A Comprehensive Motion Compensation Method for In-Plane and Out-of-Plane Motion in Dynamic Contrast-Enhanced Ultrasound of Focal Liver Lesions

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A COMPREHENSIVE MOTION COMPENSATION METHOD FOR IN-PLANE AND OUT-OF-PLANE MOTION IN DYNAMIC CONTRAST-ENHANCED ULTRASOUND OF FOCAL LIVER LESIONS

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Abstract—Contrast-enhanced ultrasound (CEUS) acquisitions of focal liver lesions are affected by motion, which has an impact on contrast signal quantification. We therefore developed and tested, in a large patient cohort, a motion compensation algorithm called the Iterative Local Search Algorithm (ILSA), which can correct for both periodic and non-periodic in-plane motion and can reject frames with out-of-plane motion. CEUS cines of 183 focal liver lesions in 155 patients from three hospitals were used to develop and test ILSA. Performance was evaluated through quantitative metrics, including the root mean square error and $R^2$ in fitting time/intensity curves and standard deviation value of B-mode intensities, computed across cine frames), and qualitative evaluation, including B-mode mean intensity projection images and parametric perfusion imaging. The median root mean square error significantly decreased from 0.032 to 0.024 ($p < 0.001$). Median $R^2$ significantly increased from 0.88 to 0.93 ($p < 0.001$). The median standard deviation value of B-mode intensities significantly decreased from 6.2 to 5.0 ($p < 0.001$). B-Mode mean intensity projection images revealed improved spatial resolution. Parametric perfusion imaging also exhibited improved spatial detail and better differentiation between lesion and background liver parenchyma. ILSA can compensate for all types of motion encountered during liver CEUS, potentially improving contrast signal quantification of focal liver lesions. (E-mail: elkaffas@stanford.edu) © 2022 World Federation for Ultrasound in Medicine & Biology. All rights reserved.

Key Words: Motion compensation, Contrast-enhanced ultrasound, Focal liver lesion.

INTRODUCTION

Contrast-enhanced ultrasound (CEUS) is a widely used imaging modality for characterization of focal liver lesions (FLLs). In CEUS, microbubble contrast agents are typically administered to the patient as a bolus injection. Analysis of the contrast wash-in and wash-out has exhibited clinical utility for imaging of the liver (Dietrich et al. 2012; American College of Radiology 2017; Burrowes et al. 2017). The analysis can be done qualitatively or quantitatively. Previous studies have reported that quantitative approaches are effective in certain tasks, including characterization of FLLs (Pei et al. 2013) and monitoring of therapeutic response (Roccarina et al. 2015).

In the liver, however, CEUS acquisitions in the liver are inevitably affected by motion, despite the operator’s intention to minimize this. This in turn can have a major impact on contrast signal quantification, often rendering results unreliable. Motion can result from periodic diaphragm movement caused by respiration or from non-periodic movements, such as intentional or unintentional probe movement, large diaphragm movement after long breath holding and patient movement (Wu et al. 2018).

Acquisition protocols have been proposed to mitigate effects from motion. For example, in visualization of an FLL, the ultrasound probe should be aligned in the same
axis of respiratory movement to allow for only in-plane motion and to minimize out-of-plane motion (Dietrich et al. 2018). However, the liver is anatomically protected by ribs. FLLs in some segments of the liver cannot be visualized by such ideal probe orientations. Moreover, during the long acquisition of CEUS cines, there may be some circumstances that cause large amplitude of motion or out-of-plane motion. To this end, motion compensation (MC) algorithms come into play, to correct for in-plane motion and reject frames with out-of-plane motion prior to application of quantitative methods for characterization of FLLs (Rognin et al. 2010; Anaye et al. 2011; Streba et al. 2012; Gatos et al. 2015; Kondo et al. 2017).

Various MC methods for CEUS cines have been proposed. Typically, in such algorithms, a region of interest (ROI) is drawn over the focal liver lesion on the reference frame, which is determined either manually by the user (Ta et al. 2014) or automatically (Zhang et al. 2019). Previous MC methods have focused on specific types of motion, for example, in-plane periodic respiration (Mulé et al. 2011; Ta et al. 2014; Schäfer et al. 2015; Kaizhi et al. 2018; Zhang et al. 2019), non-periodic respiration (Wan et al. 2021) and out-of-plane motion (Ta et al. 2014; Schäfer et al. 2015). Development of a comprehensive MC algorithm that works for all types of motion remains a challenge. Our aim, therefore, was to develop an MC algorithm called Iterative Local Search Algorithm (ILSA), which can compensate both periodic and non-periodic in-plane motion and can reject frames with out-of-plane motion. These motion types are commonly encountered in real-world clinical practice. We quantitatively and qualitatively evaluated ILSA on a large multi-institutional clinical data set of CEUS cines collected during ultrasound exams for HCC surveillance in three medical centers.

METHODS

Data set

Data to develop and test ILSA were obtained retrospectively from an ongoing larger multi-institutional study approved by the institutional review board of Stanford University (Palo Alto, CA, USA), Thomas Jefferson University (Philadelphia, PA, USA) and Foothills Medical Center (Calgary, AB, Canada) (NCT03318380). Written informed consent was obtained from each patient prior to data collection. All data were de-identified and analyzed anonymously (Health Insurance Portability and Accountability Act of 1996 (HIPAA) compliant). We obtained CEUS cines from 155 patients who underwent evaluation of focal liver lesions. Because some patients had more than 1 lesion, a total of 183 lesions were included for final analysis, comprising 28, 72 and 83 lesions from each participating institution (anonymized). Characterization of the lesions by CEUS Liver Imaging Reporting and Data System (LI-RADS) category (American College of Radiology 2017) and definitive diagnosis by computed tomography (CT)/magnetic resonance imaging (MRI)/pathology are summarized in Table 1.

During the evaluation of FLLs by CEUS, a bolus of ultrasound contrast was injected into the peripheral circulation of the patient, then the pattern of contrast enhancement of the lesion and surrounding liver parenchyma was observed. Sonographers positioned the probe over the lesion and attempted to maintain the probe still during recording of the cines. The mean ± standard deviation (SD) duration of the cines was 40 ± 23 s. The mean ± SD frame rate was 9.9 ± 3.9 frames/s (FPS). All data had side-by-side B-mode and corresponding contrast-enhanced data during the acquisition. This allows for simultaneous evaluation of the lesion in B-mode and contrast enhancement pattern. All data were stored in DICOM format.

Iterative Local Search Algorithm

We developed ILSA based on iterative local search. ILSA receives as input user-defined regions of interest (ROIs). The users are allowed to draw a ROI(s) on the lesion on the B-mode in at least one frame. It then tracks the lesion on B-mode and translates the corresponding coordinates to the contrast-enhanced window. The in-plane tracking iteratively searches for the area with maximum normalized correlation coefficient (Bradski 2000) (eqn [1.1]) with the reference ROI(s). The search is confined within a local region, which updates based on prior information from previously tracked frames. Finally, frames with out-of-plane motion are eliminated by applying a correlation threshold, which is automatically determined during the iterative tracking process. Figure 1 schematically describes ILSA. Pseudocode for ILSA is described in Appendix S1 (online only).

Table 1. Characterization of the lesions by CEUS LI-RADS category and definitive diagnosis by computed tomography/magnetic resonance imaging/pathology

<table>
<thead>
<tr>
<th>CEUS LI-RADS category</th>
<th>Benign</th>
<th>Malignant</th>
<th>Total</th>
</tr>
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<tr>
<td>LR-1</td>
<td>7 (100%)</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>LR-3</td>
<td>8 (33.3%)</td>
<td>16 (66.7%)</td>
<td>24</td>
</tr>
<tr>
<td>LR-4</td>
<td>7 (20.6%)</td>
<td>27 (79.4%)</td>
<td>34</td>
</tr>
<tr>
<td>LR-5</td>
<td>0</td>
<td>103 (100%)</td>
<td>103</td>
</tr>
<tr>
<td>LR-M</td>
<td>0</td>
<td>15 (100%)</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>22 (12.0%)</td>
<td>161 (88.0%)</td>
<td>183</td>
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</tbody>
</table>

CEUS = contrast-enhanced ultrasound; LI-RADS = Liver Imaging Reporting and Data System.
where \( \overline{R} \) is a mean normalized correlation coefficient, computed across all user-defined reference ROI(s). \( R(x, y) \) is a normalized correlation coefficient calculated using eqn (1.2); \( T(\cdot, \cdot) \) is a coordinate in the search region; \( T \) is the reference ROI; \( F \) is the set of user-defined reference ROIs; and \( N \) is the number of user-defined reference ROI(s).

\[
R(x, y) = \frac{\sum_{x', y'} (T'(x', y') \cdot I'(x + x', y + y'))}{\sqrt{\sum_{x', y'} (T'(x', y')^2 \cdot \sum_{x', y'} I'(x + x', y + y'))}}
\]

where \( R(x, y) \) is the normalized correlation coefficient; \( (x, y) \) is a coordinate in the search region; \( (x', y') \) is a coordinate in the reference ROI; \( T'(x', y') \) is normalized pixel intensity at the coordinate \( (x', y') \) within the reference ROI, as calculated using eqn (1.3); and \( I'(x + x', y + y') \) is normalized pixel intensity at the coordinate \( (x + x', y + y') \) within the search region, as calculated with eqn (1.4).

\[
T'(x', y') = T(x', y') - \frac{1}{w \cdot h} \cdot \sum_{x', y'} T(x', y')
\]

where \( T'(x', y') \) is normalized pixel intensity at the coordinate \( (x', y') \) within the reference ROI; \( T(x', y') \) is pixel intensity at the coordinate \( (x', y') \) within the reference ROI; \( w \) and \( h \) are the width and height of the reference ROI, respectively; \( \frac{1}{(w \cdot h)} \cdot \sum_{x', y'} T(x', y') \) is mean pixel intensity calculated across all coordinates \( (x', y') \) within the reference ROI; and \( x' \) and \( y' \) have values of 0, 1, 2, \ldots, \( w-1 \). \( y' \) and \( y'' \) have values of 0, 1, 2, \ldots, \( h-1 \).

\[
I'(x + x', y + y') = I(x + x', y + y') - \frac{1}{w \cdot h} \cdot \sum_{x', y'} I(x + x', y + y')
\]

where \( I'(x + x', y + y') \) is normalized pixel intensity at the coordinate \( (x + x', y + y') \) within the search region; \( I(x + x', y + y') \) is pixel intensity at the coordinate \( (x + x', y + y') \) within the search region; \( w \) and \( h \) are the width and height of the reference ROI; \( I \) is the set of user-defined ROI(s) (in eqn [1.1]) of the lesion in one or more reference frames on the B-mode window. It creates an initial search region \( I \) that covers the input ROI \( T \) defined by the user, with additional surrounding area around the lesion. The additional surrounding area extends beyond each of the four sides of the input ROI by the number of pixels as calculated with eqn (2). This calculation does not depend on the spatial resolution of the cine; thus, it ensures a stable physical distance extended beyond the input ROI. Then, in each frame, ILSA searches all possible positions (exhaustive search) within the initial search region \( I \) to find the position that maximizes the normalized correlation coefficient \( max_{x,y} (R(x, y)) \) to the reference ROI(s) \( T \). If the user provides more than one reference ROI \( T \), ILSA calculates the mean normalized correlation coefficient \( \overline{R} = \frac{1}{T} \sum_{T \in F} max_{x,y} (R(x, y)) \) across all reference ROIs. A list of normalized correlation coefficients of all cine frames is obtained. ILSA selects the median of the listed normalized correlation coefficients as an initial threshold for frame inclusion. ROIs with normalized correlation coefficients greater than the initial threshold are included as initial candidate ROIs (Fig. 2).

\[
d = \frac{H}{30}
\]

where \( d \) is the number of pixels that the additional surrounding area extends beyond each of the four sides of the ROI; and \( H \) is the number of pixels along the vertical axis of the entire B-mode acquisition window. Let \( w_{ROI} \) and \( h_{ROI} \) be the width and height (in pixels) of the ROI, respectively; and \( w_{SR} = w_{ROI} + 2d \) and \( h_{SR} = h_{ROI} + 2d \) would be the width and height of the search region, respectively.
Step 2. Forward and backward tracking from reference frames. This step performs forward and backward tracking of the lesion from each reference ROI (T in eqn [1.1]) (Fig. 3). The tracking process comprises three modules, as follows.

Module 1: In-plane motion tracking. ROI tracking starts from each user-defined reference ROI (T) in the reference frame. The local search region (I) is formed by expanding the reference ROI (T) to cover the expected maximal movement of the lesion in the next frame (eqn [2] describes calculation of the search region). The purpose of constructing the local search region (I) is to limit the search space, and to minimize the risk of matching other irrelevant structures present in the entire ultrasound scene. Then, in the next frame, ILSA performs an exhaustive search within the local search region (I) to find the area with maximum normalized correlation coefficient (\( \bar{R} \)). The area would be included into the pool of candidate ROIs (green-outlined boxes in Fig. 3) only if the normalized correlation coefficient (\( \bar{R} \)) reaches the threshold that was initialized in step 1. In the subsequent frames, the local search region (I) (white-outlined boxes in Fig. 3) is updated based on prior information from the tracked ROI in the preceding frame.

Module 2: Elimination of frames with out-of-plane motion. During the in-plane tracking process, if the searched maximum normalized correlation coefficient (\( \bar{R} \)) does not reach the threshold, the frame would be considered as having out-of-plane motion and thus be eliminated. In this case, ILSA gathers history of all previous tracked ROIs, except for ROIs the center coordinates of which are outliers (less than the first quartile \(-1.5\text{IQR}\), or greater than the third quartile \(+1.5\text{IQR}\) of all ROIs’ center coordinates), and then forms a local search region by union of the ROIs, with additional surrounding area (red-outlined boxes in Fig. 3). The local search region is used in the tracking process until an area with a normalized correlation coefficient (\( \bar{R} \)) above the threshold is found. Then, the in-plane tracking resumes.

Module 3: Automatic threshold adjustment. In the first iteration, ILSA uses the initial threshold determined from step 1. This initial threshold is intentionally set at a high value to include only the ROIs that are highly correlated with the reference ROIs (T). This ensures that the ROIs included in the first iteration include the lesion.
However, several frames with the lesion would be eliminated in the first iteration. To solve this, we iteratively run ILSA and automatically adjust the threshold in each iteration. At the end of each iteration, the candidate ROIs are kept in memory. In the subsequent iteration, the threshold is decreased by a value of 0.02 to include more candidate ROIs. Locations of the candidate ROIs from the preceding iteration are then compared with the candidate ROIs in the corresponding frames in the subsequent iteration. If the locations exactly match, ILSA keeps the updated set of candidate ROIs, proceeds to the next iteration and continues to decrease the threshold in each iteration. Otherwise, it means that the added candidate ROIs belong to the frames without lesions. If these frames without lesions were further tracked, the candidate ROIs would drift away from the true location of the lesion. To prevent this, ILSA stops and return the set of candidate ROIs from the preceding iteration as the final output. The automatic threshold adjustment algorithm is described in Figure 2.

**Step 3.** Apply motion compensation parameters to the contrast-enhanced window. Finally, the final output ROIs from the B-mode window are translated to the corresponding coordinates on the contrast-enhanced window. The motion-compensated contrast enhancement pattern of the lesion can then be used for further downstream perfusion analysis.
Experimental validation
We applied ILSA on 183 CEUS cines of focal liver lesions. Performance was evaluated quantitatively and qualitatively by various methods, as follows.

Quantitative metrics. Root mean square error and coefficient of determination in fitting TICs (Chen et al. 2020). Intensity values in the motion-compensated contrast-enhanced ROIs were used to fit time-intensity curves (TICs) using the log normal model (eqn [3]) (Strouthos et al. 2010; Dietrich et al. 2012; Turco et al. 2016, 2020). The intensity value at each time point in the TIC was calculated by averaging all intensity values within the ROI of the corresponding frame. The root mean square error (RMSE) and coefficient of determination ($R^2$) of pre-MC and post-MC TICs were compared.

$$I(t) = \frac{\text{AUC}}{\sqrt{2\pi\sigma(t-t_0)}} e^{[(\log(t-t_0)-\mu)^2/(2\sigma^2)]}$$

(3)

In our case, $I(t)$ represents ultrasound intensity at frame $t$; $t$ represents frame number; $t_0$ represents frame number at initial contrast enhancement; $\mu$ and $\sigma$ are parameters of the log normal model; and AUC is the area under the lognormal curve.

Standard deviation of B-mode intensities, computed across cine frames (Schäfer et al. 2015). This method is based on the rationale that in-plane and out-of-plane motion in the pre-MC cine would cause the lesion to move in and out of the pre-MC ROI. In contrast, the post-MC ROI in each frame in B-mode should exhibit a relatively similar appearance of the lesion. We calculated mean B-mode intensity within the ROI in each frame. Then, the SD of the mean B-mode intensities was computed across all cine frames. Pre-MC and post-MC SD values were compared. If ILSA is effective, the post-MC SD value should be lower than the pre-MC SD value.

Qualitative evaluation. B-mode mean intensity projection (Ta et al. 2014). B-mode mean intensity projection was created by averaging the pixel intensities of B-mode ROI cine (dimension: time $\times$ width $\times$ height) along the time dimension, yielding a 2-D matrix (dimension: width $\times$ height). We compared B-mode mean intensity projections between the pre-MC and post-MC data. Motion in the pre-MC cine would cause loss of spatial resolution in the mean intensity projection image. The mean intensity projection image of the post-MC data should reveal qualitative improvement in spatial resolution.

Parametric perfusion imaging obtained on pixel-level TICs (Wan et al. 2021). We extracted TICs at each pixel in the contrast-enhanced ROI and estimated the following parameters: peak intensity, peak time (time at which peak intensity occurs), appearance time (time at which 10% of peak intensity occurs) and wash-in time (time interval between appearance time and peak time). The parameter values from all pixels within the ROI were used to create parametric perfusion imaging (PPI). If ILSA is effective, PPI of the post-MC data should reveal improved spatial details and better differentiation between the lesion and background liver parenchyma.

Subgroup analyses
To illustrate the generalizability of ILSA, we performed quantitative evaluation (RMSE, $R^2$ of TIC fitting and SD of B-mode intensities) sub-grouped by hospital, lesion longest diameter (< 2 cm and ≥2 cm) and lesion echogenicity (hyperechoic, hypo-echoic, iso-echoic and mixed echogenicity).

Sensitivity analyses
We performed sensitivity analyses to determine the effects of different input setups on the performance of ILSA. Different combinations of ROI sizes and frame rates were used. Experimented variations of ROIs were (i) ROI fitted to the lesion, and (ii) ROI including surrounding area around the lesion, which was created by extending the ROI fitted to the lesion on all four sides by half of the distance ($d$) defined in eqn (2). Experimental frame rates were either “full” (defined as the original frame rates of the cines) or “half” (defined as half of the frame rates of the cines, that is, the cines were temporally downsampled every other frame).

Statistical analyses
Quantitative evaluation metrics (RMSE, $R^2$ and SD) were summarized by median values. A Wilcoxon signed-rank test was used to test statistically significant differences between the pre-MC and post-MC RMSE, $R^2$ and SD values. Two-tailed $p$-values $<$0.05 were considered to indicate statistical significance. Boxplots of pre-MC and post-MC quantitative metric values were visualized. We also plotted baseline pre-MC values against the difference in pre-MC and post-MC values, to interpret whether changes in the values differ among cases with low or high baseline pre-MC values. All analyses were performed in Python Version 3.7 (Python Software Foundation, Wilmington, DE, USA).

RESULTS
Root mean square error and coefficient of determination in fitting TICs
There was an improvement in the TIC signal of the post-MC data compared with the pre-MC data (Fig. 4).
Median RMSE significantly decreased from 0.032 to 0.024 ($p < 0.001$) (Fig. 5a). The decrease in RMSE was more pronounced in cases with high pre-MC RMSE values (Fig. 5b). The median $R^2$ significantly increased from 0.88 to 0.93 ($p < 0.001$) (Fig. 5c). The increase in $R^2$ was more pronounced in cases with low pre-MC $R^2$ values (Fig. 5d).

**Standard deviations of B-mode intensities, computed across cine frames**

The median SD value of B-mode intensities, computed across cine frames, significantly decreased from 6.2 to 5.0 ($p < 0.001$) (Fig. 6a). The decrease in SD value was more pronounced in cases with high pre-MC SD values (Fig. 6b).

**Subgroup analyses for the quantitative evaluation**

We further performed quantitative evaluation (RMSE, $R^2$ of TIC fitting and SD of B-mode intensities) sub-grouped by hospital, lesion longest diameter ($< 2$ cm and $\geq 2$ cm) and lesion echogenicity (hyperechoic, hypo-echoic, iso-echoic and mixed echogenicity). There was improvement of post-MC data in all subgroups, as outlined in Table 2.

**Effects of different input setups on the performance of ILSA**

Performance results of ILSA using different combinations of ROI sizes (ROI fitted to the lesion or ROI including area surrounding the lesion) and frame rates (“full” or “half”), as assessed by the RMSE, $R^2$ of TIC fitting and SD of B-mode intensities, are outlined in Table 3.

**Image of B-mode mean intensity projection and parametric perfusion images formed with pixel-level TICs**

Comparison between pre-MC and post-MC B-mode mean intensity projection images and the parametric perfusion images of various parameters are illustrated in Figure 7. The post-MC B-mode mean intensity projection images have improved spatial resolution, compared with the pre-MC images (Fig. 7a). The post-MC parametric perfusion images also have improved spatial details and better differentiation between lesion and background liver parenchyma (Fig. 7b–e).

**Computation speed**

The 183 cines used for the experiments have a mean $\pm$ SD duration of 40 $\pm$ 23 s, 380 $\pm$ 248 frames and a frame rate of 9.9 $\pm$ 3.9 FPS. ILSA achieved a computation speed of 21.7 $\pm$ 8.1 FPS using Intel Xeon CPU @ 2.20 GHz (Family 6 Model 79).

**DISCUSSION**

In this study, we developed ILSA, which works well for all types of motion encountered during CEUS examinations of the liver, including periodic and non-periodic in-plane motion, and can reject frames with out-of-plane motion. Both quantitative and qualitative validation in 183 FLLs revealed improvement of post-MC data, compared with pre-MC data. We also determined
the generalizability of ILSA by validation on a large multi-institutional data set of CEUS data.

Although the overall quantitative and qualitative evaluation results indicated that ILSA improved the CEUS data, we observed that there were some cases where RMSE (Fig. 5b), $R^2$ (Fig. 5d) and SD (Fig. 6b) values of post-MC data were inferior to pre-MC data. On visual inspection of the plots, most of the problematic cases already had good baseline pre-MC metric values (low RMSE, high $R^2$ and low SD). In these cases, MC is not necessary, and application of the MC algorithm might not lead to large improvement. For these cases, the quantitative metrics comparing pre-MC and post-MC TICs did not indicate a clear improvement. Yet, the B-mode mean intensity projection and parametric perfusion images revealed improvements after application of ILSA. This highlights the importance of using both quantitative and qualitative methods to evaluate the contribution of MC algorithms.

Fig. 5. Comparison between pre-MC and post-MC RMSE and $R^2$ values. (a, c) Boxplots comparing pre-MC and post-MC RMSE and $R^2$ values. Green triangles denote mean values. (b, d) Plots between baseline pre-MC values and changes in the values after the Iterative Local Search Algorithm was applied. MC = motion compensation; RMSE = root mean square error.
The types of motion appearing in the CEUS cines is an important consideration in designing MC algorithms. In-plane motion caused by respiration is common during CEUS acquisition. Because the normal respiration is periodic, many algorithms perform respiratory gating or use signal filtering methods to identify cine frames in the same phase of respiration (Mulé et al. 2011; Ta et al. 2014; Kaizhi et al. 2018; Zhang et al. 2019). However, irregular breathing can also occur. A method based on optimal transport has been proposed to compensate motion caused by irregular breathing (Wan et al. 2021).

Another type of motion is out-of-plane motion, which can negatively affect the quality of data as the lesion completely disappears from the viewing plane. One study performed out-of-plane motion filtering by calculating correlation between each frame and the reference frame and then applying adaptive thresholds to filter out frames with out-of-plane motion (Ta et al. 2014). Another study used a semi-automatic approach by calculating a correlation matrix among all frames in the cine.

<table>
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<tr>
<th>Sub-group</th>
<th>N</th>
<th>RMSE</th>
<th>$R^2$</th>
<th>SD</th>
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<tr>
<td></td>
<td></td>
<td>Pre-MC</td>
<td>Post-MC</td>
<td>Pre-MC</td>
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<tr>
<td>All</td>
<td>183</td>
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<td>Hospital C</td>
<td>83</td>
<td>0.030</td>
<td>0.019</td>
<td>0.970</td>
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<td>Lesion longest diameter</td>
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<tr>
<td>&lt; 2 cm</td>
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</tbody>
</table>

RMSE = root mean square error; SD = standard deviation; MC = motion compensation. *All evaluation results are summarized by median. Names of hospitals were anonymized. The order A, B and C does not follow the order of hospitals described under Methods.
The correlation matrix is visualized, in which out-of-plane motion exhibits a specific pattern. The user then draws temporal regions on the visualized correlation matrix to exclude frames with out-of-plane motion (Schäfer et al. 2015).

The strength of ILSA is that it can compensate a wide range of motion types present during acquisition of CEUS in clinical routine. Compared with previous studies that proposed MC algorithms that work for only specific types of motion (Ji et al. 2011; Mulé et al. 2011; Kaizhi et al. 2018; Zhang et al. 2019), ILSA can compensate either periodic or non-periodic in-plane motion and can reject frames with out-of-plane motion. ILSA is also robust to variation in the baseline quality of CEUS data. Our data set is collected from three hospitals with different baseline qualities of pre-MC CEUS data (Table 2). ILSA was able to generalize to variations and thus performed well across data from all three sites. Moreover, ILSA performed consistently well on different lesion characteristics (diameter and echogenicity) and input setups (ROI size and frame rate). The effects of other imaging parameters (e.g., mechanical index [MI]) on the performance of ILSA were not the focus of our current study and may be explored in future studies.

ILSA has some limitations. First, it still requires the user to manually draw ROI(s) in at least one frame.

### Table 3. Performance results of ILSA using different combinations of ROI size and frame rate

<table>
<thead>
<tr>
<th>ROI size</th>
<th>Frame rate</th>
<th>RMSE</th>
<th>(R^2)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pre-MC</td>
<td>Post-MC</td>
<td>Pre-MC</td>
</tr>
<tr>
<td>Fitted to the lesion*</td>
<td>Full*</td>
<td>0.032</td>
<td>0.024</td>
<td>0.88</td>
</tr>
<tr>
<td>Fitted to the lesion</td>
<td>Half</td>
<td>0.032</td>
<td>0.024</td>
<td>0.88</td>
</tr>
<tr>
<td>Including surrounding area</td>
<td>Full</td>
<td>0.032</td>
<td>0.023</td>
<td>0.88</td>
</tr>
<tr>
<td>Including surrounding area</td>
<td>Half</td>
<td>0.032</td>
<td>0.023</td>
<td>0.88</td>
</tr>
</tbody>
</table>

ILSA = Iterative Local Search Algorithm; MC = motion compensation; RMSE = root mean square error; ROI = region of interest; SD = standard deviation.

* The baseline algorithm, performance results of which are reported throughout the article, used the ROI fitted to the lesion and “full” frame rate.

![Fig. 7. Comparison of pre-MC and post-MC images. (a) B-Mode mean intensity projection images. The post-MC B-mode mean intensity projection images reveal improved spatial resolution, compared with the pre-MC images. (b–e) PPI of peak intensity, peak time, appearance time and wash-in time, respectively. Post-MC PPI reveals improved spatial details and better differentiation between lesion and background liver parenchyma. MC = motion compensation; PPI = parametric perfusion imaging.](image-url)
this regard, performance of ILSA may partly depend on quality of ROI(s) drawn by the user. Nonetheless, we designed ILSA to optionally receive ROIs in more than one reference frame. When the mean normalized correlation coefficient (eqn [1.1]) is computed over more reference frames, the calculated mean normalized correlation coefficient value would be more robust and thus enable better lesion tracking performance. Second, ILSA can compensate for only translational motion. We intentionally designed ILSA to perform transformation in only 2 degrees of freedom (DoFs), including translation in the x- and y- directions. In clinical practice, the motion of FLLs almost always manifests as translational motion in CEUS cines. The rotational motion is very subtle. A previous study also found that transformation based on 2 DoFs (translation in x- and y-directions) yielded the best MC results, compared with those based on 3 DoFs (translation and rotation) and 4 DoFs (translation, rotation and scaling) (Bakas et al. 2019). Another advantage of excluding rotational transformation is that it reduces the risk of rotational drift on encountering noisy and fast-changing appearance of CEUS cine frames. Lastly, ILSA was designed on the assumption, based on clinical observations, that sonographers try to keep the ultrasound probe still. In cases in which very fast movement repeatedly occurs throughout the CEUS acquisition, the adaptive local search region might fail to cover the possible locations of the lesion during frame transition. However, this scenario is unlikely to occur in practice. ILSA should work well for most cases encountered during standard clinical practice.

CONCLUSIONS

We have proposed ILSA for MC of CEUS of FLLs. It can compensate for all types of motion, including periodic and non-periodic in-plane motion, and can reject frames with out-of-plane motion. Performance was experimentally validated by various quantitative and qualitative methods. ILSA can ultimately improve the quality of perfusion analysis of FLLs by CEUS.