An efficient model to guide prospective T2-weighted 4D magnetic resonance imaging acquisition

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(Received 12 April 2017; revised 7 March 2018; accepted for publication 3 April 2018; published 6 May 2018)

Purpose: To establish a mathematical model to guide prospective T2-weighted four-dimensional magnetic resonance imaging (4DMRI) acquisition and to propose an efficient solution to expedite prospective T2-weighted 4DMRI acquisition.

Methods: Prospective T2-weighted 4DMRI acquisition was characterized by a mathematical model with 4DMRI acquisition time as the objective function and completeness of the image set, acquisition timing, image contrast, and image artifacts as constraints. Given the irregular nature of human respiration, an efficient solution based on the greedy strategy (ESGS) was proposed. The efficiency of the ESGS method was validated using healthy human subjects. Comparisons were made with the previous 4DMRI method incorporating the prefixed-order respiratory state splitting (PO-RSS) technique.

Results: 4DMRI image sets acquired using the ESGS and PO-RSS methods had similar image quality. The average time to acquire a 4DMRI image set covering 60 slices at 10 respiratory states was reduced by 30%, from 13.1 min using the PO-RSS method to 9.0 min using the ESGS method. It was demonstrated that high-quality T2-weighted 4DMRI could be obtained within a reasonable amount of time and all slices within each of the three-dimensional volumes were indeed acquired at the same respiratory state.

Conclusions: The ESGS method substantially reduces the acquisition time for T2-weighted 4DMRI, making it ready for clinical evaluation to obtain abdominal tumor motion for radiotherapy treatment planning. © 2018 American Association of Physicists in Medicine [<https://doi.org/10.1002/mp.12923>]

Key words: efficient solution, greedy strategy, mathematical model, prospective 4DMRI, T2 weighted

1. INTRODUCTION

Four-dimensional (4D) magnetic resonance imaging (MRI) is of great interest due to its potential in radiotherapy motion management.^{1–6} Compared to 4D computed tomography (4DCT),^{7–12} 4DMRI has better soft tissue contrast and involves no ionizing radiation. It provides a powerful tool for studying tumor and/or organ motion for abdominal cancer. Tumor motion information can be used to derive internal target volume (ITV) for radiotherapy treatment planning using either the entire motion range for nongated radiation therapy or a selected range for gated radiation therapy.¹³ Appropriate ITV treatment margins are determined to maintain a balance between sufficient target dose coverage and sparing of surrounding radiosensitive organs-at-risk (OARs).

In general, 4DMRI can be classified into two categories: retrospective binned 4DMRI^{5,6,14–20} and prospectively triggered 4DMRI.^{3,21,22} Retrospective 4DMRI sorts images into various respiratory states retrospectively using respiratory signal acquired through either external or internal surrogates. Respiratory signal obtained through external surrogates needs to

be acquired simultaneously with image acquisition, whereas respiratory signal obtained through internal surrogates needs to be acquired either in between individual images (e.g., navigator signal) or every few k-space lines (e.g., self-gating projection profile). Retrospective sorting can also be achieved using image-based respiratory surrogates such as body area.¹⁴ Retrospective 4DMRI does not involve real-time respiratory signal processing. It is relatively easy to implement. However, it is more susceptible to breathing irregularity because breathing pattern changes are not handled in real-time, which may result in inaccurate respiratory sorting. Prospective 4DMRI monitors respiratory signal through either external or internal surrogates and adjusts timing of image acquisition in real time. Although phase-based prospective 4DMRI is still susceptible to breathing irregularity such as breathing period variations, amplitude-based prospective 4DMRI, on the other hand, is very robust to breathing irregularity. This is because in amplitude-based prospective 4DMRI, images are acquired only when the predetermined conditions are met. As a result, breathing irregularity may increase 4DMRI acquisition time, instead of causing inaccurate respiratory binning, and image artifacts.

In 2013, Hu et al.²¹ demonstrated the feasibility of using a prospective amplitude triggering system to achieve T2-weighted 4DMRI. Compared to previous 4DMRI techniques based on balanced steady-state free precession (bSSFP) or fast spoiled gradient echo, T2-weighted 4DMRI has better tumor tissue contrast. The original proof-of-concept T2-weighted 4DMRI method, however, did not handle the missed trigger issue²² efficiently. A missed trigger refers to a situation in which a predefined respiratory state (or trigger) either does not appear because of irregular shallow breathing, or occurs before the end of image acquisition of the previous slice and therefore gets ignored by the MRI scanner. In the prefixed-order 4DMRI acquisition, each missed trigger is followed by multiple skipped triggers because these are not paired with the slice currently under image acquisition. As the number of respiratory states increases, the available image acquisition time between adjacent respiratory states decreases. When the available image acquisition time drops below what is required for two-dimensional (2D) image acquisition of a slice which usually happens at mid-inhalation and mid-exhalation, missed triggers occur frequently, which results in a large number of skipped triggers in the prefixed-order 4DMRI and thus substantially increases 4DMRI acquisition time. To reduce missed triggers caused by decreased time interval between respiratory states, Du et al.²² developed a method termed prefixed-order respiratory state splitting (PO-RSS). In the PO-RSS method, respiratory states are interleaved into two groups to increase time interval between respiratory states and reduce the chance of missed triggers. Although the PO-RSS method is able to reduce the average acquisition time to 13.2 min (range, 8.9–18.3 min) to obtain a T2-weighted 4DMRI image set covering 60 slices at 10 respiratory states, it is still relatively long for clinical evaluation. The relatively long scan time (e.g., >10 min) not only compromises patient comfort, but also increases the chance of voluntary motion which may complicate interpretation of 4DMRI. Even though there are no clear criteria for long scan time, we feel that <10 min of scan time would be acceptable because each individual MRI scan in a clinical MRI exam usually lasts 4–6 min.

To expedite 4DMRI image acquisition, we proposed a mathematical model and an efficient solution to guide T2-weighted 4DMRI image acquisition. Given the irregular nature of human respiration, it may not be practical to find a global optimal solution that minimizes 4DMRI acquisition time. A good approximation, however, is achievable using the greedy strategy²³ which selects a locally optimal choice at each individual stage with the hope of achieving a global optimum. The proposed solution, termed as efficient solution based on the greedy strategy (ESGS), was validated and compared with the previous PO-RSS method using healthy human subjects.

2. MATERIALS AND METHODS

Respiratory signals and MRI images were acquired from healthy human subjects. The use of human subjects in this

study was approved by the Institutional Review Board at Washington University in St. Louis.

2.A. Mathematical model to guide prospective 4DMRI acquisition

Prospective 4DMRI acquisition can be generalized by a mathematical model in which 4DMRI acquisition time is the objective function that needs to be minimized. The acquisition model is subject to constraints as described in the constraint optimization problem (COP) (1).

- Minimize:* 4DMRI acquisition time
- Subject to:*
1. Acquire all slices at all respiratory states
 2. Ensure no timing conflict in data acquisition
 3. Select imaging parameters to achieve given contrast
 4. Control image artifacts
- (1)

From the generalized model described in the COP (1), we can obtain specific requirements that are needed to guide T2-weighted 4DMRI acquisition. In the model, the objective is to minimize 4DMRI acquisition time. For prospective 4DMRI, image acquisition for a slice at a respiratory state is triggered when the respiratory signal matches that specific respiratory state, which is defined by the predetermined respiratory amplitude and stage (inhalation or exhalation). Assume that the timestamp of a trigger in 4DMRI acquisition is expressed as $t_{s,d}$ where s represents the slice and d indicates the respiratory state, 4DMRI acquisition time can be determined by the maximum timestamp of all triggers, or $\max(t_{s,d})$ for $s \in [1, S]$ and $d \in [1, D]$, where S and D represent the total number of slices and respiratory states, respectively. With the ESGS method, image acquisition of slices at individual respiratory states may not always follow the sequential order (i.e., from slice 1 to S or from respiratory state 1 to D). Therefore, $\max(t_{s,d})$ indicates image acquisition of the last slice and last respiratory state in time, rather than the last slice in position or the last respiratory state in respiration.

There are four constraints in the model. The first one is to ensure completeness of the 4DMRI image set, namely, images from all slices and respiratory states are acquired. Mathematically, this can be expressed as $\forall s \in [1, S] \ \& \ \forall d \in [1, D]$. The second constraint is to avoid timing conflicts in image acquisition. Specifically, time between two consecutive triggers has to be longer than image acquisition time (T_{Shot}) for a single slice at a specific respiratory state, or $abs(t_{s1,d1} - t_{s2,d2}) > T_{Shot}$, given $s1 \neq s2$ or $d1 \neq d2$. The third constraint is to select appropriate imaging parameters to achieve the desired contrast. For T2-weighted 4DMRI, echo time (TE) is within the range of 60–120 ms, and repetition time (TR) is typically longer than 6 s. The fourth constraint is

to control image artifacts. A specific image artifact related to T2-weighted 4DMRI is the slice cross-talk effect. It is caused by the fact that slice excitation profiles are not perfectly rectangular²⁴ and manifests as signal intensity variation between slices, which becomes noticeable when images are grouped into a three-dimensional (3D) volume and displayed in orientations other than the original acquisition orientation. The slice cross-talk effect becomes less severe when slices are further apart in location. To minimize this artifact, a constraint needs to be implemented so that once an image is acquired from a slice, no adjacent slices will be allowed for image acquisition for a given amount of time ($T_{crosstalk}$), e.g. $T_{crosstalk} = 4$ s for $abs(s1 - s2) \leq 4$ and $T_{crosstalk} = 3$ s for $4 < abs(s1 - s2) \leq 7$.

Therefore, for prospectively triggered T2-weighted 4DMRI, COP (1) becomes:

$$\begin{aligned}
 & \text{Minimize : } \max(t_{s,d}) \text{ for } s \in [1, S] \text{ \& } d \in [1, D] \\
 & \text{Subject to : } 1. \quad \forall s \in [1, S] \text{ \& } \forall d \in [1, D] \\
 & \quad 2. \quad abs(t_{s1,d1} - t_{s2,d2}) > T_{Shot} \text{ given } s1 \neq s2 \text{ or } d1 \neq d2 \\
 & \quad 3. \quad TE \text{ uses a preselected fixed value within } [60, 120] \text{ milliseconds} \\
 & \quad \quad TR = abs(t_{s,d1} - t_{s,d2}) \geq 6 \text{ seconds given } d1 \neq d2 \\
 & \quad 4. \quad abs(t_{s1,d1} - t_{s2,d2}) > T_{crosstalk} \\
 & \text{where } T_{crosstalk} = \begin{cases} 4 \text{ seconds} & \text{if } 0 < abs(s1 - s2) \leq 4 \\ 3 \text{ seconds} & \text{if } 4 < abs(s1 - s2) \leq 7 \\ 0 \text{ seconds} & \text{if } abs(s1 - s2) = 0, \text{ or } > 7 \end{cases}
 \end{aligned} \tag{2}$$

For prospectively triggered T2-weighted 4DMRI, assume the number of respiratory states is D and the respiratory amplitudes at the end-of-exhalation and end-of-inhalation are A_{eoe} and A_{eoi} , respectively. Then, the respiratory amplitude ($A_{trig,d}$) and stage ($S_{trig,d}$) that correspond to each respiratory state (or trigger) can be determined by Eq. (3).

$$\begin{cases} A_{trig,d} = A_{eoe} + (d - 1)A_{step} & \text{for } d \in [1, \frac{D}{2}] \\ S_{trig,d} = \text{inhalation} \\ A_{trig,d} = A_{eoi} - (d - \frac{D}{2} - 1)A_{step} & \text{for } d \in [\frac{D}{2} + 1, D] \\ S_{trig,d} = \text{exhalation} \end{cases}$$

where $A_{step} = (A_{eoi} - A_{eoe}) / (D/2)$

Respiratory signal can be acquired using any surrogates (e.g., internal navigator or respiratory bellows). We used a pneumatic respiratory bellows (Philips Healthcare, Best, the Netherlands) wrapped around a human subject's abdomen. A_{eoe} and A_{eoi} were obtained in the preparation stage²¹ immediately before 4DMRI acquisition. A tolerance window of $\pm 5\%$ of the respiratory range was used. Image acquisition started when respiratory amplitude fell within $A_{trig,d} \pm A_{tol}$, where $A_{tol} = 0.05(A_{eoi} - A_{eoe})$.

2.B. Efficient solution based on greedy strategy

Due to the irregular nature of human respiration, an efficient solution is proposed based on the greedy strategy. In the ESGS method, slices and respiratory states are not acquired in a specific order. Respiratory signal is constantly monitored throughout 4DMRI acquisition. When a match is found with any of the respiratory states, the ESGS method identifies a slice that satisfies all the constraints in COP (2) and has not been acquired at that respiratory state to start image acquisition. This process continues until images from all slices and respiratory states have been acquired. At any stages, if multiple slices satisfy all the constraints for a given respiratory state, the one that is closest to the previously acquired slice is selected. The flowchart of the ESGS method is illustrated in Fig. 1.

2.C. Compatibility with previous acquisition methods

All previous T2-weighted 4DMRI methods are solutions to the mathematical model proposed in this study, even though they may not be the most efficient one. Previous

FIG. 1. Flowchart of 4DMRI acquisition using the ESGS method. Here $count_s$ is to check if slice s has waited enough time since last acquisition (≥ 6 s). An acquisition variable $mark_{s,d}$ (false or true) is used to indicate if slice s has been acquired at respiratory state d .

methods have low acquisition efficiency because they have unnecessary constraints. For example, Hu et al.²¹ and Du et al.²² proposed methods in which slices were paired with predetermined respiratory states and a MRI image for a given slice at a specific respiratory state was acquired only when the predetermined respiratory state appeared. These methods are referred to as the prefixed-order (PO) methods. Due to the irregular nature of human respiration, missed triggers are unavoidable in 4DMRI acquisition. The efficacy of 4DMRI acquisition depends heavily on how missed triggers are handled. In the PO methods, if a trigger is missed, 4DMRI acquisition is paused until the same respiratory state appears again which is at least one respiratory cycle later, ignoring all other respiratory states that appear in between. These skipped triggers place an unnecessary constraint, which reduces 4DMRI acquisition efficiency. The ESGS method, however, handles missed triggers differently. Instead of waiting for the same trigger to appear again, it takes whatever trigger that appears next to continue 4DMRI acquisition. Therefore, it is capable of achieving much higher 4DMRI acquisition efficiency.

In the previous PO-RSS method, 60 slices were interleaved into 6 packages with 10 slices per package. 4DMRI acquisition was based on individual packages. Within a package, slices were separated by 6 slice thicknesses. In-between packages, image acquisitions for physically adjacent slices were separated by at least the multiplication of the number of slices per package and T_{shot} ($10T_{shot} = 3,800$ ms). In reality, the temporal separation was longer than the $10T_{shot}$ theoretical limit due to time intervals between 2D image acquisitions. As a coarse estimate, the average separation, or available relaxation time, was about 13.1 s given the average simulated PO-RSS 4DMRI acquisition time of 13.1 min, use of 6 packages, and 10 respiratory states. It provided sufficient amount of time for adjacent slices to recover. Thus, the cross-talk effect was minimal in the PO-RSS method. In the ESGS method, slices are no longer acquired in a prefixed order. There exists a possibility that slices physically adjacent to each other may be acquired consecutively, creating the cross-talk artifact. Therefore, in the ESGS method, a specific constraint is required to control the cross-talk artifact.

2.D. 4DMRI acquisition

The ESGS and PO-RSS methods were implemented using a single-shot turbo spin echo (TSE) sequence in the Philips PARADISE pulse sequence programming environment (Philips Healthcare, Best, the Netherlands, version R2.5.3). The PO-RSS method was implemented in the same manner as described in the previous publication.²² T2-weighted 4DMRI was acquired using a Philips Achieva 1.5T MRI scanner (Philips Healthcare, Best, the Netherlands). Key imaging parameters for 4DMRI acquisition are listed below. Sixty slices were acquired at each of the 10 respiratory states. The slice thickness was 3.0 mm. The in-plane field of view was 375×260 mm² and the in-plane spatial resolution was 1.5×1.5 mm². To produce T2 weighting, TE of 75 ms and

TR of more than 6 s were used in image acquisition. Parallel imaging (acceleration factor of 2) and partial Fourier (70% k-space coverage) techniques were used to reduce the 2D image acquisition time for a slice (T_{shot}) to 380 ms. The respiratory states were determined according to Eq. (3) using 20 s of respiratory signal acquired in the preparation stage. Ten respiratory states were used to equally sample the respiratory range based on the respiratory amplitude and stage (0%, 20%↑, 40%↑, 60%↑, 80%↑, 100%, 80%↓, 60%↓, 40%↓, and 20%↓), where 0% and 100% represented end-of-exhalation and end-of-inhalation, respectively, and “↑” and “↓” represented the inhalation stage and exhalation stage, respectively. Since respiratory states were determined based on respiratory signal acquired during the preparation stage, each individual 4DMRI acquisition had its own respiratory states (or triggers). The respiratory states determined in different 4DMRI scans should be pretty similar for the same human subject, but may not be exactly the same. 4DMRI images were acquired in the sagittal orientation. Based on respiratory states, the acquired 2D images were grouped into 3D volumes and displayed in the coronal orientation.

The constraint to reduce the slice cross-talk artifact was estimated based on theoretical analysis. In the abdomen area, longitudinal relaxation times (T_1) of typical organs, such as liver and kidney, are around 600–700 ms.²⁵ About 99% of the magnetization can be recovered using a $T_{crosstalk}$ of 4 s ($1 - e^{-4000/700} = 0.99$). Therefore, in the ESGS method, a conservative setting for the cross-talk constraint would be $T_{crosstalk} = 4$ s for $abs(s1 - s2) \leq 4$ and $T_{crosstalk} = 3$ s for $4 < abs(s1 - s2) \leq 7$.

To evaluate the acquisition efficiency of the ESGS method and compare it with that of the PO-RSS method, we simulated 4DMRI acquisition using respiratory signals from 11 healthy human subjects (age average: 25.5 yr, age range: [20, 36], 2 female and 9 male). Among the 11 respiratory signals, 7 overlapped with those in our previous study²² and 4 were newly acquired. The current study excluded three respiratory signals from the previous study²² because these were from human subjects who also had new respiratory signals acquired and used in the simulation study. For comparison, we acquired 4DMRI image sets using both the ESGS and PO-RSS methods from a healthy human subject. For all 4DMRI image acquisition, images were acquired in the sagittal orientation. These 4DMRI image sets were reformatted and displayed in the coronal orientation to assess effectiveness of respiratory binning.

To evaluate the cross-talk effect, we developed a quantitative metric called interslice image intensity variation (*ISIIV*). *ISIIV* is defined as the percentage change in image intensity between two adjacent slices.

$$ISIIV = \frac{I(s) - I(s-1)}{(I(s) + I(s-1))/2} \quad (4)$$

To reduce the effect of imaging noise on *ISIIV*, we use average signal intensity within a 30×30 mm² region of interest (ROI) at the uniform region of the liver in individual slices,

instead of signal intensity of a single voxel, to calculate *ISIIV*. To exclude blood vessels and air cavities, histogram analysis was utilized. Specifically, we plotted the histogram of voxel intensities within the ROI, identified the peak on histogram that corresponded to the liver (the bin with the highest occurring frequency), found the two intensity bins that had 20% of the highest occurring frequency on both side of the liver peak, and excluded voxels with intensities outside the range defined by the above two intensity bins. For the remaining voxels, only those with image intensities within $\pm 2\sigma$ of the average signal were used in calculation of *ISIIV*. The analysis was only focused on the liver to avoid anatomy induced signal change.

3. RESULTS

In the simulation study based on respiratory signals of healthy human subjects, acquisition time was obtained for 4DMRI incorporating the PO-RSS and ESGS techniques (Table I). The average acquisition time was 13.1 min for the PO-RSS method and 9.0 min for the ESGS method. Compared to the PO-RSS method, the ESGS method was able to reduce the average 4DMRI acquisition time by 30%. The improvement was statistically significant ($P < 0.001$ base on one-tailed paired Student's *t*-test). In Table I, we also listed the number of skipped triggers for the PO-RSS and ESGS methods. The ESGS method has substantially less skipped triggers. Skipped triggers in the ESGS method were due to two factors: (a) no slices could be selected because of constraints and (b) all slices were already acquired for a given respiratory state but the 4DMRI acquisition was not finished yet. Figure 2 shows 4DMRI acquisition schemes from a representative human subject using both the PO-RSS and ESGS methods, which clearly demonstrates the improvement in acquisition efficiency by using the ESGS method.

It was expected that image quality should be similar between the PO-RSS and ESGS methods despite image

acquisition efficiency. Although in general effective TR in the ESGS method was shorter than that in the PO-RSS method, it should not impact image quality because longitudinal magnetization already got fully recovered ($>99.5\%$) after $TR = 6T_1$ (~ 4000 ms for liver and kidney). Further waiting time ($TR > 6T_1$) would not result in any meaningful signal change increase (99.5% vs 100%). Besides effective TR, all other imaging parameters used in the PO-RSS and ESGS methods were exactly the same. Therefore, the two 4DMRI acquisition methods should have comparable image quality. A comparison of image quality between the PO-RSS and ESGS methods is shown in Fig. 3, which matches with our expectation. Qualitatively, the image quality is comparable between the two 4DMRI image sets [Figs. 3(a) and 3(b)]. In the reformatted images displayed in the coronal orientation, no obvious cross-talk artifacts are observed in both 4DMRI image sets. Also, no obvious abrupt changes are observed along the lung–liver boundary in both 4DMRI image sets, indicating that images were binned correctly into corresponding respiratory states. Figure 3(c) shows the *ISIIV* of the PO-RSS and ESGS methods for the respiratory state 0%.

Quantitatively, we calculated the *ISIIV* for each of the 10 respiratory states in a relatively uniform region of the liver which was ± 3.6 cm in the left/right direction from the approximate center of the liver in the reconstructed coronal images. The maximum, average, and standard deviation of the *ISIIV* for each respiratory state were listed in Table II. There was no statistically significant difference between the PO-RSS and ESGS methods (based on the two-tailed paired Student *t*-test), confirming that the two methods have similar level of the cross-talk effect.

Figure 4(a) shows T2-weighted images from a representative sagittal slice acquired using the ESGS method at 10 respiratory states. The acquired T2-weighted 4DMRI was also reformatted and displayed in the coronal orientation [Fig. 4(b)]. A movie that shows the respiratory motion in a sagittal slice can be found in Video S1. No obvious abrupt changes are found along the lung–liver boundary, indicating that all images within a 3D volume were acquired at the same respiratory state. To provide an intuitive idea of how images look like when slices are not acquired in the same respiratory state, we artificially shifted a few slices 3 respiratory states out of their appropriate respiratory state and displayed images in the coronal orientation, as shown in Fig. 4(c). The artifacts caused by incorrect binning are obvious and can be easily detected at the lung–liver boundary. The streak lines are more obvious along the upper boundary of the liver than along the lower boundary of the liver because (a) motion around the upper boundary of the liver is larger than that around the lower boundary of the liver²⁶ and (b) the contrast between the lung and the liver is more dramatic than that between the liver and the kidney.

4. DISCUSSION

The primary focus of this study was to advance our motion management capability by developing a novel

TABLE I. Acquisition time for 4DMRI incorporating the PO-RSS and ESGS methods.

Subject signals	PO-RSS (min)	ESGS (min)	Time reduction (%)	PO-RSS skipped triggers	ESGS skipped triggers
1	10.8	7.7	28	1426	690
2	13.0	9.7	26	1349	548
3	16.9	9.5	44	1733	465
4	13.8	9.2	34	1647	662
5	13.5	7.9	42	1627	600
6	11.5	7.8	32	1455	628
7	9.5	7.5	21	1190	550
8	15.6	10.4	33	1577	484
9	12.1	9.1	25	1409	546
10	18.3	12.2	33	1852	727
11	8.9	7.6	15	1196	717
Ave	13.1	9.0	30	1496	602
<i>P</i> value	<0.001		–

FIG. 2. Simulated 4DMRI acquisition using (a) the PO-RSS method and (b) the ESGS method. The respiratory signal was from a representative healthy human subject (a.u. stands for arbitrary unit). The lines represent the respiratory signal and the dots represent the time points that 2D images are acquired from individual slices and respiratory states. The zoomed in time duration between 330 and 385 s is also displayed. [Color figure can be viewed at wileyonlinelibrary.com]

prospective 4DMRI method suitable for clinical evaluation. Only healthy human subjects were involved in this study. Even though their ages may not match the ages of a clinical patient population, the irregular nature of respiration exists in both groups. Therefore, use of healthy human subjects is justifiable in methodology development. There is a possibility that patients may have more irregular respiration. In that case, 4DMRI acquisition time is likely to increase. This possibility will be investigated in future studies.

There are two potential imaging artifacts directly related to respiratory motion. One is blurring within individual images and the other is imperfect respiratory binning causing anatomy discontinuity across slices. Blurring is due to motion of internal anatomy during k-space data acquisition for a single slice. It usually happens when multishot acquisition techniques, or a very long acquisition window, are utilized. In multishot acquisition techniques, acquisition of the entire k-space data for a slice is divided into multiple segments to

reduce the acquisition window. If these segments are acquired at different respiratory levels, they contain different anatomy information which, after k-space data combination and image reconstruction, may result in blurring artifact. Similarly, blurring artifact can also be caused by a very long acquisition window. In our 4DMRI acquisition, we use a single-shot technique with a short acquisition window (~ 250 ms). Since majority of anatomy information is encoded in the central part of k-space which can be acquired in even shorter amount of time (~ 100 ms), anatomy change within this 100 ms is only 1.0 mm given a typical respiratory motion range of 1.5 cm, and an exhalation to inhalation time of 1.5 s. Thus, motion-induced blurring artifact is rather minimal. In prospective respiratory amplitude triggered 4DMRI, use of the triggering window ($\pm 5\%$) can cause imperfect respiratory binning. For each respiratory state, images from individual slices may be acquired at any respiratory levels within the triggering window, causing slight anatomy discontinuity

FIG. 3. A comparison of image quality between the (a) PO-RSS and (b) ESGS methods. Images displayed here were from the respiratory state 0%. For both methods, 4DMRI images were acquired in the sagittal orientation (1st column) and reformatted and displayed in the coronal orientation (2nd column). To evaluate the cross-talk effect quantitatively, interslice image intensity variation (ISIIV) in a uniform region of the liver was plotted for both methods (c). The x-axis indicated the lateral distance from the approximate center of the liver in the reconstructed coronal images. These results confirmed comparable image quality between the two methods. [Color figure can be viewed at [wileyonlinelibrary.com](#)]

TABLE II. ISIIV of the PO-RSS and ESGS methods for the 10 respiratory states.

Respiratory state	ISIIV (max)		ISIIV (ave)		ISIIV (STD)	
	PO-RSS (%)	ESGS (%)	PO-RSS (%)	ESGS (%)	PO-RSS (%)	ESGS (%)
0%	4.68	3.89	1.22	1.39	1.14	0.90
20%↑	5.90	5.26	1.84	1.30	1.43	1.03
40%↑	3.21	7.40	1.19	2.29	0.84	1.69
60%↑	8.07	6.92	2.16	1.40	1.99	1.52
80%↑	9.39	6.03	1.48	1.89	2.04	1.60
100%	6.34	5.10	1.61	1.68	1.30	1.20
80%↓	2.66	5.33	0.82	1.61	0.59	1.29
60%↓	6.27	5.27	1.80	1.79	1.51	1.17
40%↓	6.40	6.04	1.14	1.98	1.32	1.38
20%↓	6.41	4.87	2.00	1.53	1.66	1.12
Ave	5.93	5.61	1.53	1.69	—	—
P value	0.65		0.44		—	

between slices, which may be easily detected when images are reformatted and displayed in orientations other than the acquired orientation. In our 4DMRI acquisition, the range of anatomy discontinuity between slices is expected to be within ± 0.75 mm given a $\pm 5\%$ triggering window and a typical respiratory motion range of 1.5 cm. For motion-induced blurring or anatomy discontinuity artifacts, respiratory states at end-of-inhalation and end-of-exhalation are less affected compared to those at mid-inhalation and mid-exhalation. At end-of-inhalation and end-of-exhalation, anatomy changes within the data acquisition window are smaller. Therefore, they are less susceptible to blurring artifact. Also, the effective triggering window is more likely to be 5%, instead of $\pm 5\%$, at end-of-inhalation and end-of-exhalation because

these are at the end of motion range, which makes them less susceptible to anatomy discontinuity artifact.

Although the previous PO-RSS method and the proposed ESGS method both belong to the prospective acquisition method, the ESGS method provides substantial improvement in acquisition efficiency compare to the previous PO-RSS method. Use of the Greedy algorithm substantially reduces the number of skipped triggers and successfully avoids unnecessary waiting time. Therefore, it is able to achieve better acquisition efficiency. Since the Greedy algorithm makes locally optimal choices at individual stages with the hope of achieving a global optimum, theoretically there is a possibility that it may not achieve the global optimal solution. In certain cases, they may even produce worst possible solutions.²⁷ However, in the ESGS method, the main effect is to remove unnecessary waiting time. Therefore, it proves to be more efficient than the PO-RSS method.

Because of the appealing tumor tissue contrast, T2-weighted 4DMRI has been investigated by several other groups as well.^{25,26} For example, Tryggstad et al. utilized the single-shot TSE sequence to continuously acquire 2D MRI images and retrospectively bin these 2D images into appropriate respiratory states. When images are continuously acquired, TR is fixed. Therefore, this method is able to provide relatively consistent signal intensity among slices even without using any constraints. On the other hand, continuous image acquisition and retrospective binning make this method more susceptible to breathing irregularity. In addition, there is a possibility that some slices may have more than necessary samplings, whereas others may have insufficient samplings of respiration. For 4DMRI methods based on 3D acquisition techniques, slice cross-talk is less of an issue due to volume excitation and 3D image reconstruction. However, they are more susceptible to blurring artifact due to the long acquisition time that is required to adequately sample a 3D k-space volume.

FIG. 4. T2-weighted 4DMRI was acquired in the sagittal orientation using the ESGS method. Images from a representative slice at 10 respiratory states were displayed (a) in the sagittal orientation and (b) in the coronal orientation. The white lines indicate the liver dome at end of exhalation (0%). No obvious abrupt changes were shown along the lung–liver boundary in images displayed in the coronal orientation, indicating all slices within a 3D volume were acquired at the same respiratory state. A synthetic example (c) shows how the coronal image looks like when slices are not acquired at the same respiratory state.

The image artifact constraint in COP (1) is important for the ESGS method. For example, slice cross-talk artifact may appear in 4DMRI due to use of variable TR. In MRI, the slice profile is not perfectly rectangular because of the truncation effect caused by finite duration of radiofrequency pulses. Because slice thickness is defined at the full width at half maximum, some spins in slices adjacent to the acquired slice are unavoidably excited. These spins have different effective TR compared with other spins in the same slice. These spins, if not allowed sufficient time to return to the equilibrium, contribute differently to MRI signal for different slices, causing signal variation across slices. Enforcing a constraint for slice cross-talk in COP (2) can minimize image nonuniformity. To determine constraints for image artifacts it usually involves a tradeoff between image quality and acquisition efficiency. If constraints are too strong, it can substantially increase 4DMRI acquisition time. If constraints are too weak, image artifacts may be observed in 4DMRI images. In addition, these constraints also depend on anatomy of interest. For example, an acceptable set of constraints for the liver may not be acceptable for blood vessels because of large

difference in T_1 between the liver and the blood. In this work, our primary goal was to demonstrate the feasibility of the ESGS method. For the feasibility validation purpose, one set of constraints that produced acceptable image quality would be sufficient. Optimizing constraints (e.g. $T_{crosstalk}$) for individual disease sites, although important, is beyond the scope of the current study and will be investigated in future.

A limitation of the prospective amplitude triggered 4DMRI method is that substantial pattern change in respiratory amplitude may significantly increase 4DMRI acquisition time. For example, irregular deep breathing in the preparation stage may result in a much longer 4DMRI acquisition time because end-of-inhalation and end-of-exhalation respiratory states determined in the preparation stage are less likely to appear in the 4DMRI acquisition stage. Since this type of breathing irregularity happens in the short preparation stage (20 s), it can be detected fairly quickly after 4DMRI acquisition starts. In this case, it is recommended to restart the 4DMRI sequence and rerun the preparation stage for better determination of respiratory states. Baseline drift is another breathing irregularity that may prolong 4DMRI acquisition

time due to increased chance of nonappearance for some respiratory states. Baseline drift may be addressed through implementation of advanced algorithms that estimates and compensates baseline drift in real time. We will explore this approach in future.

Currently, we split respiratory states equally into inhalation and exhalation because of the hysteresis effect in which the tumor may take different paths during inhalation and exhalation. This allows full characterization of tumor motion during the entire respiration cycle. In this study, 10 respiratory states were selected (5 during inhalation and 5 during exhalation). This is based on the number of bins that has been typically used in clinical 4DCT. Although more respiratory states may be used in 4DMRI acquisition, it inevitably increases 4DMRI acquisition time. A tradeoff has to be made between temporal sampling of respiratory motion and 4DMRI acquisition time.

Besides T2-weighted 4DMRI, the proposed mathematical model has the potential to accommodate other MRI sequences into 4DMRI acquisition to achieve different image contrasts such as T1 weighting or diffusion weighting.²⁸ In these cases, the general description of the constraints may remain the same as those in COP (1). The specific constraints, however, need to be adapted accordingly. In this study, MRI images were acquired in the sagittal orientation. If there is a need, they may also be acquired in any other orientations through manipulation of the gradient system, which is an intrinsic benefit of MRI compared to CT.

5. CONCLUSION

We demonstrate the feasibility of using the ESGS method to substantially reduce 4DMRI acquisition time while maintaining the capability of providing T2 weighting. High-quality T2-weighted 4DMRI can be obtained within an average acquisition time of 9.0 min, making it feasible for clinical evaluation.

ACKNOWLEDGMENT

This work is supported in part by National Institutes of Health grant 1R21CA167092.

CONFLICT OF INTEREST

None declared.

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SUPPORTING INFORMATION

Additional supplemental material may be found online in the Supporting Information section at the end of the article.

Video S1. A movie showing the respiratory motion in a representative sagittal slice.