Single Shot Quantification of Gas-Filled Microbubbles with Ultrasound

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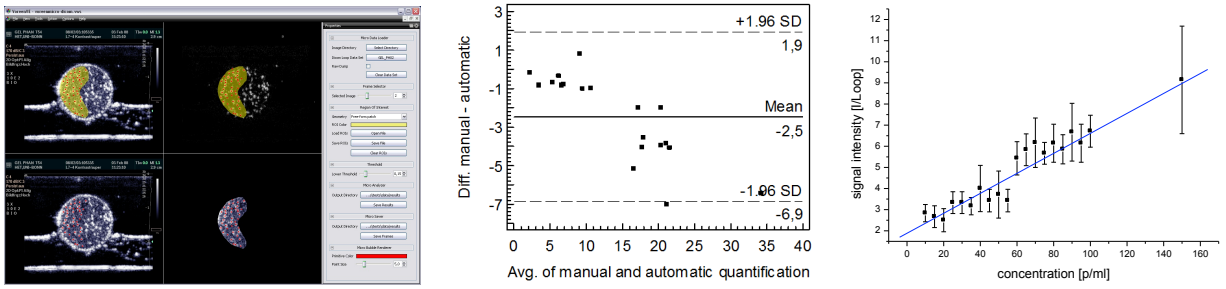

(a) (b) (c)

Figure 1: *(a) User-interface of the proposed system, (b) Bland-Altman plot comparing automatic microbubble quantification with manual ground truth for a gel phantom, (c) correlation graph for signal intensity and microbubble concentration for the gel phantom.*

1 Introduction

Gas-filled microbubbles (MBs) are well-established echo-enhancers that are wildly used as diagnostic tool in various medical fields. Above a certain sound pressure level, MBs burst and emit a strong signal called "stimulated acoustic emission" (SAE), which can be detected through ultrasound imaging. Since the amplitude of the SAE signal is high enough to distinguish individual MBs within a given tissue, and it has already been shown that MBs can be coated with target-specific tracers, the SAE effect is a promising tool for highly sensitive molecular imaging with ultrasound. For a practical use of SAE for molecular imaging, however, reliable and efficient quantification of MBs within different tissues is necessary.

In this work, we present a novel semi-automatic technique for the quantification of MBs, called "single shot quantification" (SSQ). In contrast to previous approaches [Reinhardt et al. 2005], SSQ does not require a scan of the entire organ, but allows to determine the MB concentration by analyzing a time series of ultrasound frames which are scanned at a *single position*. The proposed technique has been implemented in a software system (see Fig. 1(a)) based on the Voreen framework [Meyer-Spradow et al. 2009].

2 Our Approach

As an initial step, the user marks one or multiple regions of interest (ROIs) to specify the regions, in which the system should quantify the MBs. For the following automatic quantification, we distinguish two cases:

1. For low particle concentrations, the MB disintegration results in discrete SAE signals that can actually be *counted*.
2. Higher MB concentrations prohibit the detection of individual MBs, and the particle count has to be derived from the *signal intensity* within the ROI.

For discrete SAE signals, the MBs usually appear as local intensity maxima. Simply counting the number of local maxima within a ROI, however, does not result in a sufficiently accurate MB quantification, even if pixels of low intensity are masked by a global intensity threshold. This is on the one hand due to the presence of tissues with a strong ultrasound echo similar to the SAE signal, and on the other hand because MBs occasionally appear as multiple adjacent intensity maxima instead of a single one. In order to isolate the MBs, we perform a sequence of image processing operations on the frame series. At first, the background signal is determined by averaging frames without MB signals. The resulting background frame is then subtracted from each frame of the input series, as shown in the top-right view in Figure 1(a) with overlaid ROI and detected MBs for the currently selected time-step. In order to merge adjacent intensity maxima representing a single MB, a Gaussian blur is applied to each background difference frame, followed by a non-maximum suppression that reduces each MB signal to a single pixel. Finally, a background difference threshold t_b is applied in order to filter out those local intensity maxima which are caused by noise, and the remaining pixels are counted. The described image processing pipeline has two free parameters: the standard deviation σ of the Gaussian filter and the background difference threshold t_b. Since we assume a low concentration of MBs ($< 200\,p/ml$), σ can be chosen rather high and turned out to be rather uncritical. For ultrasound frames of dimensions 768x576, σ values between 2.5 and 4.0 gave reliable results. t_b is adjusted by the user according to visual inspection of the detection results. We have evaluated the reliability of our approach by applying it to scans of a gel phantom with a stationary MB distribution. A Bland-Altman analysis indicates high agreement between the automatic detection of MBs and manual ground truth, with the system being slightly more sensitive than the human eye (see Fig. 1(b)).

For the automatic quantization of MBs at higher concentrations, we have investigated the relationship between the average intensity-background difference within a ROI and the corresponding MB count. For the gel phantom, the intensity-background difference exhibits a high correlation with the detected number of SAE events as well as with the injected MB concentration (see Fig. 1(c)). Thus, we can obtain the MB count from the intensity value, by using the linear mapping depicted in Fig. 1(c). Since the analysis so far has been conducted on stationary MB distributions, the next step is to evaluate the applicability of our approach to dynamic MBs.

References

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