Scientific Article

Simulating intrafraction prostate motion with a random walk model

Tobias Pommer PhD [a,b,c,]*, **Jung Hun Oh PhD** [c],
Per Munck af Rosenschöld PhD [a,c], **Joseph O. Deasy PhD** [c]

[a] *Department of Oncology, Section of Radiotherapy, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark*
[b] *Section of Radiotherapy Physics and Engineering, Department of Medical Physics, Karolinska University Hospital, Stockholm, Sweden*
[c] *Department of Medical Physics, Memorial Sloan-Kettering Cancer Center, New York, New York*

Abstract

Purpose: Prostate motion during radiation therapy (ie, intrafraction motion) can cause unwanted loss of radiation dose to the prostate and increased dose to the surrounding organs at risk. A compact but general statistical description of this motion could be useful for simulation of radiation therapy delivery or margin calculations. We investigated whether prostate motion could be modeled with a random walk model.

Methods and materials: Prostate motion recorded during 548 radiation therapy fractions in 17 patients was analyzed and used for input in a random walk prostate motion model. The recorded motion was categorized on the basis of whether any transient excursions (ie, rapid prostate motion in the anterior and superior direction followed by a return) occurred in the trace and transient motion. This was separately modeled as a large step in the anterior/superior direction followed by a returning large step. Random walk simulations were conducted with and without added artificial transient motion using either motion data from all observed traces or only traces without transient excursions as model input, respectively.

Results: A general estimate of motion was derived with reasonable agreement between simulated and observed traces, especially during the first 5 minutes of the excursion-free simulations. Simulated and observed diffusion coefficients agreed within 0.03, 0.2 and 0.3 mm²/min in the left/right, superior/inferior, and anterior/posterior directions, respectively. A rapid increase in variance at the start of observed traces was difficult to reproduce and seemed to represent the patient's need to adjust before treatment. This could be estimated somewhat using artificial transient motion.

Conclusions: Random walk modeling is feasible and recreated the characteristics of the observed prostate motion. Introducing artificial transient motion did not improve

the overall agreement, although the first 30 seconds of the traces were better reproduced. The model provides a simple estimate of prostate motion during delivery of radiation therapy.

Introduction

External radiation therapy targets the tumor while attempting to spare the surrounding healthy tissue. Tumor motion during radiation therapy delivery (ie, intrafraction motion) requires additional margins and leads to irradiation of healthy tissue both from enlarged margins and because surrounding tissue may drift into the high-dose area. Prostate cancer is commonly treated with radiation therapy, and prostate motion has been investigated in several studies with a wide range of localization modalities, including x-ray imaging,[1] magnetic resonance imaging,[2] ultrasound,[3] and electromagnetic monitoring.[4-6] The impact of motion in radiation therapy has been studied from treatment margin and dosimetric perspectives.[7-11] Several methods have been proposed for motion compensation in various stages of clinical implementation.[12-15]

Several investigations have been conducted on biomechanical modeling of pelvic organs and their interaction, with some focusing specifically on the implementations and implications of radiation therapy.[16-20] Söhn et al modeled prostate motion on the basis of principal component analysis to determine eigenmodes for interfractional motion and deformation of the prostate, rectum, and bladder.[21] A study by Ballhausen et al proposed a random walk model to describe intrafraction prostate motion using population-based drift vectors, diffusion constants, and Monte Carlo simulations.[22]

A random walk is a model in which the object of interest is subject to external forces and moves stochastically in accordance with probability distributions. The motion is characterized by each step being independent of previous steps, whereas the displacement at a certain time is dependent on the displacement at an earlier time. The variance in position for many samples increases linearly with time. The authors considered intrafraction motion as a time-dependent process with displacements that accumulate over time and argued that the random walk model would be suitable because it does not require knowledge of the external forces that affect the prostate.

A follow-up study used ultrasound to record prostate motion during 84 radiation therapy fractions for 6 patients.[23] The motion data were analyzed to find the best fit to 3 models: a static noise model in which each position is independent of the previous position, a stationary process model in which the prostate moves unobstructed within a certain volume, and a random walk model. The random walk model was favored for all 6 patients, and the variance was found to continuously increase within the investigated timeframe (5-8 minutes).

Using real-time electromagnetic guided prostate positioning during radiation therapy, Langen et al noted 2 main types of prostate motion: a sudden, transient motion and a slow, drifting motion.[4] The former was mostly directed anteriorly and superiorly and the latter inferiorly and posteriorly (see Fig 1 in Langen et al[4]). The suggested mechanisms for the motion were changes in rectal volume and bladder filling, pushing the prostate anteriorly/superiorly and posteriorly/inferiorly, respectively.

In this study, we aim to simulate prostate motion using a random walk model with simulation parameters on the basis of observed motion with special attention to modeling the transient motion that occurred in the observed data. Whereas Ballhausen et al[22] primarily recreated the motion characteristics of time averages, this study will analyze each observed prostate motion trace to use as input for the model and compare the simulations with the observed data at a time resolution of seconds. Furthermore, we intend to differentiate between the slow and rapid motion components (ie, transient motion and prostate drift). The purpose of this study is to test whether it is possible to recreate the properties of patient data using a random walk model, if necessary with simulated transient motion.

Methods and materials

A dataset of prostate motion traces recorded with electromagnetic tracking at 10 Hz during 548 radiation therapy fractions (mean length 607 seconds) for 17 patients was used in this study.[4] The traces contained only translational information, and prostate rotation was thus not considered in this study. The motion traces were set to start at the origin at the beginning of the trace and were filtered with an averaging filter with a filter length of 10 data points (average time scale of 1 seconds) to remove high-frequency noise. A single observer qualitatively categorized the traces (Fig 1) by reviewing all traces and deciding whether transient motion was present. The review was done 3 times, and the majority decision was used. Transient motion was considered as rapid motion
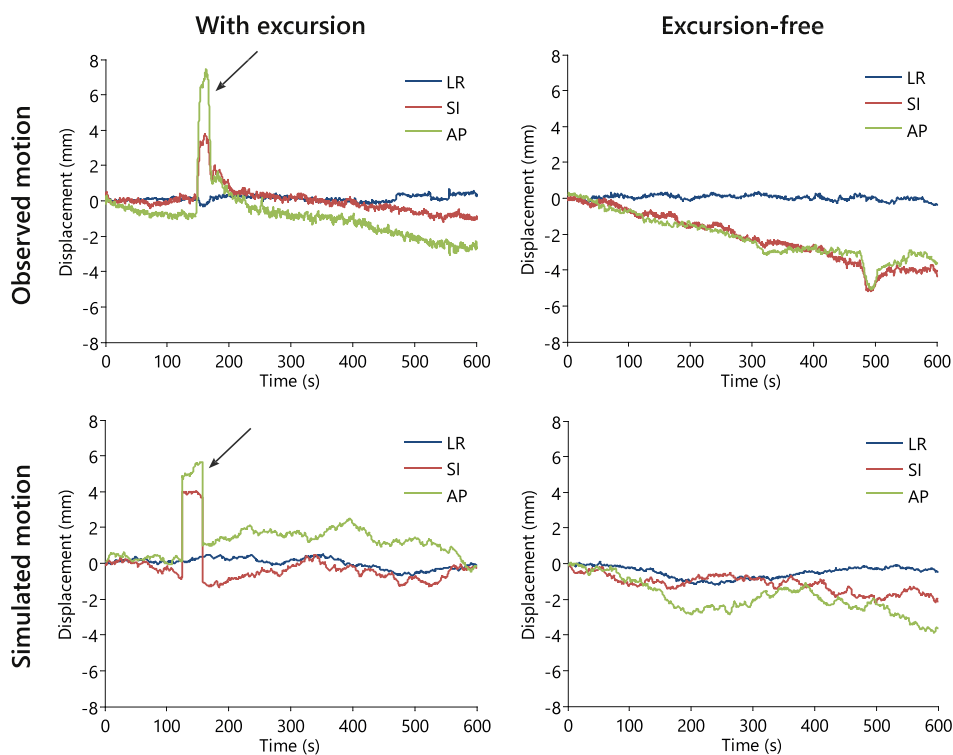
Figure 1 Examples of observed (top) and simulated (bottom) prostate motion with (left, arrow) and without (right) a transient excursion. The simulated traces were selected from the large number of simulated traces to resemble the observed traces.

(ie, occurring within a few seconds) of at least a few millimeters in the anterior/superior direction followed by a return to approximately the original position. The returning motion could be as fast as or sometimes comparably slower than the initial transient motion. The categorization allowed for the use of a subgroup of the traces as input for the random walk and for comparison of simulated traces with a subgroup of observed traces.

Random walk model

The random walk model was essentially a Monte Carlo model that repeatedly selected a step size and direction on the basis of a set of fixed probabilities. The probabilities were obtained by analysis of the observed traces (all traces [n = 548], excursion-free traces only [n = 320], or traces with excursions only [n = 228]). Two matrices were calculated from the observed traces that were used as input for the model: a matrix that described the probability of prostate motion in all combinations of the cardinal directions as well as no motion and continuous step size distributions (one for each direction) with the observed length of the prostate motion steps between each sampling point. The actual matrix values are given in the online supplement. The motion traces were simulated one at a time by step-wise motion with the direction sampled on the basis of a random number from the direction matrix and the step size randomly sampled from the step size

distributions. The simulations were conducted with the same time steps as the observed traces (0.1 seconds during 600 seconds and for 548 traces).

The transient motion in the observed traces occurred over several consecutive sampling points. With a random walk model, using small steps only, a simulation of the observed traces was found to be challenging because the same direction with several relatively large and improbable consecutive steps was required to reproduce them (Fig 1). Therefore, the possibility of adding artificial transient motion was added to the model (Fig 1). A random number was generated to decide whether a transient motion step, directed superiorly and anteriorly, would occur instead of a random walk step. The size of the large step was randomly chosen between 0 mm and a maximum step length of 5.5 mm to maximize the agreement with the observed traces (Fig 1).

The same step was used for the 2 directions, whereas the left/right direction was unaffected (in agreement with the observation that transient excursions had a very small impact on the left/right position of the prostate). The probability of transient motion was set to give the approximately same number of excursions as the observed traces (0.12 min^{-1} for simulations compared with 0.11 min^{-1} for the observed traces, motivated by the choice of not having a minimum value for the size of the simulated transient motion). The method is illustrated in Figure 2. After the transient motion occurred within the model, the likelihood of a new (second) transient step was
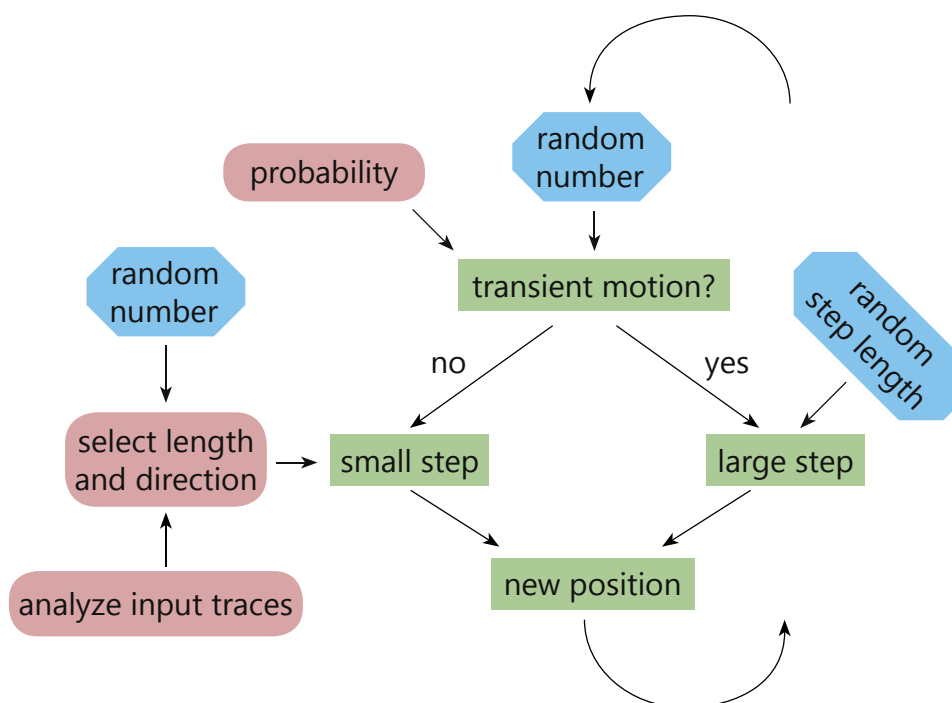
Figure 2   Overview of the steps in the random walk simulation. Artificial transient motion was created with a large step, alternately directed anteriorly/superiorly and then posteriorly/inferiorly. For simulations 1 and 3, the probability of transient motion was set to 0.

increased by a factor of 10 (Fig S1). When the second transient step would occur, it would be assigned the exact opposite direction and the same magnitude as the initial first transient motion, thus effectively returning the prostate to its approximate starting position.

Simulations

Four simulations with different combinations of input parameters and choice of evaluation were used in this study and are presented in Table 1. For each simulation, 548 motion traces were obtained with the random walk model and evaluated against observed traces. The purpose of each simulation was as follows:

- Simulation 1: to reproduce the motion of all observed traces without artificial transient excursions

- Simulation 2: to reproduce the motion of all observed traces using artificial transient excursions
- Simulation 3: to reproduce the motion of excursion-free observed traces without artificial transient excursions
- Simulation 4: to reproduce the motion of observed traces with excursions using artificial transient excursions

Evaluation

To quantify the agreement between simulated and observed traces, 2 metrics were calculated: the difference between the average position of the simulated traces and the average position of the observed traces and the difference in the position variance among the simulated traces and the position variance among the observed

Table 1   Performed simulations using either motion data from all observed traces or only traces without transient excursions as input

Simulation	Input parameters	Simulated Excursions	Comparison
1	All traces	No	All traces (n = 548)
2	No excursion traces	Yes	All traces (n = 548)
3	No excursion traces	No	No-excursion traces (n = 320)
4	All traces	Yes	With-excursion traces (n = 228)

Note: Artificial transient excursions were added to emulate the transient excursions in the observed data. For each simulation, 548 traces were obtained with the random walk model.
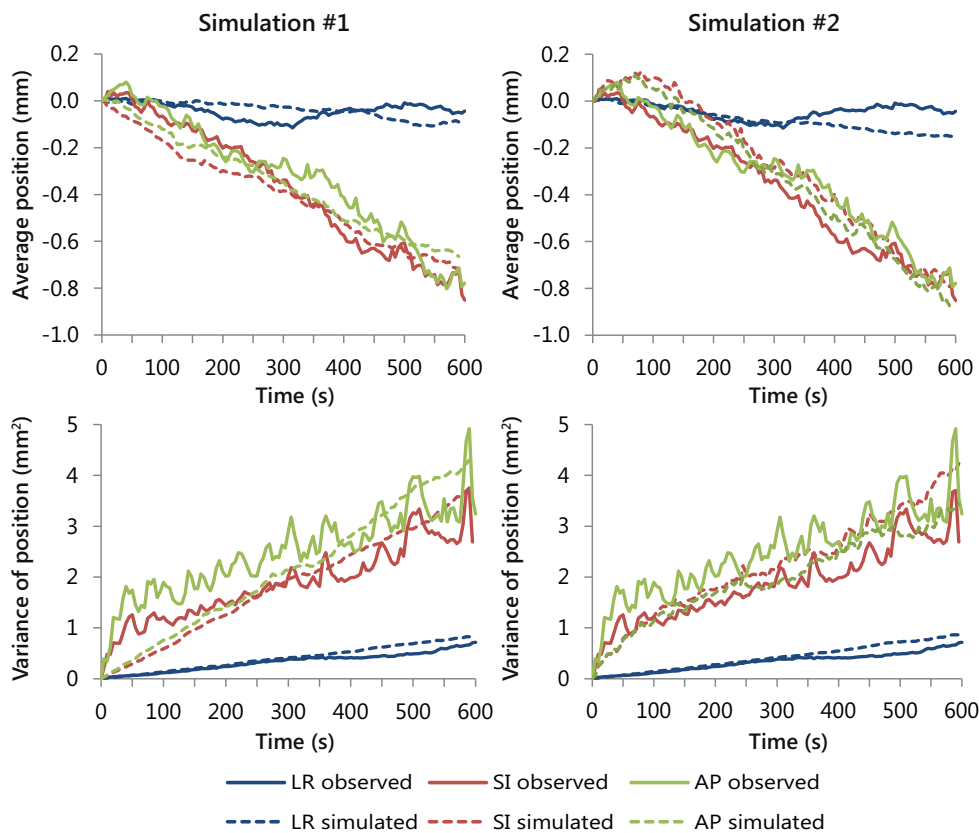
Figure 3 Time-resolved results from simulations 1 (left) and 2 (right; solid lines), comparing metrics from simulated traces (n = 548) to the observed traces (n = 548; dashed lines). Simulation 1 used a random walk model with model input from all traces, and simulation 2 added artificial transient excursions and used observed traces without excursions as model input.

traces. For the first metric, the average of the difference was evaluated, but for the second metric, the standard deviation of the difference was evaluated. For both metrics, the evaluation was done for each 100-second interval up to 600 seconds.

The diffusion coefficient was calculated in each dimension for each set of traces (either simulated or observed) according to:

$$D = \frac{1}{2} \cdot \frac{x^2}{t}, \tag{1}$$

where D is the diffusion coefficient, and x^2 is the average of the squared displacement at time t for all traces in the dataset (either simulated or observed). The diffusion coefficient was calculated at $t = 4$ min and $t = 8$ minutes, which was chosen to reflect an intermediate and a long time elapsed since patient setup (where the prostate displacement was assumed to be 0).

Results

The 548 prostate motion traces in the dataset lasted an average of 10.1 minutes. Among these, 228 had one or several excursions (the maximum number for a single

trace was 13), whereas 320 had no transient excursions (Fig 1). The overall probability of transient motion was 0.11 min^{-1}. In general, there was a good agreement between simulated and observed traces (Figs 3 and 4). Simulations 1 and 2, which attempted to recreate the behavior of all observed traces, showed similar agreement of the average position (average difference in the 0-600–second interval of 0.06 mm and 0.07 mm, respectively; Fig S2), but simulation 2 better reproduced the rapid increase in variance at the start of the observed traces (Fig 3).

For simulation 3, the random walk without added transient excursions was compared with observed traces without transient excursions. Excellent agreement with the observed traces was observed, especially for the 0 to 300 seconds time interval (Fig 4, left). After approximately 400 seconds, the variance of the observed traces seemed to reach toward a threshold whereas the variance of the simulated traces, in accordance with the random walk model, increased linearly. Lastly, for simulation 4, artificial transient excursions were added to the model, all traces were used as input, and the results were compared with the observed traces with excursions. The average position of the observed traces could not be reproduced (average difference 0.19 mm). However,
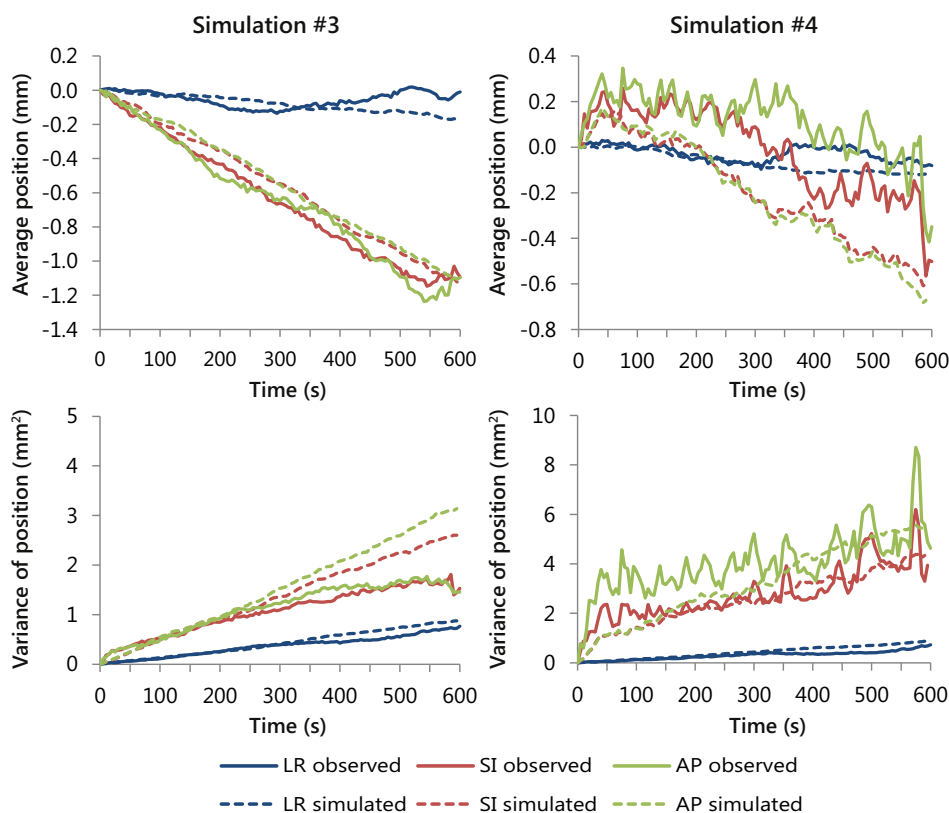
Figure 4 Results from simulations 3 (left) and 4 (right; dashed lines) compared with the observed traces (solid lines). Simulation 3 used a random walk model with input from and was compared with traces without transient excursions. Simulation 4 used the random walk model with input from all traces with added artificial excursions and was compared with motion traces that contained one or several excursions. Note the different scales on the Y axes.

some qualitative agreement with the observed variance could be seen (Fig 4; right).

The calculated diffusion coefficients for the simulations and the corresponding dataset of observed traces agreed well (Table 2), especially for simulation 3 at 4 minutes and simulation 4 at 8 minutes. The difference between simulated and observed diffusion coefficients was less than 0.03, 0.2 and 0.3 mm²/min in the left/right, superior/inferior, and anterior/posterior directions, respectively. Even though the difference was the smallest for simulation 3 at 4 minutes, it was also the largest at 8 minutes for simulation 3 (Fig 4; left).

The differences between repeated simulations with 548 simulated traces were small enough to be disregarded (Fig S1).

Discussion

The aim of this study was to model observed prostate motion using a random walk model either with or without artificial transient excursions. The observed motion consisted of motion data from radiation therapy regimens for 17 patients. Two simulations in this study aimed to model the motion in the entire dataset using a random walk model with input from all observed traces and using a random walk model with input from only excursion-free traces while adding artificial transient excursions. Both approaches resulted in reasonable agreement, suggesting the applicability of a random walk approach to modeling prostate motion, even if it includes transient excursions (ie, large and rapid prostate movements).

A characteristic of the random walk model is that the displacement variance increases linearly with time with no maximum. There was a quick increase in variance at the start of the observed traces, which was better reproduced with added transient motion than without it. Meanwhile, for the observed traces without transient motion, the variance increased linearly for several minutes but seemed to reach a maximum toward the end of the traces (Fig 4; left). The attempt to model the motion of the excursion-free traces produced excellent agreement for the approximately first 5 minutes and gave further reason to consider the random walk model as a viable alternative for prostate motion modeling for the timespan of a conventional radiation therapy fraction. With the increased availability of flattening filter free beams, 5 minutes also will remain the relevant timeframe for hypofractionated prostate treatments. The difference between the observed traces in Figures 3 (right) and 4

Table 2 Diffusion coefficients, D (mm^2/min), for observed and simulated traces, calculated with equation (1)

	Simulated D			Observed D		
	LR	SI	AP	LR	SI	AP
$t = 4$ min						
Simulation 1	0.01	0.33	0.36	0.01	0.38	0.57
Simulation 2	0.01	0.39	0.45	0.01	0.38	0.57
Simulation 3	0.01	0.19	0.22	0.02	0.19	0.26
Simulation 4	0.01	0.59	0.99	0.01	0.74	1.22
$t = 8$ min						
Simulation 1	0.03	0.65	0.86	0.01	0.54	0.81
Simulation 2	0.03	0.62	0.76	0.01	0.54	0.81
Simulation 3	0.03	0.53	0.65	0.02	0.37	0.40
Simulation 4	0.03	0.79	1.56	0.01	0.81	1.56

LR, left/right; SI, superior/inferior; AP, anterior/posterior.

(right) is that excursion-free traces have been removed in the latter. When comparing the figures, it is clear that the large variation in variance was due to transient excursions.

Using a random walk model to simulate prostate motion was recently proposed by Ballhausen et al.[22,23] The authors showed that treatment margins calculated assuming a random walk are smaller than those calculated on the basis of a Gaussian approximation[22] and give compelling support for the use of a random walk model on the basis of prostate motion from 6 patients.[23] The present study complements those results by isolating the effect of transient excursions on the applicability of the random walk model. Clearly, any random walk model will find it difficult to recreate the rapid motion shown in Figure 1A, and a fit to prostate motion including such motion might overestimate the effect of the drifting component of prostate motion.

Despite these challenges, reasonable agreement was achieved with the random walk model in this study (Fig 3; left). Even better agreement was found between simulated motion and excursion-free motion, which further suggests that the random walk model is suited for modeling prostate drift. Approximately half of the traces had one or several transient excursions with an average of 0.11 excursions per minute. As long as the prostate quickly returns to its original position, these would have a marginal impact on treatment and the required margins. If, however, the timing of pretreatment imaging happens to coincide with an excursion or the prostate does not quickly return to its original position, the prostate will be misplaced during that treatment fraction.

Intrafraction prostate motion is arguably becoming more relevant with the increased prevalence of daily pretreatment prostate imaging. Interfraction correction (ie, correcting the target position before treatment) can be considered a first-order correction and intrafraction a second-order correction. Intrafraction corrections should

ideally include not only translations but also rotations and deformations. Studies that model deformation are, to the authors' knowledge, limited to interfractional motion.[21] Modeling intrafraction motion with rotations and deformations as well as translations is a potential topic of future research. Other potential areas of improvement include a more sophisticated model of long-term trends (eg, where variance may subside with time as observed for the excursion-free traces), a more sophisticated model of short-term noise (eg, the patient is getting comfortable), and patient-specific modeling.

Conclusions

The random walk model could successfully recreate the characteristics of observed prostate motion from 17 patients, especially when considering only motion from treatment fractions without transient excursions during the first 5 minutes. Although the motion model cannot predict the exact noisy trajectory for any given patient, the model agrees well with the time-average trends. The transient excursions caused a rapid increase in prostate displacement variance, which was difficult to recreate without the use of artificial excursions. The overall agreement was, however, still satisfactory. This suggests that the random walk model is applicable for prostate motion modeling and can be used for simulations of radiation therapy delivery or treatment margin calculation.

Acknowledgments

Supplementary data

Supplementary material for this article (http://dx.doi.org/10.1016/j.adro.2017.03.005) can be found at www.advancesradonc.org.

References

1. Kitamura K, Shirato H, Seppenwoolde Y, et al. Three-dimensional intrafractional movement of prostate measured during real-time tumor-tracking radiotherapy in supine and prone treatment positions. *Int J Radiat Oncol Biol Phys.* 2002;53:1117-1123.
2. Ghilezan MJ, Jaffray DA, Siewerdsen JH, et al. Prostate gland motion assessed with cine-magnetic resonance imaging (cine-MRI). *Int J Radiat Oncol Biol Phys.* 2005;62:406-417.
3. Huang E, Dong L, Chandra A, et al. Intrafraction prostate motion during IMRT for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2002;53:261-268.

4. Langen KM, Willoughby TR, Meeks SL, et al. Observations on real-time prostate gland motion using electromagnetic tracking. *Int J Radiat Oncol Biol Phys*. 2008;71:1084-1090.

5. Bittner N, Butler WM, Reed JL, et al. Electromagnetic tracking of intrafraction prostate displacement in patients externally immobilized in the prone position. *Int J Radiat Oncol Biol Phys*. 2010;77:490-495.

6. Kupelian P, Willoughby T, Mahadevan A, et al. Multi-institutional clinical experience with the Calypso System in localization and continuous, real-time monitoring of the prostate gland during external radiotherapy. *Int J Radiat Oncol Biol Phys*. 2007;67:1088-1098.

7. Zhang P, Mah D, Happersett L, Cox B, Hunt M, Mageras G. Determination of action thresholds for electromagnetic tracking system-guided hypofractionated prostate radiotherapy using volumetric modulated arc therapy. *Med Phys*. 2011;38:4001-4008.

8. Litzenberg DW, Balter JM, Hadley SW, et al. Prostate intrafraction translation margins for real-time monitoring and correction strategies. *Prostate Cancer*. 2012;2012:130579.

9. Lips IM, van der Heide UA, Kotte AN, van Vulpen M, Bel A. Effect of translational and rotational errors on complex dose distributions with off-line and on-line position verification. *Int J Radiat Oncol Biol Phys*. 2009;74:1600-1608.

10. Li HS, Chetty IJ, Enke CA, et al. Dosimetric consequences of intrafraction prostate motion. *Int J Radiat Oncol Biol Phys*. 2008;71: 801-812.

11. Langen KM, Lu W, Ngwa W, et al. Correlation between dosimetric effect and intrafraction motion during prostate treatments delivered with helical tomotherapy. *Phys Med Biol*. 2008;53:7073-7086.

12. 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;48:1187-1195.

13. Sawant A, Venkat R, Srivastava V, et al. Management of three-dimensional intrafraction motion through real-time DMLC tracking. *Med Phys*. 2008;35:2050-2061.

14. Wilbert J, Meyer J, Baier K, et al. Tumor tracking and motion compensation with an adaptive tumor tracking system (ATTS): system description and prototype testing. *Med Phys*. 2008;35:3911-3921.

15. Depuydt T, Verellen D, Haas O, et al. Geometric accuracy of a novel gimbals based radiation therapy tumor tracking system. *Radiother Oncol*. 2011;98:365-372.

16. Alterovitz R, Goldberg K, Pouliot J, et al. Registration of MR prostate images with biomechanical modeling and nonlinear parameter estimation. *Med Phys*. 2006;33:446-454.

17. Bharatha A, Hirose M, Hata N, et al. Evaluation of three-dimensional finite element-based deformable registration of pre- and intraoperative prostate imaging. *Med Phys*. 2001;28: 2551-2560.

18. Hensel JM, Menard C, Chung PW, et al. Development of multiorgan finite element-based prostate deformation model enabling registration of endorectal coil magnetic resonance imaging for radiotherapy planning. *Int J Radiat Oncol Biol Phys*. 2007;68:1577-1583.

19. Yan D, Jaffray DA, Wong JW. A model to accumulate fractionated dose in a deforming organ. *Int J Radiat Oncol Biol Phys*. 1999;44: 665-675.

20. Jaillet F, Shariat B, Vandorpe D. Deformable object reconstruction with particle systems. *Comput Graph*. 1998;22:189-194.

21. Söhn M, Birkner M, Yan D, Alber M. Modelling individual geometric variation based on dominant eigenmodes of organ deformation: implementation and evaluation. *Phys Med Biol*. 2005; 50:5893-5908.

22. Ballhausen H, Reiner M, Kantz S, Belka C, Söhn M. The random walk model of intrafraction movement. *Phys Med Biol*. 2013;58: 2413-2427.

23. Ballhausen H, Li M, Hegemann NS, Ganswindt U, Belka C. Intrafraction motion of the prostate is a random walk. *Phys Med Biol*. 2015;60:549.