HHS Public Access

Author manuscript

IEEE Trans Ultrason Ferroelectr Freq Control. Author manuscript; available in PMC 2018 April 24.

Published in final edited form as:

IEEE Trans Ultrason Ferroelectr Freq Control. 2017 October ; 64(10): 1514–1525. doi:10.1109/TUFFC.2017.2737948.

Segmentation of 3-D High-Frequency Ultrasound Images of Human Lymph Nodes Using Graph Cut With Energy Functional Adapted to Local Intensity Distribution

Jen-wei Kuo,

Department of Electrical and Computer Engineering, New York University Tandon School of Engineering, Brooklyn, NY 11201 USA

Jonathan Mamou [Member Senior, IEEE],

F. L. Lizzi Center for Biomedical Engineering, Riverside Research, New York, NY 10038 USA

Yao Wang [Fellow, IEEE],

Department of Electrical and Computer Engineering, New York University Tandon School of Engineering, Brooklyn, NY 11201 USA

Emi Saegusa-Beecroft,

University of Hawaii, Honolulu, HI USA, and also with the Kuakini Medical Center, Honolulu, HI 96817 USA

Junji Machi, and

University of Hawaii, Honolulu, HI USA, and also with the Kuakini Medical Center, Honolulu, HI 96817 USA

Ernest J. Feleppa [Life Fellow, IEEE]

F. L. Lizzi Center for Biomedical Engineering, Riverside Research, New York, NY 10038 USA

Abstract

Previous studies by our group have shown that 3-D high-frequency quantitative ultrasound (QUS) methods have the potential to differentiate metastatic lymph nodes (LNs) from cancer-free LNs dissected from human cancer patients. To successfully perform these methods inside the LN parenchyma (LNP), an automatic segmentation method is highly desired to exclude the surrounding thin layer of fat from QUS processing and accurately correct for ultrasound attenuation. In high-frequency ultrasound images of LNs, the intensity distribution of LNP and fat varies spatially because of acoustic attenuation and focusing effects. Thus, the intensity contrast between two object regions (e.g., LNP and fat) is also spatially varying. In our previous work, nested graph cut (GC) demonstrated its ability to simultaneously segment LNP, fat, and the outer phosphate-buffered saline bath even when some boundaries are lost because of acoustic attenuation and focusing effects. This paper describes a novel approach called GC with locally adaptive energy to further deal with spatially varying distributions of LNP and fat caused by inhomogeneous acoustic attenuation. The proposed method achieved Dice similarity coefficients

of 0.937 ± 0.035 when compared with expert manual segmentation on a representative data set consisting of 115 3-D LN images obtained from colorectal cancer patients.

Index Terms

Graph cuts (GCs); lymph node (LN); segmentation; ultrasound

I. Introduction

High-frequency (i.e., >20 MHz) ultrasound (HFU) provides fine-resolution images, on the order of $100 \mu\text{m}$, because of its short wavelengths (i.e., $\sim 75 \mu\text{m}$ at 20 MHz) and small focal-zone beam diameters. Our previous work has shown that high-frequency 3-D quantitative ultrasound (QUS) has the potential to differentiate fully metastatic from cancer-free dissected human lymph nodes (LNs) by quantifying tissue microstructure inside the LN parenchyma (LNP) [1]–[4]. A key limitation of our previous studies was our use of semiautomatic segmentation methods, which still required a certain amount of human supervision [5].

Accurate knowledge of whether LNs associated with a primary tumor are metastatic or nonmetastatic is crucial for optimal treatment planning and patient management [6]. For colorectal cancer patients undergoing colectomy, at least 12 LNs are harvested from each specimen by pathologists. In current clinical practice, only one central cross section of each dissected LN is stained and evaluated under a microscope by a pathologist due to labor and costs constraints. This severe spatial undersampling results in unsatisfactory rates of false-negative determinations in cases of small off-center foci of metastatic cancer [1]. The goal of our QUS studies is to guide the pathologists toward suspicious regions within LNs and markedly reduce the false-negative rate, particularly for micrometastases, i.e., foci with sizes between 0.2 and 2.0 mm.

Fig. 1(a) shows a representative HFU image of a human LN immersed in a phosphate-buffered saline (PBS) bath. Two different LN tissue types are visible: LNP (inside) and fat (surrounding). In order to perform QUS processing successfully, a 3-D segmentation method is required to restrict QUS processing to LNP and to correct accurately for ultrasound attenuation [2]. Furthermore, accurate segmentation can provide detailed LNP shape information, which can be used to produce additional bio-markers of cancer.

Automatic LN segmentation in HFU images faces several challenges, such as speckle noise, low contrast between LNP and fat, implicit boundary, and spatially varying intensity distributions caused by acoustic attenuation and focusing effects. Therefore, obtaining satisfactory results with intensity information alone is not possible. To illustrate this point, Fig. 1(c) shows the result of a K-means analysis, which clusters voxels based on their intensities. Compared with manual segmentation result, some LNP voxels with high intensity are mislabeled as fat, and some LNP voxels with low intensity are mislabeled as PBS. Due to speckle noise and spatially varying intensity distributions in HFU images, other intensity-based segmentation methods such as region growing [7] would also yield unsatisfactory results.

In addition to intensity information, we take advantage of structural information. As shown in Fig. 1(b), LNP, fat, and PBS are in a nested configuration. Some approaches based on graph cuts (GCs) can segment multiple objects at the same time and preserve some structural relationship between these objects in the segmentation result. Ishikawa [8] described representing different objects by separate layers of a graph, and showed that a multiobject segmentation problem can be solved as a binary GC problem if the energy term satisfies certain convex conditions. Although objects in the segmentation result under his structure have a nested relationship, he did not consider how to take advantage of it. To exploit the known generic relationships between objects (e.g., containment, attraction, and exclusion), Delong and Boykov [9] described a multiregion GC. However, Delong and Boykov's model requires manually selected seeds to define the missing boundary between objects with similar intensity distributions. In order to deal with the missing boundary in a nested structure automatically, Kuo *et al.* [10] described nested GC (NGC). In NGC, the missing boundary of an inner object can be defined by the convex hull of its outer object automatically. Kuo *et al.* [11] applied NGC to segmenting LNs and overcame the missing boundary between LNP and PBS. Level-set-based approaches can also be used to preserve the nested relationships in segmentation processing. Nosrati and Hamarneh [12] described a level-set version of Delong and Boykov's model. In addition, multiphase level-set approach also works well to preserve nested relationships by deforming multiple noncrossing nested level-set functions. Bui *et al.* [13] described a three-phase level-set method to segment LNs. Compared with GC-based methods, level-set-based methods can avoid grid bias and can permit faster calculations, but they require proper initialization or initial seeds to avoid converging to a local minimum. Bui *et al.* [14] used random-forest classification to presegment images and initiate a level-set approach.

Intensity-distribution estimation is another challenge in LN segmentation. To obtain satisfactory segmentation, accurate intensity distributions for the three components of isolated LNs are required. Some clustering algorithms, such as K-means or expectation maximization (EM), may be able to categorize the intensity values of all voxels into three distributions to represent target objects. However, these approaches often yield unsatisfactory segmentation results for larger LNs [Fig. 1(c)], where the intensity distribution fluctuates significantly with depth because of acoustic attenuation and focusing effects. In addition, attenuation effects may become so extreme that fat boundaries become invisible [see the red arrow in Fig. 1(a)]. To mitigate the attenuation and missing-boundary problems, we used depth-dependent intensity profiles to model the depth-dependent variation of intensity mean and standard deviation (STD) in [11]. Using an EM-based iterative framework, depth-dependent profiles were estimated by a spline-based fitting process from the previous segmentation result, and the segmentation result was obtained by NGC using the estimated depth-dependent profiles. Instead of using an EM-based framework to update profiles, level-set-based approaches can also update profiles during deformation. Bui *et al.* [15] developed a method, which applied depth-dependent profiles, called statistical transverse slice level set (STS-LS). Nevertheless, depth-dependent profiles are unable to deal with intensity inconsistency within the same depth caused by inhomogeneous acoustic attenuation as shown in Fig. 2. Fig. 2(c) shows the segmentation result obtained using a depth-dependent profile [11]. Compared with the manual

segmentation result in Fig. 2(b), some fat regions (red arrow) are mislabeled as LNP because the fat on the right (green arrow) at the same depth is much brighter than the fat on the left. In this case, depth-dependent profiles are unable to model the intensity variations accurately. Using local distribution to differentiate LNP and the fat can solve the error caused by intensity inconsistency within the same depth. Bui *et al.* [13] have used a local-region-based gamma distribution to segment LNs. Level-set-based methods are good in applying local intensity distributions to differentiate regions. Since level-set-based methods deform the contour gradually, the local distributions can be updated by the boundary accordingly. However, updating distributions in local regions is computationally expensive. Furthermore, using local-region-based distributions with level-set-based methods is likely to result in convergence to a local minimum when the image is noisy. In contrast, GC-based approaches generally set the similarity cost by predefined intensity distributions. Because the boundary is unknown, the local region is hard to be determined in advance.

The graph-based segmentation algorithm is a kind of region merging algorithm that can do segmentation without predefined distributions. Felzenszwalb and Huttenlocher [16] proposed a method called efficient graph-based algorithm (EGB), which maps pixels in an image to connected vertices in a graph and merges vertices into subgraphs. EGB treats all pixel as different subgraphs initially, and clusters similar subgraphs gradually. It applies pairwise region comparison predicate (PRCP) to determine the minimum internal difference between pairs of subgraphs, and merge two subgraphs when the difference of the mean intensity of these two subgraphs is lower than the minimum internal difference. To segment ultrasound images, Huang *et al.* [17] proposed robust graph-based (RGB) segmentation algorithm, which applied a novel PRCP that takes into account local statistics and signal-to-noise ratio. Furthermore, Zheng and Huang [18] extended the RGB method to segment 3-D ultrasound images. To deal with large-scale voxel mergence, Chang *et al.* [19] proposed to apply hypothesis testing to measure the similarity when the subgraphs are larger than certain threshold. However, the graph-based algorithm cannot cluster all subgraphs in a target object with noise and high spatially varying intensity distributions and find the boundary between properly.

In order to deal with the spatially varying intensity distributions of LNP and fat and intensity inconsistency within the same depth, we propose a novel way to segment LNP and fat based on the locally observed intensity statistics. We call this method GC with locally adaptive energy (GC-LAE), which can differentiate LNP and fat voxels according to the similarity of distributions in local regions. Fig. 3 illustrates the difference between level-set-based methods, graph-based segmentation methods, and the proposed method. Fig. 3(b) shows the way level-set-based method takes advantage of local distributions. In Fig. 3(b), the black dashed line indicates the boundary of foreground found by a level-set-based method. The similarity between the red pixel and both foreground and background can be defined by the distributions within the local region inside the red dashed line. The intensity distribution of the foreground is obtained by the pixels inside the red and black dashed lines, and the intensity distribution of the background is obtained by the pixels inside the red dashed line and outside the black dashed line. These intensity distributions are updated with the deformation. Different from level-set-based methods, graph-based segmentation methods define local intensity distributions by subgraphs. Fig. 3(c) illustrates a possible segmentation

result of graph-based segmentation methods. There are three subgraphs (white, light gray, and dark gray) in Fig. 3(c), and these subgraphs are connected by edges in red. Graph-based methods obtain one intensity distribution for each region and compare the similarity of intensity distributions between connecting subgraphs. If the difference of the mean intensity of two connecting subgraphs is smaller than some threshold, they will be merged together. However, graph-based segmentation methods start from treating each pixel as a subgraph and therefore are sensitive to noise and may not be able to segment an object in its entirety when it has large intensity variation. The proposed method, called GC-LAE, can separate target image into a foreground and a background by predefined local intensity distributions. Generally, GC-based approaches cannot define local regions like level-set-based methods because we cannot know the boundary [black dashed line in Fig. 3(b)] in advance. If we define the local region of a pixel by the region centered on this pixel, the local regions of two connecting pixels will have some overlap and reduce the dissimilarity. To solve this problem, GC-LAE defines the local region according to the direction of edges. As illustrated in Fig. 3(d), the local regions of two connecting pixels (red and green) can be defined in the same direction of the edge between them and be nonoverlapping. When the local region is small and the boundary of the foreground is smooth, the intensity dissimilarity of the local region of pixels at the cut boundary (black dashed line) can be well preserved. With the proposed energy function, GC-LAE can make the cut forced by the local intensity dissimilarity, which is insensitive to the noise present in ultrasound images. To further deal with the blurry boundary in ultrasound images, GC-LAE can give pixels having larger distance to the edge higher weights to obtain local intensity distributions. In contrast to level-set-based approaches, GC-LAE can always achieve the global minimum of the defined energy function.

The GC-LAE alone cannot be applied to the entire image volume to successfully separate all three regions. We introduce a robust framework combining NGC and GC-LAE to segment LNs. It first applies NGC to the entire image volume to obtain an initial segmentation into three nested regions: the PBS, fat, and LNP. The resulting LNP and fat regions are then combined to form the LN-mask. Then it applies GC-LAE to the LN-mask to refine the segmentation of LNP and fat. The resulting segmentation is used to update the intensity distributions of the three regions. Finally, the NGC is applied again using these updated distributions to obtain the final segmentation of three nested regions. This framework is fully automatic and does not require any manual initialization or predefined intensity distributions.

This paper is organized as follows. Section II describes the graph structure of GC-LAE and defines LAE term and global energy term. Section III introduces the whole framework combining GC-LAE and NGC. Section IV illustrates the segmentation results and compares the performance of NGC with depth-dependent profiles [11], random forest classification (RFC)+STS-LS [14], and the proposed method. Section V discusses the clinical significance and the future work and concludes this paper.

II. Graph Cut With Locally Adapted Data and Edge Costs

GC [20] is a segmentation method that can segment all voxels in a 3-D volume into two regions by minimizing an energy functional. Generally, the energy consists of a data term and a smoothness term. The data term is the sum of the cost at each voxel that is typically inversely proportional to the likelihood of a voxel belonging to the assigned region, determined from the voxel's intensity and the assumed intensity distribution of the assigned region. In GC, all voxels pairs that are directly adjacent to each other in 3-D by 6-, 18-, or 26-connectivity are considered in the neighborhood set. The smoothness term is the sum of the cost between every two voxels in a defined neighborhood set, which typically represents the cost if these two voxels are assigned into two different regions. Based on the defined energy functional, one can set up a corresponding graph, which includes all voxels as nodes as well as two additional nodes called source (region 1) and sink (region 2). The link cost between a voxel and source (resp. sink) is equal to the data cost corresponding to assign the voxel to region 1 (resp. region 2). The edge cost between every two neighboring voxels defines the link cost between the two corresponding nodes. The segmentation problem is defined as finding a minimal cut, which separates voxels that are connected to the source (hence assigned to region 1) and those connected to the sink (hence assigned to region 2) with a minimal total sum of link cost along the cut.

A. Energy Definition

1) Locally Adaptive Energy—In GC-LAE, the LAE of each edge is defined by the similarity of their corresponding local regions. As shown in Fig. 3(d), the LAE of an edge between two connecting voxels (red and green points) is defined by the similarity of its local regions (red and green dashed lines). Because we know the location of the two voxels and the direction of the edge connecting them, we can define the local regions for the red and green voxels, respectively, to make them nonoverlapping [as shown in Fig. 3(d)]. Fig. 4(a) illustrates how we define the local region for different pairs of voxels. The intensity distribution of local regions can be modeled by preferred model. To avoid the effect of blurry boundary, it is possible to give pixels in local regions having larger distances to the edge higher weights to obtain the intensity distributions. In this experiment, the intensity distributions of local regions are modeled by Gaussian distribution with unitary weight. We define the LAE of a pair of neighboring voxels p and q based on the product of the probability of voxel p belonging to the local distribution of voxel q , and the probability that q belonging to the local distribution of p . Maximizing the product of these probabilities is equivalent to minimizing the sum of the negative log likelihood of these probabilities. Let x_p denote the assigned label of voxel p , and I_p the image intensity at this voxel. We call the region with higher intensity the foreground (Region 1), which is connected to the source (S), and the region with lower intensity the background (Region 2), which is connected to the sink (T). $C_{x_p x_q}$ denotes the LAE cost between voxel p and q with assigned labels x_p and x_q . When we label voxel p as S and voxel q as T , the cost will be C_{ST} . When we label voxel p as T and voxel q as S , the cost will be C_{TS} . Assuming the local distribution over each neighborhood is Gaussian, when the assigned labels for the two voxels are the same, the LAE costs C_{SS} and C_{TT} between voxels p and q are defined as follows:

$$C_{SS} = C_{TT} = \frac{(I_p - \mu_q)^2}{2\sigma_q^2} + \frac{(I_q - \mu_p)^2}{2\sigma_p^2}$$

where μ_p and σ_p denote the mean and the STD of the local distribution of voxel p , respectively. When the assigned labels for the two voxels are different, we assign the following LAE costs:

$$\begin{aligned} C_{ST} &= \frac{(I_p - (\mu_q + k\sigma_q))^2}{2\sigma_q^2} + \frac{(I_q - (\mu_p - k\sigma_p))^2}{2\sigma_p^2} \\ C_{TS} &= \frac{(I_p - (\mu_q - k\sigma_q))^2}{2\sigma_q^2} + \frac{(I_q - (\mu_p + k\sigma_p))^2}{2\sigma_p^2}. \end{aligned} \quad (1)$$

With the above definition, when the difference between voxel p (resp. q) and μ_q (resp. μ_p) is larger than $(k\sigma_q/2)$ [resp. $(k\sigma_p/2)$], the cost of having the same label is larger than the cost of having different labels, and therefore such energy definition encourages a cut between the two pixels. The introduction of the $(k\sigma/2)$ term in the definition of (1) has a similar effect as the minimum internal difference used in graph-based segmentation methods, but GC-LAE does not treat it as a hard constraint. We can change the parameter k based on the expected difference of local distributions between two regions.

The minimization of the total energy cost between all voxels belonging to the neighborhood set can be formulated as a GC problem, with the graph structure shown in Fig. 4(b). We connect node p and q to the source S and sink T by two edges with zero cost and three edges with link costs denoted by B , C , and D respectively. These link costs can be derived from previously defined energy costs: C_{SS} , C_{ST} , C_{TS} , and C_{TT} by solving the following equation, following the original idea of GC [21]:

$$\begin{bmatrix} C_{SS} & C_{ST} \\ C_{TS} & C_{TT} \end{bmatrix} = A \begin{bmatrix} 1 & 1 \\ 1 & 1 \end{bmatrix} + B \begin{bmatrix} 1 & 1 \\ 0 & 0 \end{bmatrix} + C \begin{bmatrix} 0 & 1 \\ 0 & 1 \end{bmatrix} + D \begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix}$$

where A is a constant that can be ignored. Fig. 4(b) illustrates the cuts corresponding to C_{ST} and C_{TS} .

2) Global Energy—In addition to LAE term, we can also add a global energy term based on predefined intensity distributions. Considering that the intensity distribution varies with the depth in ultrasound images due to depth-dependent acoustic attenuation, we estimate the mean intensity and STD of each region (LNP or fat) at each depth, and assign the same mean and variance to all voxels at the same depth. In this paper, we connect all nodes shown in Fig. 4(b) to both source (for FAT) and sink (for LNP) nodes by additional edges, and define the cost of these edges using the following sigmoidal functions:

$$W_p(I_p) = \begin{cases} \alpha \frac{1}{1 + \exp\left(\frac{I_p - \mu_{\text{LNP},p}}{\sigma}\right)} & \text{node } p \text{ to } T \\ \exp\left(\frac{I_p - \mu_{\text{FAT},p}}{\sigma}\right) & \\ \alpha \frac{\exp\left(\frac{I_p - \mu_{\text{FAT},p}}{\sigma}\right)}{1 + \exp\left(\frac{I_p - \mu_{\text{FAT},p}}{\sigma}\right)}, & \text{node } p \text{ to } S \end{cases} \quad (2)$$

where $\mu_{\text{LNP},p}$ and $\mu_{\text{FAT},p}$ stand for the mean of LNP and fat at voxel p , respectively. The slope σ is defined as $(\mu_{\text{FAT},p} - \mu_{\text{LNP},p})/8$ in this experiment. α is the weight of this global energy term, with respect to the LAE. In Section IV, we show results with and without using the global energy term.

III. Overall Algorithm for Lymph Node Segmentation

Fig. 5 shows the overall procedure for the proposed segmentation method, and the corresponding images are illustrated in Fig. 6. The algorithm basically contains three parts. First, NGC [10] is used to segment the LN-mask, which contains LNP and the fat, from PBS. Second, after obtaining the LN-mask, GC-LAE is applied to separate LNP and fat voxels inside the LN-mask. Third, NGC is applied again to segment all three objects simultaneously to further refine the segmentation result by explicitly making use of the nested relationship between these three regions.

A. 3-D HFU Data Acquisition

LN dissection, histological preparation, and HFU data acquisition protocols were previously described in detail [2]. Briefly, LNs were dissected from patients with histologically proven cancers at the Kuakini Medical Center (KMC) in Honolulu, HI. Individual freshly dissected LNs were placed in a PBS solution at room temperature and scanned. Radiofrequency (RF) signals were acquired using a single-element transducer with a 12.2-mm focal length, an f-number of 2, and a center frequency of 25.6 MHz. The RF echo signals were digitized at 400 MS/s using an 8-b A/D board. 3-D HFU data were acquired from each LN by scanning adjacent planes with a uniform plane and A-line spacing of 25 μm . The present segmentation study was carried out using a representative database of 3-D HFU envelope data from 115 LNs (19 metastatic and 96 cancer-free LNs) from 67 colorectal-cancer patients. The Institutional Review Boards (IRBs) of the University of Hawaii and the KMC approved the participation of human subjects in the study. All participants were recruited at KMC and gave written informed consent as required by the IRBs.

B. Initialize LN-Mask

We initialize the LN-mask, which contains only LNP and fat [Fig. 6(c)], using the NGC method. In [11], NGC was used to separate three nested regions (PBS, fat, and LN) simultaneously based on the depth-dependent intensity distributions of each region. We first estimated the mean and STD of PBS by probabilistic random sample consensus (RANSAC) described in Section III-B.1. By assigning probabilities to candidate PBS voxels based on

their intensities, RANSAC [22] obtained good estimations in a few tries (i.e., ~ 5). Fig. 6(b) shows the resulting probability map where bright voxels have a higher probability of belonging to PBS than dark voxels. After obtaining the distribution of PBS, we define PBS threshold, which is the intensity threshold between PBS and the LN-mask [I^T in (3)], to differentiate PBS and LN-mask. With the data term defined by the PBS threshold (3), NGC is able to obtain an accurate LN-mask [Fig. 6(c)]. Note that NGC can separate LN and PBS even when the lower part of LN is almost as dark as PBS due to acoustic attenuation.

1) RANSAC-Based PBS Distribution Estimation—Because the PBS region is generally very dark and can be approximated as a constant, we need to estimate only its mean intensity. To accomplish this, we used a probabilistic RANSAC approach. We assigned a probability of being PBS to each voxel, and randomly selected candidate PBS voxels from all voxels according to these probabilities. In each sampling, the mean of all selected candidate voxels was calculated, and the voxels that had intensities within a distance threshold to the mean intensity were identified and considered to be inliers for the PBS. The mean value determined from the sampling that led to the largest inlier set was the final estimated intensity mean for the PBS. We further computed the STD of the inlier voxels, and used a Gaussian function with the mean and STD as the probability density function for the PBS. This probability density function was employed by the NGC algorithm to separate PBS from LN-mask region in the next step.

To determine the probability that a voxel belongs to the PBS, we first calculated the mean over all voxels. Because the PBS voxels are typically darker than LNP and fat voxels, a true PBS voxel is likely to have an intensity much lower than the overall mean value. Therefore, we set the probability to zero for all voxels whose intensities are above the overall mean. For a voxel whose intensity is lower than the overall mean, we set the probability $P(I_p)$ to be proportional to the difference $d(I_p)$ between the mean and the intensity of voxel p , using

$$P(I_p) = d(I_p) / \max_{j \in \mathcal{U}} d(I_j)$$

where $\mathcal{U}$ is the set of voxels j with $d(I_j) > 0$. Fig. 6(b) shows the probability defined by the intensity difference. In each sampling, we chose 20% of voxels in $\mathcal{U}$. In our experiment, we conducted five random samplings and chose the largest inlier set from these five samplings to estimate the mean intensity and STD of PBS voxels.

2) Segment PBS by NGC—In Fig. 6(a), LNP (dark and light) is inside the fat (light), and these two objects are inside the PBS (dark). In this example, NGC limited the region of LNP inside the convex hull of the fat and defined the missing boundary between LNP and PBS as a straight line [illustrated in Fig. 6(c)]. Using the conventional GC approach would have falsely labeled the lower part of LNP as PBS. We briefly describe the NGC algorithm below. A more detailed description can be found in [10].

NGC is designed to simultaneously segment multiple objects with a nested relationship, i.e., an inner object is contained in an outer object, and NGC only needs to have the intensity distribution of each object. (which can be either global distributions or locally adaptive

location-dependent distributions, e.g., depth dependent). NGC applies duplicated layers to represent different objects. Each node in layer i corresponds to a voxel in the image and has an associated binary variable x_p^i , with $x_p^i = 1$ indicating voxel p is assigned to region i , $x_p^i = 0$ otherwise. To determine x_p^i , we minimize the following energy function:

$$E(x_p^i, i \in \mathcal{L}, p \in \mathcal{P}) = \sum_{i \in \mathcal{L}} \left(\sum_{p \in \mathcal{P}} D_p^i(x_p^{i-1}, x_p^i) + \alpha_i \sum_{p, q \in \mathcal{N}} V_{p, q}^i(x_p^i, x_q^i) \right) \quad (3)$$

$$D_p^i(x_p^{i-1}, x_p^i) = \begin{cases} 0 & x_p^i = x_p^{i-1} \\ W_p^{i-1, i} & x_p^i \neq x_p^{i-1} \end{cases}$$

$$W_p^{i-1, i}(I_p) = \begin{cases} \frac{1}{1 + \exp\left(\frac{I_p - I^T}{\sigma}\right)}, & i \text{ is PBS} \\ \frac{\exp\left(\frac{I_p - I^T}{\sigma}\right)}{1 + \exp\left(\frac{I_p - I^T}{\sigma}\right)}, & i \text{ is fat} \\ \frac{\min\left(1, \exp\left(\frac{I_p - I^T}{\sigma}\right)\right)}{1 + \exp\left(\frac{I_p - I^T}{\sigma}\right)}, & i \text{ is LNP} \end{cases}$$

$$V_{p,q}^i(x_p^i, x_q^i) = \begin{cases} 0 & x_p^i = x_q^i \\ 1 & x_p^i \neq x_q^i \end{cases} \quad (4)$$

where $\mathcal{L}$ denotes the set of layer indices, $\mathcal{P}$ is the set of voxels, and $\mathcal{N}$ defines neighborhood set (we used 18-connectivity to define the neighborhood structure in 3-D). V^i and D^i stand for the regularization term and data term, respectively. We define $V_{p,q}^i$ as in (4) so that the total regularization cost for layer i is the total boundary length of region i . Minimizing such a length will lead to smoother boundaries. Data term D_p^i is defined as the log likelihood that pixel intensity I_p belongs to object i . Because the goal here is to separate PBS from target HFU image, we consider only the case where each object has either high or low intensity.

As illustrated in Fig. 6(a), the intensity of PBS is “low,” the intensity of the fat is “high,” and the lower part of LNP is “low” and the higher part of LNP is “high.” Therefore, we define the energy terms by a sigmoid function as in (3). The parameters I^T and σ are determined based on the observed intensity distribution of PBS in the previous step. We use Gaussian distribution to model PBS. In (3), PBS threshold I^T is defined as $\mu_{\text{PBS}} + 3\sigma_{\text{PBS}}$, and σ is defined as $\sigma_{\text{PBS}}/2$. Fig. 6(c) shows the segmentation result obtained using NGC. The white region contains LNP and fat, and the PBS is labeled in black. The details of NGC can be found in [10].

C. LNP Segmentation From the LN-Mask

In LN images, the intensity distribution of a given object may not be uniform even at a constant depth. To deal with the spatially varying intensity distributions, we apply the GC-LAE method described in Section II to the LN-mask. The parameter k should be set based on the degree of intensity dissimilarity between LNP and fat. Our experience revealed that using a fixed k value led to difficulties in obtaining satisfactory segmentation results for images with nonuniform contrast variations. Therefore, we performed GC-LAE multiple times using several k values, and fuse these results to obtain the confident regions of LNP and fat. Finally, we applied NGC to obtain the final segmentation result. The method to automatically select k values is described in Section III-D.

1) Segment LNP and Fat by GC-LAE—In the proposed framework, we apply GC-LAE in two rounds. In the first round, GC-LAE is applied with the LAE only. The top row in Fig. 7 shows the segmentation results of GC-LAE obtained by several different k in the first round. Because the contrast between LNP and the fat at left hand side (green arrow) is low, GC-LAE may segment some LNP voxels as the fat region when k is small or segment all fat voxels on the left as LNP when k is high.

As demonstrated, there is not a single value for k that will work well in all regions. Therefore, we apply GC-LAE with several different k values, and then fuse the results. The automatic selection of up to three k values is described in Section III-D. We use the

intersection of the LNP regions obtained with different k as the confident region for LNP [white region in Fig. 7(a, bottom)], and we use the intersection of the fat regions as the confident region for fat [pink region in Fig. 7(a)]. From these confident regions, we determine the mean and STD of LNP and the fat at different depths. To suppress the noise in the resulting mean and STD values, we further fit the mean and STD profiles along the depth into two separate spline functions using the spline-based approach with RANSAC [22].

In the second round, GC-LAE is applied with LAE term and the global energy term [see (2)]. The global energy is defined by the depth-dependent profiles obtained from the confident regions in the first round. The bottom row of Fig. 7 shows the segmentation results of GC-LAE with global energy that have more accurate boundary on the left. Similar to the first round of GC-LAE, we can fuse these results to obtain new confident regions for both LNP and fat, and derive the new depth-dependent mean and STD profiles.

2) Update PBS Threshold—Before applying NGC for the final refinement, the depth-dependent PBS threshold I_p^T in (3) is defined as $\mu_{\text{LNP},p} - \sigma_{\text{LNP},p}$ and σ_p in (3) is defined as $\sigma_{\text{LNP},p}/2$.

D. Automatic Selection of Several k Values

Small LNs (≤ 3.6 mm) have higher contrast between LNP and fat than large LNs (>3.6 mm) because they typically suffer less severe attenuation effects. For small LNs, a larger k value is preferred to get rid of unwanted noise. For large LNs, a smaller k value is preferred to find all boundaries. Fig. 8 shows the segmentation results of GC-LAE for three values of k . The top row of Fig. 8 shows a small LN (2.7 mm), and the bottom row shows a large LN (7.9 mm). As shown in Fig. 8, an improper k value may lead to extremely poor results. In the top LN, the segmentation results of GC-LAE when $k = 1.5$ and $k = 2.5$ are poor because GC-LAE may be too sensitive to noise when the value of k is too small. In the bottom LN, GC-LAE may be unable to differentiate objects when the value of k is too large.

In our experiment, we apply GC-LAE with k values from one to four with interval 0.5, and then we use the fat ratio inside the inner mask to determine proper k automatically. The inner mask is defined as the area with distance over 70% of the largest distance to the boundary of LN-mask. The bright region in Fig. 8 shows the inner masks of corresponding LNs. After getting the inner mask, we compute the fat ratio inside the inner mask. As indicated in Fig. 8, poor results tend to have larger fat ratio. In this experiment, we choose up to three k values having fat ratio under 0.32. The automatically selected k values of the top LN are 3, 3.5, and 4 and those of the bottom LN are 1 and 1.5.

E. Refinement Process

NGC is used to refine the result of GC-LAE to guarantee the nested relationship among PBS, fat, and LNP, and obtain the final segmentation result. As described in Section III-C.2, we obtain depth-dependent PBS parameters I_p^T and σ_p based on the GC-LAE segmentation result. We also generate seeds for the fat and LNP regions based on the previous segmentation result. NGC can correct the errors of GC-LAE such as the mislabeled “halo”

voxels outside the fat shown in Fig. 6(d) [indicated by the green arrow in Fig. 6(e)]. The final segmentation result of NGC is shown in Fig. 6(f).

Initial seeds for the LNP and fat regions are obtained from the confident regions obtained by the second round GC-LAE (the bottom row of Fig. 7). As shown in Fig. 9(a), we first obtained a fused segmentation map from the GC-LAE results. The voxel values T_p in black, blue, purple, and pink regions are 0, 1, 2, and 3, which are the number of times that each voxel is considered to be fat by the three segmentation results. The pink region is considered the confident fat region, and the black region is the confident LNP region. As can be seen, there are some “halo” pixels outside the pink region that are falsely considered as LNP. We apply a morphological opening to remove the halo region of confident LNP region and define the remaining region as the seeds of LNP. We also set confident fat region as seeds for the fat region. Furthermore, we remove any fat (pink) regions that are completely contained by LNP seeds through connectivity analysis, so that the fat seeds lie only on the outer boundary of the LN-mask. As shown in Fig. 9(b), pink pixels are the final seeds for fat, and the white pixels are the seeds for LNP.

To make NGC more likely to cut along the boundary between LNP and fat regions obtained by GC-LAE, we define the edge cost between voxels by the sum of the three binary segmentation results obtained using GC-LAE with different values of k as shown in Fig. 9(a). Making use of the fact that the fat region is outside the LNP and should have intensity higher than the LNP, we define the edge cost, $V_{p,q}$ as

$$V_{p,q} = \begin{cases} 1 & T_p > T_q \\ 4 & T_p = T_q \\ \propto & T_p < T_q \end{cases}.$$

Note that T_p is set as $T_q + 1$ when p is outside the LN-mask and q is inside the LN-mask. By this setting, NGC will tend to cut the LNP-fat boundary along the boundary of GC-LAE segmentations.

For fat-PBS boundary, we do not change the edge cost, so NGC cuts the fat-PBS boundary by the intensity and the new depth-dependent PBS threshold obtained in Section III-C.2. Fig. 9(c) and (d) compares the result of NGC based on the segmentation results of GC-LAE with and without global energy. The result based on GC-LAE with global energy obtained more accurate LNP-fat boundary on the left.

IV. Results

In this paper, we compared the result of the current described method with two other methods: our own prior work called NGC with depth-dependent profile [11] and the method developed in [14] called STS-LS with RFC.

The NGC method is based on the EM framework [11]. In the expectation phase, NGC is applied to segment LNP, fat, and PBS simultaneously. In the maximization phase, the mean

and STD of the intensity in each depth of each object are obtained by the previous segmentation result of NGC. A spline-based fitting method is applied to fit the mean intensity (resp. STD) of each object as a function of depth to establish the depth-dependent profiles of each objects. These depth-dependent profiles are used in the NGC during the expectation phase of next iteration. The iteration stops when the segmentation result of NGC is converged.

The STS-LS with RFC algorithm contains an initialization step and a refinement step [14]. In the initialization step, 15 features are extracted for each voxel, and RFC is employed to obtain an initial segmentation result. In the refinement step, the initial result is refined by a three-phase local-region-based level-set segmentation method. The Gamma distribution is used to model the envelope data of HFU images. During the contour evolution, Gamma distribution parameters are estimated locally in transverse slices (i.e., depth dependent).

A. Illustrative Results

Fig. 10 displays the segmentation results of four typical LNs to illustrate the advantages and disadvantages of the three different segmentation methods. RTS-LS with RFC and NGC with depth-dependent profiles segment LNP mainly by intensity information, and GC-LAE-based methods segment LNP mainly by the intensity similarity of local regions.

1) LNs With Clear Boundary and Consistent Intensity Distributions—The top LN has clear boundary and consistent intensity distributions. Therefore, all four segmentation methods can obtain satisfactory results. However, RFC + STS – LS may converge to a false local minimum during deformation as shown in the top of Fig. 10(c). In contrast, the GC-based approach can avoid this kind of error.

2) LNs With Clear Boundary and Nonhomogeneous Acoustic Attenuation—As discussed in Section I, depth-dependent profiles may not perform adequately in the presence of inconsistent profiles, where the intensity of voxels within the same depth in one object may not be consistent. To illustrate this point, the second rows of Fig. 10(c) and (d) show the segmentation result of RFC + STS – LS and NGC with depth-dependent profiles, respectively. Comparing these results with the manual segmentation result in Fig. 10(b), we can identify a fat region on the left mislabeled as LNP because the fat in the right region of the image at the same depth is brighter than the fat in left. In this case, NGC with depth-dependent profiles and RFC + STS – LS were unable to correctly segment the fatty region on the left. Because the contrast between LNP and fat is strong enough on the left side of the LN, GC-LAE was able to find the boundary correctly [Fig. 10(e) and (f)] independent of whether the global-energy term is used.

3) LNs With Blurry Boundary and Low Intensity Difference Between LNP and the Fat—GC-LAE determines a boundary based on the similarity of local intensity distributions. Therefore, it may not be able to find the boundary correctly when the boundary is blurry. In the third LN of Fig. 10, the boundary between LNP and the fat in middle is extremely blurry and the intensity difference between them is low. In this case, GC-LAE cannot find the boundary correctly even with global energy because of insufficient contrast,

but RFC + STS – LS and NGC with depth-dependent profiles were able to provide better segmentation results according to intensity distributions. RFC + STS – LS obtain the best results in this case by updating intensity distributions gradually with deformation.

4) LNs With Blurry Boundary and High Intensity Difference Between LNP and the Fat—The bottom row of Fig. 10 shows a transverse slice of an LN with a “blurry” boundary at the upper left corner, and the intensity of the fat on right is much brighter than LNP. In this case, RFC + STS – LS remained at a false local minimum during the segmentation of this LN. NGC with depth-dependent profiles performed better, but it was adversely influenced by the blurry boundary. GC-LAE without global information also incorrectly segments some bright voxels of LNP as fat. In this example, GC-LAE with a global-energy term has the best performance. Using the additional information provided by the depth-dependent profiles, the resulting boundary nearly matches the true boundary.

B. Results in Our Database

To evaluate the segmentation result, we use Dice similarity coefficient (DSC), which is defined as

$$DSC = 2 |X \cap Y| / (|X| + |Y|)$$

where X and Y are the results of the segmentation algorithm and the ground truth (i.e., manual expert segmentation), respectively. DSC evaluates the similarity between two segmentation results X and Y .

Table I shows the segmentation results for the 42 colorectal LNs used in [14], which is a subset of the images in the complete data set. We compare the performance of the RFC + STS – LS, NGC with depth-dependent profiles, and the current described GC-LAE-based method with and without depth-dependent profiles. Table I demonstrates that the GC-LAE outperforms two other methods by obtaining highest average DSC in all three objects.

Table II shows the DSC values for 115 LNs of our whole database, which includes the 42 LNs used in Table I. It compares the performance of NGC with depth-dependent profiles, the described method without global energy (one round of GC-LAE), and the proposed method with global energy (two rounds of GC-LAE). As shown in Table II, GC-LAE obtained higher average DSC than NGC with depth-dependent profile method in all three objects. With the information of depth-dependent profiles, GC-LAE can obtain more accurate results in LNP and fat segmentation and lead to better accuracy. In general, the total pixel number of the fat is less than the total number of LNP region. Therefore, with the same number of errors, the DSC of the fat will be lower than that of the LNP.

C. Computation Time

In NGC with depth-dependent profiles and GC-LAE, we down sample all testing HFU images by an integer factor between two or four to yield an image whose dimensions are always smaller than $100 \times 100 \times 100$ to reduce the execution time. Table III lists the average execution time in minutes per LN over 54 colorectal LNs used in [15] and 115 LNs

including breast LNs. (These times were obtained using a PC with a 2.6-GHz i7 processor using MATLAB 2016b without use of GPUs or any parallel computing.)

V. Discussion and Conclusion

A. Weight of Global Energy

The coefficient a in (2) controls the dependency of the solution on the global energy term, which is defined by the depth-dependent profiles obtained from confident regions as described in Section III-C. Because every connected voxel pairs contribute to the LAE term, the weight a_p of voxel p should be defined as a constant a times the number of pairs in the neighborhood set of p . When the a value is infinity, the segmentation result of the proposed framework will be close to the result of NGC with depth-dependent profiles. Therefore, the segmentation results shown in Fig. 10(d)–(f) can be considered as those obtained when a is infinity, zero, and in between ($a = 5$). When inhomogeneous acoustic attenuation exists (e.g., the second row in Fig. 10), a lower a (i.e., <100) is preferred to avoid the effect of the inhomogeneous intensity. When the contrast between LNP and fat is small (e.g., the fourth row in Fig. 10), a higher a (i.e., >0.1) is required to accurately determine the boundary by depth-dependent intensity distributions. In this paper, we defined $a = 5$, and therefore the weight $a_p = 5 \times 18$ when voxel p is 18-connectivity.

B. Clinical Significance

The goal of our QUS studies is to enable the pathologist to target suspicious regions within the LN for histologic evaluation. This new segmentation algorithm makes the complete QUS analysis process automatic from 3-D HFU data acquisition to using QUS to identify suspicious regions. Section IV-B clearly establishes that the new segmentation method performs successfully, but it does not provide information about how QUS estimates may be affected by superior segmentation. As shown in Fig. 11, the average effective scatterer size (D) estimates obtained using manual segmentation and the proposed automatic segmentation agreed well. The mean difference was $-0.066 \mu\text{m}$, and the 95% limits of agreement (i.e., mean ± 1.96 STDs) were -1.02 and $+0.89 \mu\text{m}$. As illustrated in [2] and [3] and also visible in Fig. 11, D is a very important QUS parameter for detection of metastatic LNs. Therefore, our segmentation method does not degrade metastases detection using QUS, while providing a completely automatic framework.

C. Future Work

1) Interobserver and Intraobserver Variabilities—The gold standard used for evaluating our segmentation algorithm came from a single expert, and because there exists no other means to carefully segment the 3-D ultrasound data, no absolute means exist to evaluate the quality of the expert segmentation. Therefore, it is reasonable to expect that different experts would give slightly different results. Future studies will be performed to quantify interobserver and intraobserver variabilities. Nevertheless, when blindly presented with automatic segmentation and manual segmentation images, our expert was unable to differentiate them.

2) Breast LNs—Our database also includes more than 100 axillary LNs acquired from breast-cancer patients; axillary LNs have a different topology than the LNs acquired from colorectal cancers. In particular, they often contain fatty deposits inside the LNP creating new challenging aspects for automatic segmentation. In future studies, we will meet this challenge by modifying the GC-LAE framework to segment these internal fatty deposits. Now, a two-layer NGC is used to separate LNP, fat, and PBS. Because fatty deposits are inside the LNP, they also satisfy a nested relationship, and we can extend the two-layer NGC to three-layer NGC to segment these fatty deposits as well.

3) Other HFU Segmentation Problems—The new segmentation method presented here was successfully applied to HFU data acquired from freshly excised human LNs, but the ability to segment objects with spatially varying intensity distributions is essential and applicable to a wide range of imaging applications where HFU is used. HFU images usually suffer from inhomogeneous acoustic attenuation, and GC-LAE could help segment objects in such images.

D. Conclusion

This paper describes a novel fully automatic framework to segment LNP, fat, and PBS simultaneously in LN images. The algorithm combines CG-LAE and NGC. NGC generates an LN-mask, which contains only LNP and fat, while GC-LAE further separates LNP and fat. GC-LAE is insensitive to the direction of attenuation and performs well in the presence of inhomogeneous acoustic attenuation in HFU images. Compared with our previous work using NGC with depth-dependent profiles in an EM-based framework, the new framework is superior in handling inhomogeneous intensity distributions and can find the LNP–fat boundary even when the intensity contrasts between the two are spatially varying greatly.

The proposed framework further refines the results of GC-LAE by NGC, which can exploit the nested relationship between PBS, fat, and LNP to obtain anatomically correct segmentation. With NGC, the missing boundary between LNP and PBS is well defined by the convex hull of fat. NGC always achieves the global minimum of the defined energy functional. Compared with level-set-based approaches for LN segmentation, the described framework is less vulnerable to converging to a false local minimum during deformation and therefore is not dependent on initialization values.

References

1. Saegusa-Beecroft E, et al. Three-dimensional quantitative ultrasound for detecting lymph node metastases. *J Surgical Res.* 2013; 183(1):258–269.
2. Mamou J, et al. Three-dimensional high-frequency backscatter and envelope quantification of cancerous human lymph nodes. *Ultrasound Med Biol.* 2011; 37(3):345–357. [PubMed: 21316559]
3. Mamou J, et al. Three-dimensional high-frequency characterization of cancerous lymph nodes. *Ultrasound Med Biol.* 2010; 36(3):361–375. [PubMed: 20133046]
4. Coron, A., et al. A quantitative ultrasound-based method and device for reliably guiding pathologists to metastatic regions of dissected lymph nodes. *Proc. 9th IEEE Int. Symp. Biomed. Imag. (ISBI);* May 2012; p. 1064–1067.
5. Coron, A., et al. Three-dimensional segmentation of high-frequency ultrasound echo signals from dissected lymph nodes. *Proc. IEEE Ultrason. Symp., (IUS);* Nov. 2008; p. 1370–1373.

6. Resch A, Langner C. Lymph node staging in colorectal cancer: Old controversies and recent advances. *World J Gastroenterol*. 2013; 19(46):8515–8526. [PubMed: 24379568]
7. Gonzalez, RC., Woods, RE. *Digital Image Processing*. 3. Upper Saddle River, NJ, USA: Prentice-Hall; 2006.
8. Ishikawa H. Exact optimization for Markov random fields with convex priors. *IEEE Trans Pattern Anal Mach Intell*. Oct; 2003 25(10):1333–1336.
9. Delong, A., Boykov, Y. Globally optimal segmentation of multi-region objects. *Proc. IEEE 12th Int. Conf. Comput. Vis*; Oct. 2009; p. 285-292.
10. Kuo JW, Mamou J, Aristizábal O, Zhao X, Ketterling JA, Wang Y. Nested graph cut for automatic segmentation of high-frequency ultrasound images of the mouse embryo. *IEEE Trans Med Imag*. Feb; 2016 35(2):427–441.
11. Kuo, J-W., Mamou, J., Wang, Y., Saegusa-Beecroft, E., Machi, J., Feleppa, EJ. A novel nested graph cuts method for segmenting human lymph nodes in 3D high frequency ultrasound images. *Proc. IEEE 12th Int. Symp. Biomed. Imag. (ISBI)*; Apr. 2015; p. 372-375.
12. Nosrati MS, Hamarneh G. Local optimization based segmentation of spatially-recurring, multi-region objects with part configuration constraints. *IEEE Trans Med Imag*. Sep; 2014 33(9):1845–1859.
13. Bui, TM., et al. Level-set segmentation of 2D and 3D ultrasound data using local gamma distribution fitting energy. *Proc. IEEE 12th Int. Symp. Biomed. Imag. (ISBI)*; Apr. 2015; p. 1110-1113.
14. Bui, TM., et al. Random forest classification and local region-based, level-set segmentation for quantitative ultrasound of human lymph nodes. *Proc. IEEE Int. Ultrason. Symp. (IUS)*; Oct. 2015; p. 1-4.
15. Bui TM, et al. Local transverse-slice-based level-set method for segmentation of 3D, high-frequency ultrasonic backscatter from dissected human lymph nodes. *IEEE Trans Biomed Eng*. Jul; 2016 64(7):1579–1591. [PubMed: 28113305]
16. Felzenszwalb PF, Huttenlocher DP. Efficient graph-based image segmentation. *Int J Comput Vis*. Sep; 2004 59(2):167–181.
17. Huang QH, Lee SY, Liu LZ, Lu MH, Jin LW, Li AH. A robust graph-based segmentation method for breast tumors in ultrasound images. *Ultrasonics*. 2012; 52(2):266–275. [PubMed: 21925692]
18. Zheng, L., Huang, Q. A graph-based segmentation method for 3D ultrasound images. *Proc. IEEE 31st Chin. Control Conf. (CCC)*; Jul. 2012; p. 4001-4005.
19. Chang H, Chen Z, Huang Q, Shi J, Li X. Graph-based learning for segmentation of 3D ultrasound images. *Neurocomputing*. Mar.2015 151:632–644.
20. Boykov Y, Veksler O, Zabih R. Fast approximate energy minimization via graph cuts. *IEEE Trans Pattern Anal Mach Intell*. Nov; 2001 23(11):1222–1239.
21. Kolmogorov V, Zabih R. What energy functions can be minimized via graph cuts? *IEEE Trans Pattern Anal Mach Intell*. Feb; 2004 26(2):147–159. [PubMed: 15376891]
22. Fischler MA, Bolles R. Random sample consensus: A paradigm for model fitting with applications to image analysis and automated cartography. *Commun ACM*. 1981; 24(6):381–395.

Biographies

Jen-wei Kuo was born in Taipei, Taiwan, in 1982. He received the B.S. degree in electronics engineering from National Chiao Tung University, Hsinchu, Taiwan, in 2005, the M.S. degree in electronics engineering from National Taiwan University, Taipei, in 2008, and the M.S. degree in computer science and the Ph.D. degree in electrical and computer engineering from New York University, New York, NY, USA, in 2012 and 2016, respectively.

He was a Post-Doctoral Associate at New York University, where he was involved in high frequency ultrasound image segmentation, three-dimensional shape decomposition, and machine learning-based shape analysis.

Jonathan Mamou (S'03–M'05–SM'11) was born in Saint-Germain-En-Laye, France, in 1978. He graduated from the Ecole Nationale Supérieure des Télécommunications, Paris, France, in 2000, and received the M.S. and Ph.D. degrees in electrical and computer engineering from the University of Illinois at Urbana–Champaign, Urbana, IL, USA, in 2002 and 2005, respectively.

He is currently a Research Manager with the F. L. Lizzi Center for Biomedical Engineering, Riverside Research in New York, NY, USA. He is the Coeditor of the book *Quantitative Ultrasound in Soft Tissues* published by Springer in 2013. His fields of interests include theoretical aspects of ultrasonic scattering, ultrasonic medical imaging, ultrasound contrast agents, and biomedical image processing.

Dr. Mamou is a fellow of the American Institute of Ultrasound in Medicine (AIUM) and a member of the Acoustical Society of America. He served as the Chair of the AIUM High-Frequency Clinical and Preclinical Imaging Community of Practice. He is an Associate Editor of *Ultrasonic Imaging* and the IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency control, and a reviewer for numerous journals.

Yao Wang (F'04) received the B.S. and M.S. degrees in electronic engineering from Tsinghua University, Beijing, China, in 1983 and 1985, respectively, and the Ph.D. degree in

electrical and computer engineering from the University of California at Santa Barbara, Santa Barbara, CA, USA, in 1990.

Since 1990, she has been on the faculty of Electrical and Computer Engineering, Tandon School of Engineering of New York University (formerly Polytechnic University), Brooklyn, NY, USA. She is the leading author of a textbook titled *Video Processing and Communications*, and has authored over 250 papers in journals and conference proceedings. Her current research interests include video communications, multimedia signal processing, and medical imaging.

Dr. Wang has served as an Associate Editor of the IEEE Transactions on Multimedia and the IEEE Transactions on Circuits and Systems for Video Technology. She was a recipient of the New York City Mayor's Award for Excellence in Science and Technology in the Young Investigator Category in 2000. She is a co-winner of the IEEE Communications Society Leonard G. Abraham Prize Paper Award in the field of communications systems in 2004 and the IEEE Communications Society Multimedia Communication Technical Committee Best Paper Award in 2011. She was a Keynote Speaker at the 2010 International Packet Video Workshop.

Emi Saegusa-Beecroft received the M.D. and Ph.D. degrees from the Tokyo Jikei University School of Medicine, Tokyo, Japan, in 2002 and 2013, respectively.

She was with the Department of Orthopedic Surgery at the Tokyo Jikei University Hospital. After working at hospitals and clinics in Tokyo, Chiba, Saitama, and the U.S. Naval Hospital Yokosuka, she became a Research Fellow at the University of Hawaii in 2009. She is a researcher at the Department of Surgery, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, USA, where she is also with the Office of Global Health. With Dr. J. Machi, M.D., Ph.D., FACS, as her mentor, she contributed several book chapters in the field of ultrasound. Her main research interests include quantitative ultrasound for the detection of lymph node metastases in breast, colorectal, and gastric-cancer patients, surgical pathology, and global medical education.

Dr. Saegusa-Beecroft is a member of the American College of Surgeons, the American Institute of Ultrasound in Medicine, the U.S. and Canadian Academy of Pathology, the Japanese Orthopedic Association, the Japanese Association of Orthopedics and Traumatology, and the Japan College of Rheumatology.

Junji Machi received the M.D. degree from Juntendo University, Tokyo, Japan, in 1977, and the Ph.D. degree from the University of Illinois, Illinois, IL, USA, in 1984.

He completed surgical residency training at Pittsburgh, and moved to the University of Hawaii in 1995. He is currently a Professor of surgery and an Assistant Director of the Office of Global Health/Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, USA, and is a Surgeon-Researcher-Educator. He is a pioneer of intraoperative and laparoscopic ultrasound in the U.S., and has authored several books including *Ultrasound for Surgeons* (first and second editions) and *Abdominal Ultrasound for Surgeons*. His professional interests and research activities include abdominal ultrasound and quantitative ultrasound as well as abdominal surgeries and global surgical and medical education.

Dr. Machi is a fellow of the American Institute of Ultrasound in Medicine and a National Ultrasound Faculty of the American College of Surgeons.

Ernest J. Feleppa (M'82–SM'99–LSM'12–LF'15) was born in New York City, NY, USA, in 1940. He received the baccalaureate in physics from Cornell University, Ithaca, NY, USA, in 1961, and the Ph.D. degree in biophysics at Columbia University, New York, NY, USA, in 1968.

After a year of post-doctoral research in physiology and genetics, he became a member of the research staff at Riverside Research, New York, NY, in 1969, where he pursued research in coherent optics, environmental systems, and education-management systems before joining the Biomedical-Engineering Laboratory at Riverside Research. He undertook research in ultrasonic tissue characterization applied to the eye, liver, kidney, thrombi, plaque, prostate, and lymph nodes that laid the foundation for modern quantitative ultrasound. After serving as Assistant Manager, Manager, and Associate Director of the Biomedical Engineering Laboratory, he became its Research Director in 2005.

Fig. 1.

(a) Target HFU image. (b) Manual segmentation result by an expert. LNP is white and fat region is pink. The vertical axis is depth. (c) Segmentation result obtained by K-means.

Fig. 2.

(a) Target HFU image. (b) Manual segmentation result. (c) Segmentation result obtained by NGC with depth-dependent profile.

Fig. 3.

(a) Target toy image. (b) Illustration of level-set-based methods. The force on the red pixel is defined by the intensity distributions within the red dashed line. (c) Illustration of graph-based segmentation methods. Red lines indicate the connections between subgraphs. (d) Illustration of GC-LAE. The similarity between two connecting pixels (red and green) of an edge is defined by the similarity between these pixels and their corresponding local regions (dashed lines in the opposite color).

Fig. 4.

(a) Colored dashed lines indicate the corresponding local regions of pixels in different neighborhood sets. (b) Energy cost between p and q can be made by three nonzero edges depending on the region assignment of p and q . The red line associated with C_{ST} indicates the energy cost when voxel p is labeled as source S and voxel q is labeled as sink T .

Fig. 5.
Flow of the proposed framework.

Fig. 6.

Images corresponding to steps listed in Fig. 5. (a) Target HFU image. (b) Probability of belonging to PBS for all voxels. (c) LN-mask obtained by NGC with the estimated distribution of PBS. (d) Segmentation result of GC-LAE in the first round when $k = 3$. (e) Segmentation result of GC-LAE with global energy when $k = 3$. (f) Final result obtained using NGC to refine (e).

Fig. 7.

(a) HFU image and the confident regions obtained by fusing results in the top rows of (b)–(d). (b)–(d) Top row shows the segmentation results obtained by GC-LAE with different values of k in the first round (no global energy). Bottom row shows the segmentation results obtained by GC-LAE in the second round with different k values (with global energy).

Fig. 8. HFU image and its segmentation results obtained by GC-LAE with different k values. The height of the top LN is 2.7 mm, and the height of the bottom LN is 7.9 mm.

Fig. 9.

(a) Fusion of the binary segmentation maps by GC-LAE using different k values. The region outside the LN-mask is in white. The blue, purple, and pink regions are detected as fat in one, two, and three segmentation results, respectively. (b) LNP seeds are in white and the fat seeds are in pink. (c) Final NGC result based on the results of GC-LAE with global energy (i.e., using two rounds of GC-LAE). (d) Final NGC result based on the results of GC-LAE without global energy (i.e., using only one round of GC-LAE).

Fig. 10.

(a) Target HFU image. (b) Manual segmentation result. (c) Result of RFC + STS – LS. (d) Result of NGC with depth-dependent profiles. (e) Result of the proposed method without global energy (one round of GC-LAE). (f) Result of the proposed method with global energy (two rounds of GC-LAE).

Fig. 11.

Difference versus the mean of the average effective scatterer size estimated by the result of manual segmentation and proposed method on 115 LNs.

TABLE I

Mean and STD of DSC for the Segmented LNP Regions by Different Methods in 42 Colorectal LNs

	RFC+STS-LS	NGC with Depth-dependent profile	GC-LAE with global energy
LNP	0.937±0.020	0.939±0.025	0.949±0.023
Fat	0.828±0.094	0.813±0.082	0.837±0.076
PBS	0.961±0.009	0.957±0.012	0.961±0.013

TABLE II

Mean and STD of DSC for the Segmented LNP Regions by Different Methods in 115 LNs

	NGC with Depth-dependent profile	GC-LAE without global energy	GC-LAE with global energy
LNP	0.929±0.037	0.934±0.041	0.937±0.035
Fat	0.793±0.098	0.818±0.090	0.822±0.085
PBS	0.956±0.016	0.959±0.016	0.959±0.016

TABLE III

Average Execution Time of the Proposed Method in Minutes

	STS-LS	NGC with Depth-dependent profile	GC-LAE
54 LNS	19.4 ± 17.4	2.4 ± 1.6	4.4 ± 1.8
115 LNs			4.4 ± 3.0

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript