time, to compare each prediction with the simultaneous actual target position, since it is optically localized in real-time. In this way, we will be able to calculate the tumor tracking at same frequency of the external signals.

The neural networks' architecture, although it was selected to achieve a compromise between tracking accuracy and computational time, it is not the result of a specific optimization study. In order to implement a patient-specific optimization, it would be necessary to identify the best architecture before irradiation, thus relying only on the imaging data point used by Synchrony to build the model. However, considering the CyberKnife treatments duration, which is (on average on the 20 patients) approximately 72 minutes, the architecture that provides the lowest tracking errors at the beginning of the session may be inadequate later on, due to modifications occurred in internal/external correspondence model.

In conclusion, the study that we presented confirms the need for complex strategies in the implementation of models for tumor tracking. Moreover, even if the proposed method needs further optimization and validation, it has been shown that artificial neural networks can be considered a valuable instrument in developing tumor tracking methods.

V. References

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