Perfusion Curves Modelling for Evaluating of Ultrasound Image Registration

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Abstract. Estimation of the tissue perfusion parameters using ultrasound contrast agent can help to improve diagnosis occlusion of coronary arteries thus it can helps to prevent myocardial infarction. Precise registration of ultrasound time sequence is precondition for automatic and reliable perfusion analysis. Many image registration methods were developed, but ultrasound image registration is a still a challenging area. In this paper, a registration based on mutual information metric is presented using multiple regions of interest and parallel approach. Another focus is put on the registration evaluation using specific properties of acquired ultrasound sequences.

1 Introduction

Heart diseases and especially myocardial infarction, also known as heart attack, are leading causes of death for man and women all over the world [11]. Myocardial infarction is the interruption of blood supply to part of the heart, causing some heart cells to die. This commonly starts by occlusion of coronary arteries. In this first phase patient have no significant problems (chest pain, dyspnoea, etc.), but part of the myocardium is not sufficiently perfused. It can be early diagnosed using the perfusion analysis of myocardium based on dynamic contrast- enhanced ultrasound imaging (DCE-US) [1].

DCE-US using ultrasound contrast agents (UCAs) has extended diagnostic possibilities of echocardiography. These agents are usually formed as gas-filed (perfluorocarbon, sulphur hexafluoride etc.) microbubbles coated by some shell (lipid, polymer etc.), see [16]. UCA is administrated into the blood stream and can be easily detected due to their non-linear behavior [5]. In the last two decades the UCAs became a standard tool in different clinical and experimental applications, including echocardiography [12].

There are two main applications of UCA in echocardiography. The first application is focused on the measurement of ventricular volume and ejection fraction [20]. The second application deals with perfusion analysis [8], [9]. First results indicate usefulness for qualitative and quantitative estimation of perfusion parameters [6] in a spite of many practical problems.

One of the main issues in perfusion analysis in echocardiography is the suppression of displacements in the successive frames in the recorded sequence. This is mainly due to the movement of patient, breathing and movement of the ultrasound probe. It means that image registration must be performed first to search for an optimal geometrical transformation of the frames with respect to one reference image from the sequence. Correctly registered sequence is necessary condition for accurate evaluation of perfusion curves (time curves expressing the changes of contrast agent concentration within the small region of myocardium), which can be used for estimate of several tissue parameters (e.g. capillary flow) [6]. These parameters are evaluated in the standardized segments of myocardium [2].

This paper is organized as follows: Section 2 describes data acquisition and image properties, Section 3 presents used registration method, Section 4 describes proposed method of evaluation of image registration and Section 5 involves results and discussion.

2 Data Acquisition and Image Properties

The SonoVue contrast agent has been applied for DCE-US echocardiography (2-chambers view or 4-chambers view) of human heart in our experiments. SonoVue is certified contrast agent for clinical use. It is a suspension of stabilized SF6 (sulfur hexafluoride) microbubbles in saline solution. The size of these microbubbles is between 1 and 10 μm (more about SonoVue parameters in [23]).

A bolus of SonoVue was injected to the blood stream of healthy volunteer followed by a saline flush bolus. The acquired sequence was gated by ECG signal to record two kinds of sequences: one from the end-systolic heart phase (R-wave) and second from the end-diastolic heart phase (end of T-wave). ATL Philips HDI 5000 was used for recording the sequences of images during the contrast agent time distribution.

Specific interference noise (speckle), spatial invariant resolution, variable contrast caused by scene and frequency dependent attenuation and usually low and spatial-variant contrast makes the registration difficult. Most of developed methods for ultrasound registration assume that character of the registered images doesn't change (monomodal registration methods) [19]. That means that the contrasts of the images to be registered are very close to each other. In perfusion analysis each sequence (from 60 to 100 frames) starts with the first phase, called pre-contrast. This phase is without UCA, the myocardium is brighter than blood in chambers. In second contrast phase UCA is diluted in blood and myocardium is darker than blood in chambers. If UCA completely outflow the image behavior is similar to the first phase. The contrast of the images varies in time and signal to noise ratio is changing too, which relates to the passage of the UCA through tissue [10]. This implies that multimodal approach should be considered.

The speckle noise, which depends on various parameters, mainly the frequency used for imaging, geometry of an ultrasound transducer and imaged tissue, should be reduced for the accurate registration. Many methods for speckle reduction have been developed. In [18] the adaptive method has been presented. Authors in [26] used nonlinear diffusion filtering of bandpass ultrasound images in Laplacian pyramid domain. Filter based on anisotropic diffusion is well known method and can be also used for speckle reduction [21], [25]. In our case, fast median filtering was chosen (mask size 9 by 9), because it can be used for rough speckle suppression [25], [18], [13].

3 Registration Method

The proposed registration method of recorded ultrasound sequence is based on mutual information (MI) matching criterion. Mutual information $I(A, B)$ of two random images A and B measures the degree of dependence between A and B. We can express MI as a function of marginal probability density functions $p(a)$ and $p(b)$, and joint probability density $p(a, b)$:

$$I(A, B) = \sum_{a,b} p(a, b) \cdot \log(\frac{p(a, b)}{p(a)p(b)}). \tag{1}$$

The MI is defined on the overlapping images and more definitions can be found in literature [24], [4]. For example, if the images overlap only in one pixel the MI is at maximum, but the quality of registration is not optimal. To suppress the effect of increasing MI with decreasing registration quality we use normalized mutual information (NMI) [3]. NMI is defined via marginal and joint entropies $H(A)$, $H(B)$ and $H(A, B)$ as:

$$I(A, B) = \frac{H(A) + H(B)}{H(A, B)} \tag{2}$$

We presumed rigid transformation model (translation and rotation) for images in sequence.

The NMI value is usually evaluated only for specific region of interest (ROI), which also holds in our case. Furthermore, we have used two disjoint ROIs, because only well recognized boundaries and objects with specular reflections should be used during registration (valves, myocardium).

In this first developing phase, we have used the robust approach without any optimization, to ensure that global maximum will be found. Thus NMI was computed for each combination of translation and rotation of the registered image regards to the reference image. Possible translation in x-coordinate and y-coordinate was set to interval $(-20; 20)$ pixels and rotation was set to interval $(-7°; 7°)$. If we consider the step size 1 pixel and 1°, the NMI had to bee evaluated for 6147 values for each registered image pair (around 450000 values for typical sequence).

Parallel approach was therefore used to speed up our method. Sequence S was manually split to subsequences S_n because we presumed images with the similar characteristics in subsequence. The reference image from each subsequence was randomly set and the other subsequence images are registered (in parallel threads) with respect to this reference. Then the mean images were computed from registered sequences, which are used to register whole sequences to each other.

Our approach was implemented in Matlab environment with Parallel Computing Toolbox and Distributed Computing Server and can run on the computer with multicore processors or on the multiple computers connected into one computing cluster.

Algorithm for images sequence registration is presented below in pseudo-code:
Input: Sequence S of grayscale images (resolution 576x640 pixels), vectors $\vec{d_x}$, $\vec{d_y}$ of bounds for translation and vector $\vec{\phi}$ of bounds for rotation.
Output: Registered images sequence S_{REG}.

1. Set multiple ROIs → set mask M for registration.
2. Mask sequence S.
3. Split sequence S to N subsequences S_n.
4. Set fixed image A_n in each subsequence S_n, moving images in subsequences are $B_i = S - A_n$.
5. Initialize Matlabpool workers.
6. **parfor i = 1:length(S)** Do in parallel.
7. **for k = 1:length($\vec{\phi}$)**
8. rotate moving image B_i of angle $\phi(\vec{k})$
9. **for l = 1:length($\vec{d_x}$)**
10. **for m = 1:length($\vec{d_y}$)**
11. Shift B_i in (x, y) direction of $(\vec{d_x}(l), \vec{d_y}(m))$ pixels.
12. Compute $NMI_{k,l,m}$ between A_n and B_i in M.
13. **end**
14. **end**
15. **end**
16. Find position of $max(NMI_{k,l,m})$ → find parameters $\vec{d_x}, \vec{d_y}, \vec{\phi}$.
17. Apply transformation on B_i → save the registered subsequence $S_{n,reg}$.
18. **end**
19. Compute mean images I_n from $S_{n,reg}$.
20. Register I_n together.
21. Save registered sequence S_{REG}.

4 Evaluation of image registration

Evaluation of image registration is nontrivial problem, because the errors can be dragged into the registration process in each stage. We can evaluate registration using objective and subjective criteria. The mean image, obtained from whole sequence, can be used for subjective evaluation. The mean image of registered sequence should be sharper and with higher contrast than mean image computed from unregistered sequence. The dilution curve mode can be used for objective evaluation and will be described in the paragraphs below.

The basic dilution model is shown on Fig. 1a). Bolus (with UCA concentration equal c_0) is injected into inflow pipe. The bolus is diluted in chamber (volume V) and then flows out of the chamber. Typical dilution curve ($c(t)$) without recirculation, measured in defined ROI, is shown in Fig. 1b).

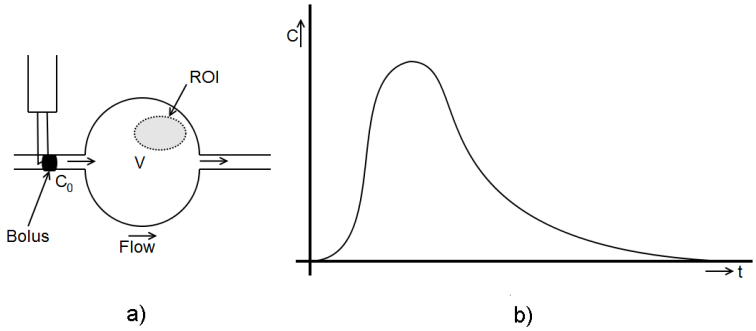


Fig. 1: a) Basic diluction model. b) Perfusion curve.

During perfusion analysis a fast UCA bolus is administrated into blood stream and the concentration proportional to brightness in the region of interest (ROI) is measured. The selected ROI defines a specific myocardial tissue for perfusion analysis. One of the main quantitative parameters related to the myocardium blood-flow on microvascular level is the mean transit time (MTT). MTT represents average time it takes the UCA bolus to pass through ROI in seconds. Additional perfusion parameters can be estimated [7].

The measured dilution curve should be approximated by known function in order to eliminate the noise and artifacts. Several models can be applied.

Mathematical models are based on the shape similarity between the perfusion curve $c(t)$ and specific mathematical function used for data fitting. The Log-Normal distribution is usually used as favorite function in dilution techniques, see [17]. Ideal bolus (infinitely short injection) is theoretically needed for model, but in practice very fast bolus injection in comparison to MTT is assumed.

Compartment modeling is based on a mathematical description of a small ideal mixing chamber with a unidirectional UCA washout and with a constant flow rate. Parts of cardiovascular system e.g. left ventricular, part of some artery, perfused myocardium can be set as compartment. UCA concentration $f_c(t)$ described by multicompartment model leads to Erlang distribution [14]:

$$f_{Erlang}(t) = c_0 \frac{e^{-\frac{t}{\tau}} (\frac{t}{\tau})^{k-1}}{(k-1)!}, \tag{3}$$

where k is number of compartments and τ is time constant depending on blood flow rate.

Generalization of this model, where k is non-integer, is also used and is called Gamma distribution [14]:

$$f_{Gamma}(t) = c_0 \frac{e^{-\frac{t}{\tau}} (\frac{t}{\tau})^{k-1}}{\Gamma(k)}, \tag{4}$$

where $\Gamma(k)$ is gamma function.

The local density random walk (LDRW) model was used for fitting the measured perfusion curves. This model has been utilized for estimation of the ejection fraction using UCA, which is also based on dilution curve fitting [15]. The LDRW model can be used also for perfusion analysis describing an ideal injection of the UCA bolus and its behavior in a straight infinitely-long tube. Due to a constant blood velocity and Brownian motion of the UCA bubbles, the time-varying concentration can be described [15] as:

$$f_{LDRW}(t) = \frac{1}{\mu} e^{\lambda} \sqrt{\frac{\lambda\mu}{2\pi t}} e^{-\frac{\lambda}{2}\left(\frac{t}{\mu}+\frac{\mu}{t}\right)}, \tag{5}$$

where μ is the mean transit time through the modeled tube and λ determines the UCA behavior in blood stream.

5 Result and Discussion

The fast bolus imaging method results in a perfusion curve extracted from myocardial ROI, which is shown in Fig. 2. To compare, perfusion curves extracted from unregistered and registered sequence are shown in Fig. 3.

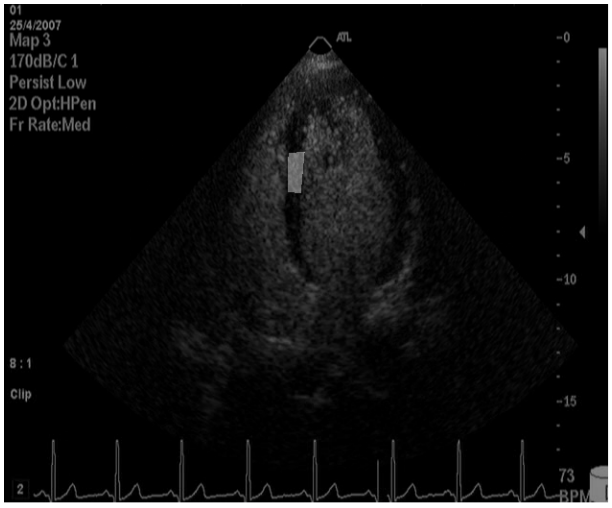


Fig. 2: Position of ROI for extracting perfusion curves.

Random peaks on perfusion curve evaluated from unregistered sequence are clearly visible. This is due the movement of tissue in ROI in sequence caused probably by breathing. These peaks are almost suppressed on perfusion curve evaluated from registered sequence.

Lognormal, Erlang, Gamma distribution and LDRW model were used for estimation of mean MTT of myocardium in our experiment. Results are shown in Fig. 3. The perfusion curve of unregistered sequence is deformed by many random peaks, see Fig. 4b), and mean estimated $MTT_{unreg} = 15.86\,s$ with variance $Var(MTT_{unreg}) = 3.47$. In Fig. 4a) is shown the peaks on the perfusion curve of registered sequence are almost suppressed and mean estimated $MTT_{reg} = 11.185\,s$ with variance $Var(MTT_{reg}) = 0.19$.

The mean estimated $MTT_{reg} = 11.185\,s$ corresponds with result published in [22], where is shown the MTT of normal human myocardium is around 8–13 s.

Developed registration method was tested also on images sequence taken without UCA. The result of registration is shown in Fig. 5 as mean image of sequences. Mean image of registered sequence, in Fig. 5b), is sharper and detailed than mean image of unregistered sequence in Fig. 5a). Resembling results was achieved for registration of sequence taken during perfusion analysis using UCA, see Fig. 6.

Developed algorithm was speed up 4 times using parallel algorithm than single thread implementation. Registration process of sequence takes approximately 16000 seconds

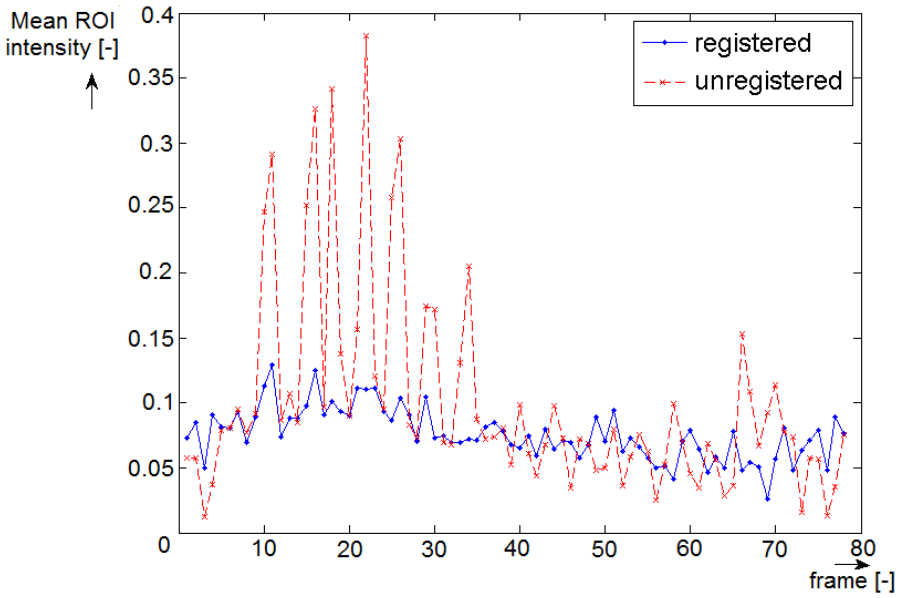


Fig. 3: Perfusion curves of selected ROI of myocardium using registered and unregistered sequence.

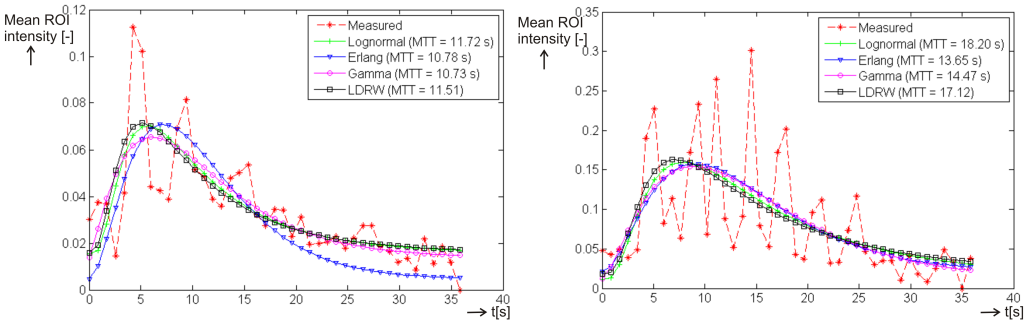
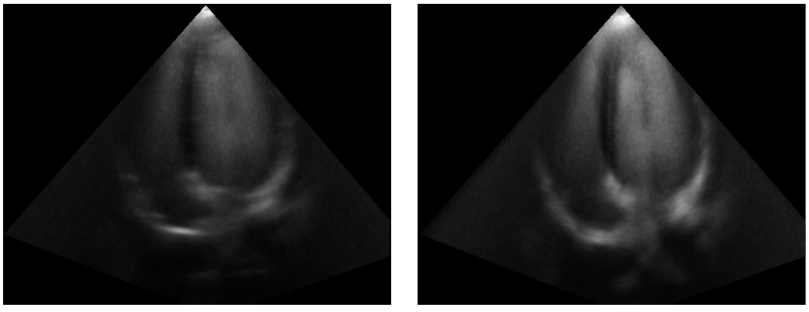


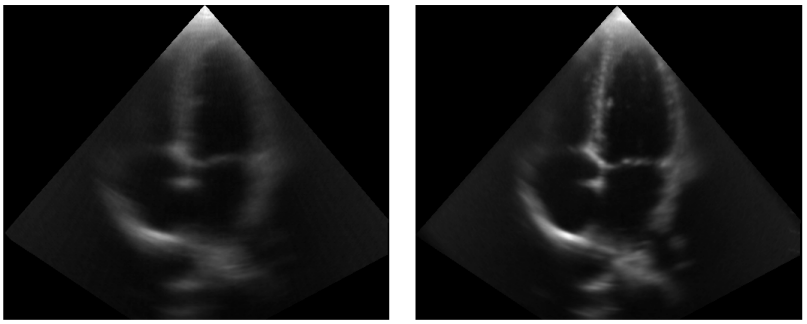
Fig. 4: Evaluation of perfusion curves to estimate MTT using Lognormal, Erlang, Gamma distribution and LDRW model from a) registered sequence; b) original unregistered sequence. Mean ROI intesity corresponds to the UCA concentration.



a) Mean image of original sequence b) Mean image of registered sequence

Fig. 5: Mean images of images sequence taken during UCA propagation.

computed in single thread on CPU Intel Q9400, 4GB RAM. Parallelized registration process of sequence (80 images) takes only 3500 second computed using 6 threads (cluster of two computers: Intel Q9400, 4GB RAM and Intel E7300, 2GB, three threads on each computer).



a) Mean image of original sequence b) Mean image of registered sequence

Fig. 6: Mean images of images sequence taken without UCA.

6 Conclusion

A modified NMI-based method using subsequential approach with parallel computing was presented. Moreover, new metric for the evaluation of registration quality based on MTT variance was described. Proposed methods were successfully tested on sequence taken on healthy volunteer.

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References

[1] Caiani, E. G., Korcarz, C. E., Collins, K. A.., Lang, R. M., Mor-Avi, V.: Simultaneous Quantitative Assessment of Myocardial Perfusion and Function Using analysis of Color-Encoded Contrast-Enhanced Images. Computers in Cardiology 2003; 30:181–184

[2] Cerqueira, M. D., Weissman, N. J., et. al.: Standarized Myocardial Segmentation and Nomenclature for Tomographic Imaging of Heart. Dallas, 2002

[3] Collignon, A., Maes, F., Delaere, D., Vandermeulen, D., Suetens, P. Marchal, G.: Automated Multi-Modality Image Registration Based on Information Theory. Information Processing in Medical Imaging, Dordrecht, 1995:263–274

[4] Hajnal, J. V., Hill, D. L. G., Hawkes, D. J. (Eds.): Medical Image Registration. CRC Press, Florida, 2001

[5] Hoff, L.: Acoustic Characterization of Contrast Agents for Medical Ultrasound Imaging. Kluwer Academic Publisher, Dordrecht, 2001:263–274

[6] Hossack, J. A., Yinbo, L., Zquan Y., French, Ba. A.: Assessment of Transient Myocardial Perfusion Defects in Intact Mice using a Microbubble Contrast Destruction / Refill Approach. Proc. of. 2004 IEEE Ultrasonic Symposium, Montreal, Canada, 2004:9–12

[7] Jackson, A., Buckley, D. L., Parker, M.: Dynamic Contrast-Enhanced Magnetic Resonance Imaging in Oncology, Springer, Berlin, 2005

[8] Kaul, S., Senior, R., Dittrich, H., Raval, U., Khattar, R., Lahiri, A.: Detection of Coronary Artery Disease with Myocardial Contrast Echocardiography: Comparison With 99mTc-Sestamibi Single-Photon Emision CT. Circulation 96, 785–792 (1997)

[9] Kolar, R., Jirik, R., Harabis, V., Mezl, M., Bartos, M.: Advanced Methods for Perfusion Analysis in Echocardiography. Psychological Research, in press 2010

[10] Kolar, R., Jirik, R., Harabis, V., Nylund, K., Gilja, O. H.: Registration of Ultrasound Contrast Images for Perfusion Analysis. Proceedings of 2009 IEEE International Ultrasonic Symposium, Rome, 2009

[11] Kosuge, M., Kimura, K., Ishikawa, T., et al.: Differences Between Men and Women in Terms of Clinical Features of ST-segment Elevation Acute Myocardial Infarction. Circulation Journal 2006; 70:222–226

[12] Linder, J. R.: Molecular Imaging of Cardiovascular Disease with Contrast-enhanced Ultrasonography. Nature Reviews Cardiology 2009; 6:475–481

[13] Loupas, T., McDicken, W. N., Allan, P. L.: An Adaptive Weighted Median Filter for Speckle Suppression in Medical Ultrasonic Images. IEEE Transactions on Circuits and Systems 1989; 36:129–135

[14] Mischi M, den Boer JA, Korsten: On the physical and stochastic representation of an indicator dilution curve as a gamma variate. Physiologic Measurement 2008; 29: 281-294

[15] Mischi, M., Jansen, A., Kalker, A., Korsten, H.: Identification of ultrasound contrast agent dilution systems for ejection fraction measurements. IEEE Transactions on Ultrasonics, Ferroelectrics and Frequency Control 2005; 52:410–420

[16] Quaia, E.: Contrast Media in Ultrasonography: Basic Principles and Clinical Applications. Springer-Verlag, Berlin Heidelberg, 2007

[17] Rognin, N. G., Frinking, P., Costa, M., Arditi, M.: In-vivo Perfusion Quantification by Contrast Ultrasound, Circulation 2001; 104:2582–2587

[18] Rui, Li., Zhuoxin, S., Cishen, Z.: Adaptive Filter for Speckle Reduction with Feature Preservation in Medical Ultrasound Images. Intl. Conf. on Control, Automation, Robotics and Vision, Hanoi, Vietnam, 2008

[19] Shekhar, R., Zagrodsky, V., Garcia, M. J., Thomas, J. D.: Registration of Real-Time 3-D Ultrasound Images of The Heart for Novel 3-D Stress Echocardiography. IEEE Transaction on Medical Imaging 2004; 23:1141–1149

[20] Malm, S., Frigstad, S., Sagberg, E., Larsson, H., Skjaerpe, T.: Accurate and Reproducible Measurement of Left Ventricular Volume and Ejection Fraction by Contrast Echocardiography: A Comparison With Magnetic Resonance Imaging. Journal of the American College of Cardiology 2004; 44:1030–1035

[21] Michailovich, O., Tannenbaum, A.: De-specling of medical ultrasound images. IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control 2006; 53:64–78

[22] Mohlenkamp, S., Beighley, P. E., Pfeifer, E. A., Behrenbeck, T. R., Sheedy, P. F., Ritman, E. L.: Intramyocardial Blood Volume, Perfusion and Transit time in Response to Embolization of Different Sized Microvessels. Cardiovascular Research 2003; 57:843–852

[23] Schneider, M.: Characterization of SonoVue. Echocardiography 2007; 16:743–746

[24] Vajda, I.: Theory of Statistical Inference and Information. Kluwer Academic Publisher, 1989

[25] Yang, Z., Fox, M. D.: Speckle Reduction and Structure Enhancement by Multichannel Median Boosted Anisotropic Diffusion. EURASIP Journal on Applied Signal Processing 2004; 16:2492–2502

[26] Zhang, F., Yoo, M. Y., Koh, L. M., Kim, Y.: Nonlinear Diffusion in Laplacian Pyramid Domain for Ultrasonic Speckle Reduction. IEEE Transactions of Medical Imaging 2007; 26:200–211