A02-3 Function Integrated Diagnostic Assistance Based on Multidisciplinary Computational Anatomy Models

- Progress Overview FY2015 -

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***Abstract*—This paper describes the purpose and summary of our recent progress and achievement in the research work, which is a part of the research project "Multidisciplinary Computational Anatomy and Its Application to Highly Intelligent Diagnosis and Therapy," founded by Grant-in-Aid for Scientific Research on Innovative Areas, MEXT, Japan. The main purposes of our research in this project are to establish a scientific principle of multidisciplinary computational anatomy and to develop computer-aided diagnosis (CAD) systems based on such anatomical models for organ and tissue functions. In FY2015, we proceeded with the preparation for sub projects, such as the database establishment, and started the investigation in earnest. Several progresses have been achieved with the promising results, which encourage the continual effort for success of this project.**

I. Introduction

Modern medical imaging devices have granted the visualization of metabolic and functional information of a body, raising the enormous interest in quantitative image analysis. The multimodality image diagnosis with a large volume of anatomic and functional information leads to increasing demands for an intelligent support system that allows for advanced visualization, information integration, and disease highlighting. Such systems can assist an accurate and efficient diagnosis, reporting, and treatment planning. In order to develop the advanced systems, our goals in this project are to establish a scientific principle of multidisciplinary computational anatomy and to develop

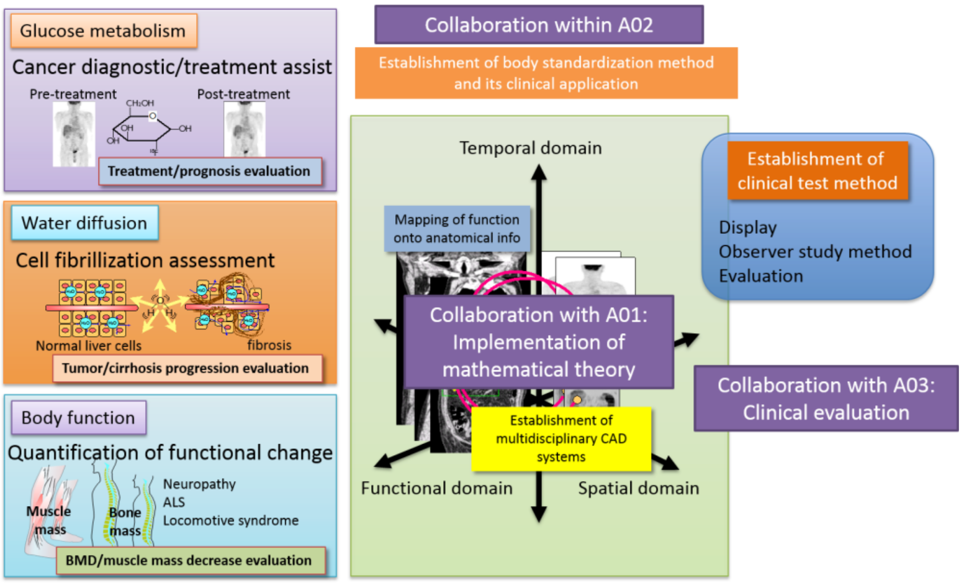


Fig. 1. Schematic diagram of the research project

anatomical and functional models for diagnosis of organ and tissue functions.

In the previous studies, we developed computational anatomy models of various organs in CT images [1]. In current project, we not only continue to improve model construction and application but also focus on establishment of computational models for functional imaging. These models can be effectively combined to process multidisciplinary information.

As A02-3, our roles in this project are to investigate image analysis methods based on the anatomic and functional information fusion and to establish a methodology of computer-aided diagnostic (CAD) systems for organ and tissue functions. Figure 1 shows the schematic diagram of the research project.

In the following sections, the progress we made in FY2015 for each of the major topics will be presented.

II. Recent Achievements

A. *Statistical Image Analysis of Torso FDG-PET/CT Images for Cancer Quantification*

1) Purpose: Standardized uptake value (SUV) on Fludeoxyglucose (FDG) positron emission tomography (PET) is used for evaluating regional activities of glucose metabolism related to cancer development. Radiologists have to understand the SUV ranges or typical normal/abnormal values based on the patients' physiological accumulations. Ideas of statistical image analysis are widely accepted for brain function analysis in dementia diagnosis. We have developed a new scheme by applying such analysis idea to torso FDG-PET diagnosis. The purpose of this study is to verify the effectiveness of the statistical approach in torso FDG-PET imaging.

2) Methods: Institutional Review Board (IRB)-approved cases (49 normal and 10 abnormal) were used in this study. The proposed scheme consisted of the following steps: (1) anatomical standardization of images, (2) normal model construction, and (3) Z-score calculation. Bounding boxes surrounding target organ regions on CT images were determined automatically using our organ recognition method [2]. The normal model contains the mean and standard deviation (SD) of SUVs for each voxel after the standardized cases were summarized [3]. Figure 2 shows an overview of the standardization scheme for FDG-PET images. The Z-score was obtained on the basis of the mean and SD stored in the normal model by comparing with the standardized abnormal cases voxel by voxel. To validate the Z-score index, we manually extracted 451 normal and 397 abnormal spots in liver and right lung images. SUV and Z-score in each region were obtained after the statistical analysis. We evaluated the discrimination performance based on the receiver operating characteristic (ROC) analysis method.

3) Recent Achievement: The discrimination performance of SUV and Z-score for the liver and the lung ROIs was measured by using the area-under-the-ROC-curves (AUCs). Each AUC was over 0.97. When the ROIs were pooled, the AUCs of Z-score and SUV were 0.98 and 0.96, respectively. The discriminant performance of the Z-score was slightly better than that of SUV with statistical significance when the ROIs were pooled. Figure 3 shows the ROC curves (right) and the distributions (left) of normal and abnormal spots on FDG-PET images.

4) Discussion: The discriminant performance of the Z-score was slightly better than that of SUV when the ROIs were pooled. The results suggest a possibility of the new quantitative determination method to support knowledge of SUV ranges as FDG accumulations in each organ. In addition, a combination of SUV and Z-score may provide a high discrimination accuracy when readers interpret torso FDG-PET images.

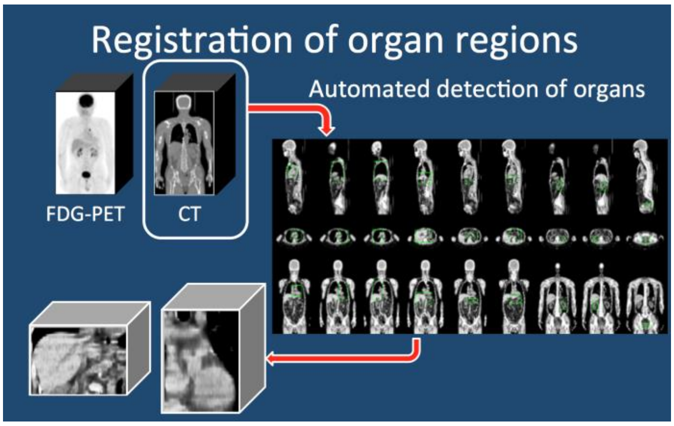


Fig. 2. Overview of organ detection and registration

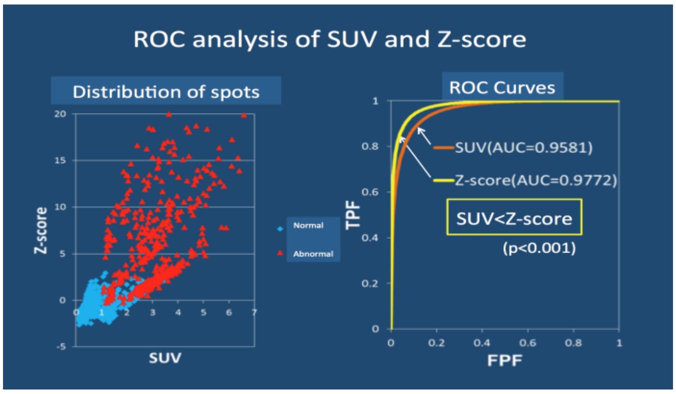


Fig. 3. Distributions of normal and abnormal spots and ROC curves for discrimination of the spots by using SUV and Z-score

5) Conclusion: Statistical image analysis of torso FDG-PET images may provide a new index for the interpretation.

B. Detection and Analysis of Lung and Breast Tumors Using PET/CT Images

1) Purpose: Lung cancer is the leading cause of death for males and females worldwide; it is essential to detect the lung cancer at an early stage. PET/CT examination is widely used for detection of early cancer, since it has the high sensitivity and high specificity by using both anatomical and functional information of the body. However, radiologists have to examine more than 1,000 images per patient; it is difficult to maintain the diagnostic accuracy avoiding reading errors. In this study, we develop the automated schemes of lung tumor detection and evaluation of malignancy using the PET/CT images.

2) Methods: In this study, we will develop the lung CAD scheme by combining the PET/CT images and supplementary information.

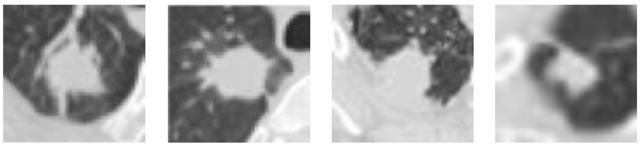
In the previous year, we developed the hybrid detection method of lung tumors using both CT and PET information. As for the existing detection method using CT image, it was difficult to detect low-contrast lesions that touch to normal organs such as the chest wall or blood vessels in the lung. In this study, we plan to develop the improved scheme using active contour filters to detect the "difficult tumors" from the previous CAD scheme [4-6].

In this year, we investigated the analytical method of determining the malignancy of tumors by a combination of anatomical, functional and supplementary information. At the same time, we are constructing a large scale PET/CT image database with pathological information to verify the analytical result of malignancy. Furthermore, using the same approach as lung CAD, we investigated the automated detection method of breast tumors in PET/CT images.

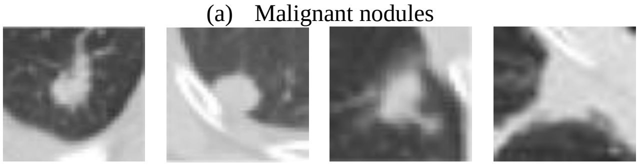
3) Recent Achievement: We have developed the analytical method of determining the malignancy of tumors by a combination of anatomical and functional information [7]. In order to characterize the lung nodules, twelve types of shape and functional features are calculated from two-phase PET/CT images. And then, malignancy is determined by the random forest method.

For the evaluation of the developed method, we collected 30 cases (21 malignant and 9 benign nodules) of early and delayed phased PET/CT images in patients who underwent both the PET/CT scan and the biopsy by bronchoscopy. As a result of evaluation, most of the malignant nodules were identified correctly under the condition that a half of benign nodules were judged correctly (Fig. 4). These results indicate that the proposed method may be useful to decrease the biopsy inspection with the greater physical burden on the patient.

As for the breast region, we developed an automated detection method of breast tumors using whole-body PET/CT images [8-10]. In this study, highly uptake regions in PET images inside the breast region extracted using CT images were detected as tumor candidates. Initial evaluation using 10 cases of screening PET/CT images revealed that the

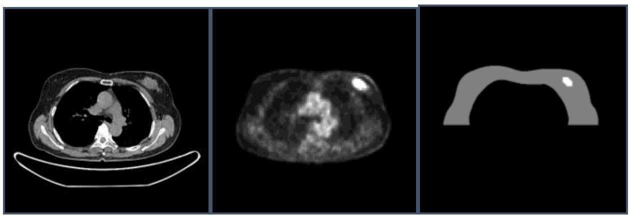


(a) Malignant nodules



(b) Benign nodules

Fig. 4. Examples of malignant (a) and benign (b) nodules judged correctly by our method



(a) (b) (c)

Fig. 5. Detection result of breast tumor. (a) CT image, (b) PET image, and (c) Segmentation and detection result. Gray and white regions show the breast and tumor, respectively

sensitivity of detection was 83.3 % with the FPs per case of 1.0. Figure 5 shows the detection example of breast tumor.

C. Automated Analysis of Increased Uptake Regions in the Bone Scintigraphy Using SPECT/CT Images

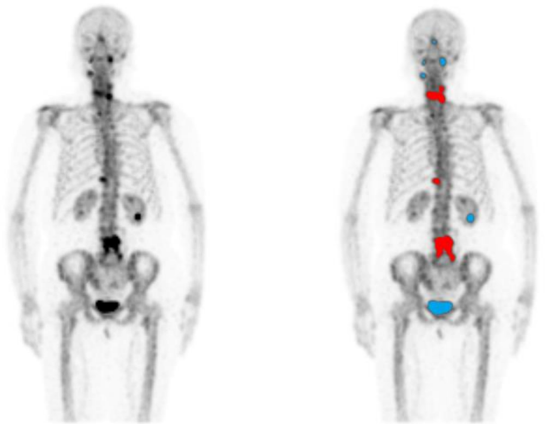
1) Purpose: As an examination of bone scintigraphy, two-dimensional examination is conducted using a gamma-ray camera. Recently, some institutions introduced a whole body SPECT/CT examination. By using SPECT/CT images, it is possible to analyze the uptake regions of the SPECT image while utilizing the information of the bone obtained from the CT image; remarkable improvement of accuracy is expected compared to the existing methods.

However, because the diagnosis using SPECT/CT is based on qualitative judgment, it is difficult to evaluate uptake regions quantitatively and three-dimensionally. In this study, therefore, we develop an automated analytical technique of increased uptake regions using both SPECT and CT images to evaluate the bone metastases and malignancy of tumors.

2) Methods: In this study, we will develop the CAD scheme to evaluate the bone metastasis and its malignancy by combining the anatomical and functional information obtained from CT and SPECT images, respectively.

In the current year, we continued to investigate the imaging properties of tumors in SPECT/CT images using a bone-simulated phantom. Based on these results, we developed the automated analytical method of tumors in SPECT/CT images. At the same time, we are constructing the SPECT/CT database for evaluation.

3) Recent Achievement: We conducted preliminary evaluation using 20 cases of clinical images. As a result, hot spots were detected correctly, and measured volume by proposed method and manual measured volume were well matched [11-13] (Figs. 6 and 7).



(a) (b)

Fig. 6. Automated detection result of hot spots. (a) Original SPECT image, and (b) Detection result. Red region is the detected region and blue is the eliminated one.

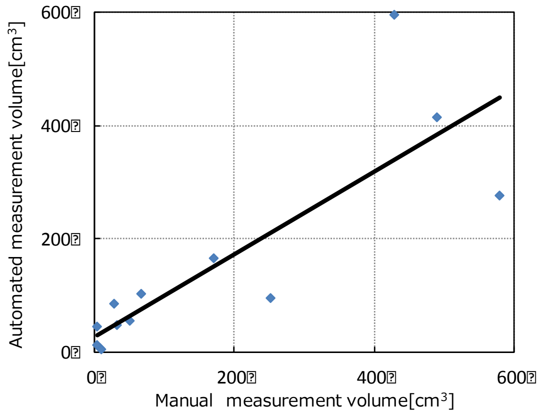


Fig. 7. Relation between the manual and automated measurements

D. Automated Analysis of Breast Tumor Using Unenhanced MR Images

1) Purpose: Breast cancer incidence tends to rise globally and the mortality rate for breast cancer is increasing in Japan. There are various screening modalities for breast cancer, and MRI examinations with high detection rate are used for high-risk groups, which are genetically prone to develop breast cancer. However, these examinations require contrast agents for dynamic imaging and may harm the screening examinees. In this study, we develop an automated analytical scheme of breast tumor using unenhanced MR images.

2) Methods: In this study, we will develop the CAD scheme using anatomical and functional information obtained by plural image sequences without contrast agents.

In this year, we improved the analytical method of the anatomical structure of mammary glands using unenhanced T1-weighted MR images. Furthermore, we developed the automated detection scheme of breast tumor using functional feature obtained by diffusion-weighted MR images [14-17].

3) Recent Achievement: We developed three-dimensional Gabor filter to analyze the orientation of mammary glands in the breast [18,19]. The orientations of mammary glands that extracted from filtered image are analyzed using histogram. Figures 8 (a) and (b) show histograms of orientation in normal and abnormal cases. As a result, big difference was observed between two cases.

The proposed tumor detection method was evaluated using 54 cases of MR images and evaluated its usefulness. Example of detected tumors is shown in Fig.9. The detection sensitivity was 75 % and FPs/case was 3.1. These results indicate that the proposed method may be useful for the analysis of breast using unenhanced breast MR images.

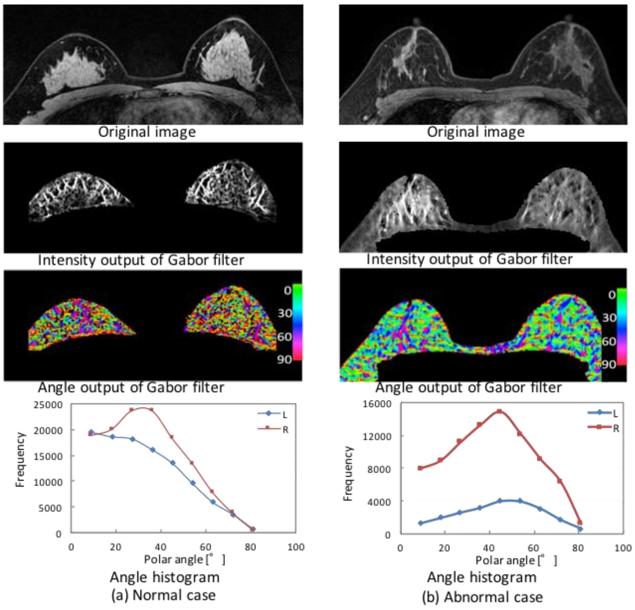


Fig. 8. Experimental result of orientation analysis

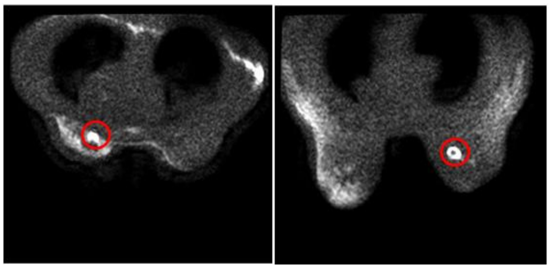


Fig. 9. Examples of tumors detected correctly by our method (Red circle)

E. *Fundamental Techniques for Quantifying and Modeling the Human Anatomy and Functions based on CT and MR Images*

1) Purpose: The goal of this research is to accomplish automatic quantifications of human functions based on anatomy from multiple image modalities such as CT and MR of individual patients for supporting the diagnosis and surgery planning. The purpose of this work is to generate a universal model that can be used to automatically recognize human anatomy and estimate function values directly from multiple image modalities. The core of the proposed approach is to train a deep network for image-pixel-wise classification and straightforward regression of human function based on a large database that statistically covered human population.

2) Methods and Results: We planned to build an image database that supports the investigations of this research work. This database includes multiple modality images to demonstrate anatomical and functional information of human body. In previous work, we have collected over 4,000 patient cases of torso CT scans and 10 cases of whole body MR images that show water diffusion functions of different tissue types. In this year, we expanded our dataset by adding 50 whole body CT scans and 100 pelvic MR (T2+Difusion Weighted Image (DWI)) scans. We also had our research protocol examined by Research Ethics Committee of Gifu University Hospital and obtained the permission to use those image data for this research purpose.

Automated organ segmentation was the fundamental part of this work. We put effort into achieving robustness and generality as well as the high accuracy of the segmentation processes by reducing the complexity. In previous works, we integrated different methods that were developed specifically for different organ segmentation problems into a simple and universal approach. This approach was the use of a common mechanism to solve the different types of organ segmentation under the ad-hoc (organ-specific) feature spaces that are optimized respectively for each organ type by using machine-learning and data-driven methods [20]. In this year, we improved the proposed approach by unifying the ad-hoc feature spaces for different organ types into one shared feature space, and optimized it for all the organs simultaneously. Actually, we regarded the problem of multiple organ segmentations of 3D medical images as a voxel-to-label classification and accomplished this simple classification process via a deep convolutional neural network. Our preliminary results showed the potential capability of this new approach for multiple organ and tissue segmentations on CT images.

We regard the functional quantification task as the image regression and registration problem. In our previous work, we focused the motions and deformations of diaphragm and liver by tracing changes of targets' shapes on a time series of CT or MR scans from the same patient [21]. In this work, we plan to use functional images such as DWI directly and combine them with the anatomical structures that are obtained from MR or CT images. The challenge in this work is 3D image registration between different image modalities with high accuracy. We propose a method to accomplish the multi-modality image-registrations based on corresponding landmarks on the different images. The preliminary results on investigation of the local image similarity for landmark detections have been presented in [22,23]. A novel quantification method for dense of mammary glands on CT image was also proposed in [24].

User-interface that shows the results of organ segmentation is an important element of this research work. In previous work, we developed a system to effectively communicate with doctors for using and evaluating the organ segmentation results of our research in a PACS system. This system was employed to visualize the uterus structures and fibroids in 3D using MR images to help doctors to make the surgical plans [25]. In this year, we applied 3D printing and molding techniques to generate hands-on physical models that show patient specific uterus structures requested by surgeons (Fig.10). Stiffness of the uterus body has also been considered into the model generations. The usefulness and accuracy of these models have been demonstrated in two actual surgical operations [26].

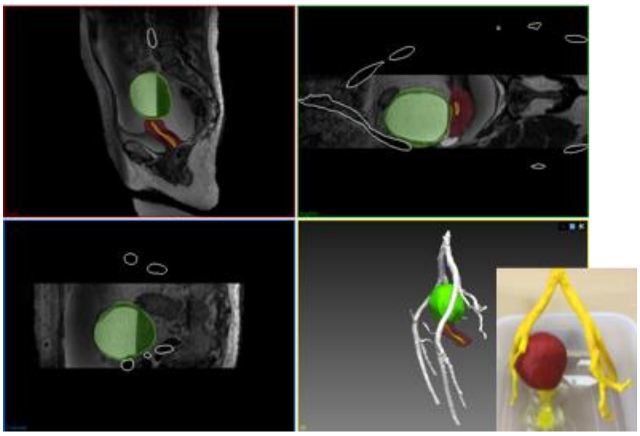


Fig. 10. Physical model generation for uterus surgical planning based on organ segmentations and 3D printing.

3) Conclusion: This research work aims to recognize the anatomical structures and quantify some useful functions of human body using the multiple CT and MR images. We propose an all-in-one approach to solve these problems straightforwardly by using a deep network and confirmed its capability in the preliminary experiment. Our segmentation results were used to generate the physical models which were employed in surgical planning for uterine fibroids movements. The usefulness of the models has been confirmed by the doctors.

F. A Model-Based Approach to Recognize Skeletal Muscle Region for Muscle Function Analysis

1) Purpose: In Japan, CT device is widespread, and torso CT images and whole-body CT images are occasionally obtained. In the super-aging society, accurate measurement of skeletal muscle volume is helpful for rehabilitation and extension of healthy life expectancy. Our purposes are to develop a quantitative analysis method of whole body muscles and to assess the change in muscle function using this method.

2) Methods: In this FY, we propose three types of approaches for muscle recognitions.

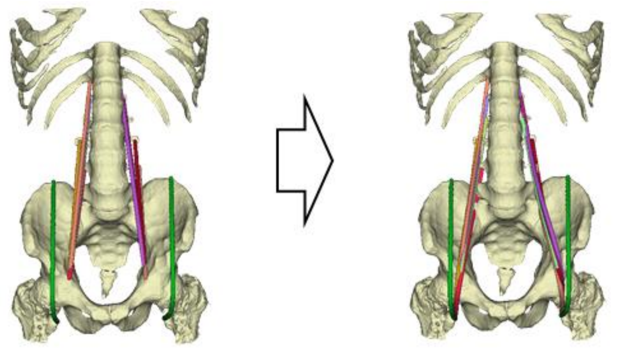
In torso region, we previously achieved the site-specific recognition of muscles in CT images. In deep muscle region, the automatic recognitions of the psoas major muscles [27] and iliac muscles [28] were achieved. These muscles are related to walking ability and postural maintenance. The recognition method of these muscle was controlled separately using a model-based technique. However, these muscles were anatomically related to each other. In this FY, we attempted to generate a composite model of the muscle fibers in iliopsoas muscle regions [29].

In whole-body CT, in order to enable the whole-body analysis of muscle regions, we propose a muscle recognition method based on a dynamic deformation technique. In addition, we explicate our site-specific recognition method to cases of amyotrophic lateral sclerosis (ALS) [30] and validate the effectiveness of our method.

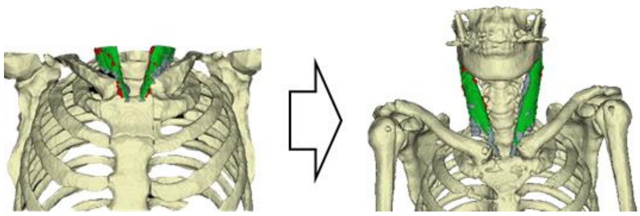
In our challenging study, the precise analysis of scapula is also started for composite analysis of the muscle in scapular region. In the automatic recognition of skeletal muscles, the positional information of the attachment sites, i.e., origin and insertion, is important. We have previously accomplished the site-specific automatic recognition of skeletal muscles using a classified skeletal image [31]. A problem of the current classified skeletal image is that fine shape characteristics of the skeleton in the attachment sites of the skeletal muscles have not been recognized. In this study, we focused on the scapula where multiple skeletal muscles are attached and developed the automatic classification method of the scapula, including the precise structure.

3) Results: In this FY, we achieved the composite model generation in iliopsoas major muscles [32,33]. We re-examined the muscle direction model in the psoas major. The recognition rate in the binding site of the psoas major and iliac muscle was improved by 8.3 % and 3.2 % respectively (Fig. 11 (a)).

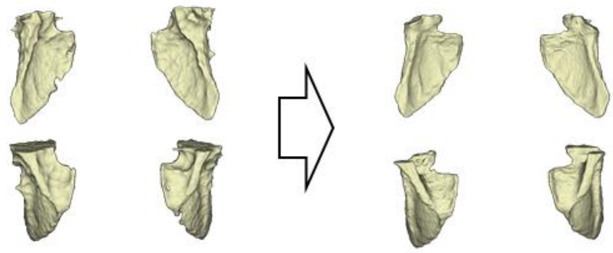
In whole-body CT, an initial study for recognizing the sternocleidomastoid muscle was performed. In the previous



(a) Composite model generation for iliopsoas



(b) Sternocleidomastoid muscle in whole-body CT



(c) Precise analysis of scapula in scapular region

Fig. 11. Recognition results of muscle in FY 2015

study, the imaging range of torso CT images was limited to the lower sternocleidomastoid muscle [34]. This study aimed to recognize the whole sternocleidomastoid muscle region in whole-body CT images. First, we propose the recognition method of the skeletal muscle in whole-body region [34,35]. Next, we construct the average shape of the sternocleidomastoid muscle using the atlas. We improved the previous method on the alignment of the atlas to consider the imaging range in whole-body CT. The average concordance rate was 60.3 % using 10 cases of whole-body CT images with abnormalities in the skeletal muscles. We successfully recognized the major area of the sternocleidomastoid muscle [36] (Fig. 11 (b)).

In the precise analysis of the scapula, we achieved the automatic recognition of the scapula using anatomical position features and gray values. We evaluated seven anatomical features that exist in the torso CT and confirmed all of the features in ten experimental cases. Also, the average matching rate was 86.0 %, which increased by 20.8 % compared to that by the conventional method. The recognized scapula was applied to the supraspinatus recognition. Compared with the conventional method, 19.0 % improvement in accuracy was accomplished and we concluded that the recognition of precise structures of the scapula can contribute significantly to the skeletal muscle recognition (Fig. 11(c)) [37,38].

G. *Development of Estimation System of Knee Extension Strength Using Image Features in Ultrasound Images of Rectus Femoris*

1) Purpose: The word “Locomotive syndrome” has been proposed to describe the state of requiring care by musculoskeletal disorders and its high-risk condition. Reduction of the knee extension strength is cited as one of the risk factors, and the accurate measurement of the strength is needed for the evaluation. The measurement of knee extension strength using the dynamometer is one of the most direct and quantitative methods. However, the measurement using the dynamometer requires a patient to exert muscular strength, and it has the risk of damage to the patient’s muscles and the peripheral tissues. Therefore, this study aims to develop a system for measuring the knee extension strength using the ultrasound images of the rectus femoris muscles obtained with non-invasive ultrasound diagnostic equipment.

2) Methods: First, we extract the muscle area from the ultrasound images. We detect edges from an original image using Canny edge detector and select the edges close to the boundary of the muscle area manually. The boundary lines of the upper and lower ends of the muscle area are determined by approximating the selected edges with curves. The area between these boundaries is defined as the muscle area.

We obtain image features using gray level co-occurrence matrix (GLCM) and the histograms of echogenicity from the muscle area. From GLCM, we obtain image features such as angular second moment and entropy. From the echogenicity histograms, the average value, standard deviation, skewness, and kurtosis are calculated. In addition, the vertical length at the center of the muscle area is considered as the thickness of the muscle.

We combine these features and physical features, such as the patient’s height, and build a regression model of the knee extension strength from the training data.

Finally, we substitute the features calculated from the test data into the regression model, and estimate their knee extension strength [39].

3) Results: We employed 168 B-mode ultrasound images of rectus femoris muscles scanned on both legs of 84 subjects (19-86 years old) for evaluation. Table 1 shows the breakdown of the subjects. The experiment was carried out with the leave-one-out method. As a result of this experiment, the correlation coefficient value between the measured values and estimated values was 0.82. Figure 12 shows the relationship between the measured strength and estimated strength. The root mean squared error (RMSE) was 7.69 kg [40].

4) Conclusion: In this study, we developed a system for estimating the knee extension strength using ultrasound images of rectus femoris muscles. The proposed method is considered to be useful as a method of measuring non-invasively knee extension strength. In the future, we plan to build a regression model considering the gender and age.

TABLE I
BREAKDOWN OF THE SUBJECTS

	Male	Female	Total
Young (19-45 years old)	23	13	36
Elder (46-86 years old)	14	34	48
Total	37	47	84

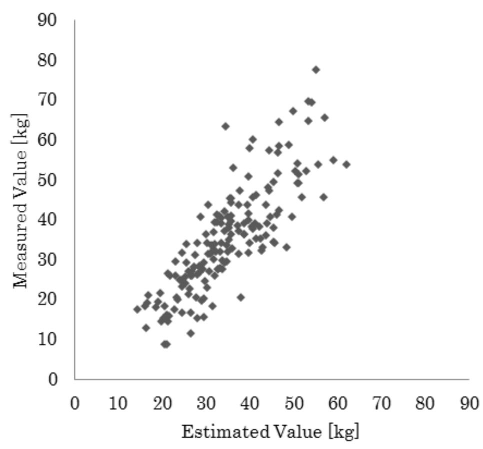


Fig. 12. Relationship between the measured value and estimated value

H. *Other Related CAD Application*

Application of the multidisciplinary computational models is not limited to the above research topics. Its principle as well as the outputs of our research has a strong potential of being applied to various problems. We are currently investigating the development of multimodality, multi-purpose CAD systems. The topics include estimation of cerebral blood flow on dynamic scintigrams [41,42], quantitative analysis of dopamine transporter imaging on brain SPECT images [43], the detection of architectural distortion on mammograms [44,45], quantitative analysis of liver on CT and MR images [46-48], retrieval of similar images for classification of breast lesions on mammograms and breast ultrasound [49,50], quantitative analysis of mandibular cortical bone on dental panoramic radiographs (DPRs) for screening osteoporosis [51-54], quantitative measurement of alveolar bone resorption on DPRs for diagnosis of periodontal diseases [55,56], detection of maxillary sinusitis on DPRs [57-59], detection of carotid artery calcifications on DPRs for screening arteriosclerosis [60], detection and analysis of blood vessels on retinal fundus images [61-64], and diagnosis of glaucoma by optic disc deformation analysis, detection of retinal nerve layer defect on retinal fundus images [65], and detection of unruptured cerebral aneurysm on MRA images.

III. Current States in International Collaboration

One of the anticipated effort in this project is to establish the scientific principle of multidisciplinary computational anatomy and to accelerate the advancement of this research field by international collaboration. We are currently working on research collaboration with renowned researchers, which include analysis of PET/CT images with Prof. Huiyan Jiang in Tohoku University, China, segmentation of mammary grands on CT images with Prof. Shuo Li in the University of Western Ontario, Canada, and analysis of liver on MR with Prof. Xuejun Zhang in Guangxi University, China. In addition, we are arranging a new collaboration on analysis of muscles with researchers in University of Bern, Switzerland.

IV. Conclusion

Our recent progresses in developing the methods for constructing the multidisciplinary models and applying the models for various multimodality image analysis were described. The preliminary results are promising, which convince us the success of our research project.

Our continuous effort toward accomplishing the project goal will proceed in next year. We will strive to advance the research by effective collaboration with other teams in this project and international groups having various strong backgrounds.

Acknowledgment

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