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Performance enhancement in respiratory tumor motion prediction

호흡에 의한 종양 움직임 예측을 위한 알고리즘 개선

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최 승 욱

A thesis of the Degree of Doctor of Philosophy

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Performance enhancement in respiratory tumor motion prediction

by

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A thesis submitted to the Department of Medicine in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in Medical Science (Radiation Applied Life Science) at Seoul National University College of Medicine

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Abstract

Introduction

The breathing motion moves internal organs and targeted regions determined by radiation therapy planning. For the radiation therapy, accurate prediction for breathing motion is of great interest as the outer targeted region treatment could endanger sensitive tissue. In this study, a prediction algorithm with adaptive support vector regression (aSVR) was proposed and compared with the adaptive neural network (ANN) algorithm considering the prediction accuracy and the computational costs of training and predicting.

Methods

Respiration data from 87 patients treated by radiation therapy, were acquired with an optical marker at 30 Hz. Five types of prediction filters with the ANN or aSVR filters, were implemented and their performance was compared according to the size of the sliding window (2.5 and 5.0 sec), and the prediction latencies (100, 200, 300, 400, and 500 msec). Training and testing of the prediction algorithms with aSVR and ANN were performed. The root mean square error (RMSE) was used as the accuracy metric.

Results

The aSVR with a radial basis function (RBF) kernel outperformed other prediction filters, including not only various types of ANN filters but also the aSVR with a linear kernel. A sliding window of 2.5 sec significantly and independently enhanced the overall accuracy. Otherwise, the training and prediction testing times were significantly prolonged in case of aSVR with an RBF kernel.

Conclusions

The aSVR filter with the RBF kernel is in all cases superior to other filters regarding its accuracy; it also shows clinically applicable results from the viewpoint of training and predicting time, which may be effective for predicting patient breathing motion and thus enhancing the efficacy of radiation therapy.

Key words: respiratory motion, breathing prediction, real-time tracking, adaptive neural network, adaptive support vector regression

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Introduction

Patient breathing motion can move internal organs and the targeted region determined by radiotherapy treatment planning based on patient-specific CT images. Radiation therapy planning with the assumption of a fixed position for internal organs and targeted regions, could, therefore, harm surrounding, sensitive, and normal tissues. It is also not efficient to perform radiation therapy only when the targeted region comes into the pre-determined safety zone, which has been the commonly used strategy of conventional radiation therapy. Consequently, for more efficient radiation therapy, patient breathing motion needs to be accurately predictable. In addition, predicting patient breathing motion is becoming more and more important for robotic radiation therapy, such as CyberKnifeTM (Accuray Inc., Sunnyvale, CA, USA), which can track the targeted region using a robot arm, intelligent estimation and planning software.

To date there have been many studies investigating prediction algorithms of patient breathing motion. Although most patients' breathing motion appears to be regular, it is, in fact, inherently very complex and irregular (1). Adaptive neural network (ANN) is well-known to precisely predict regular patterns, although it is limited in its application to irregular breathing patterns. Shirato *et al.* used an extrapolation method for respiration prediction (2). Murphy *et al.* applied an adaptive linear filter to predict the position of tumors (3). Sharp *et al.* compared the performances of linear filters, the Kalman filter, and ANN, and found that ANN was the best (4). They also showed that outlier detection can improve the prediction accuracy. Issaksson *et al.* found that the ANN filter outperformed the adaptive linear filter for predicting the position of lung tumors (5). Ren *et al.* proposed a new prediction algorithm based on an auto-regression moving average method (6). Murphy and Dieterich showed that a nonlinear neural network filter outperformed a linear neural network filter in predicting respiration (7). Murphy and Pokhrel also optimized the parameters for nonlinear neural network filters (8).

Support vector regression (SVR) was proposed in 1996 by Vapnik *et al*. (9) Since the cost function for producing the support vector machine (SVM) model does not consider training points that exist beyond the support vector margin, the model relies only on a subset of the training data, which means that the cost function for building the model ignores any training data close to the model prediction within a threshold (10). The idea of SVR is based on the computation of a linear regression function in a high-dimensional feature space where the input data are mapped via a nonlinear function to minimize the generalization error bound so as to accomplish generalized performance (9). SVR has been applied in various fields including time series and financial (noisy and risky) prediction, approximation of complex engineering analyses, convex quadratic programming, choices of loss functions, etc. (11-13)

In radiation therapy, there is slight time latency between the prediction of motion and the actual radiation exposure. Shirato *et al.* reported 0.09-sec latency between the recognition of markers and radiation exposure (2).

Therefore, considering time latency is very important for accurately predicting patient breathing motion. Recently SVR was introduced to predict respiratory tumor motions (14, 15). Riaz *et al.* compared SVR and adaptive filters and found that SVR more accurately predicts the future tumor position in the methods studied than adaptive filters (14). Krauss *et al.* compared the performance of respiratory motion prediction based on linear regression, neural networks (NN), kernel density estimation, and SVR. The small differences between the predictors emphasized the relative importance of adequate model parameter optimization compared to the actual prediction model selection (15).

Cauwenberghs and Poggio proposed incremental and decremental support vector machine learning (16), and Ma *et al.* developed accurate online SVR (AOSVR) and proved that AOSVR was faster than batch SVR (17). Parrella also developed OnlineSVR, an implementation of adaptive SVR, and compared it with LibSVM which was one of the most frequently used SVM algorithms (18, 19). Ernst *et al.* reported that OnlineSVR was a feasible tool for predicting human breathing and that it outperformed both the MULIN prediction methods and Wavelet-based multi scale auto regression (20-22). Also they noticed that the drawback of OnlineSVR was its slow prediction speed.

In this study, to evaluate optimal configuration of prediction algorithm of patient breathing motion, prediction algorithms with various parameters are proposed and compared. The organization of the manuscript is as follows:

overall methods including ANN and aSVR algorithms are described in the Materials and Methods section; prediction results using 87 actual patients' data are presented in the Results section; and, finally, the significance of this study and future anticipated research are provided in the Discussion and Conclusions sections.

Methods

Respiration data acquisition

Respiratory motion data were retrospectively acquired from 87 patients who were scanned using 4-dimensional CT protocols for radiation therapy in the Department of Radiation Therapy of Asan Medical Center. Respiration data were acquired in 30Hz using the RPM System (Real Time Position Management System, Varian Medical Systems, Palo Alto, CA, USA), which is composed of an infrared emitter, optical markers placed on the patient's abdomen to reflect the infrared light, and a camera system used to detect the reflected light. Acquired data were down-sampled to 10 Hz for faster processing (7). Because the average period of human breathing ranges from 2 to 5 sec, down-sampling to 10 Hz does not cause any problem.

We did not specify any breathing rules or regulations to the patients and had them breathe freely. Signals derived from measuring the position of optical markers were considered to be a record of the patient's breathing. These breathing data ranged in length from 3.6 to 8 min.

Prediction algorithms for respiratory motion

Five types of prediction filters, i.e. three different types of ANN and two different types of SVR, were implemented and compared for predicting respiration. Two-layered nonlinear ANNs (7) were implemented as a feed-forward network with a nonlinear activation function g as in (1):

$$P(t+\tau)=g\left(\sum_{k=1}^{M} w_{kj}^{2} g\left(\sum_{i=1}^{N} w_{ji}^{2} S(t-i)+w_{j0}^{2}\right)+w_{kj}^{2}\right) \tag{1}$$

where $P(\mathrm{t} + \tau)$ and $S(t - i)$ are the predicted respiration signals at time $t + \tau$ and the actual respiration signals at time $t - i$, which are the given the inputs, respectively. Also, N is the number of previous samples used for modeling, M is the number of input neurons, w_{ij} is a weight multiplied between node i and node j, and g is the activation function. The outputs of the input neurons were transferred to the output neuron through the activation function in a form of a tangential sigmoid function in this study. In actual implementation, three nonlinear ANNs were implemented: one with a two-layer feed-forward network with two input neurons (M=2) and another with a two-layer feed-forward network with four input neurons (M=4) in (1). The other nonlinear ANN was a three-layer feed-forward network with four input neurons and two intermediate neurons, where another summation should be included in (1). The two-layer feed-forward network is known to be sufficient to model virtually any kind of input-output relationship (23). However, the three-layer feed-forward network was also prepared for performance comparison.

In case of SVR, one with a linear kernel and the other with a radial basis function (RBF) kernel were implemented as in (2) [18]:

$$P(t)=\sum_{k=1}^{N} \theta_k \phi\left(t, S(t-i)\right)+b \tag{2}$$

where θ_k and b are regression parameters for the k-th input

(k=1,2,…,N) and ϕ is a kernel function for SVR, which is either a linear function or an RBF. The two SVR models and the three nonlinear neural network models used for respiration prediction filters are summarized in Table 1.

Table 1. Prediction algorithm prepared and compared in this study

Classifier Type	Filter	Description
ANN	ANN-22	Two-layer feed-forward ANN with two input neurons
	ANN-24	Two-layer feed-forward ANN with four input neurons
	ANN-34	Three-layer feed-forward ANN with four input neurons and two intermediate neurons
aSVR	aSVR-Linear	aSVR (Online SVR) with linear kernel
	aSVR-RBF	aSVR (Online SVR) with RBF kernel

The neural network toolbox included in MATLAB software (MathWorks Inc., Natick, MA, USA) was utilized for the implementation of ANN filters. OnlineSVR (18), an implementation of adaptive SVR, was adopted for aSVR filters. However, the MATLAB version of OnlineSVR was so slow that it was not used for this study. Instead, MATLAB interface was implemented to its C++ version. At first, LibSVM (19), another implementation of SVR, was also considered. However, as LibSVM did not provide an adaptive training feature, it was not used for this study. The overall procedure for our prediction filters was composed of training, choosing the best-trained filter, and prediction testing.

Preparing respiration data

In general, human breathing is inherently irregular. Figure 1 shows the typical respiratory motion patterns from patients with regular, relatively regular, irregular, and complex breathing.

Figure 1. Some examples of respiration signals

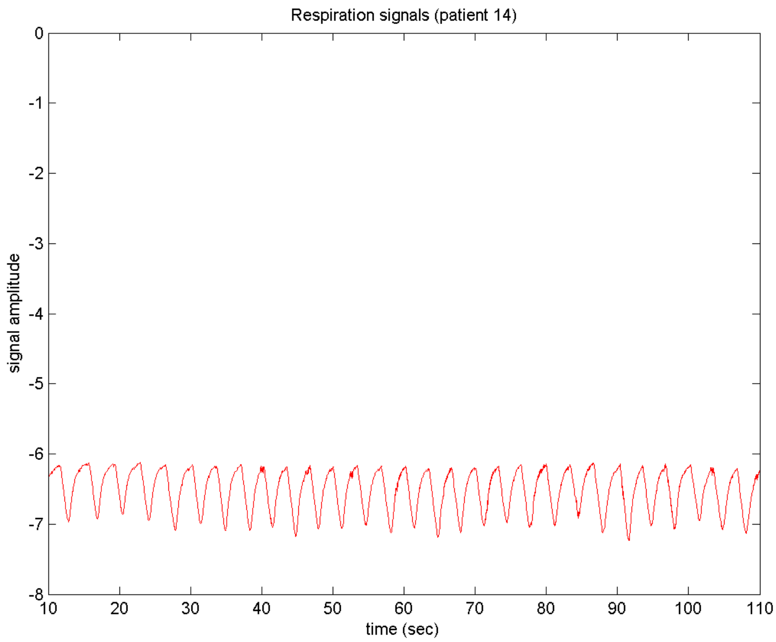

Figure 1 (a). An example of respiration signals for regular breathing

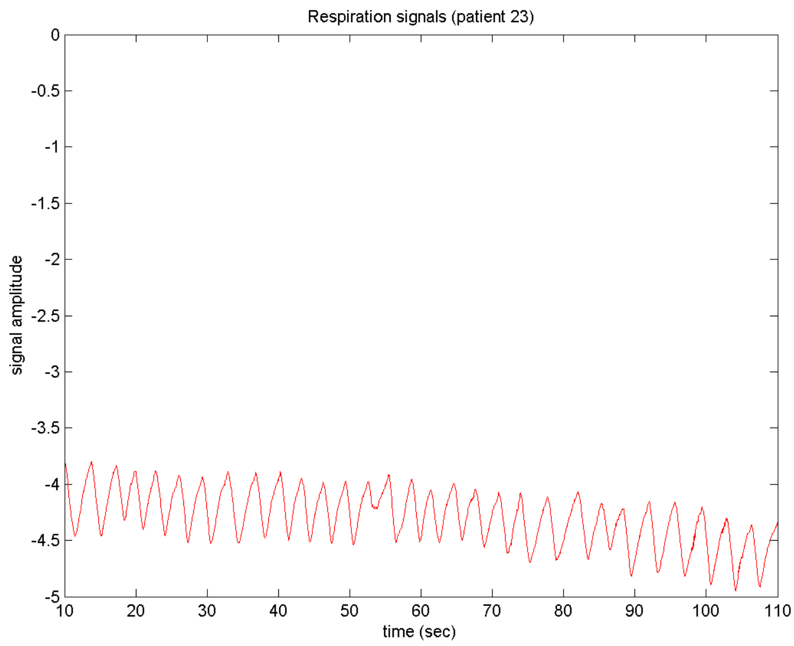

Figure 1 (b). An example of respiration signals for relatively regular breathing

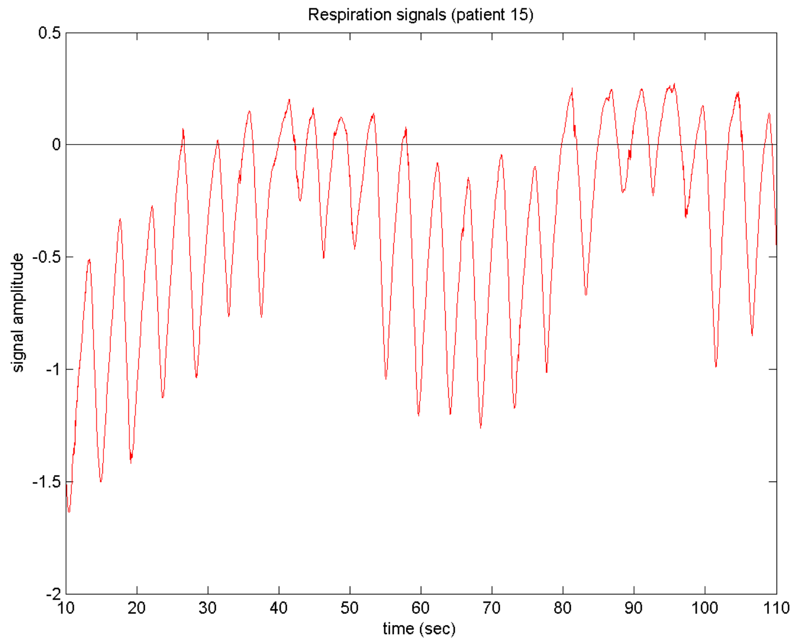

Figure 1 (c). An example of respiration signals for irregular breathing

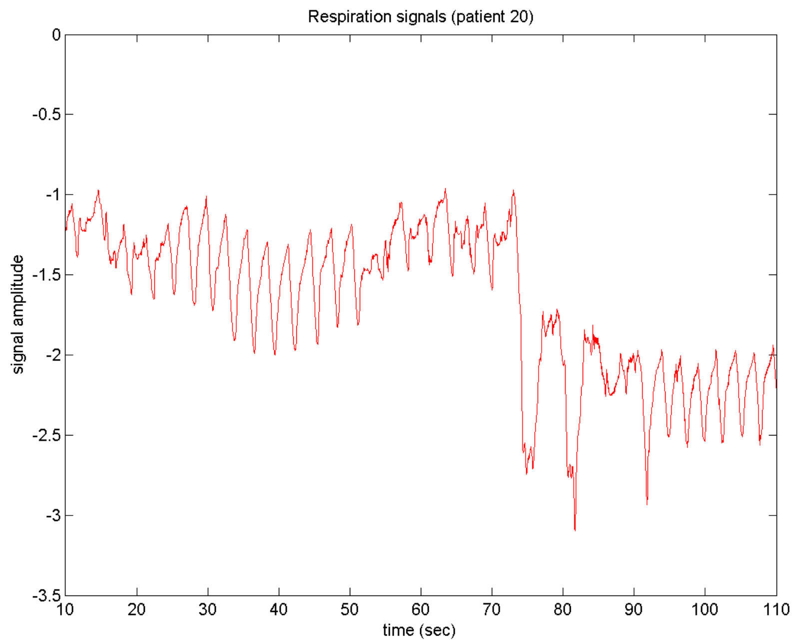

Figure 1 (d). An example of respiration signals for complex breathing

Training

Prediction filters for estimating respiratory motion should be trained with a given prediction latency τ. The first 30 sec of each patient's breathing data was used as the training data set. As for the number of training samples, two cases were considered: one with a sliding window of 2.5 sec and the other with that of 5.0 sec. For each of the two sliding windows in training, the same sliding window scheme is applied to the corresponding testing. In case of a sliding window of 2.5 sec, 25 samples were used for training because 25 samples in 10 Hz correspond to the amount of breathing in 2.5 sec. Likewise, 50 samples were required for sliding windows of 5.0 sec. The prediction filters were trained to predict the respiratory motion in the given latency τ using the sliding window of 25 and 50 signal samples from 300 breathing signal samples (30 sec * 10Hz), respectively. Therefore, in order to predict the respiration at time t, the prediction filters were trained with 25 and 50 samples prior to time $t - \tau$, respectively. The total number of trainings was 275 (300 samples – 25 samples) for a sliding window of 2.5 sec and 250 (300 samples – 50 samples) times for sliding windows of 5.0 sec. The same data set was used for training ANNs and aSVRs. Back-propagation ANNs were used to optimize the weight parameters of the neural network and make them adaptive for each patient's respiration signals. The parameters of aSVR were optimized using a brute force grid search algorithm (24).

Choosing the best prediction filters

During training of the ANN filters, weight parameters of neural networks were optimized for each patient's breathing pattern. In nonlinear neural networks, weights of connections should be randomized in order for neurons to operate independently. Therefore, whenever an ANN filter was trained, the performance of the ANN filter would be different. In order to choose the best-trained neural network, ten neural networks were trained, among which the best neural network was selected according to the prediction performance. In the case of aSVR filters, a brute-force grid search algorithm was used to choose the best prediction filters. The best aSVR filter with a linear kernel was selected after training and evaluating 25 filters with the cost parameters of 1, 3, 5, 7, and 9, and gamma parameters of 2^{-1}, 2^{-3}, 2^{-5}, 2^{-7}, and 2^{-9}. In the same manner, the best aSVR filter with RBF kernel was chosen with cost values of 2^1, 2^3, 2^5, 2^7, and 2^9 and with the same gamma values listed above. Although stabilized learning, an option in OnlineSVR, could generate more accurate results, it was disabled in this study for faster training. To evaluate the performance of ANNs and aSVRs, the next 30 sec of each patient's breathing signal data (from 30 to 60 sec) were used.

Prediction testing

To test the respiration signal after latency τ at the time of t in the ANN filter, 25 and 50 (N=25 or 50) previous sequential samples obtained prior to the time of t, were used. The predicted value $P(\mathrm{t} + \tau)$ was estimated by the filters. After evaluating the actual respiration signal, $S(\mathrm{t} + \tau)$ in the latency τ, the difference between the predicted value and the actual value were compared and the weights of the prediction filters were adjusted for adaptation of the filter.

During prediction, testing and choosing the best prediction filter, ANN and aSVR were continuously retrained in accordance with the predicted and actual values. In order to implement the adaptive training for ANN, train() and adapt() functions in MATLAB Neural Network Toolbox were used (23) while adaptive training in aSVR was implemented with user-defined functions in (18).

For each patient's data, 50 totally different combinations of conditions, i.e.

five types of prediction filters, two sliding window sizes (2.5 and 5.0 sec), and five prediction latencies, were applied. In every experiment, the accuracy, training time, and testing time were measured. The accuracy and predicting time were measured from the selected best prediction filter (10 ANNs and 25 aSVRs models were trained and evaluated). The training time was the mean time in all of the corresponding trainings.

All the training and prediction testing were performed using MATLAB software (version 2010a) on Microsoft Windows 7. MATLAB interface for C++ version of OnlineSVR was developed using Microsoft Visual Studio 2010.

Accuracy metrics and statistics

In this study, RMSE was used as an accuracy measurement method to compare the performance of the prediction algorithms:

$$\mathrm{RMSE} = \sqrt{\frac{\sum_i (D_i - P_i)^2}{n}} \tag{3}$$

where D_i is the ith observation, P_i is the prediction of the ith observation, and n is the number of observations.

RMSE measures the error between the predicted and actual observations. ANOVA and the Tukey post-hoc test were performed to compare the overall performance of each filter in all latencies with an alpha level of 0.05. Statistical analyses were performed in this study using SPSS® Statistics 20 (IBM Corp., Armonk, NY, USA).

Results

Accuracy

A total of 4,350 runs (87 patients * 50 combinations of three factors) were performed. Figure 2 illustrates examples comparing the actual and predicted signals from each prediction filter for various breathing patterns. Figure 3 is a bar chart used for comparing the mean RMSE at a latency of 100 msec.

Figure 2. Prediction accuracy of ANN-24 and aSVR-RBF filters in typical respiration motion (latency = 100 msec, sliding window = 2.5 sec)

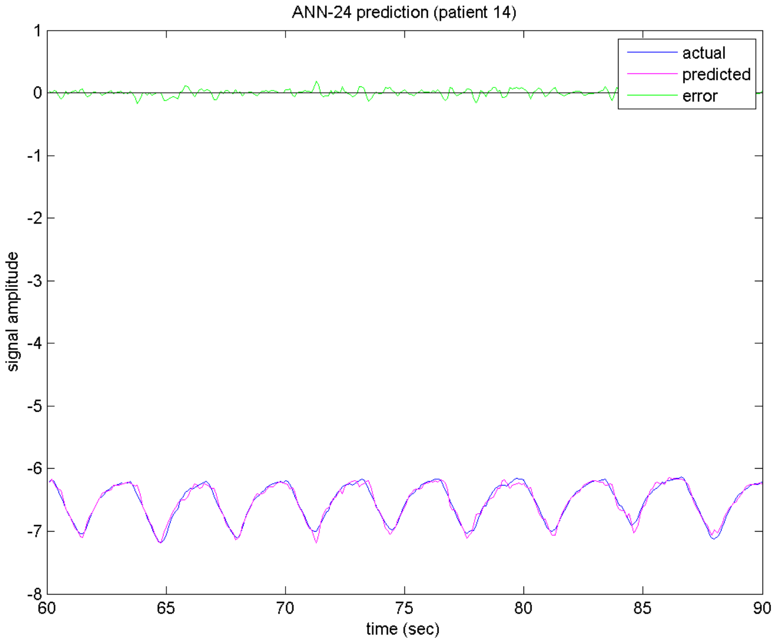

Figure 2 (a). Prediction accuracy of ANN-24 in regular breathing

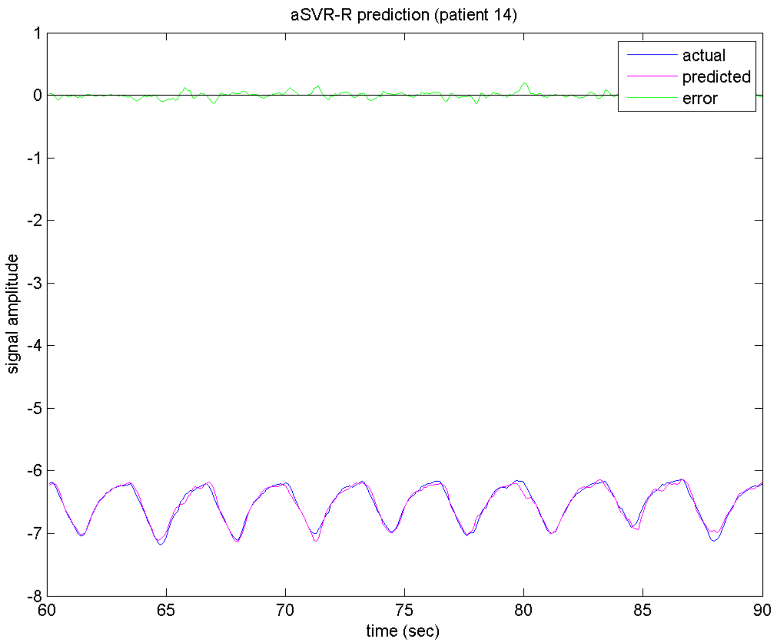

Figure 2 (b). Prediction accuracy of aSVR-RBF in regular breathing

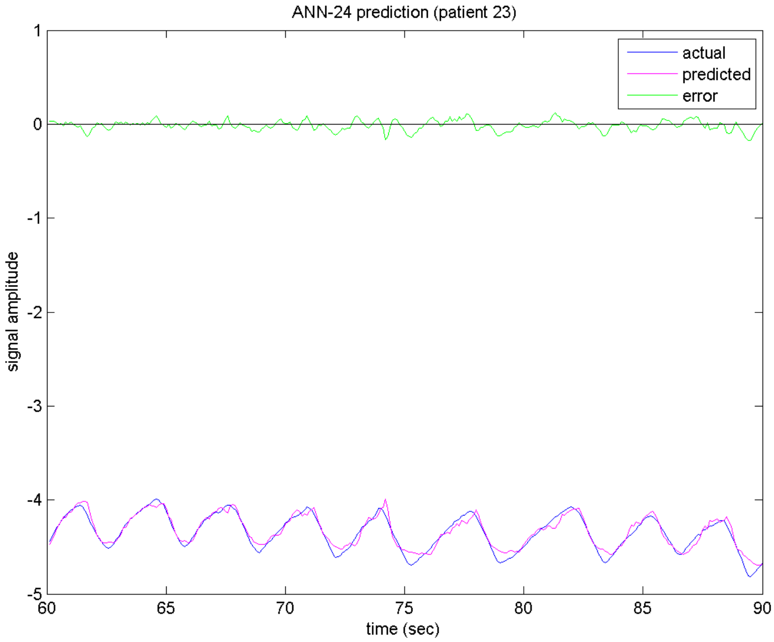

Figure 2 (c). Prediction accuracy of ANN-24 in relatively regular breathing

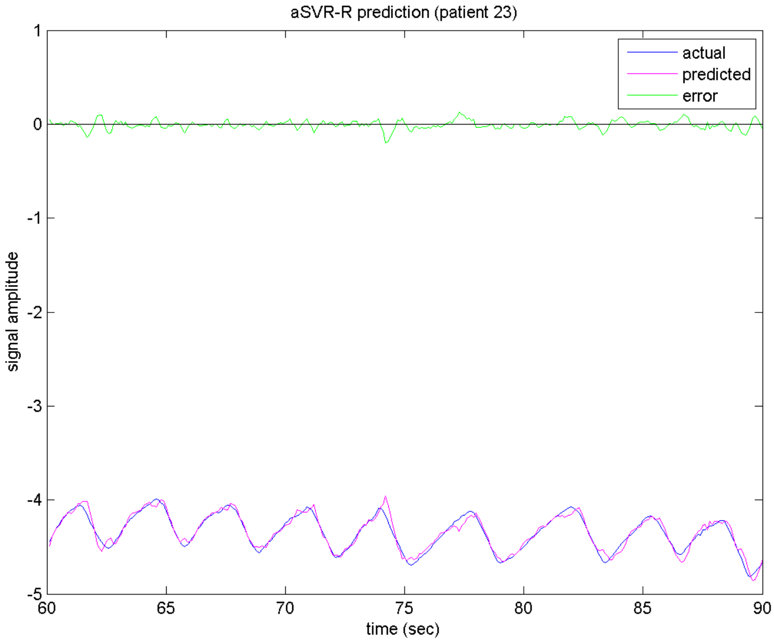

Figure 2 (d). Prediction accuracy of aSVR-RBF in relatively regular breathing

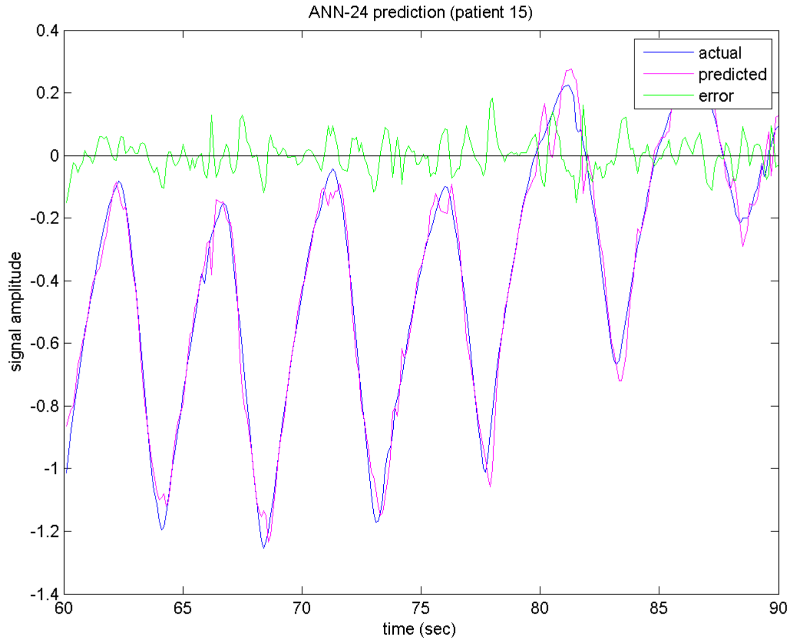

Figure 2 (e). Prediction accuracy of ANN-24 in irregular breathing

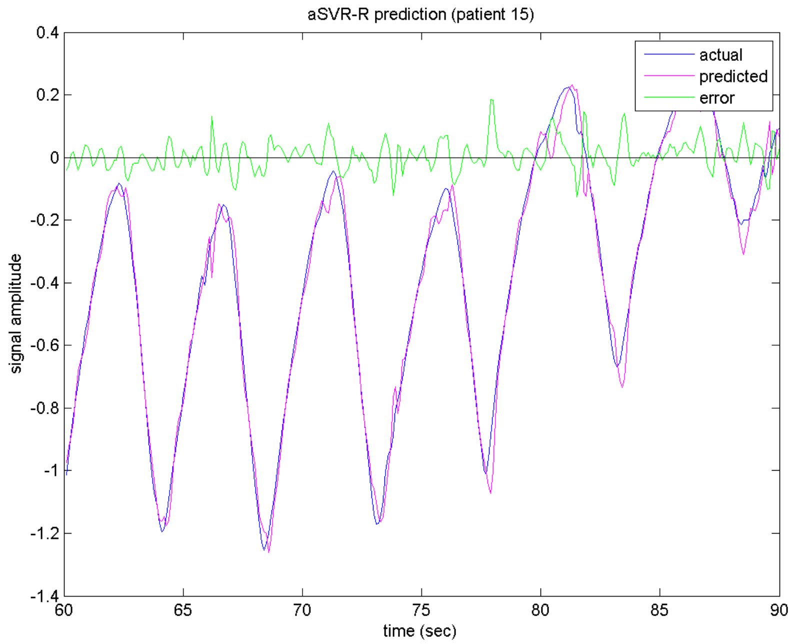

Figure 2 (f). Prediction accuracy of aSVR-RBF in irregular breathing

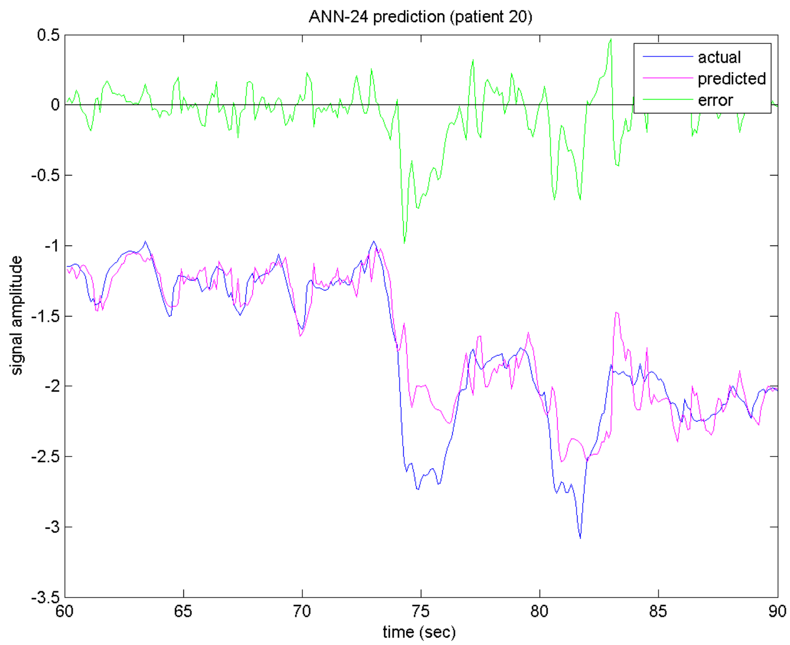

Figure 2 (g). Prediction accuracy of ANN-24 in complex breathing

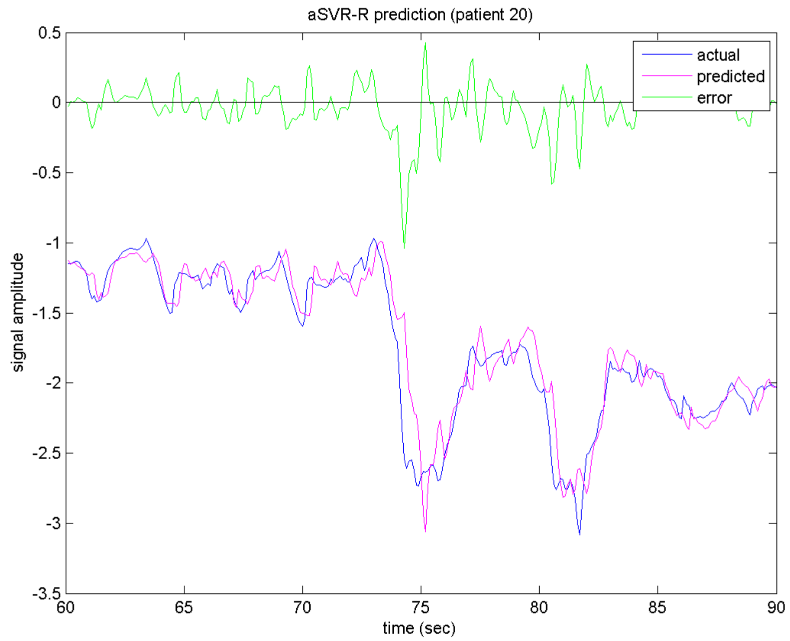

Figure 2 (h). Prediction accuracy of aSVR-RBF in complex breathing

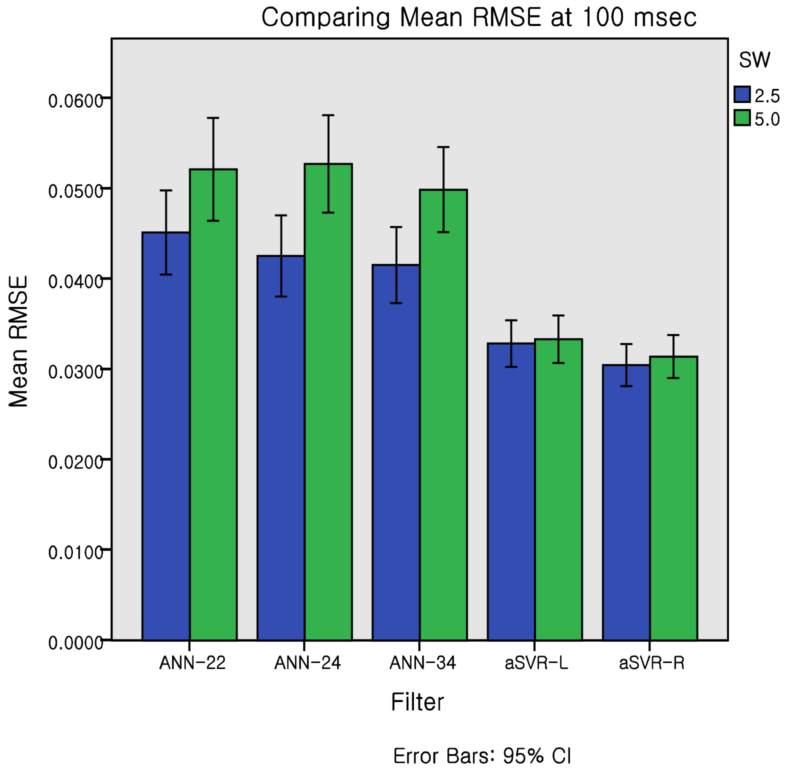

Figure 3. Mean RMSE at latency 100 msec

Table 2 summarizes the ANOVA test result for accuracy showing the factor effects; it also shows all of the single factors–latency, sliding window, and filter type which affected the accuracy. Tables 3 and 4 show the post-hoc test results for latencies and filter types, respectively. Accuracy at latency 100 msec was significantly the best, followed by those at 200, 300, 400, and 500 msec, sequentially. Regarding the type of prediction filter, aSVR with an RBF kernel significantly showed the best accuracy, and aSVR with a linear kernel was the next best. Both aSVR filters were significantly more accurate than all of the ANN filters, although the differences among the ANN filters were not significant. In addition, predictions at a sliding window with 2.5 sec were significantly more accurate than those with 5.0 sec.

Table 2. Factor effects regarding the accuracy, i.e. latency, sliding window, and filter type

Factor	Level	*p*-value	RMSE comparison
Latency (in msec)	100, 200, 300, 400, 500	0.000*	100 <† 200 <† 300 <† 400 <† 500
Sliding window (in sec)	2.5, 5.0	0.000*	2.5 <‡ 5.0
Filter	ANN-22, ANN-24, ANN-34, aSVR-Linear, aSVR-RBF	0.000*	aSVR-RBF <† aSVR-Linear <† ANN-22, ANN-34, ANN-24
Sliding window · Filter		0.000*	
All other factor combinations		> 0.05	

*The difference is significant (ANOVA).
†The difference is significant (Tukey method).
‡ The difference is significant (*t*-test).

Table 3. Post-hoc test on the accuracy for latencies

Latency	Mean RMSE in homogeneous subset				
	1	2	3	4	5
100	.041233				
200		.067603			
300			.094536		
400				.121326	
500					.146593
p-value	1.000	1.000	1.000	1.000	1.000

Table 4. Post-hoc test on the accuracy for filter types

Filter	Mean RMSE in homogeneous subset		
	1	2	3
aSVR-RBF	.078786		
aSVR-Linear		.089854	
ANN-22			.100310
ANN-34			.101087
ANN-24			.101254
p-value	1.000	1.000	.991

Supplemental Table 1 shows the accuracy in each condition and compares the different types of prediction filters (paired *t*-test). Supplemental Tables 2 shows the effect of window size in each condition, respectively (paired *t*-test). In almost all cases, a sliding window with 2.5 sec provided significantly better results.

Training and predicting time

Table 5 shows the ANOVA test result for training times. Almost all other factors affected the training times. Tables 6 and 7 show the post-hoc test results for latencies and filter types, respectively. The training times at latencies 100 and 500 were significantly faster than those at latencies 300 and 200. In addition, the training times of aSVR filters were significantly slower than those of ANN filters. The aSVR filter with an RBF kernel required a longer training time than the others. Supplemental Table 3 lists the training times for each condition.

Table 5. Factor effects regarding the training time, i.e. latency, sliding window, and filter type

Factor	Level	*p*-value	Training time comparison
Latency (in msec)	100, 200, 300, 400, 500	0.000	100 <† 400, 500, 300, 200
Sliding window (in sec)	2.5, 5.0	0.000	
Filter	ANN-22, ANN-24, ANN-34, aSVR-Linear, aSVR-RBF	0.000	ANN-22, ANN-24 <† ANN-34 <† aSVR-Linear <† aSVR-RBF
Latency · Sliding window		0.801*	
Latency · Sliding window · Filter		0.396*	
All other factor combinations		< 0.05	

*The difference is not statistically significant (ANOVA).

†The difference is significant (Tukey method).

Table 6. Post-hoc test on the training time for latencies

Latency	Mean training time in homogeneous subset		
	1	2	3
100	.791226		
400		.825821	
500		.832799	
300		.837419	.837419
200			.868350
p-value	1.000	.857	.060

Table 7. Post-hoc test on the training time for filter types

Filter	Mean training time in homogeneous subset			
	1	2	3	4
ANN-22	.395273			
ANN-24	.397582			
ANN-34		.486107		
aSVR-Linear			1.243330	
aSVR-RBF				1.633323
p-value	1.000	1.000	1.000	1.000

In the same manner, Table 8 summarizes the ANOVA test result for predicting times. Tables 9 and 10 show the post-hoc results for latencies and filter types, respectively. Sliding window did not affect the predicting time in most cases. The predicting time at a latency of 100 msec was significantly faster, although no significance was seen among those at other latencies. Similar to training times, an aSVR filter with an RBF kernel was significantly slower than other filters. Supplemental Table 4 shows the predicting times in each condition.

Table 8. Factor effects on the predicting time, i.e. latency, sliding window, and filter type

Factor	Level	*p*-value	Predicting time comparison
Latency (in msec)	100, 200, 300, 400, 500	0.000	100 <† 400, 300, 200, 500
Sliding window (in sec)	2.5, 5.0	0.146	
Filter	ANN-22, ANN-24, ANN-34, aSVR-Linear,	0.000	ANN-24, ANN-22 <† ANN-34 <† aSVR-Linear <† aSVR-RBF

aSVR-RBF	
Latency · Sliding window	0.580*
Latency · Sliding Window · Filter	0.181*
All other factor combinations	< 0.05

*The difference is not statistically significant (ANOVA).
†The difference is significant (Tukey method).

Table 9. Post-hoc test on the predicting time for latencies

Latency	Mean predicting time in homogeneous subset	
	1	2
100	.016099	
400		.018227
300		.018448
200		.018469
500		.018921
p-value	1.000	.268

Table 10. Post-hoc test on the predicting time for filter types

Filter	Mean predicting time in homogeneous subset			
	1	2	3	4
ANN-24	.014670			
ANN-22	.014819			
ANN-34		.016321		
aSVR-Linear			.019999	
aSVR-RBF				.024354
p-value	.993	1.000	1.000	1.000

Discussion

Considering the various classifiers and factors, five types of clinically applicable prediction filters were implemented and tested with 87 real human patients' breathing motion data. The accuracies, training times, and predicting times were evaluated, their statistical meaning was analyzed, and the best classifier and factor combination was determined. The aSVR filters showed better prediction performance in respiratory tumor motion than ANNs. In particular, the aSVR filter with the RBF kernel (aSVR-RBF) significantly outperformed any other prediction filter, including the aSVR filter with a linear kernel (aSVR-Linear). In addition, aSVR-RBF including sliding window with 2.5 sec significantly enhanced the accuracy in most cases.

Although the complexity of aSVRs using OnlineSVR was high, as Ernst *et al.* commented (21), the required times for prediction (approximately 19 to 27 msec) are relatively not too slow compared with those for other filters used in this study. Without using the stabilized learning, the aSVR filter outperforms other filters with the prediction latencies (100 to 500 msec), which indicates that the aSVR-RBF filter is efficient enough for practical usage in clinical applications. However, in cases of the stabilized learning used to optimize the internal parameters of OnlineSVR, the training was too slow, i.e. in some cases it took approximately 10 min.

Krauss *et al.* reported that ANN shows slightly better performance than SVR (15), and argued that model parameter tuning might be essential for fair predictor comparisons. However, unlike Krauss's report, in this study, the aSVR filter with the RBF kernel outperformed ANN filters with various configurations. This would be caused by the adaptiveness of OnlineSVR, which was described in Section Methods, resulting in a more adequate prediction model.

Previous studies used the root mean square error (RMSE) (14, 15, 21, 22) or the normalized RMSE (nRMSE) (5, 7, 8) as the accuracy metric. However, the use of nRMSE as the accuracy metric is questionable as it creates a bias toward errors that occur at signals with small magnitudes. In other words, predictions with errors evenly distributed throughout the entire signals are likely to get higher nRMSE than predictions with errors concentrated around peaks of breathing waves, given the same RMSE. The latter is of more concern in tumor tracking for radiotherapy purposes.

There are several limitations to this study. As the length of the breathing data used for this study was relatively short, more and longer data sets will be required in order to more precisely evaluate the algorithms. However, previous studies used the breathing data of only a small number of patients, i.e. 12 (15) or 14 (14), or they used computer-generated breathing data (21). In general, it is well known that breathing patterns are very different substantially between patients (1), which means that the change of breathing patterns by patients could be higher than that of the breathing pattern by time. Therefore, in this study, we used 87 actual patients' data, which would lead to more practical results. Another limitation of this study is the total length of training samples. The first 30 sec of breathing data was used for training. Nevertheless, we focused on an evaluation of the robustness of the prediction algorithm on various types of respiratory patterns.

In future studies, there should be several considerations. In this study, we did not take the difference of breathing patterns into account. If a specific prediction algorithm could be applied depending on respiratory patterns, a better result would be anticipated. In order to do so, a study on quantitatively categorizing human breathing patterns would be required. In addition, since regular breathing may have some outliers that do not follow the normal pattern, other research on detecting such outliers should be performed.

While the brute-force grid search method used in this study compared only 25 combinations, i.e. five cost and five gamma values, and chose the best aSVR filter among them, a more elaborate search algorithm is needed in order to improve performance. Furthermore, we may consider a respiratory simulated phantom study in order to evaluate the accuracy and efficiency of our algorithm.

Conclusions

The aSVR filter with the RBF kernel is in all cases superior in accuracy to the ANNs and the aSVR filter with the linear kernel, and it shows clinically applicable results from the viewpoint of training and predicting time, both of which may be effective for predicting patient breathing motion and enhancing the efficacy of radiation therapy.

References

1. Benchetrit G. Breathing pattern in humans: diversity and individuality. Respir Physiol. 2000;122(2-3):123-9.

2. Shirato H, Shimizu S, Kunieda T, et al. Physical aspects of a real-time tumor-tracking system for gated radiotherapy. Int J Radiat Oncol Biol Phys. 2000;48(4):1187-95.

3. Murphy M, Jalden J, Isaksson M. Adaptive filtering to predict lung tumor breathing motion during image-guided radiation therapy. Comput Assist Radiol Surg–CARS 2002. 2002:539-44.

4. Sharp GC, Jiang SB, Shimizu S, Shirato H. Prediction of respiratory tumour motion for real-time image-guided radiotherapy. Phys Med Biol. 2004;49(3):425-40.

5. Isaksson M, Jalden J, Murphy MJ. On using an adaptive neural network to predict lung tumor motion during respiration for radiotherapy applications. Med Phys. 2005;32(12):3801-9.

6. Ren Q, Nishioka S, Shirato H, Berbeco RI. Adaptive prediction of respiratory motion for motion compensation radiotherapy. Phys Med Biol. 2007;52(22):6651-61.

7. Murphy MJ, Dieterich S. Comparative performance of linear and nonlinear neural networks to predict irregular breathing. Phys Med Biol. 2006;51(22):5903-14.

8. Murphy MJ, Pokhrel D. Optimization of an adaptive neural network to predict breathing. Med Phys. 2009;36(1):40-7.

9. Smola A, Vapnik V. Support vector regression machines. Adv Neural Inf Process Syst. 1997;9:155-61.

10. Cortes C, Vapnik V. Support-Vector Networks. Mach Learn. 1995;20(3):273-97.

11. Vapnik V, Golowich SE, Smola A. Support vector method for function approximation, regression estimation, and signal processing. Adv Neural Inf Process Syst. 1996;9.

12. Schölkopf B, Bartlett P, Smola A, Williamson R. Support vector regression with automatic accuracy control. International Conference on Artificial Neural Networks (ICANN'98): Springer-Verlag, 1998; p. 111-6.

13. Burges CJC. A tutorial on Support Vector Machines for pattern recognition. Data Min Knowl Disc. 1998;2(2):121-67.

14. Riaz N, Shanker P, Wiersma R, et al. Predicting respiratory tumor motion with multi-dimensional adaptive filters and support vector regression. Phys Med Biol. 2009;54(19):5735-48.

15. Krauss A, Nill S, Oelfke U. The comparative performance of four respiratory motion predictors for real-time tumour tracking. Phys Med Biol. 2011;56(16):5303-17.

16. Cauwenberghs G, Poggio T. Incremental and decremental support vector machine learning. Adv Neural Inf Process Syst. 2001:409-15.

17. Ma J, Theiler J, Perkins S. Accurate on-line support vector regression. Neural Comput. 2003;15(11):2683-703.

18. Parrella F. Online support vector regression. Italy: Department of Information Science University of Genoa, 2007.

19. Chang CC, Lin CJ. LIBSVM: A Library for Support Vector Machines. Acm T Intel Syst Tec. 2011;2(3):27.

20. Ernst F. Compensating for quasi-periodic motion in robotic radiosurgery: Springer Science+ Business Media, LLC, 2012.

21. Ernst F, Schweikard A. Forecasting respiratory motion with accurate online support vector regression (SVRpred). Int J Comput Assist Radiol Surg. 2009;4(5):439-47.

22. Ernst F, Schweikard A. A survey of algorithms for respiratory motion prediction in robotic radiosurgery, 2009.

23. Beale MH, Hagan MT, Demuth HB. Neural Network Toolbox User's Guide. 2012a ed: MathWorks, 2012; p. 2-14.

24. Hsu CW, Chang CC, Lin CJ. A practical guide to support vector classification (Technical report). Department of Computer Science and Information Engineering, National Taiwan University; 2003; Available from: http://www.csie.ntu.edu.tw/~cjlin/papers/guide/guide.pdf.

Appendix A. Supplemental Tables

Supplemental Table 1. Accuracy comparison of latency

Latency	Sliding window	Filter		*p*-value			
				ANN-24	ANN-34	aSVR-Linear	aSVR-RBF
100	2.5		RMSE	0.0426±0.0211	0.0416±0.0197	0.0329±0.0121	0.0305±0.0109
		ANN-22	0.0452±0.0219	0.018*	0.003*	0.000*	0.000*
		ANN-24	0.0426±0.0211		0.242†	0.000*	0.000*
		ANN-34	0.0416±0.0197			0.000*	0.000*
		aSVR-Linear	0.0329±0.0121				0.000*
	5.0		RMSE	0.0528±0.0253	0.0499±0.0221	0.0334±0.0124	0.0314±0.0111
		ANN-22	0.0522±0.0267	0.592†	0.103†	0.000*	0.000*
		ANN-24	0.0528±0.0253		0.036*	0.000*	0.000*
		ANN-34	0.0499±0.0221			0.000*	0.000*
		aSVR-Linear	0.0334±0.0124				0.000*
200	2.5		RMSE	0.0678±0.0272	0.0670±0.0256	0.0602±0.0227	0.0530±0.0193
		ANN-22	0.0695±0.0273	0.043*	0.002*	0.000*	0.000*
		ANN-24	0.0678±0.0272		0.255†	0.000*	0.000*
		ANN-34	0.0670±0.0256			0.000*	0.000*
		aSVR-Linear	0.0602±0.0227				0.000*
	5.0		RMSE	0.0813±0.0329	0.0796±0.0306	0.0609±0.0227	0.0555±0.0202
		ANN-22	0.0813±0.0340	0.967†	0.243†	0.000*	0.000*
		ANN-24	0.0813±0.0329		0.152†	0.000*	0.000*
		ANN-34	0.0796±0.0306			0.000*	0.000*

		aSVR-Linear	0.0609±0.0227				0.000*
300	2.5		RMSE	0.0932±0.0382	0.0929±0.0374	0.0895±0.0357	0.0762±0.0298
		ANN-22	0.0956±0.0394	0.056†	0.042*	0.002*	0.000*
		ANN-24	0.0932±0.0382		0.726†	0.029*	0.000*
		ANN-34	0.0929±0.0374			0.082†	0.000*
		aSVR-Linear	0.0895±0.0357				0.000*
	5.0		RMSE	0.1109±0.0446	0.1079±0.0445	0.0902±0.0360	0.0807±0.0313
		ANN-22	0.1081±0.0486	0.191†	0.911†	0.000*	0.000*
		ANN-24	0.1109±0.0446		0.068†	0.000*	0.000*
		ANN-34	0.1079±0.0445			0.000*	0.000*
		aSVR-Linear	0.0902±0.0360				0.000*
400	2.5		RMSE	0.1191±0.0526	0.1204±0.0527	0.1189±0.0491	0.0997±0.0404
		ANN-22	0.1172±0.0469	0.212†	0.021‡	0.524†	0.000*
		ANN-24	0.1191±0.0526		0.241†	0.946†	0.000*
		ANN-34	0.1204±0.0527			0.559†	0.000*
		aSVR-Linear	0.1189±0.0491				0.000*
	5.0		RMSE	0.1367±0.0606	0.1413±0.0614	0.1188±0.0479	0.1064±0.0428
		ANN-22	0.1347±0.0564	0.194†	0.001‡	0.000*	0.000*
		ANN-24	0.1367±0.0606		0.003‡	0.000*	0.000*
		ANN-34	0.1413±0.0614			0.000*	0.000*
		aSVR-Linear	0.1188±0.0479				0.000*
500	2.5		RMSE	0.1411±0.0611	0.1441±0.0664	0.1471±0.0610	0.1227±0.0504
		ANN-22	0.1416±0.0606	0.709†	0.074†	0.101†	0.000*
		ANN-24	0.1411±0.0611		0.095†	0.050†	0.000*
		ANN-34	0.1441±0.0664			0.385†	0.000*
		aSVR-Linear	0.1471±0.0610				0.000*

		RMSE	0.1671±0.0802	0.1661±0.0784	0.1467±0.0547	0.1316±0.0547
	ANN-22	0.1577±0.0690	$0.001^{\ddagger}$	$0.001^{\ddagger}$	0.001^{*}	0.000^{*}
5.0	ANN-24	0.1671±0.0802		$0.685^{\dagger}$	0.000^{*}	0.000^{*}
	ANN-34	0.1661±0.0784			0.000^{*}	0.000^{*}
	aSVR-Linear	0.1467±0.0547				0.000^{*}

- Note: mean±SD

[*] The column side is significantly more accurate than the row side (paired *t*-test).

[†] The difference between the row and the column side is not significant (paired *t*-test).

[‡] The row side is significantly more accurate than the column side (paired *t*-test).

Supplemental Table 2. Accuracy comparison on the sliding window

Latency (in msec)	Filter	RMSE SW = 2.5 sec[(c)]	RMSE SW = 5.0 sec[(d)]	*p*-value	Difference (d-c)/c (in %)
100	ANN-22	0.0452±0.0219	0.0522±0.0267	0.000*	15.48
	ANN-24	0.0426±0.0211	0.0528±0.0253	0.000*	23.94
	ANN-34	0.0416±0.0197	0.0499±0.0221	0.000*	20.04
	aSVR-Linear	0.0329±0.0121	0.0334±0.0124	0.000*	1.48
	aSVR-RBF	0.0305±0.0109	0.0314±0.0111	0.000*	3.10
200	ANN-22	0.0695±0.0273	0.0813±0.0340	0.000*	16.91
	ANN-24	0.0678±0.0272	0.0813±0.0329	0.000*	19.99
	ANN-34	0.0670±0.0256	0.0796±0.0306	0.000*	18.78
	aSVR-Linear	0.0602±0.0227	0.0609±0.0227	0.010*	1.10
	aSVR-RBF	0.0530±0.0193	0.0555±0.0202	0.000*	4.84
300	ANN-22	0.0956±0.0394	0.1081±0.0486	0.012*	13.11
	ANN-24	0.0932±0.0382	0.1109±0.0446	0.020*	18.93
	ANN-34	0.0929±0.0374	0.1079±0.0445	0.119†	16.18
	aSVR-Linear	0.0895±0.0357	0.0902±0.0360	0.000*	0.78
	aSVR-RBF	0.0762±0.0298	0.0807±0.0313	0.000*	5.91
400	ANN-22	0.1172±0.0469	0.1347±0.0564	0.000*	14.92
	ANN-24	0.1191±0.0526	0.1367±0.0606	0.000*	14.83
	ANN-34	0.1204±0.0527	0.1413±0.0614	0.000*	17.41
	aSVR-Linear	0.1189±0.0491	0.1188±0.0479	0.937†	-0.05
	aSVR-RBF	0.0997±0.0404	0.1064±0.0428	0.000*	6.69
500	ANN-22	0.1416±0.0606	0.1577±0.0690	0.000*	11.35
	ANN-24	0.1411±0.0611	0.1671±0.0802	0.000*	18.43

ANN-34	0.1441±0.0664	0.1661±0.0784	0.000*	15.24
aSVR-Linear	0.1471±0.0610	0.1467±0.0547	0.641†	-0.32
aSVR-RBF	0.1227±0.0504	0.1316±0.0547	0.000*	7.23

- Note: RMSE = mean±SD

* The cases with a window size of 2.5 sec are significantly more accurate than those with a window size of 5.0 sec (paired *t*-test).

† The difference between the case with a window size of 2.5 and that with a window size of 5.0 sec is not significant (paired *t*-test).

Supplemental Table 3. Training times in each condition (in sec)

L[*1]	S[*2]	ANN-22	ANN-24	ANN-34	aSVR-Linear	aSVR-RBF
100	2.5	0.5211±0.2158	0.3659±0.0813	0.5036±0.1621	0.9122±0.3226	1.3897±0.4266
	5.0	0.4965±0.2637	0.4144±0.0873	0.5500±0.1622	1.4694±0.6399	1.2893±0.3273
200	2.5	0.4801±0.2681	0.3955±0.1231	0.4846±0.1700	1.0192±0.2363	1.6782±0.3625
	5.0	0.3785±0.1033	0.4385±0.0923	0.5169±0.1021	1.7252±0.5244	1.5668±0.3282
300	2.5	0.3578±0.0965	0.3609±0.0652	0.4437±0.1037	0.9734±0.1970	1.7703±0.3380
	5.0	0.3503±0.0988	0.4284±0.0891	0.5061±0.1090	1.5828±0.4014	1.6005±0.2875
400	2.5	0.3456±0.0961	0.3485±0.0542	0.4268±0.0842	0.9061±0.1598	1.8009±0.3161
	5.0	0.3425±0.1378	0.4204±0.0568	0.4917±0.0670	1.5056±0.3649	1.6702±0.2933
500	2.5	0.3511±0.1587	0.3652±0.0563	0.4255±0.0705	0.8625±0.1556	1.8264±0.3203
	5.0	0.3292±0.0612	0.4381±0.0793	0.5123±0.0885	1.4769±0.3405	1.7408±0.3257

- Note: Training time = mean±SD

[*1] L = Latency in msec

[*2] S = Sliding window in sec

Supplemental Table 4. Prediction times in each condition (in sec)

L[*1]	S[*2]	ANN-22	ANN-24	ANN-34	aSVR-Linear	aSVR-RBF
100	2.5	0.0142±0.0003	0.0140±0.0003	0.0156±0.0003	0.0149±0.0090	0.0202±0.0130
	5.0	0.0139±0.0006	0.0138±0.0006	0.0154±0.0007	0.0142±0.0083	0.0249±0.0162
200	2.5	0.0147±0.0018	0.0144±0.0018	0.0160±0.0020	0.0209±0.0107	0.0244±0.0136
	5.0	0.0151±0.0003	0.0151±0.0003	0.0168±0.0003	0.0190±0.0090	0.0284±0.0137
300	2.5	0.0143±0.0011	0.0141±0.0011	0.0156±0.0013	0.0227±0.0102	0.0247±0.0119
	5.0	0.0151±0.0007	0.0151±0.0007	0.0168±0.0008	0.0201±0.0102	0.0260±0.0116
400	2.5	0.0144±0.0006	0.0142±0.0006	0.0158±0.0007	0.0236±0.0113	0.0234±0.0119
	5.0	0.0150±0.0001	0.0150±0.0001	0.0166±0.0001	0.0199±0.0093	0.0244±0.0106
500	2.5	0.0152±0.0011	0.0149±0.0011	0.0166±0.0013	0.0245±0.0121	0.0236±0.0120
	5.0	0.0162±0.0017	0.0162±0.0017	0.0180±0.0019	0.0203±0.0103	0.0236±0.0100

- Note: Testing time = mean±SD

[*1] L = Latency in msec

[*2] S = Sliding window in sec

국문초록

서론

방사선 치료에서 호흡을 정확하게 예측하는 것은 매우 중요하다. 왜냐하면 호흡 운동에 의해 인체 내부 장기와 더불어 방사선 치료 계획에서 설정한 방사선 조사 표적도 움직이게 되는데, 이 때 예민한 정상 조직이 방사선에 피폭되어 손상될 수 있기 때문이다. 본 연구에서는 정확한 호흡 예측을 위해 적응적 서포트 벡터 회귀 (adaptive support vector regression; aSVR) 알고리즘을 제안하고 이의 예측 정확도, 훈련 시간, 예측 시간을 적응적 신경회로망(adaptive neural network; ANN)을 이용하였을 때와 비교하였다.

방법

방사선치료 대상 환자 87명으로부터 광학식 마커 방식으로 호흡 데이터를 30 Hz로 획득하였다. 5가지 종류의 ANN 및 aSVR 필터를 구현하고 슬라이딩 윈도우의 크기(2.5초 또는 5초), 예측 지연시간(latency) (100, 200, 300, 400, 500 msec)을 달리하며 성능을 측정하고 비교하였다. 훈련 및 예측은 10 Hz로 다운샘플한 데이터를 이용하였고, 정확도 측정 기준으로는 제곱평균제곱근(root mean square error; RMSE)를 사용하였다.

결과

레이디얼 베이시스 함수(radial basis function; RBF) 커널을 가진 aSVR 필터가 선형 커널을 가진 aSVR 필터 및 다른 모든 ANN 필터들보다 우수한 예측력을 보여주었다. 2.5초의 슬라이딩 윈도우를 사용하는 것이 5초의 슬라이딩 윈도우를 사용할 때에 비해 더 나은 결과를 보여주었다. aSVR 필터, 그 중에서도 RBF 커널에 기반한 aSVR 필터가 훈련 및 예측에 가장 많은 시간이 소요되었다. 슬라이딩 윈도우의 크기는 예측시간에 영향을 주지 않았다.

결론

RBF 커널에 기반한 aSVR 필터가 가장 우수한 예측 성능을 나타내었으며 훈련 및 예측 시간에 있어서도 임상에 적용할 수 있는 수준의 결과를 보여주었다. 이는 방사선 치료의 효율을 향상시키는데 효과가 있을 것으로 기대한다.

주요어: 호흡 운동, 호흡 예측, 실시간 추적, 적응적 신경회로망, 적응적 서포트 벡터 회귀

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