Lesion Type Classification by Applying Machine-Learning Technique to Contrast-Enhanced Ultrasound Images

Kazuya TAKAGI†, Nonmember, Satoshi KONDO†, Member, Kensuke NAKAMURA††, and Mitsuyoshi TAKIGUCHI††, Nonmembers

SUMMARY One of the major applications of contrast-enhanced ultrasound (CEUS) is lesion classification. After contrast agents are administered, it is possible to identify a lesion type from its enhancement pattern. However, CEUS image reading is not easy because there are various types of enhancement patterns even for the same type of lesion, and clear classification criteria have not yet been defined. Some studies have used conventional time intensity curves (TICs), which show the vessel dynamics of a lesion. It is possible to predict lesion type from the TIC parameters, such as the coefficients obtained by curve fitting, peak intensity, flow rate and time to peak. However, these parameters are not always provide sufficient accuracy. In this paper, we prepare 1D Haar-like features which describe intensity changes in a TIC and adopt the Adaboost machine learning technique, which eases understanding of which features are useful. Hyperparameters of weak classifiers, e.g., the step size of a Haar-like filter length and threshold for output of the filter, are optimized by searching for those parameters that give the best accuracy. We evaluate the proposed method using 36 focal splenic lesions in canines 16 of which were benign and 20 malignant. The accuracies were 91.7% (33/36) when inspected by an experienced veterinarian, 75.0% (27/36) by linear discriminant analysis (LDA) using conventional three TIC parameters: time to peak, area under curve and peak intensity, and 91.7% (33/36) using our proposed method. McNemar testing shows the p-value to be less than 0.05 between the proposed method and LDA. This result shows the statistical significance of differences between the proposed method and the conventional TIC analysis method using LDA.

key words: contrast-enhanced ultrasound, computer-aided diagnosis, lesion classification, Adaboost, Haar-like

1. Introduction

Contrast-enhanced ultrasound (CEUS) is commonly used to distinguish between benign and malignant lesions in the clinical context [1]–[4]. After contrast agents are administered, echo patterns change due to the inflow and outflow of the contrast agents that vary according to lesion type. The outflow of a contrast agent is faster in malignant lesions, making it possible to predict the lesion type from the change in echo patterns.

A major problem with CEUS is that physicians do not find it easy to read the images, principally because there are various types of enhancement patterns even for the same type of lesion, whether benign or malignant. This causes difficulty in establishing clear criteria for classifying lesions, and why it is said that the diagnostic results for CEUS depend on the reading skills of the physician. We believe that a computer-aided diagnosis can help the physician’s diagnosis [5], [6].

There are several quantitative approaches which use a time intensity curve (TIC) to classify lesions with CEUS [7]–[10]. A TIC shows the temporal change in intensity in the target region of interest (ROI), and TIC parameters such as time to peak (TTP), area under curve (AUC) and peak intensity (PI) are obtained, as shown in Fig. 1. However, these parameters do not always provide sufficient information for clearly classifying the lesion types. A novel approach is therefore required to extract features that differ from the conventional TIC parameters.

In this paper, we adopt the following three approaches for the TIC-based lesion classification.

1. A 1D Haar-like feature is adopted [11], [12] that can describe intensity changes within a specified time window in TIC, such as when the intensity increases or decreases and by how much it increases or decreases.

2. Adaboost [13] is adopted to classify lesions using the 1D Haar-like features of the TIC. Adaboost is a machine-learning algorithm that compiles a strong classifier from a collection of weak classifiers to perform simple classifications. Since Adaboost provides the contribution factor of each weak classifier as a

![Fig. 1 TIC parameters: Time to peak (TTP), area under curve (AUC) and peak intensity (PI).](https://example.com/fig1.png)

---


doi.org/10.1587/transinf.2013EDP7464

Copyright © 2014 The Institute of Electronics, Information and Communication Engineers
training result, it can also be used as an analysis tool to highlight features useful for lesion classification.

3. We optimize the hyperparameters of the weak classifiers. This optimization is performed by searching for parameters that provide the best accuracy.

2. Proposed Method

In TIC analysis, observation of intensity changes is important, i.e., when or how the intensity changes. Our proposed method introduces 1D Haar-like features to describe the intensity changes. Moreover, the proposed method adopts Adaboost, a machine-learning technique, to classify lesions using the 1D Haar-like features of the TIC. We describe how to generate TIC in Sect. 2.1 below. The details of our proposed method are described in Sects. 2.2, 2.3 and 2.4.

2.1 TIC Generation

We used CEUS image sequences as input. As shown in Fig. 2, each frame of the sequence includes two images: a contrast image and a tissue image. Both tissue and contrast images are acquired simultaneously. Contrast image is reconstructed from harmonic components of ultrasound echoes. In details two successive pulses are transmitted whose phase or amplitude are modulated and these two echoes are combined with the specific weighting to extract harmonic components [14]–[16]. On the other hand tissue image is reconstructed from fundamental components of one of these two echoes.

The proposed method tracks a region of interest (ROI) to compensate pulsative and breathing motion. Further motion noises including off-plane motion are corrected by a model fitting technique described later. The tissue image is used for tracking an ROI since the echoes in the tissue image are independent of the contrast agent (we will describe later how we specify the ROI). The positions of the tracked ROIs in the tissue images are mapped onto the corresponding positions in the contrast images and a TIC is obtained from the contrast images. The intensity of the TIC is calculated as average intensity inside the ROI in the contrast images.

A TIC is obtained using the following steps.

1. A frame is selected from a CEUS image sequence and is used as the reference frame for tracking the ROI. The selected frame should be one which empirically shows strong enhancement.
2. Two ROIs are manually set in the reference frame. An example is shown as the solid circles in Figs. 2 (b) and (c). One ROI is set on a lesion and the other is set on the parenchyma.
3. Two TICs are obtained from the ROIs in the contrast image. The ROIs are automatically tracked using a template matching the tissue image, as shown in Fig. 3. The ROIs in the reference frame are used as templates for template matching.
4. Obtain the arrival time of contrast agents at the parenchyma region from the TIC of the parenchyma region. The arrival time can be detected automatically using a pattern-matching filter whose output value increases with the rise pattern in the TIC. The reason for obtaining the arrival time from the TIC of the parenchyma region is that it is difficult to obtain the arrival time from the TIC of the lesion region in some cases due to weak enhancement.
5. The base time ($t = 0$) of the TIC of the lesion region is set with the arrival time of the contrast agents to the parenchyma region, as shown in Fig. 4.
6. A model function is fitted to the TIC of the lesion region using a nonlinear least-squares fitting method. We use the gamma function as the model function.

Fig. 2  CEUS image of the focal splenic lesions of canines. Regions of interest (ROIs) of a lesion and parenchyma and TIC for those ROIs. (a) TIC, (b) ROIs in a contrast image are used for TIC generation and (c) a tissue image is used for ROI tracking.

Fig. 3  The ROI position in each frame is corrected by the estimated displacement between the current frame and the reference frame.
Parameters for a weak classifier. A weak classifier is defined by the starting frame of the window in fitted TIC: $s_j$, the window length in the frame: $l_j$, the threshold for intensity change: $t_j$, and intensity change direction: $d_j$.

When we train a classifier, we prepare training samples which include CEUS image sequences for both benign and malignant cases. We obtain fitted TIC of the lesion ROI using the procedure described in Sect. 2.1. The input to the weak classifier is an intensity change $c_j$ inside a time window obtained by a 1D Haar-like filter as

$$c_j = \sum_{i=s_j}^{s_j+l_j/2} T_i - \sum_{i=s_j+l_j/2+1}^{s_j+l_j} T_i,$$

where $T_i$ is the value of fitted TIC at the $i$-th frame, $s_j$ is the starting frame of the $j$-th window, and $l_j$ is the length of $j$-th window. Each weak classifier checks the amount of the intensity change inside the time window, $c_j$. Each weak classifier is characterized by four parameters: (a) starting frame (time) of the window in fitted TIC $s_j$, (b) the window length in frame (time) $l_j$, (c) a threshold for the intensity change $t_j$, and (d) intensity change direction $d_j$ which takes +1 or −1, i.e., either an increase or a decrease, as shown in Fig. 5. The output from the weak classifier $h_j$ is decided by intensity change $c_j$, which is calculated using Eq. (1), a threshold $t_j$, and a direction $d_j$,

$$h_j = \begin{cases} 1 & \text{if } d_j \cdot c_j > t_j \\ -1 & \text{otherwise} \end{cases}.$$

When no intensity changes, $h_j$ takes −1 regardless of the value of $d_j$ because the value of $c_j$ takes 0.

In each boosting round, one weak classifier with the lowest error $e$ is selected from all the weak classifiers, and the weight of the selected weak classifier is obtained from this error $e$. The boosting is stopped when a obtained in Eq. (3) is smaller than a threshold value (0.001 in our experiments).

$$a = \log \frac{1 - e}{e}$$

The starting position of the window $s_j$, threshold $t_j$ and window length $l_j$ are given as

$$s_j = s_{\text{step}} \cdot p(j),$$

$$t_j = t_{\text{min}} + t_{\text{step}} \cdot q(j)$$

and

$$l_j = l_{\text{min}} + l_{\text{step}} \cdot r(j),$$

respectively. $s_{\text{step}}$ is the step size of the starting position of the window in a time (frame) axis. $p(j)$ is an integer value which shows a step index. Its maximum value is given as FLOOR($l/l_{\text{step}}$) where $l$ is the TIC length and FLOOR() is a rounding-off operation. Similarly, $t_{\text{min}}$ and $t_{\text{step}}$ are the minimum value of the threshold and the step size of the threshold for the intensity, respectively. $q(j)$ is a step index and its maximum value is given as FLOOR($t_{\text{max}} - t_{\text{min}})/t_{\text{step}}$.
where \( t_{\text{max}} \) is the maximum value of the threshold. Finally \( l_{\text{min}} \) and \( l_{\text{step}} \) are the minimum value of the window length and the step size of the window length, respectively. \( r(j) \) is a step index and its maximum value is defined as FLOOR\((l_{\text{max}} - l_{\text{min}})/l_{\text{step}}\) where \( l_{\text{max}} \) is the maximum value of the window length.

Figure 6 shows examples of both the starting position of the window and window length. In this example the minimum value of the window length is equal to the step size, i.e., \( l_{\text{min}} = l_{\text{step}} = l_1 \). For example, \( l_6 \) is given as \( l_6 = l_{\text{min}} + l_{\text{step}} \cdot r(6) = l_1 + l_1 \cdot 1 = 2l_1 \). These hyperparameters of weak classifiers \( l_{\text{min}}, l_{\text{max}}, l_{\text{step}}, l_{\text{min}}, \text{and } l_{\text{step}} \) affect the classification accuracy. Therefore the proposed method exhaustively searches for the optimal hyperparameters. Here, the step size of the starting position of the window is excluded from the optimization because the optimal value of this parameter could be solely found in preliminary experiments. The optimization procedure is as follows.

1. The search range parameters are set: a minimum search range value of the window length \( L_{\text{min}} \), a maximum search range value of the window length \( L_{\text{max}} \), a search step size of the window length \( L_{\text{step}} \), a minimum search range value of threshold \( T_{\text{min}} \), a maximum search range value of the threshold \( T_{\text{max}} \), and a search step size of the threshold \( T_{\text{step}} \). Note that these parameters are constant values and are different from \( l_{\text{min}}, l_{\text{max}}, l_{\text{step}}, l_{\text{min}}, l_{\text{max}} \) and \( l_{\text{step}} \).
2. The accuracy with a leave-one-out validation for every combination of hyperparameters \( (L_{\text{min}}, L_{\text{max}}, L_{\text{step}}, L_{\text{min}}, L_{\text{max}}, L_{\text{step}}) \).
3. The hyperparameters which give the best accuracy are selected.

2.3 The Classification Step

When classifying a new image sequence, the following steps are applied.

1. The fitted TIC of the lesion ROI is obtained using the same procedure as described in Sect. 2.1.
2. The outputs of the weak classifiers, which are selected in the training step, are calculated.
3. The lesion type, i.e., benign or malignant, is classified by the strong classifier which combines the outputs of the weak classifiers with their weights.

\[
h_j = \begin{cases} 
1 & \text{if } \sum_{k=1}^{m} w_k \cdot h_k(x) \geq 0 \\
-1 & \text{otherwise} 
\end{cases}
\]

where \( x \) is the fitted TIC and \( m \) is the number of weak classifiers. \( h_k \) and \( w_k \) are the output and the weight of the k-th weak classifier, respectively. When \( h_k(x) \) is equal to 1, we classify a target lesion as benign; if not, as malignant.

3. Experimental Data

The study population was recruited from canines with single or multiple focal splenic lesions detected by conventional ultrasonography in the Veterinary Teaching Hospital of the Graduate School of Veterinary Medicine, Hokkaido University [20]. Sonazoid (Daiichi-Sankyo, Tokyo, Japan) was used as the contrast agent. Contrast-enhanced ultrasonography was performed with an ultrasound machine (Aplio XG, Toshiba Medical Systems, Tochigi, Japan) with a 5-11MHz broadband linear probe (PLT-704 AT, Toshiba Medical Systems).

A single focal zone was placed at the deepest part of the lesion. The MI was set at 0.1-0.2 to minimize microbubble destruction. The gain was set so that few signals from the underlying splenic parenchyma were present. The cranial abdomen was shaved and the canines were restrained in dorsal recumbency. Scan planes were chosen to show both a splenic lesion and normal parenchyma in one image. Sonazoid (0.12 mL microbubbles/kg) was injected via an intravenous catheter in the cephalic vein. Catheters were flushed with saline (0.9% NaCl) solution immediately after the injection. Real-time imaging was performed from preinjection to 1 minute after injection of Sonazoid for the vascular phases. All images were recorded on a hard disk for off-line analysis.

The final diagnosis was confirmed by histology or cytology.

4. Experimental Results

We conducted two experiments. In the first, we evaluated the effectiveness of the hyperparameter optimization...
scheme. In the second experiment, we compared our proposed method with conventional methods. We used 36 clinical image sequences of canines with focal splenic lesions that included 16 benign and 20 malignant lesions. All the image sequences were provided in 8-bit grayscale AVI format. The dynamic range and frame rate were set to 45 dB.

![Accuracy distribution for the 5,590 combinations of the hyperparameters. Each accuracy is obtained with leave-one-out cross-validation.](image)

**Table 1**  Experimental result on classification accuracy and output of the 1D Haar-like filter of the highest weight classifier. The accuracies of the proposed method, SCAD-SVM and LDA are obtained with leave-one-out cross-validation.

| No. | Lesion type               | Classification result | Output of the highest weight classifier |
|-----|---------------------------|-----------------------|-----------------------------------------|
|     |                           | Veterinarian | Proposed method | SCAD-SVM | LDA | Filtered value [dB] | Is greater than 4dB ? |
| 1   | Benignancy                |             |                 |          |     | 8.7               | Yes                   |
| 2   | Nodular hyperplasia       |             |                 |          |     | 5.7               | Yes                   |
| 3   |                           |             |                 |          |     | 13.2              | Yes                   |
| 4   |                           |             |                 |          |     | 8.0               | Yes                   |
| 5   |                           |             |                 |          |     | 4.3               | Yes                   |
| 6   |                           |             |                 |          |     | 7.5               | Yes                   |
| 7   |                           | NG         | NG              | NG       | 2.6 |                   |                       |
| 8   |                           |             |                 |          |     | 7.8               | Yes                   |
| 9   |                           |             |                 |          |     | 7.1               | Yes                   |
| 10  |                           |             |                 |          |     | 5.6               | Yes                   |
| 11  |                           |             |                 |          |     | 4.2               | Yes                   |
| 12  |                           |             | NG              | 4.2      |     |                   |                       |
| 13  | Hematoma                  |             | NG              | NG       | 5.6 |                   | Yes                   |
| 14  |                           |             | NG              | NG       | 2.4 |                   |                       |
| 15  | Extramedullary hematopoiesis | NG     | NG              | NG       | 0.0 |                   |                       |
| 16  |                           |             |                 |          |     | 6.8               | Yes                   |
| 17  | Malignancy                |             |                 |          |     | -0.2              |                       |
| 18  | Hemangiosarcoma           |             | NG              |          | 2.9 |                   |                       |
| 19  |                           |             | NG              |          | -0.3|                   |                       |
| 20  |                           |             |                 |          |     | 0.5               |                       |
| 21  |                           |             |                 |          |     | 0.2               |                       |
| 22  |                           |             | NG              | 3.9      |     |                   |                       |
| 23  |                           |             |                 |          |     | 0.2               |                       |
| 24  |                           |             |                 |          |     | 0.1               |                       |
| 25  |                           |             |                 |          |     | 0.3               |                       |
| 26  | Lymphoma                  |             |                 |          |     | 0.6               |                       |
| 27  |                           |             |                 |          |     | 0.6               |                       |
| 28  | Histiocyticsarcoma        |             | NG              |          | -1.0|                   |                       |
| 29  |                           |             | NG              |          | 1.6 |                   |                       |
| 30  | Cartinoma                 |             |                 |          |     | 1.2               |                       |
| 31  |                           |             |                 |          |     | 3.9               |                       |
| 32  | Fibrohistiocytic nodule   | NG         |                 |          |     | 3.4               |                       |
| 33  |                           |             |                 |          |     | 3.4               |                       |
| 34  | Leiomyosarcoma            |             | NG              |          | 3.1 |                   |                       |
| 35  | Osteosarcoma              |             | NG              |          |     | 1.9               |                       |
| 36  | Granuloma                 |             |                 |          |     | 1.9               |                       |
| Accuracy | | 33/36 | 33/36 | 30/36 | 27/36 |
|          | | 91.7% | 91.7% | 83.3% | 75.0% |
and 30 fps, respectively, in all.

The TIC length \( l \), used for the classification, was set to 30 seconds. The first 10 seconds of fitted TIC show the intensity changes before the contrast agents are injected.

The step size of the starting position of the window \( s_{\text{step}} \) was 1 second. In optimizing the hyperparameters of the weak classifiers described in Sect. 2, the search range parameters \( L_{\text{min}}, L_{\text{max}}, l_{\text{step}}, T_{\text{min}}, T_{\text{max}} \) and \( T_{\text{step}} \) were set to 2 seconds, 16 seconds, 2 seconds, 0 dB, 16 dB and 2 dB, respectively. We finally prepared 5,590 patterns that were a combination of 65 patterns for window length and 86 patterns for threshold. ROIs were set by a CEUS-experienced veterinarian.

4.1 Effect of Our Optimization Scheme on TIC Analysis Resolution

Figure 7 shows the accuracy of the 5,590 combinations of hyperparameters. Each accuracy is the result of leave-one-out cross-validation. The accuracies range from 44.4% at worst to 91.7% at best. This wide accuracy range shows that the hyperparameter optimization scheme works effectively.

4.2 Comparison between Our Proposed Method and Other Methods

We compared our proposed method with the following conventional methods.

1. Linear discriminant analysis (LDA), which uses three conventional TIC parameters: time to peak (TTP), area under the curve (AUC) and peak intensity (PI) [7]–[10]. For TTP, arrival time (frame) is the time when the contrast agent arrives at the parenchyma; this is the same as in our proposed method. The AUC is defined as the integral value of the intensity from the arrival time (frame) to peak time (frame) in this study.

2. Support vector machine [17], [18] with smoothly clipped absolute deviation (SCAD-SVM) [19] which uses 176 features. These 176 features are outputs of the 1D Haar-like filter where \( L_{\text{min}}, L_{\text{max}} \) and \( l_{\text{step}} \) are set to 2 seconds, 16 seconds and 2 seconds, respectively. This is one of the finest settings concerning the step size of window length in the proposed method.

3. A subjective reading by a CEUS-experienced veterinarian.

Accuracies of the classification were evaluated by leave-one-out cross-validation. Table 1 shows the experimental results. The accuracies were 91.7% (33/36), achieved by an experienced veterinarian, 75.0% (27/36) by LDA, 83.3% (30/36) by SCAD-SVM, and 91.7% (33/36) using the proposed method. The proposed method gave 538 combinations of hyperparameters of weak classifiers that gave the best accuracy, and these combinations misclassified the same three samples. A McNemar test revealed the p-value to be less than 0.05 between our proposed method and LDA (see Table 2). This result shows the statistical significance of the differences between our proposed method and conventional TIC analysis method using LDA. On the other hand, in the comparison with the SVM and subjective reading, the p-values were greater than 0.05, so our proposed method did not show any statistically significant difference from the latter two methods.

5. Discussion

In this section, we discuss following two points: one is the contribution factors to accuracy and the other is the selected features in the training step of the proposed method.

5.1 Contribution Factors to Accuracy

The proposed method obtained better accuracy than LDA with three TIC parameters but there was no significant difference between the proposed method and SCAD-SVM. In comparison with SCAD-SVM we used the same 176 features which were obtained with the finest hyperparameter setting (except threshold parameter) in the proposed method. This indicates that Haar-like filter and hyperparameter optimization contribute to good accuracy.

5.2 Selected Features

As a result of optimizing the hyperparameters of weak classifiers, we obtained 538 combinations that yielded a maximum 91.7% accuracy. Most of these combinations gave the same strong classifiers when we performed Adaboost training with all the training samples, and we were able to summarize them into 19 strong classifiers. Each strong classifier had 2, 3, 4 or 10 weak classifiers, and the highest weight weak classifier was the same: the starting position of the window was 1 second before the arrival time to the parenchyma region, the window length was 12 seconds, the threshold for the intensity change was 4 dB, and the intensity was rising. If the output of the 1D Haar-like filter meets these conditions, the probability that the lesion is a benign type is high.

Figure 8 shows the relationship between fitted TICs and the highest weight classification window for 6 cases. The fitted TICs show the arrival times for malignant lesions.

| Table 2 | P-value of the McNemar Test. Bold shows the statistical significance of differences. |
|---------|---------------------------------|
|          | Veterinarian | Proposed method | SVM-SCAD | LDA |
| Veterinarian | -          | 0.480           | 0.450    | 0.077 |
| Proposed method | 0.480     | -               | 0.450    | **0.041** |
| SVM-SCAD   | 0.450      | 0.450           | -        | 0.505 |
| LDA        | 0.077      | **0.041**       | 0.505    | -    |
to be earlier than those for benign types. Moreover, the intensities of malignant lesions decrease faster than the intensities of benign lesions. The intensity difference of a benign lesion inside the window is therefore higher than that of a malignant lesion. It is generally reported that the inflow and outflow of contrast agent is faster in malignant lesions, since malignant lesions have neovascular vessels. The training results support this observation. The two rightmost columns in Table 1 show the output of the 1D Haar-like filter of the highest weight weak classifiers for all cases. Most of the benign samples meet the threshold condition (greater than 4 dB) of the highest-weighted weak classifiers. In this way, 1D Haar-like feature provides good accuracy and useful features that are easily understood.

6. Conclusion

In this paper, we propose a lesion type classification using a machine learning technique applied to contrast-enhanced ultrasound images. In the classification step, we set two ROIs manually and the remaining process is automatically performed. In the experiment using focal splenic lesions in canines, the proposed method achieved 91.7% accuracy and outperformed conventional methods by employing linear discriminant analysis using three TIC parameters (time to peak, area under curve and peak intensity). However in comparison with the support vector machine using the output of a 1D Haar-like filter, which is the finest setting related to the step size of window length there was no significant advantage.

Therefore our contributions using our proposed approach are that 1) we adopt the 1D Haar-like filter to describe an intensity change in the TIC; 2) we optimize the hyperparameters of the weak classifiers to achieve the best accuracy. Moreover, from the training result we can tell which time window is important in the TIC for classifying lesion types, and this knowledge can assist the physician with his or her diagnosis.

The size of the clinical data in this study is relatively small, but we believe that we have succeeded in demonstrating the potential of our proposed method. In future studies, we intend to increase the volume of data and evaluate the validity of the proposed method for a larger data set.

There is, however, an operator dependency when setting ROIs, especially the parenchyma ROI. We would in future like to evaluate how ROI setting affects the performance of our method.

References

[1] F. Moriyasu and K. Itoh, “Efficacy of Perflubutane Microbubble-Enhanced Ultrasound in the Characterization and Detection of Focal Liver Lesions: Phase 3 Multicenter Clinical Trial,” AJR Am. J. Roentgenol., vol.193, no.1, pp.86–95, July 2009.
[2] M. Kudo, K. Hatanaka, and K. Maekawa, “Sonazoid-enhanced Ultrasound in the Diagnosis and Treatment of Hepatic Tumors,” J. Med. Ultrason., vol.16, no.2, pp.130–139, 2008.
[3] K. Numata, et. al., “Contrast enhanced ultrasound of hepatocellular carcinoma,” World J Radiol., vol.28, no.2, pp.68–82, Feb. 2010.
[4] H. Kanemoto, et al., “Vascular and Kupffer imaging of canine liver and spleen using the new contrast agent Sonazoid,” J. Vet. Med. Sci., vol.70, no.11, pp.1265–1268, Nov. 2008.
[5] K. Sugimoto, F. Moriyasu, N. Kamiyama, and K. Doi, “Computer-aided diagnosis for the classification of focal liver lesions by use of contrast-enhanced ultrasonography,” Med Phys., vol.35, no.5, pp.1734–1746, May 2008.
[6] K. Sugimoto, J. Shiraishi, F. Moriyasu, and K. Doi, “Computer-aided diagnosis for contrast-enhanced ultrasound in the liver,” World J. Radiol., vol.28, no.2, pp.215–223, June 2010.
[7] A. Ignee, M. Jedrejczyk, G. Schuessler, W. Jakubowski, and C.F. Dietrich, “Quantitative contrast enhanced ultrasound of the liver for time intensity curves–Reliability and potential sources of errors,” Eur J Radiol, vol.73, no.1, pp.153–158, Jan. 2010.
[8] H. Zhuang, Z.G. Yang, H.J. Chen, Y.L. Peng, and L. Li, “Time-intensity curve parameters in colorectal tumours measured using double contrast-enhanced ultrasound: Correlations with tumour angiogenesis,” Colorectal Dis., vol.14, no.2, pp.181–187, Feb. 2012.
[9] S. Ohlerth, E. Ruefli, V. Poirier, M. Roos, and B. Kaser-Hotz, “Contrast harmonic imaging of the normal canine spleen,” Vet. Radiol. Ultrasound, vol.48, no.5, pp.451–456, Sept.-Oct. 2007.
[10] H. Kanemoto, et. al., “Vascular and Kupffer imaging of canine liver
and spleen using the new contrast agent Sonazoid,” J. Vet. Med. Sci., vol.70, no.11, pp.1265–1268, Nov. 2008.
[11] P. Viola and M. Jones, “Robust real-time object detection,” Second International Workshop on Statistical Learning and Computational Theories of Vision Modeling, Learning, Computing and Sampling, July 2001.
[12] P. Wilson and J. Fernandez, “Facial feature detection using Haar classifiers,” Journal of Computing Sciences in Colleges archive, vol.21, Issue 4, pp.127–133, April 2006.
[13] Y. Freund and R.E. Schapire, “A decision-theoretic generalization of on-line learning and an application to boosting,” Journal of Computer and System Sciences, vol.55, no.1, pp.119–139, 1997.
[14] P. Burns, R. Stephanie, and D. Simpson, “Pulse inversion imaging of liver bloodflow: Improved method for characterizing focal masses with microbubble contrast,” Invest. Radiol., vol.35, no.1, pp.58–71, Jan. 2000.
[15] P.J. Phillips, “Contrast pulse sequences (CPS): Imaging nonlinear microbubbles,” IEEE Ultrason. Symp. Proc. 2001.
[16] M. Crocco, M. Palmese, C. Sciallero, and A. Trucco, “A comparative analysis of multi-pulse techniques in contrast-enhanced ultrasound medical imaging,” Ultrasonics, vol.49, pp.120–125, 2009.
[17] K.R. Muller, S. Mika, G. Ratsch, K. Tsuda, and B. Scholkopf, “An introduction to kernel-based learning algorithms,” IEEE Trans. Neural Network, vol.12, no.2, pp.181–201, March 2001.
[18] http://www.support-vector-machines.org/
[19] F. Jianqing and L. Runze, “Variable Selection via Nonconcave Penalized Likelihood and its Oracle Properties,” Journal of American Statistical Association, vol.96, issue 45, pp.1348–1360, 2001.
[20] K. Nakamura, et. al., “Contrast-Enhanced Ultrasonography for Characterization of Focal Splenic Lesions in Dogs,” Journal of Veterinary Internal Medicine, vol.24, pp.1290–1297, 2010.

Kazuya Takagi received his B.S. and M.S. degrees at Chiba University in 1999 and 2001, respectively. He joined Matsushita Electric Industrial Co., Ltd. (now Panasonic Corporation) in 2001 and Panasonic Healthcare Co., Ltd. in 2012. He is now with Konica Minolta, Inc.

Satoshi Kondo received his B.S., M.S. and Ph.D. degrees at Osaka Prefecture University in 1990, 1992 and 2005, respectively. He joined Matsushita Electric Industrial Co., Ltd. (now Panasonic Corporation) in 1992 and Panasonic Healthcare Co., Ltd. in 2012. He is now with Konica Minolta, Inc. His research interests are in the fields of medical image processing and machine learning. He was also a participant in international standardization activities such as IEEE1394 Trade Association, ITU-T VCEG and ISO/IEC MPEG and DICOM. He holds over 100 patents on H.264/MPEG-4 AVC video coding standard.

Kensuke Nakamura received his D.V.M. and Ph.D. degrees in Veterinary Medicine from Hokkaido University in 2005 and 2011, respectively. Since 2011, he has worked as an assistant professor at Graduate school of Veterinary Medicine, Hokkaido University.

Mitsuyoshi Takiguchi received his BVSc, MS, and PhD degrees in Veterinary Medicine from Hokkaido University in 1987, 1989, and 1999, respectively. In 1996, he stayed in University of Illinois, Department of Veterinary Clinical Sciences to study diagnostic radiology. He now is a professor of Veterinary internal medicine at Hokkaido University Graduate School of Veterinary Medicine.