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Independent Component Analysis Filter for Small Vessel Contrast Imaging During Fast Tissue Motion

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***Abstract*— Suppressing tissue clutter is an essential step in blood flow estimation and visualization, even when using ultrasound contrast agents. Blind source separation (BSS)-based clutter filter for high-framerate ultrasound imaging has been reported to perform better in tissue clutter suppression than the conventional frequency-based wall filter and nonlinear contrast pulsing schemes. The most notable BSS technique, singular value decomposition (SVD) has shown compelling results in cases of slow tissue motion. However, its performance degrades when the tissue motion is faster than the blood flow speed, conditions that are likely to occur when imaging the small vessels, such as in the myocardium. Independent component analysis (ICA) is another BSS technique that has been implemented as a clutter filter in the spatiotemporal domain. Instead, we propose to implement ICA in the spatial domain where motion should have less impact. In this work, we propose a clutter filter with the combination of SVD and ICA to improve the contrast-to-background ratio (CBR) in cases where tissue velocity is significantly faster than the flow speed. In an *in vitro* study, the range of fast tissue motion velocity was 5–25 mm/s and the range of flow speed was 1–12 mm/s. Our results show that the combination of ICA and SVD yields 7–10 dB higher CBR than SVD alone, especially in the tissue high-velocity range. The improvement is crucial for cardiac imaging where relatively fast myocardial motions are expected.**

***Index Terms*— Blind source separation (BSS), clutter filter, contrast-enhanced ultrasound (CEUS), slow blood flow, tissue motion.**

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I. Introduction

CONTRAST-ENHANCED ultrasound (CEUS) imaging is a diagnostic tool in clinical practice that enables the assessment of microvascular flow and perfusion [1]–[4]. By intravascular injection, encapsulated microbubbles act as ultrasound contrast agents (UCAs) that lit up the otherwise hypoechoic blood regions since they produce strong backscatter signal upon ultrasound insonification. This enhancement improves ultrasound sensitivity to detect vascular flow and allows quantitative evaluation of microvascular flow [5]. Regional microvessel characterization with CEUS, such as characterizing focal liver lesions [2], [6] and renal masses [1], has been recommended and is performed in clinical practice. Moreover, CEUS for detecting myocardial blood flow and perfusion has been used for decades [7], [8], albeit with a limited accuracy to detect regional perfusion deficits [9], [10]. Actually, resolving the flow of contrast agents in the myocardial vascular structure, rather than just detecting the presence of contrast agents, could improve diagnostic assessment [11], [12]. However, quantitative CEUS results have significant variations due to scanner settings, patients' physiological variations, and factors relating to the microbubbles [13], [14]. Cardiac imaging has additional problems due to substantial tissue motion. The peak cardiac motion around the location of the left coronary artery has a speed of up to 56 mm/s [15]. This rapid motion causes strong tissue clutter artifacts that impair the contrast signal visibility [16].

In the past decades, two main approaches have been developed to suppress the strong tissue clutter that conceals the microbubble flow signal. The first one is frequency-based wall clutter filters for ultrasonic flow imaging, which operate in the temporal domain [17], [18]. It works with the assumption that the flow inside the vessel is faster than the tissue motion, which is not the case with the combination of slow flow in the microvasculature and the fast-moving tissue, causing spectral contents overlap in temporal domain [19]. The second approach is by using contrast specific imaging techniques that exploit the nonlinear properties of microbubbles [20]. One option is by imaging of the harmonic signals of the transmit frequency (subharmonic, second harmonic, and superharmonic) [21]–[23]. The alternative is by transmitting a sequence

of pulses that cancel the linear tissue components when combined, yet retain nonlinear contrast signal components, such as pulse inversion (PI) [24], amplitude modulation (AM) [25], and power modulated pulse inversion/contrast pulse sequences (PMPI/CPS) [26]. However, ultrasound also propagates nonlinearly through tissue, which diminishes the contrast between tissue and microbubble nonlinear signal, thus reducing contrast visibility [27]. Moreover, since the nonlinear signals have lower signal amplitude and multiple transmit-receive events are combined, noise can become a significant factor [28]. Finally, contrast-specific pulsing sequences need very well-controlled transmit signals to work optimally in actual clinical settings [29].

More recently, blind source separation (BSS) techniques, which attempt to estimate the original sources of signal mixtures without the information of the mixing process and the sources, received a lot of attention as clutter filters [30]. Singular value decomposition (SVD) [31], [32] and independent component analysis (ICA) [33] have shown potential to outperform conventional temporal filters, as they discriminate the clutter and flow signal by their spatiotemporal statistical properties instead of just temporal information. This however means that a BSS clutter filter assumes that the *underlying* statistics in, and between, the image pixels are stationary. This is not necessarily true in medical imaging: In the presence of motion, clutter statistics per pixel can change over time since the image moves over the pixels. Hence, the motion within the sample period should be limited, and sufficient framerate is required, to maintain coherence throughout the filtering interval [34]. Low temporal sampling rates (provided by conventional line-by-line scanning) cause loss of spatiotemporal coherence, which makes clutter removal ineffective.

Breakthroughs in ultrafast ultrasonic imaging have enabled the acquisition of more than 1000 images/s, which is an order of magnitude higher than conventional line-by-line scanning. The fast acquisition is achieved by transmitting broad beams that scan the whole field of view with a limited number of beams, instead of line-by-line focused beams [35], [36]. Along with coherent compounding of multiple transmission events (e.g., angled plane-waves), the ultrafast ultrasound approach can produce high temporal sampling images without significant quality degradation compared to line-by-line scanning [37], [38].

SVD is a BSS method based on eigen decomposition that uses second-order statistics (i.e., variance) as the objective function, projecting the data onto orthogonal subspaces and ranking the singular vectors based on their eigenvalues. SVD filtering of high-framerate ultrasound images has been proven to be significantly more effective than conventional temporal filtering for clutter suppression in the flow imaging of small vessels [39]. Typically, SVD filters assume that the tissue, flow, and noise components can be decomposed into distinct rank subspaces, ordered (decreasingly) by the magnitude of their eigenvalues. Subsequently, a threshold can be applied to remove the unwanted components, with a low rank threshold for tissue removal and a separate high rank threshold for noise suppression. Several estimators have been investigated, and it was reported that the optimal threshold could be estimated using the correlation matrix of the spatial singular vectors [40]. However, SVD performance to suppress clutter drops off significantly with slower flow rate and faster tissue motion [39], [41]. The SVD filter operates on the assumption that the tissue signal has a low spatiotemporal correlation with the microbubble signal. However, their spatiotemporal correlation increases with tissue motion as the tissue encloses the vessels, which causes the decomposition to be less effective. Motion compensation on beamformed images before an SVD filter was investigated but the contrast to background ratio (CBR) improvement was not significant [41]. A combination of nonlinear imaging schemes (AM) with SVD was also investigated and was shown to attain worse CBR than only SVD filter [42]. Finally, clustering the ranks based on the singular values, spatial correlation, and mean Doppler frequency with the K-means algorithm instead of choosing a threshold was proposed to improve the clutter and flow distinction [43]. Although K-means clustering improves the performance, it is still limited by the efficacy of SVD to separate clutter and flow into different components. It could not resolve the case when the tissue motion is significantly faster than the flow speed, which causes the resulting decomposed components to still consist of mixtures of clutter and flow signals.

ICA is another BSS technique that has been investigated as clutter filter [44], where SVD transforms data onto a basis with orthogonal vectors; ICA seeks to transform the data onto a basis with statistically independent vectors. In doing so, ICA might provide better results than SVD when the components are correlated in time. With the assumption that the microbubbles are sparser than tissue signal [30], [39], their respective statistical distribution is different and independent of each other, regardless of the tissue motion. Recently, Tierney *et al.* [45] have shown that in combination with ultrafast ultrasound imaging, ICA is better than SVD in detecting slow flow when the tissue velocity is low and displacement is small. However, their ICA implementation over long SVD ensemble and component selection based on power Doppler image relies upon the assumption that large displacement does not occur through the ensemble period. Such assumption is likely to be violated in cardiac imaging, where fast tissue motion and large displacement exist throughout the cardiac cycle.

With the aim of detecting slow flow during high velocity tissue motion, we propose a combination of SVD and ICA as a clutter filter with high-framerate CEUS plane-wave images. Instead of implementing ICA on the spatial singular vectors that represent the flow signals in the entire SVD ensemble duration, we use ICA on a prefiltered images in a short time window, where the flow location is almost static. SVD is used as a prefilter to remove any semistatic clutter and tissue components. Subsequently, the ICA algorithm is employed to further isolate microbubble signal from the residual clutter. Here, it operates as a spatial filter on a subset of images that are almost spatially stationary, enabled by the ultrafast imaging framerate. The signal that consists of microbubble or clutter signal will be unmixed based on their distinct statistical distribution [46]. We chose the fourth-order statistics (normalized kurtosis) as the selection parameter in ICA as it is correlated with ultrasound scatter density [30], [47]. We evaluated and compared the performance of our proposed

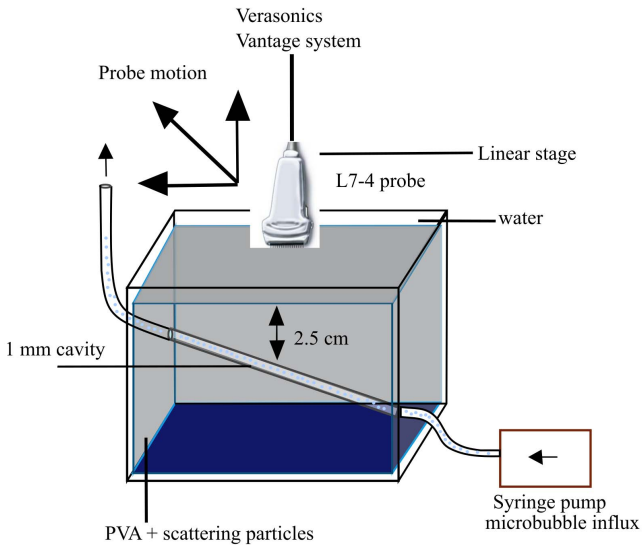

Fig. 1. Experimental setup to investigate the effect of probe motion and flow speed. The flow phantom consists of tissue-mimicking material (gray area) and a 1-mm wall-less cavity to emulate a small vessel. The probe was attached to a linear stage and moved during an acquisition while microbubbles were continuously injected.

filter to SVD in an *in vitro* setup where the induced motion simulates realistic cardiac velocity and in a range of slow flow speeds.

II. Methods

A. In Vitro Setup

A tissue-mimicking wall-less flow phantom was used for *in vitro* data acquisition (see Fig. 1). The phantom was made from a suspension of 10% w/v polyvinyl alcohol (PVA) and 1% w/v silicon carbide as background scattering particles, with one completed freeze-thaw thermal cycle. Diluted in-house phospholipid-coated microbubbles (F-type [48], concentration $\sim 7.6 \times 10^5$ MB/mL), which have similar performance to the commercially available Target-Ready MicroMarker (FUJIFILM VisualSonics, Inc., Toronto, ON, Canada), were used. They were continuously infused through a 1-mm diameter channel by a syringe pump (AL-1000, World Precision Instruments, Sarasota, FL, USA). An ultrasound probe (see below) was attached to a linear motorized stage. Rigid tissue motion was emulated by moving the probe during image acquisition in various directions. The diagonal direction had 45° angle with both the vertical and horizontal directions, in-plane with the probe image plane; see arrows on left-top in Fig. 1. Initially, the tube was located at 2.5 cm depth inside the image; as the probe was moving away from the phantom, the depth was up to 4.3 cm.

To test the efficacy of the filter performance, two series of experiments were performed: the first investigated the effect of tissue motion while keeping flow speed constant (Table I) and the second investigated the effect of flow speed while keeping the tissue motion constant (Table II). These velocities are realistic for cardiac imaging except for peak-early diastolic and peak-early systolic motion [15]. Reported flow speeds in this channel were calculated by the ratio of the flow rate (provided by the perfusion pump setting) and the channel cross-sectional area and hence is the average flow speed, not peak flow speed.

TABLE I
Parameters of Probe Motion Experiment

Probe motion experiment	
Probe axis	Diagonal, axial, lateral
Probe velocity	0, 5, 10, 15, 20, 25 mm/s
Average flow speed	6 mm/s

TABLE II
Parameters of Flow Speed Experiment

Flow speed experiment	
Probe axis	Diagonal
Probe velocity	25 mm/s
Average flow speed	1, 2, 3, 6, 8, 12 mm/s

B. Ultrasound Acquisition and Beamforming

RF acquisitions were performed with a linear transducer array (L7-4, Philips ATL, Bothell, WA, USA), connected to a Vantage 256 system (Verasonics Inc., Redmond, WA, USA). Each experiment was repeated three times. The transmission sequence consisted of five tilted plane waves from $-7°$ to $7°$ with $3.5°$ increments with a pulse repetition frequency of 5000 Hz. The transmitted pulses had a center frequency of 5.2 MHz (four cycles, fundamental imaging)at a mechanical index (MI) of 0.05, measured with a standard hydrophone setup (30 mm from the transducer). Delay-and-sum beamforming and angular compounding were performed with the Ultrasound Toolbox [50] in MATLAB (2020B, the Mathworks, Natick, MA, USA, 2020) on a 0.5λ resolution grid.

C. Two-Step BSS Framework Rationale

A sequence of beamformed CEUS images (s) can be modeled as a linear mixture of three independent components: tissue clutter signal (c), microbubble signal (b), and noise (n)

$$s(x, z, t) = c(x, z, t) + b(x, z, t) + n(x, z, t) \quad (1)$$

where x is the lateral position, z is the axial position, and t is the time. To accurately assess the flow signal, the clutter and noise need to be removed from the signal mixture. However, only the observed mixture signal is available, and both the mixing process and the source signals are unknown.

Demené *et al.* [39] have implemented an SVD filter by rearranging the $s(x, z, t)$ as a 2-D Casorati matrix S where the dimension is $(n_x \times n_z, n_t)$. It was assumed that the tissue clutter has high internal spatiotemporal coherence and is uncorrelated with the flow signal. Therefore, clutter and microbubble signal are expected to be projected into separate

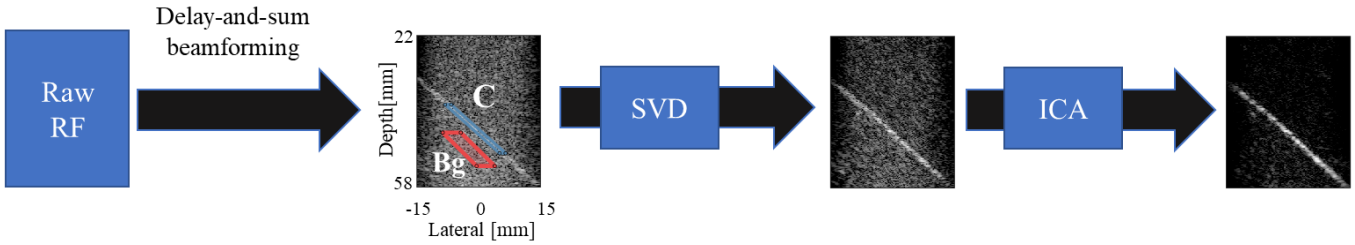

Fig. 2. Overview of the BSS filter framework. Example of ROI for calculating CBR. C (blue box) was used for contrast signal strength and Bg (red box) was used for background signal strength. Image is displayed with 40-dB dynamic range.

singular vectors. The strong tissue clutter would be accumulated in the first few ranks. The microbubble flow signal then can be retrieved by adding the components above an estimated rank threshold.

Although SVD works effectively when the tissue motion is not significantly faster than the flow speed, its performance drops off relatively proportional with tissue motion velocity and inversely proportional with flow velocity [39], [41]. In such case, the assumption of independent motion between tissue and flow is violated as they are temporally correlated. Since SVD maximizes the variance in the spatiotemporal domain, the projected components do not necessarily correspond to isolated signal sources (c, b, n). They could still consist of clutter and microbubble signal mixture, which makes SVD filtering by ranks removal ineffective. As a result, further filtering is needed to resolve flow signal, when it is significantly slower than the tissue motion velocity.

Differently than SVD, ICA finds maximally independent components from linear signal mixtures. The principle lies in the central limit theorem, which states that the linear combination of independent components is closer to a Gaussian distribution than the components prior to the mixing process. Accordingly, a measure of non-Gaussianity can be used as an objective to obtain maximally independent components; presuming that the sources are independent and have distinct non-Gaussian distribution. The pixel value in ultrasound images $s(x, z, t)$ is a linear summation of tissue, microbubbles, and noise that are spatially independent and have different scatterer density, thus distinct spatial distribution. ICA then can be implemented in the spatial domain to retrieve these initial signal components, whereas subsequent images act as independent observations of the spatial distribution. Thus, motion should be less of a factor in spatial domain, compared to the SVD filter that operates in spatiotemporal domain.

Normalized kurtosis (or fourth-order marginal cumulant of a distribution) is adopted as the ICA objective function as it is a measure of non-Gaussianity and has been employed to characterize ultrasound scatterers spatial density/sparsity [30], [47]. However, it is sensitive to other components that have sparse distribution such as strong specular reflections and noise, in the image, which could be falsely detected as microbubble signal. To improve ICA detection robustness, we therefore propose to first remove the more coherent tissue components, and the incoherent noise, with SVD. This prefiltered data then will be processed by ICA to further separate the contrast signal from the residual tissue signal. The overview of the processing framework is shown in Fig. 2.

1) SVD as a Prefilter: The input of our ICA implementation is several observations of the signal mixtures that consist of similar spatial structure, i.e., a limited number of subsequently recorded images without coherent plane-wave compounding. High-framerate imaging with tilted plane wave transmissions assure that a similar underlying spatial structure is present in a short ensemble of images, and the SVD filtering [39] is separately performed on the subsets of equal transmission angle. The ensemble length for this SVD prefiltering is found by parametric testing (see Appendix). The noise threshold (nn) is found by the maximum acceleration of the normalized ordered singular values [49]. Additionally, this search starts after 20% of the total singular values number to avoid finding the clutter cutoff. After removing the noise components, the spatial covariance technique is employed to find the clutter cutoff (nc) [50]. Clutter filtering in this first step is described as

$$\widetilde{S_{bc}}(x, z, t, \alpha) = \sum_{i=nc}^{nn} \lambda_i U_i(x, z, \alpha) V_i(t, \alpha) \tag{2}$$

where $\widetilde{S_{bc}}(x, z, t, \alpha)$ is the filtered images on each transmission angle α, λ are the singular values, U are the spatial singular vectors, and V are the temporal singular vectors. An example of the described rank selection is shown in Fig. 3.

2) ICA Filtering: ICA is then implemented on the output of the SVD filter in the first step to further separate microbubble signal and clutter.

The algorithm was applied to an observation window (y) of an ensemble length (el), which arranged as a Casorati matrix with dimension ($n_x \times n_z, n_\alpha \times n_{\text{el}}$). The angled images (without coherent compounding) were used as an input to provide different observations of the imaged object and to preserve framerate. Sequential observation windows were constructed from $\widetilde{S_{bc}}$. The ensemble length should be short to keep the stationarity of the superimposed signal but long enough to provide several observations of the mixture; we tested a range of ensemble lengths to find the reasonable tradeoff, as reported in the Appendix. Both real and imaginary parts of the signal were used. Prewhitening, which normalized the observed data to achieve faster convergence, is not performed because removing the eigenvalue of the components highlighted the clutter or noise components that were not removed by SVD. The robust ICA algorithm was chosen because it can process

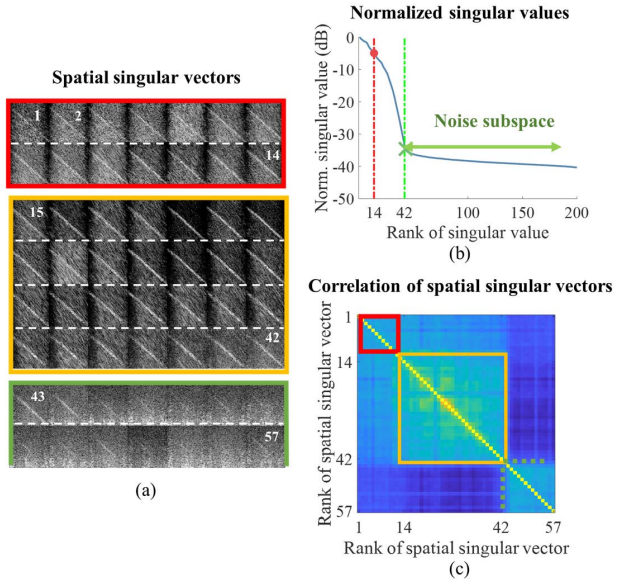

Fig. 3. Example of SVD rank selection. (a) Spatial singular vectors from rank 1 to 57. Components 1–14 are deemed as clutter although some minor bubble signal is present, 15–42 are the mixtures of bubble and clutter, and 43 until 200 are noise. (b) Normalized singular values that were used to determine the noise subspace. (c) Correlation of spatial singular vectors.

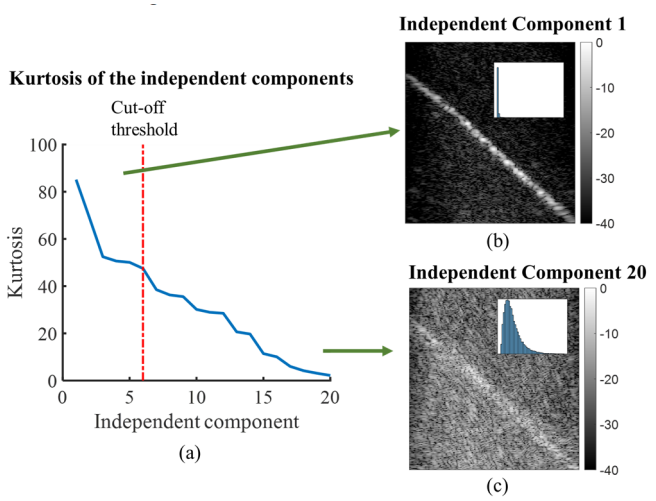

Fig. 4. Example of ICA ranking. (a) Kurtosis of all the calculated independent components. (b) and (c) B-mode images of some selected components in logarithmic scale and their respective normalized histogram of the pixel magnitude as inset. (b) Independent component with highest kurtosis. (c) Independent component with lowest kurtosis.

complex-valued signals and does not require prewhitening to achieve fast convergence [51]. It is applied on each window to maximize the non-Gaussianity of the estimated sources

$$y = WS \tag{3}$$

where W is the temporal mixing matrix and S is the maximally independent spatial components. Since no prewhitening is applied, the resulting independent components are direct linear combination of the observation window. The components are then sorted by their normalized kurtosis value (S_{sort}). Since microbubble signals are sparser and thus have higher kurtosis than tissue, the approximated microbubble signal ($\widetilde{s_b}$) is retrieved from the mixture by adding the components (nk) that have kurtosis higher than a defined threshold

$$\widetilde{s_b}(x, z) = \sum_{i=1}^{nk} S_{\text{sort}}(x, z, i). \tag{4}$$

The kurtosis threshold needs to be adjusted based on the distribution of the microbubbles that are present in the images. Empirically, we found kurtosis threshold of 45 worked well for our dataset and we used this value for all subsequent analysis. Since the noise has been reduced in the prefilter step, only one threshold is needed. An example of the described rank selection is shown in Fig. 4.

D. Postprocessing

To perform quantitative analysis, regions of interest (ROIs) were manually drawn (Fig. 2) on the tube (contrast) and PVA (background), which then automatically followed (by a global motion estimator via 2-D cross correlation) the tube and PVA while the probe was moving. CBR was then calculated to evaluate the filters' performances to suppress clutter signal, defined as

$$\text{CBR} = 20\log_{10}\left(\frac{\overline{\text{rms}}_{\text{contrast}}}{\overline{\text{rms}}_{\text{background}}}\right) \tag{5}$$

where $\overline{\text{rms}}$ is the time-averaged root-mean-square signal strength in a time interval (0.4 s) during which the probe velocity was constant.

III. Results

A. Implementation of SVD and ICA Filters

Several SVD ensemble lengths were tested for different probe speeds, but no significant differences was observed for the results with different ensemble lengths [see Appendix Fig. 8(a)]. We chose an ensemble length of 200 frames for all subsequent analyses. Several ensemble lengths for the ICA implementation were also examined [see Appendix Fig. 8(b)]. An ensemble length of 20 frames, which provided the optimal CBR, was chosen.

An example of an acquisition analysis and the result of the filter implementations are shown in Fig. 5. The CBR in the filtered images correlated with the probe velocity, while the CBR in the unfiltered images was not influenced by the probe motion, as expected. During the time interval when the probe was not moving, both SVD and SVD + ICA filter achieved similar CBR (~33 dB). However, SVD + ICA outperformed SVD alone during probe motion. When the probe speed exceeds 10 mm/s (t = 0.5:1.15 s), the CBR of SVD + ICA improves up to 10.5 and 20.4 dB compared to SVD alone and the unfiltered signal, respectively. SVD performance declined proportionally with the probe velocity (24.5 dB difference between static and peak probe velocity), while SVD + ICA retained more stable performance during motion on average. Note that this experiment had a contrast flow speed of 6 mm/s, and thus, the flow speed is significantly

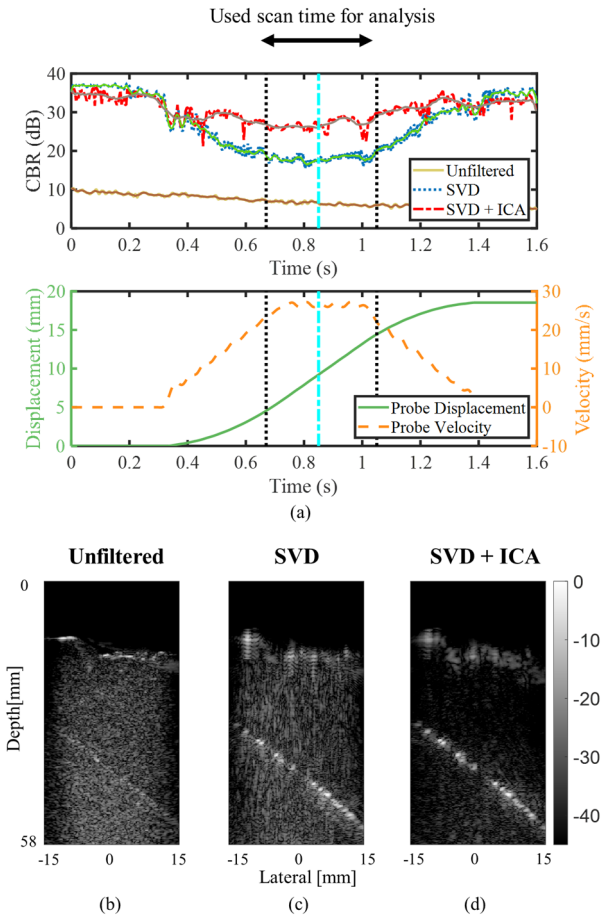

Fig. 5. Effect of probe motion. (a) CBR during 25-mm/s probe axial motion experiment and sample images during constant nominal velocity ($t = 0.85$ s, cyan line) after processing. (b) Unfiltered beamformed image. (c) SVD. (d) SVD + ICA.

lower than the peak probe speed. As visible in Fig. 5, the curves showed a frame-to-frame variation; 20-frames moving average trend lines were calculated. The standard deviation compared to the trend line of the CBR of SVD + ICA line was 1.2 dB, SVD was 0.8 dB, and the nonfiltered showed low frame-to-frame variations (0.15 dB).

B. Effect of Probe Motion

The filters' performance during various probe motions is shown in Fig. 6. In the static situation, simple SVD filter achieved 3 dB higher CBR. However, SVD + ICA consistently outperformed simple SVD during motion experiments, especially in the high velocity ranges (15–25 mm/s). The mean differences between the two filters in the high velocity ranges were 6.7 dB (axial), 6.9 dB (lateral), and 9.9 dB (diagonal). CBR for SVD declined proportionally with the probe speed across the motion direction (∼3 dB per 5 mm/s probe speed increment), except for diagonal motion of 20–25 mm/s. This downward trend results in a significant CBR difference (9.1 dB in average) between the slowest and the fastest probe speed after SVD filtering. On the other hand, the CBR obtained by

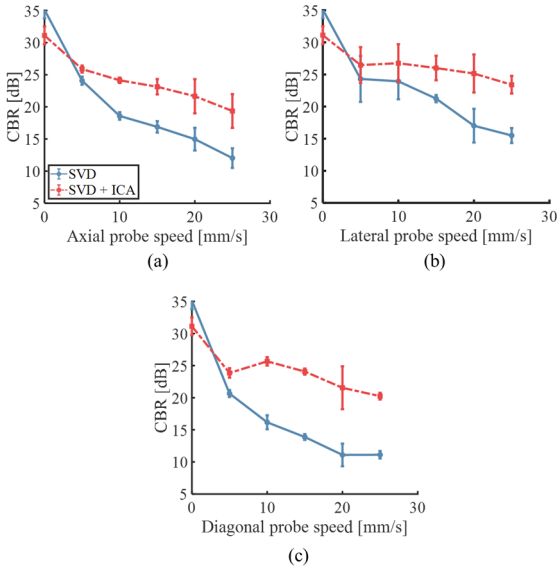

Fig. 6. Contrast-to-background values after processing by SVD and SVD + ICA for a range of probe velocities. The error bars represent the standard deviation from three repetitions. (a) Axial probe motion. (b) Lateral probe motion. (c) Diagonal probe motion.

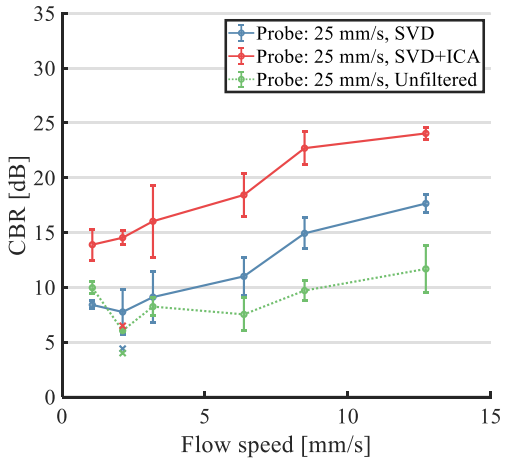

Fig. 7. Contrast-to-background values after processing by SVD and SVD + ICA for a range of flow speeds, while the probe was moving (25 mm/s) diagonally. The contrast-to-background values while the probe was static is provided as baseline reference.

SVD + ICA at 25 mm/s probe speed was only marginally lower (3.2 dB on average) than the 5-mm/s probe speed.

C. Effect of Flow Speed

The filters' performance with varying flow speeds while the probe was moving in high velocity (25 mm/s) is shown in Fig. 7. The result of one acquisition (flow speed 2 mm/s) was removed from subsequent analysis because the microbubble concentration was significantly lower than in other acquisitions, which complicated the contrast-level calculations. Both filters' performances were greatly influenced by the flow speed, where decreasing flow speed was proportional to CBR decline in both SVD and SVD + ICA. Although the SVD + ICA combination still exceeded SVD in all flow speed

(6.8 dB on average), the CBR gain reduces with increasing flow speed approaching the probe speed. The CBR for both filters increased by ∼4 dB from flow speed 6–8 mm/s; while the CBR only increased by 2.7 and 1.3 dB for SVD and SVD + ICA, respectively, from flow speed 8–12 mm/s. The unfiltered data showed a mild increase of few decibels of CBR with flow speed.

IV. Discussion

In this study, we have shown that SVD + ICA improved the clutter suppression over SVD alone in case of slow flow during realistic velocities of cardiac motion, in an *in vitro* phantom experiment. Our proposed filter framework consistently achieved better CBR than SVD during motion, especially in the fastest probe motion (25 mm/s) where ICA exceeded the CBR of the SVD filtered and unfiltered data by approximately 10 and 20 dB, respectively. In the static situation, ICA and SVD perform comparably, with slightly higher CBR with SVD alone than ICA. However, in the static condition where CBR is around 30 dB, this difference does not have any impact on the contrast visibility. The CBR improvement during motion is presumably due to ICA resolving the output of SVD that still consists of clutter and microbubbles signal mixture. ICA utilizes the different spatial distribution statistics of clutter and microbubbles instead of spatiotemporal coherence like SVD.

We performed an *in vitro* experiment where the probe motion velocities and directions were modified while keeping the flow rate fixed. The results show that SVD performance to suppress background clutter signal degrades proportionally with probe speed, while the SVD + ICA retains relatively stable clutter suppression for increasing probe speeds. The trends are consistent across all the motion directions conducted in our experiments (axial, lateral, and diagonal). The ineffectiveness of the SVD filter during motion is consistent with reports by Demené *et al.* [39] and Zhu *et al.* [41]. However, to the best of our knowledge, systematic evaluation in the high tissue velocity ranges (up to 25 mm/s) has not been reported before. As opposed to SVD, ICA filtering is affected less by motion because it operates in a short time where motion is negligible, facilitated by high-framerate imaging. This stability of signal might be beneficial to cardiac vascular flow imaging where motion should not influence the readout of the contrast signal.

The effect of different flow rates was assessed while the probe motion was kept constant at the highest velocity (25 mm/s). Clutter suppression of the SVD filter diminished proportionally with lower flow speed, as the spatiotemporal correlation between microbubbles and tissue signals increases. Combination with ICA again improves the CBR over SVD alone by 5–8 dB across all flow speeds. However, this time ICA could not retain stable CBR through different flow rates because the differences between the probe and flow speed are more significant compared to the probe motion experiment. Another possible reason is microbubble disruption. A slower flow rate inherently provides slower microbubbles replenishment, which leads to more acoustically induced deflation [52], resulting in lower CBR. The lower CBR with lower flow speed is visible in the unfiltered data in Fig. 7. By comparing the unfiltered and SVD-filtered results, it appears that the SVD filtering does not improve CBR at all upon high tissue motion and slow flow, whereas SVD + ICA does lead to higher CBR.

Unlike conventional wall frequency-based wall filters that have real physical representation and thus a meaningful threshold selection, selecting a threshold for BSS methods is not straightforward. Although SVD component selection is a well-known problem, there is still no standardized way to perform it. Initially, Demené *et al.* [39] used a qualitative approach to obtain optimal SVD threshold selection. Several efforts to solve this issue were published [40], [49], [50], [53], but we did not find any method that worked robustly for our dataset. We found that denoising the matrix by singular values acceleration [49] and using spatial correlation to find the clutter cutoffs [40], [50] worked well for our dataset. Additionally, we manually rechecked all selected automated thresholds and adapted thresholds where necessary. Since the aim of this research was to investigate ICA filter performance rather than finding a robust method to select the SVD components of the prefiltering step, we manually adjusted the slow flow acquisitions. As such, we were able to fairly compare filters at their maximum attainable CBR.

Component selection is a major issue for ICA filtering as well. In this study, we sorted the independent components by normalized kurtosis, with the assumption that the microbubble image intensity distribution is sparser than clutter signal. A threshold value that performed well for the dataset was empirically chosen and used for all analyses. The empirical approach means that the selected threshold was tuned specifically for the microbubble population in the channel of our phantom. As the kurtosis threshold defines the filtering outcome, adjusting the threshold is required for implementation on different imaging targets. This in practice might be solved by using imaging target presets, which is already customary in current clinical systems. Additionally, ensemble length is a parameter that needs to be tuned since our ICA implementation presumes negligible displacement in an observation window. The optimal ensemble length would depend on the acquisition framerate and the motion velocity. It is a tradeoff between providing spatial sample and retaining stationarity of underlying statistical structure, which hinges on the velocity of the tissue motion. The ensemble length we used for the analysis was chosen based on empirical evaluation.

Although an *in vitro* setup is more controllable compared to an *in vivo* environment, there are still some experimental uncertainties that influence the quantitative results. Microbubble concentration variabilities is always a factor in quantitative CEUS imaging as it is directly related to the backscattering magnitude and hence to the CBR "offset." The size distribution, stability, and acoustic properties of the microbubbles might be altered because they were diluted and stored in a suspending fluid prior to infusion [54]. Distinct microbubble disruption-replenishment in the varying flow experiment also contributed to the observed CBR variability, especially in the low flow settings. We excluded one acquisition (repetition number 3 of flow 2 mm/s) because of too low microbubble concentration. Yet the CBRs of the filters were always obtained from the same initial dataset; thus, they are mutually comparable. Finally, the assessment of CBR by calculating the mean of

the pixel values in the ROIs might introduce some bias toward the contrast detection sensitivity because the tube is not always completely filled with microbubbles. ROI locations that were drawn manually might have introduced some uncertainties to the CBR calculation. However, the comparison between different filters and unfiltered signal is not affected by this bias as the same ROIs in a single acquisition were used for all methods.

It should be noted that the performance of ICA depends on SVD to remove the semistatic clutter and noise. In our implementation, ICA needs the contrast signal to be stronger than the tissue signal (positive CBR) to operate. Since the prefiltering is an important step and SVD still has some concerns by itself (component selection and performance in motion), it is worth to consider other methods as a substitute for the prefilter step in the future. A possible solution could be contrast-specific detection scheme such as AM, PI, or PMPI that suppress tissue signal while retaining larger part of the contrast signal. The utilization of motion compensation before implementing the BSS filter is one of the possible improvements of the technique. However, to date, there is no standardized motion compensation algorithm that can be implemented straightforwardly. Several studies implemented various motion compensation algorithms and reported disparate improvements [41], [55], [56]. Since ICA will also benefit from a proper implementation of motion compensation, ICA should also be tested on the motion corrected images when making the comparison with only SVD filtering. Another direction of improvement would be a more robust ICA component selection. Instead of defining a fixed kurtosis threshold, fitting the components to a specific distribution like the homodyned K-distribution that gives a physical meaning [57] or the Nakagami distribution that is proven to describe *in vivo* data [58] might provide more stability compared to thresholding by normalized kurtosis. Alternatively, algorithmically defined threshold like suggested by Tierney *et al.* [45] yet adapted for high velocity case could be an option. The two-step processing induces extra computational cost. Although the computational time to perform SVD will be multiplied by the number of the transmission angles, the increase is not substantial since the time needed to process an ensemble of 200 frames is relatively short (∼2 s). On the other hand, ICA requires more substantial time (15–20 min) in the current nonoptimized implementation. However, we are trying to resolve the contrast detection and not aiming for real time or fast processing for now. In the future, more efficient operation could be implemented to reduce the computation time.

Translation to clinical application needs a further validation since our *in vitro* setup simplifies the *in vivo* conditions in several aspects. First, the myocardium tissue scatterers are inhomogeneous, which might impair the bubble detection mechanism. However, the assumptions that microbubble and tissue (myocardium) have different spatial scatterers' distribution should still be applicable. The fast-flowing microbubbles in the cardiac chamber, that are not relevant for perfusion imaging, can be removed by using a low pass filter to enhance the sparsity of the microbubble signals in the myocardium.

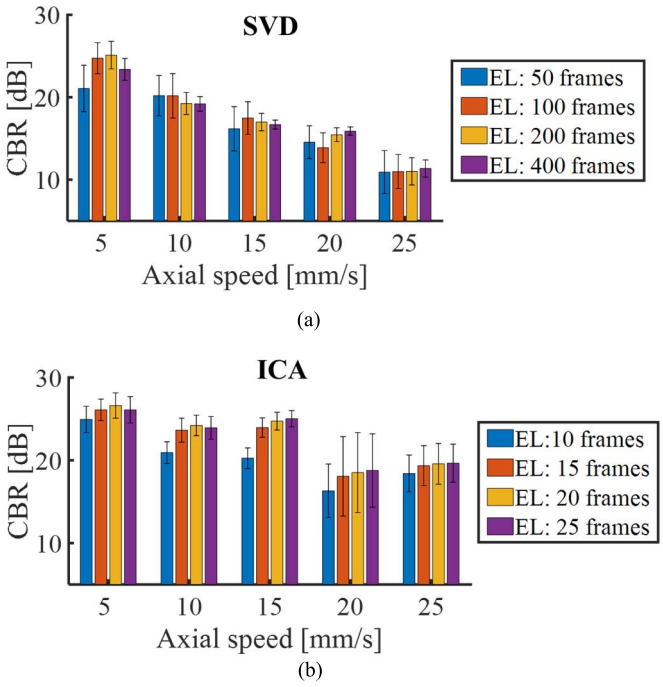

Fig. 8. (a) SVD and (b) ICA implementation for different ensemble lengths in varying probe speed.

Second, the size of the vessel determines the number of bubbles that are present, which affects the magnitude of the flow signal. The cavity diameter in our flow phantom (1 mm) is in the range of the small coronary arteries sizes. On the other hand, likely the microcapillaries (∼10 μm) could not be detected by ICA because they are small and densely populated (more than 2000 microvessels/mm^2 [7]). The fully developed speckle contrast signal from the microcapillaries will have low kurtosis and will be rejected by the filter. However, we are aiming at visualizing the small vessels and not at resolving the subresolution capillary perfusion. Third, cardiac (phased array) probe image resolution is worse and has a substantial depth-dependent resolution, compared to the linear probe that was used in this study. A possible mitigation could be implementing the beamforming and the filtering algorithm in the polar domain in which the resolution will be relatively uniform with depth. Fourth, if severe aberration changes the pixel location of the bubble in the images with different transmission angles, the assumption of our ICA implementation that the microbubbles' signal location does not change within the underlying subset of images is violated and the aberration would lead to image deterioration. Fifth, the current measurements only emulate rigid motion and visualize single channel. The nonrigid myocardial motion should not bring a new problem to our ICA implementation that operates in spatial domain; as long as the framerate is high enough to assume stationarity of the underlying statistical structure. Multiple vessels inside the field of view also should not be an issue, provided they are still sparse (see Appendix Fig. 9). Finally, changing the ICA ensemble size did not show a big impact on our *in vitro* data [Appendix Fig. 8(b)], yet it might be necessary to reinvestigate the optimal length ensemble

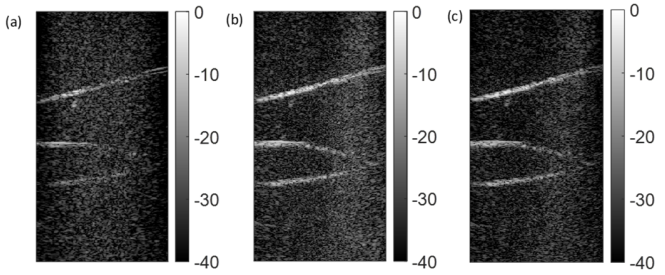

Fig. 9. Phantom images during free hand scanning after different processing. (a) Unfiltered beamformed image. (b) SVD. (c) SVD + ICA.

for *in vivo* application or eventually have that length being automatically tuned to the observed motion in the data.

V. Conclusion

We showed that ICA in combination with an SVD prefiltering step provides better contrast detection, with CBR improvement of 7–10 dB, compared to SVD alone. It is more motion-independent clutter suppression throughout various tissue motion (5–25 mm/s) and a range of flow perfusion velocity (1–12 mm/s). The improvement and stability of ICA filtering is an essential step for cardiac perfusion imaging, where high myocardial velocities are expected and stable contrast detection facilitates the interpretation.

Appendix

Ensemble length is an influential parameter for both SVD and ICA filter implementation. For this reason, we performed a quantitative evaluation (via CBR) to find the optimal ensemble length for both filters, which would be used for the results' analysis. One repetition (400 frames) of the axial probe motion dataset was processed with a range of ensemble lengths and the resulting CBR was compared. The results of the axial probe experiment processed with the SVD filter (50–400 frames) are shown in Fig. 8(a). There was no optimal ensemble length that could drastically improve the resulting CBR when the probe was moving in different speeds. The shorter ensembles (50 and 100 frames) had higher standard deviations than the longer ensembles (200 and 400 frames). Ensemble lengths of 200 frames seemed to obtain optimal results and hence were chosen for the analysis. Subsequently, the same dataset was processed with SVD filter of 200 frames ensemble and ICA filter (10–25 frames). The results are shown in Fig. 8(b). Ensemble length of ten frames consistently performed worst, compared to the rest. Ensemble length of 20 frames was chosen as it provided good tradeoff between CBR and framerate. The ensemble lengths for SVD filter (200 frames) and ICA filter (20 frames) were used for all the figures in Section III. We performed an additional free hand scanning on a phantom with multiple channels inside the field of view (Fig. 9). The flow in the channels was on the order of 8, 3, and 5 mm/s, set by two independent syringe pumps and asymmetric flow splitting. ICA improves the SVD and unfiltered image data by 1.7 and 5 dB, respectively.

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