Audiovisual biofeedback improves motion prediction accuracy

Sean Pollock, Danny Lee, Paul Keall, and Taeho Kim^{a)}

Radiation Physics Laboratory, Sydney Medical School, University of Sydney, Sydney, NSW 2006, Australia

(Received 30 October 2012; revised 17 February 2013; accepted for publication 21 February 2013; published 13 March 2013)

Purpose: The accuracy of motion prediction, utilized to overcome the system latency of motion management radiotherapy systems, is hampered by irregularities present in the patients' respiratory pattern. Audiovisual (AV) biofeedback has been shown to reduce respiratory irregularities. The aim of this study was to test the hypothesis that AV biofeedback improves the accuracy of motion prediction.

Methods: An AV biofeedback system combined with real-time respiratory data acquisition and MR images were implemented in this project. One-dimensional respiratory data from (1) the abdominal wall (30 Hz) and (2) the thoracic diaphragm (5 Hz) were obtained from 15 healthy human subjects across 30 studies. The subjects were required to breathe with and without the guidance of AV biofeedback during each study. The obtained respiratory signals were then implemented in a kernel density estimation prediction algorithm. For each of the 30 studies, five different prediction times ranging from 50 to 1400 ms were tested (150 predictions performed). Prediction error was quantified as the root mean square error (RMSE); the RMSE was calculated from the difference between the real and predicted respiratory data. The statistical significance of the prediction results was determined by the Student's *t*-test.

Results: Prediction accuracy was considerably improved by the implementation of AV biofeedback. Of the 150 respiratory predictions performed, prediction accuracy was improved 69% (103/150) of the time for abdominal wall data, and 78% (117/150) of the time for diaphragm data. The average reduction in RMSE due to AV biofeedback over unguided respiration was 26% ($p < 0.001$) and 29% ($p < 0.001$) for abdominal wall and diaphragm respiratory motion, respectively.

Conclusions: This study was the first to demonstrate that the reduction of respiratory irregularities due to the implementation of AV biofeedback improves prediction accuracy. This would result in increased efficiency of motion management techniques affected by system latencies used in radiotherapy. © 2013 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4794497>]

Key words: motion prediction, audiovisual biofeedback, motion management, system latency

I. INTRODUCTION

In external beam radiotherapy, a prevalent concern for accurate treatment delivery is the inherent latency of the treatment system. Latency refers to the time taken to register target position and the reaction time of the delivery system in addition to software limitations.^{1,2} System latencies have been estimated to be as low as 50 ms to as high as several hundred milliseconds.^{1,3} During such latency time the target may have moved, resulting in incorrect tumor targeting and increased dose to the surrounding healthy tissue.² To manage such intrafractional target movement, motion prediction is used to overcome this system latency present in such radiotherapy motion management techniques as tumor tracking and beam-gating.^{4,5} The accuracy of these motion management techniques is compromised for highly mobile tumors in the thoracic and abdominal regions, largely induced by respiration.⁶ The accuracy of such techniques is further compromised should the patient's respiration be irregular in nature.^{1,3,7,8} In the absence of motion management, target motion must be compensated by increasing the size of the planning target volume (PTV) to ensure that the tumor is being continuously irradiated across its entire range of motion.⁹ Increasing the size of the PTV also increases the dose de-

livered to the healthy surrounding tissue leading to a considerable increase in radiation-related toxicity^{10–12} and dose delivered to the healthy surrounding tissue.^{7,13–15} If patient breathing could be managed to minimize respiratory irregularities, motion management efficiency would be maximized. Such a respiratory management technique is the audiovisual (AV) biofeedback system. The AV biofeedback system has been shown to significantly reduce irregularities in a respiratory signal: reducing average cycle-to-cycle variations in respiratory displacement and period by up to 55% and 78%, respectively.¹⁶ Respiratory guidance has also been shown to reduce treatment margins about the clinical target volume (CTV), reducing the superior–inferior margins from 1.1 to 0.8 cm in gated 4D radiotherapy.¹⁷ The benefit of reducing irregular respiration using AV biofeedback has also demonstrated to be beneficial in improving motion reproducibility for respiratory-gated radiotherapy¹⁸ in addition to reducing blurring artifacts in 4D PET (Ref. 13) and CT.¹⁹

This study has further investigated the benefits of AV biofeedback by examining its impact on the accuracy of motion prediction; this has not been studied before and is the novel concept of this study. Given the findings from previous studies, in this study we test the hypothesis that AV biofeedback improves motion prediction accuracy.

II. METHODS AND MATERIALS

II.A. Study participants and respiratory data

Respiratory data have been obtained from 15 healthy human subjects across 30 MRI studies (a first and second session for each subject) in an investigation approved by the University of Sydney Ethics Committee. During the acquisition of MR images, two different respiratory signals were obtained, both of which are lung tumor surrogates: (1) external marker positioned on the abdominal wall and (2) the thoracic diaphragm.^{20–22} During each study two types of respiration were tested: (1) AV biofeedback-guided respiration and (2) unguided respiration. The second study session took place ~1 week after the first study session. As detailed in the study by Kim *et al.*,²³ the order of breathing conditions in the first session was unguided respiration followed by AV biofeedback-guided respiration; the second session reversed the order of breathing conditions that took place in the first session in order to avoid any bias against the breathing order.

II.B. Audiovisual biofeedback and respiratory data

The AV biofeedback system, developed by Venkat *et al.*,¹⁶ employs the real-time position management (RPM) system (Varian Medical Systems, Palo Alto, CA), which is responsible for attaining the real-time (30 Hz) respiratory motion of an external marker positioned on the abdomen. The respiratory motion acquired via the RPM system is used to compile a waveguide; this forms part of the visual component of AV biofeedback. Also comprising the visual component is a ball moving up and down on the visual display, whose motion corresponds to that of the external marker being tracked by the RPM system. The subject then adjusts their breathing such that the ball follows the waveguide. The audio component of AV biofeedback is music played to the subject; the music changes in speed should the ball deviate more than 15% from the waveguide.

The respiratory signals used for the prediction calculations in this study came from a previous study performed by Kim *et al.*,²³ which found that AV biofeedback substantially reduced irregularities present in abdominal wall respiratory motion as well as for the thoracic diaphragm. The abdominal wall respiratory data were acquired in real-time during the study at a rate of 30 Hz via the RPM system; the diaphragm respiratory data were acquired from the MR images acquired simultaneously with the RPM data using the MR bellows belt to temporally synchronize the RPM and MR data. Diaphragm respiratory motion information was obtained post-acquisition via a MATLAB analysis. The methods of RPM and MR temporal synchronization in addition to obtaining diaphragm motion information from the MR images are detailed by Kim *et al.*²³ The MR pulse sequence utilized in this study was the fast gradient echo (fGRE), which had an image acquisition time of 200 ms (sampling rate of 5 Hz).

II.C. Motion prediction

Following the acquisition of respiratory data from the abdomen and thoracic diaphragm, the respiratory motion of

these datasets were then predicted by a kernel density estimation (KDE) prediction algorithm developed by Ruan.²⁴ The algorithm was implemented into in-house dynamic multileaf collimator (DMLC) tracking software.^{15,25} For this study, the DMLC code was run in simulation mode with the respiratory traces (internal or external) fed into the DMLC traces as if in real-time, with the program returning the predicted motion. The KDE prediction algorithm implements a probabilistic approach in determining future position, unlike other algorithms that implement a deterministic approach.^{1,3} This probabilistic approach, rather than deterministic, makes the KDE algorithm well suited to the stochastic nature of the respiratory signals being predicted.

In this study, prediction performance was tested over a range of look-ahead prediction times (PT); the training window was kept constant. The PT corresponds to how far ahead in time the prediction algorithm is predicting and values of PT are chosen based on the system latency. System latencies have been estimated to be as low as 50 ms to as high as several hundred milliseconds.^{1,3} Higher PT values than those published are also included in our study, as more complex systems under development, such as ultrasound^{26,27} and MRI-guided systems^{28,29} will be acquiring volumetric patient anatomic information which takes longer to acquire and process than the current systems available. As such, the range of PTs tested to reproduce system latencies were from 50 to 1400 ms.

The training window is the temporal length of data to be sampled by the prediction algorithm in order to compute future position. The length of the training window has been tested in previous studies to range from 5 s,⁷ to two periods of respiration,³ to 20 s.²⁴ Across these training durations, each study noted that the prediction algorithm performed robustly. In the preliminary stages of this study, a range of training durations were tested; and apart from the very short (0.3 s) and the very long (50 s), there was not a significant variation in prediction algorithm performance. The average respiratory period of the data from this study was 4.6 ± 0.9 s; a training window of approximately two respiratory periods (9 s) was chosen here.

Prediction error was quantified as the root mean square error [RMSE, Eq. (1)] for each predicted case:

$$\text{RMSE} = \sqrt{\frac{\sum_{i=1}^n |x_{i,\text{Real}} - x_{i,\text{Predicted}}|^2}{n}}, \quad (1)$$

where x is the positional information for the real and predicted respiratory signal and n is the number of data points within such a respiratory signal.

III. RESULTS

III.A. Predicted abdominal wall respiratory motion

Across the 30 respiratory data sets and the five different prediction times tested, there was a total of 150 predicted respiratory cases, of which, 103 of 150 (69%) demonstrated a higher prediction accuracy when AV biofeedback was implemented. The magnitude and frequency of motion

TABLE I. RMSE across the five tested prediction times for AV biofeedback-guided breathing, for unguided breathing, and for the reduction of RMSE due to AV biofeedback for abdominal wall respiratory motion.

PT (ms)	RMSE ($\pm$ SD) AV biofeedback (mm)	RMSE ($\pm$ SD) unguided (mm)	Reduction in RMSE (due to AV) (%)	<i>p</i> value	AV improved prediction accuracy (fraction of studies)
50 ^a	0.2 $\pm$ 0.2	0.2 $\pm$ 0.1	−8 (no reduction)	0.34	13/30 (43%)
200	0.6 $\pm$ 0.4	0.6 $\pm$ 0.5	4	0.59	19/30 (63%)
600	1.2 $\pm$ 0.9	1.5 $\pm$ 1.2	22	0.008	23/30 (77%)
1000	1.5 $\pm$ 1.1	2.1 $\pm$ 1.6	31	<0.001	24/30 (80%)
1400	1.7 $\pm$ 1.2	2.4 $\pm$ 1.8	31	<0.001	24/30 (80%)
Average	1.0 $\pm$ 0.8	1.4 $\pm$ 1.0	26	<0.001	Total: 103/150 (69%)

^aRMSE results were acquired via interpolation due to the discrepancy between prediction time (50 ms) and acquisition time (33 ms) of the diaphragm respiratory data.

prediction results due to AV biofeedback compared to unguided respiration across the five tested prediction times and 30 studies are shown in Table I. For PT = 50 ms, RMSE results were calculated via interpolation due to the discrepancy between prediction time (50 ms) and acquisition time (33 ms) of the abdominal wall respiratory data. Linear interpolation was the technique used to interpolate these data.

For the majority of studies, the implementation of AV biofeedback improved prediction accuracy over unguided respiration; this became more prominent at higher PTs, becoming considerably more significant at PTs exceeding 200 ms.

Figure 1 illustrates the prediction results for abdominal wall respiratory motion from 3 of the 30 studies representative of the 75th, 50th, and 25th percentiles of RMSE reduction due to AV biofeedback for PT = 600 ms. The percentiles presented here are representative of the percentile rank of prediction improvement. That is, the 75th percentile result had a reduction of prediction error (RMSE), due to AV biofeedback, greater than 74% of all other results; the 50th percentile result is the median.

The reduction of RMSE, from unguided to AV biofeedback-guided motion prediction, was 37% for the 75th percentile [Figs. 1(a) and 1(b)], 22% for the 50th percentile [Figs. 1(c) and 1(d)], and 1% for the 25th percentile [Figs. 1(e) and 1(f)]. Even for the lower end of AV biofeedback's impact on prediction performance (25th percentile), there is still a marginal improvement over unguided respiratory prediction. The prediction errors (RMSE) across the five tested prediction times are shown in Fig. 2.

Figure 2 demonstrates clearly the increasing reduction of prediction error due to AV biofeedback compared to unguided respiration at higher PTs. At low PTs, prediction results demonstrate similar performance; however at PTs exceeding 200 ms [Figs. 2(c)–2(e)] the regular respiratory patterns produced by AV biofeedback clearly result in more accurate prediction results compared to unguided respiration.

III.B. Predicted diaphragm respiratory motion

Across the diaphragm respiratory data sets, 117 of 150 (78%) predicted cases demonstrated a higher prediction accuracy when AV biofeedback was implemented. The improvement of motion prediction due to AV biofeedback across the

150 predicted cases is shown in Table II. For PT = 50 ms, RMSE results were calculated via interpolation due to the large discrepancy between prediction time (50 ms) and acquisition time (200 ms) of the diaphragm respiratory data. Linear interpolation was the technique used to interpolate these data.

The results here are similar to those of abdominal wall respiration in that for the majority of predictions performed, AV biofeedback improved accuracy over unguided respiration, becoming increasingly significant at higher PTs. However, the improvement in prediction accuracy due to AV biofeedback was more significant across all PTs for diaphragm respiratory motion compared to abdominal wall respiratory motion.

Figure 3 illustrates the diaphragm prediction results from three studies representative of the 75th, 50th, and 25th percentile of RMSE reduction due to AV biofeedback for PT = 600 ms.

The reduction of RMSE from unguided to AV biofeedback-guided was 35% for the 75th percentile [Figs. 3(a) and 3(b)], 22% for the 50th percentile [Figs. 3(c) and 3(d)], and 7% for the 25th percentile [Figs. 3(e) and 3(f)]; AV biofeedback-guided respiration consistently resulted in improved prediction accuracy over unguided respiration.

The prediction errors (RMSE) across the five tested prediction times are shown in Fig. 4. Similar to abdominal wall respiratory motion prediction, AV biofeedback-guided respiratory motion of the diaphragm resulted in lower prediction error than unguided respiration, the reduction in RMSE becoming more prominent at higher PTs. However, the magnitude and significance of such improvement was larger for the diaphragm motion compared to abdominal wall motion.

III.C. First and second study sessions

There was an observed further improvement in prediction accuracy for AV biofeedback-guided respiration from the first study session to the second. In a paper by Kim *et al.* which analyzed the respiratory data that were predicted for this study, it was also found that there was a further improvement in respiratory regularity from the first study session to the second.²³ The changes in session results are shown in Table III, in which the reductions of prediction error (RMSE) due to AV biofeedback are given.

FIG. 1. The AV biofeedback guided (left: a, c, e) and unguided (right: b, d, f) abdominal wall respiratory data for $PT = 600$ ms. Solid lines represent the respiratory signal and the dotted line represents the predicted data. The bottom line is the error in prediction. (a, b): 75th percentile. (c, d): 50th percentile. (e, f): 25th percentile.

FIG. 2. Box plots of prediction error (RMSE) across prediction times: (a) PT = 50 ms, (b) PT = 200 ms, (c) PT = 600 ms, (d) PT = 1000 ms and (e) PT = 1400 ms for abdominal wall respiratory data. The crosses represent outlier data (data outside $\pm 2.7\sigma$ of the mean).

For both abdominal wall and diaphragm respiratory motion, the reduction of prediction error (due to AV biofeedback) was significantly reduced further in the second session compared to the first. For unguided respiration there was no reduction in RMSE from the first to second session; average RMSE for unguided respiration in the first session was 1.4 ± 1.0 mm, and was 1.4 ± 1.0 mm in the second session ($p = 0.8$).

IV. DISCUSSION

In this study, the impact of AV biofeedback on respiratory motion prediction accuracy was investigated. The more regular respiratory motion as produced by AV biofeedback resulted in improved motion prediction accuracy over unguided respiration.

TABLE II. RMSE across the five tested prediction times for AV biofeedback-guided breathing, for unguided breathing, and for the reduction of RMSE due to AV biofeedback for diaphragm motion.

PT (ms)	RMSE ($\pm$ SD) AV biofeedback (mm)	RMSE ($\pm$ SD) unguided (mm)	Reduction in RMSE (due to AV) (%)	<i>p</i> value	AV improved prediction accuracy (fraction of studies)
50 ^a	0.7 ± 0.5	0.8 ± 0.6	9	0.2	20/30 (67%)
200	1.4 ± 1.0	1.5 ± 1.1	9	0.1	22/30 (73%)
600	2.3 ± 1.6	3.1 ± 2.3	25	0.001	24/30 (80%)
1000	2.8 ± 1.9	4.1 ± 3.0	33	<0.001	25/30 (83%)
1400	3.0 ± 2.1	4.7 ± 3.4	36	<0.001	26/30 (87%)
Average	2.0 ± 1.4	2.8 ± 2.1	29	<0.001	Total: 117/150 (78%)

^aRMSE results were acquired via interpolation due to the large discrepancy between prediction time (50 ms) and acquisition time (200 ms) of the diaphragm respiratory data.

FIG. 3. The AV biofeedback guided (a, c, e) and unguided (b, d, f) diaphragm respiratory data from PT = 600 ms. Solid lines represent the respiratory signal, and the dotted line represents the predicted data. The bottom line is the error in prediction. (a, b): 75th percentile. (c, d): 50th percentile. (e, f): 25th percentile.

FIG. 4. Box plots of prediction error (RMSE) across prediction times: (a) PT = 50 ms*, (b) PT = 200 ms, (c) PT = 600 ms, (d) PT = 1000 ms and (e) PT = 1400 ms for diaphragm respiratory data. The crosses represent outlier data (data outside $\pm 2.7\sigma$ of the mean).

Managing tumor motion to minimize the dose delivered to healthy tissue is a prevalent issue present in radiotherapy; AV biofeedback is one such management technique to minimize respiratory irregularities. This study has further demonstrated the clinical advantages of AV biofeedback: by audio-visually guiding each subject, a more regular breathing pattern was produced that resulted in improved prediction accuracy which

would be beneficial to such motion management techniques affected by system latencies.

Of the 150 predicted cases of respiratory data, AV biofeedback improved the prediction accuracy in 103 out of 150 (69%) cases for abdominal wall respiratory data, and 117 of 150 (78%) cases for diaphragm data. The overall reduction in prediction error due to AV biofeedback was 26% ($p < 0.001$) and 29% ($p < 0.001$) for abdominal wall and diaphragm respiratory data, respectively. However, that still left 47 cases for abdominal wall motion and 33 cases for diaphragm motion that AV biofeedback did not improve prediction accuracy. Some subjects had naturally regular unguided breathing that is well suited for high prediction accuracy. Some subjects also had difficulty in following the waveguide and therefore the desired effect of regular respiration produced by AV biofeedback was diminished. In addition to this, at lower PTs there was no significant difference between the prediction performance of AV biofeedback-guided and unguided respiration. This is because, as previous studies have demonstrated, that at lower PTs the prediction algorithm is more accurately able to predict future position.^{1,3,24} Therefore, for low PTs such as 50 and 200 ms, the prediction algorithm is performing

TABLE III. Further reduction of prediction error due to AV biofeedback from the first to second study sessions.

	First session	Second session	Further reduction from first to second session	<i>p</i> value
Abdomen				
Reduction in RMSE (due to AV)	15%	34%	19%	<0.001
Diaphragm				
Reduction in RMSE (due to AV)	24%	36%	12%	0.02

sufficiently accurately for respiratory irregularities to not be a particular hindrance. Coupled with this is the nature of the respiratory signal as a result of AV biofeedback guidance: the AV biofeedback signal had a larger range of motion (8.3 mm compared to 7.1 mm for unguided respiration for abdominal wall motion; and 16.5 mm compared to 14.2 mm for unguided respiration for diaphragm motion). With a larger range of motion comes a larger magnitude of error; so despite a more regular signal being produced, the magnitude of the signal was a dominant factor in producing no statistically significant difference at lower PTs, especially since at such low PTs, the prediction algorithm is not so susceptible to respiratory irregularities. However, at PTs exceeding 200 ms, the reduction of prediction error due to AV biofeedback-guided respiration becomes increasingly significant. When considering only PTs higher than 200 ms, the percentage of cases whose prediction accuracy is improved due to AV biofeedback increases from 69% to 79% for abdominal wall motion and from 78% to 83% for the diaphragm. This is of particular importance not only for treatment systems with longer system latencies but also with the realization of more complex image-guided radiotherapy systems under development that are subject to larger system latencies.^{26–29}

RMSE for diaphragm respiratory prediction was higher than abdominal wall respiratory prediction RMSE. This is potentially due to the lower sampling rate of diaphragm respiratory data (5 Hz) compared to abdominal wall respiratory data (30 Hz); a previous study by Ren *et al.* found that a lower sampling rate resulted in a reduction in prediction accuracy.³⁰ A lower sampling rate would result in motion prediction error being more sensitive to respiratory irregularities. This is demonstrated here, with the average unguided RMSE for abdominal wall motion (30 Hz) was 1.4 ± 1.0 mm, while for diaphragm motion (5 Hz) it was 2.8 ± 2.1 mm; this resulted in a greater magnitude of improvement in prediction accuracy due to the implementation of AV biofeedback for diaphragm respiratory motion when compared to abdominal wall results. This is especially of interest with the development of ultrasound and MR image-guided treatment systems^{26–29} whose image acquisition times would limit their data sampling rates.

A number of prediction algorithms have previously been studied in regards to respiratory motion prediction such as the linear adaptive,³ neural network,^{1,3} and kernel density estimation algorithms.²⁴ While the KDE prediction algorithm performed robustly throughout respiratory data prediction in this study, given the trend of higher prediction accuracy for more regular respiratory signals found in previous studies that utilized alternate prediction algorithms,^{1,3} a similar result to what was found here would also be expected should different prediction algorithms be used.

While previous studies have indicated that no training was necessary for volunteers to follow AV biofeedback due to its low cognitive load,¹⁶ this study observed that there was a further improvement in prediction accuracy in the second session compared to the first session. This suggests that previous exposure to AV biofeedback better prepared volunteers to follow AV biofeedback more accurately. A study performed by Kim *et al.*, which analyzed the regularity of the respiratory

signals that were used for prediction in this study, found that the reduction of respiratory irregularities due to AV biofeedback was larger in the second session than the first.²³ With the increased regularity of AV biofeedback-guided respiration in the second session, motion prediction accuracy was also improved accordingly. This could be significant considering that if only one repetition of AV biofeedback was able to produce improved prediction accuracy, should this be implemented in a treatment plan comprised of numerous treatment fractions, the accuracy of motion prediction may be further improved due to more frequent exposure to AV biofeedback. Given that there was a relatively small sample size (15 human subjects) and low number of repetitions (only 1 repetition), it is difficult to ascertain the significance of this observation. Also, it is difficult to determine whether the further reduction of prediction error was due to increased familiarity with AV biofeedback or the reversal of breathing conditions from the first to second study sessions. As such, further investigation is required.

While the results of this study further develop the clinical advantages of the AV biofeedback system, a limitation was that the range of subjects was not representative of a diverse group, as it was limited to predominantly healthy young males. A future study would ideally involve the participation of cancer patients in order to directly monitor the respiratory motion of the tumor itself rather than using the diaphragm or an external marker as surrogates in healthy volunteers. Nevertheless, this study provides a valuable foundation for a future motion management cancer patient study.

By implementing AV biofeedback, respiratory irregularities (e.g., baseline shifts, deep breaths, inconsistent amplitudes) have been reduced thereby producing a more regular respiratory pattern which the KDE prediction algorithm can more accurately predict across a range of PTs. Such results demonstrate AV biofeedback as a valuable tool for motion management techniques in radiotherapy to minimize PTV and therefore minimize dose to healthy tissue, reducing radiation-related toxicity and increasing patient quality of life.

V. CONCLUSION

This study has demonstrated the benefit of utilizing AV biofeedback to improve respiratory motion prediction accuracy. Across a range of prediction times, AV biofeedback provided an increase in prediction accuracy in 103 of the 150 (69%) abdominal wall studies and 117 of the 150 (78%) diaphragm studies. However, this rate of improvement increased at higher prediction times. The overall reduction in prediction error due to AV biofeedback was 26% ($p < 0.001$) and 29% ($p < 0.001$) for abdominal wall and diaphragm respiratory data, respectively. Such improvements reveal the clinical benefit of utilizing AV biofeedback to improve motion prediction for such motion management techniques as tumor tracking and respiratory-based gating.

The results presented here confirm the hypothesis that AV biofeedback improves motion prediction accuracy; this is increasingly prevalent at higher prediction times. With the realization of real-time adaptive radiotherapy systems such as the Cyberknife Synchrony and Vero treatment systems, and

the planned introduction of couch and DMLC tracking, the reduction of prediction error through use of AV biofeedback can have a substantially beneficial impact on patient treatment accuracy.

ACKNOWLEDGMENTS

This work was supported by Sydney Medical School New Staff/Early Career Researcher Scheme Grant, NIH/NCI Grant No. R01CA93626, and an NHMRC Australia Fellowship.

^{a)} Author to whom correspondence should be addressed. Electronic mail: taeho.kim@sydney.edu.au; Telephone: 61 2 9351 3385; Fax: 61 2 9351 4018.

¹ M. J. Murphy and S. Dieterich, "Comparative performance of linear and nonlinear neural networks to predict irregular breathing," *Phys. Med. Biol.* **51**, 5903–5914 (2006).

² P. R. Poulsen, B. Cho, A. Sawant, D. Ruan, and P. J. Keall, "Detailed analysis of latencies in image-based dynamic MLC tracking," *Med. Phys.* **37**, 4998–5005 (2010).

³ M. J. Murphy and D. Pokhrel, "Optimization of an adaptive neural network to predict breathing," *Med. Phys.* **36**, 40–47 (2009).

⁴ P. Keall, V. Kini, S. Vedam, and R. Mohan, "Potential radiotherapy improvements with respiratory gating," *Australas. Phys. Eng. Sci. Med.* **25**, 1–6 (2002).

⁵ J. Nuytens, J. B. Prévost, J. Praag, M. Hoogeman, R. Van Klaveren, P. Levendag, and P. Pattynama, "Lung tumor tracking during stereotactic radiotherapy treatment with the CyberKnife: Marker placement and early results," *Acta Oncol.* **45**, 961–965 (2006).

⁶ Y. Suh, S. Dieterich, B. Cho, and P. J. Keall, "An analysis of thoracic and abdominal tumour motion for stereotactic body radiotherapy patients," *Phys. Med. Biol.* **53**, 3623–3640 (2008).

⁷ S. Vedam, P. Keall, A. Docef, D. Todor, V. Kini, and R. Mohan, "Predicting respiratory motion for four-dimensional radiotherapy," *Med. Phys.* **31**, 2274–2283 (2004).

⁸ D. A. Low, P. J. Parikh, W. Lu, J. F. Dempsey, S. H. Wahab, J. P. Hubenschmidt, M. M. Nystrom, M. Handoko, and J. D. Bradley, "Novel breathing motion model for radiotherapy," *Int. J. Radiat. Oncol., Biol., Phys.* **63**, 921–929 (2005).

⁹ L. W. Brady, H. P. Heilmann, M. Molls, S. Levitt, J. A. Purdy, C. A. Perez, and S. Vijayakumar, *Technical Basis of Radiation Therapy: Practical Clinical Applications* (Springer, Berlin, 2008).

¹⁰ M. Machtay, K. Bae, B. Movsas, R. Paulus, E. M. Gore, R. Komaki, K. Albain, W. T. Sause, and W. J. Curran, "Higher biologically effective dose of radiotherapy is associated with improved outcomes for locally advanced non-small cell lung carcinoma treated with chemoradiation: An analysis of the radiation therapy oncology group," *Int. J. Radiat. Oncol., Biol. Phys.* **82**(1), 425–434 (2010).

¹¹ L. B. Marks, S. M. Bentzen, J. O. Deasy, F. M. S. Kong, J. D. Bradley, I. S. Vogelius, I. El Naqa, J. L. Hubbs, J. V. Lebesque, and R. D. Timmerman, "Radiation dose-volume effects in the lung," *Int. J. Radiat. Oncol., Biol., Phys.* **76**, S70–S76 (2010).

¹² G. D. Hugo, J. Campbell, T. Zhang, and D. Yan, "Cumulative lung dose for several motion management strategies as a function of pretreatment patient parameters," *Int. J. Radiat. Oncol., Biol., Phys.* **74**, 593–601 (2009).

¹³ J. Yang, T. Yamamoto, B. Cho, Y. Seo, and P. J. Keall, "The impact of audio-visual biofeedback on 4D PET images: Results of a phantom study," *Med. Phys.* **39**, 1046–1057 (2012).

¹⁴ J. Y. Jin, F. F. Yin, S. E. Tenn, P. M. Medin, and T. D. Solberg, "Use of the BrainLAB ExacTrac X-Ray 6D system in image-guided radiotherapy," *Med. Dosim.* **33**, 124–134 (2008).

¹⁵ B. Cho, P. R. Poulsen, A. Sloutsky, A. Sawant, and P. J. Keall, "First demonstration of combined kV/MV image-guided real-time DMLC target tracking," *Int. J. Radiat. Oncol., Biol., Phys.* **74**, 859 (2009).

¹⁶ R. B. Venkat, A. Sawant, Y. Suh, R. George, and P. J. Keall, "Development and preliminary evaluation of a prototype audiovisual biofeedback device incorporating a patient-specific guiding waveform," *Phys. Med. Biol.* **53**, N197–N208 (2008).

¹⁷ S. Vedam, V. Kini, P. Keall, V. Ramakrishnan, H. Mostafavi, and R. Mohan, "Quantifying the predictability of diaphragm motion during respiration with a noninvasive external marker," *Med. Phys.* **30**, 505–513 (2003).

¹⁸ R. George, T. D. Chung, S. S. Vedam, V. Ramakrishnan, R. Mohan, E. Weiss, and P. J. Keall, "Audio-visual biofeedback for respiratory-gated radiotherapy: Impact of audio instruction and audio-visual biofeedback on respiratory-gated radiotherapy," *Int. J. Radiat. Oncol., Biol., Phys.* **65**, 924–933 (2006).

¹⁹ P. Keall, S. Vedam, R. George, and J. Williamson, "Respiratory regularity gated 4D CT acquisition: Concepts and proof of principle," *Australas. Phys. Eng. Sci. Med.* **30**, 211–220 (2007).

²⁰ E. Kanoulas, J. Aslam, G. Sharp, R. Berbeco, S. Nishioka, H. Shirato, and S. Jiang, "Derivation of the tumor position from external respiratory surrogates with periodical updating of the internal/external correlation," *Phys. Med. Biol.* **52**, 5443–5456 (2007).

²¹ L. I. Cerviño, A. K. Y. Chao, A. Sandhu, and S. B. Jiang, "The diaphragm as an anatomic surrogate for lung tumor motion," *Phys. Med. Biol.* **54**, 3529 (2009).

²² L. I. Cerviño, Y. Jiang, A. Sandhu, and S. B. Jiang, "Tumor motion prediction with the diaphragm as a surrogate: A feasibility study," *Phys. Med. Biol.* **55**, N221 (2010).

²³ T. Kim, S. Pollock, D. Lee, R. O'Brien, and P. Keall, "Audiovisual biofeedback improves diaphragm motion reproducibility in MRI," *Med. Phys.* **39**, 6921–6928 (2012).

²⁴ D. Ruan, "Kernel density estimation-based real-time prediction for respiratory motion," *Phys. Med. Biol.* **55**, 1311–1326 (2010).

²⁵ P. J. Keall, A. Sawant, B. Cho, D. Ruan, J. Wu, P. Poulsen, J. Petersen, L. J. Newell, H. Cattell, and S. Korreman, "Electromagnetic-guided dynamic multileaf collimator tracking enables motion management for intensity-modulated arc therapy," *Int. J. Radiat. Oncol., Biol., Phys.* **79**, 312–320 (2011).

²⁶ J. Schlosser, K. Salisbury, and D. Hristov, "Telerobotic system concept for real-time soft-tissue imaging during radiotherapy beam delivery," *Med. Phys.* **37**, 6357–6367 (2010).

²⁷ J. Schlosser, K. Salisbury, and D. Hristov, "Online image-based monitoring of soft-tissue displacements for radiation therapy of the prostate," *Int. J. Radiat. Oncol., Biol., Phys.* **83**(5), 1633–1640 (2012).

²⁸ B. Fallone, M. Carlone, B. Murray, S. Rathee, T. Stanescu, S. Steciw, K. Wachowicz, and C. Kirkby, "TU-C-M100F-01: Development of a linac-MRI system for real-time ART," *Med. Phys.* **34**, 2547 (2007).

²⁹ B. Fallone, B. Murray, S. Rathee, T. Stanescu, S. Steciw, S. Vidakovic, E. Blosser, and D. Tymofichuk, "First MR images obtained during megavoltage photon irradiation from a prototype integrated linac-MR system," *Med. Phys.* **36**, 2084–2088 (2009).

³⁰ Q. Ren, S. Nishioka, H. Shirato, and R. I. Berbeco, "Adaptive prediction of respiratory motion for motion compensation radiotherapy," *Phys. Med. Biol.* **52**, 6651–6661 (2007).