Hidefumi Kobatake · Yoshitaka Masutani
Editors

Computational Anatomy Based on Whole Body Imaging

Basic Principles of Computer-Assisted Diagnosis and Therapy

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Editors
Hidefumi Kobatake
Professor Emeritus
Tokyo University of Agriculture
and Technology
Tokyo, Japan

Yoshitaka Masutani
Hiroshima City University
Hiroshima, Japan

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Preface

The origin of research on computational anatomy can be traced back approximately a century. The famous book *On Shape and Growth* by D'Arcy Wentworth Thompson was published in 1917. Its central theme was to reveal the importance of physical laws and mechanics as the fundamental determinants of the form and structure of living organisms. In Chapter XVII of the book, "The Comparison of Related Forms," he showed that the differences in forms of related animals could be explained by relatively simple mathematical transformations.

Modern computational anatomy is emerging as a discipline focused on the quantitative analysis of variabilities in organ shape and the application of this analysis to computer-aided diagnosis (CAD) and computer-aided surgery. The spectrum of topics in computational anatomy has expanded to encompass all aspects of intelligent segmentation, modeling, recognition and understanding of complex three-dimensional (3D) objects, man–machine interface technologies, and other applications. Reflecting these developments, advanced computational anatomy provides a technical platform for a better understanding of anatomic variability, an aid in the diagnosis of disease, and a means to simulate surgical interventions.

October 2003 saw the start of an extensive research project on CAD in medical imaging, "Intelligent Assistance in Diagnosis of Multi-Dimensional Medical Images," in Japan. It was a 4-year research project supported by a Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Culture, Sports, Science and Technology (MEXT). The state-of-the-art CAD system at that time was quite limited in its capabilities. The objective of this research project was to develop a multi-organ, multi-disease CAD system that made full use of human anatomical data and diagnostic knowledge of multiple diseases. The research organization consisted of nine planned research groups and ten research groups selected from publicly offered research plans. Almost all researchers in the area of medical image processing in Japan joined this project. Typical conventional CAD systems adopted two processing steps to detect specific abnormal regions on medical images. The first one is the processing to detect candidates of suspicious regions and the second one is to identify whether they are truly abnormal. Image features such as film densities, shapes, textural characteristics, and so on, which are distinctive to a specific disease on medical images, are used to detect suspicious regions. It was *the abnormality-dependent approach.* That is, image characteristics used in the first processing step were dependent on the kinds of diseases. However, we felt that the first processing step of future CAD systems whose targets are multiple diseases of multiple organs should be to understand the normal structure of the patient from input images, with potential ability to detect abnormal regions as regions having structures and/or characteristics that are different from normal ones. This fundamentally different approach was called *the normality-dependent approach*. That is, the CAD system depended on the understanding of normal organ structure and departures from those normal structures. The development of two databases, a digital atlas of human anatomy and a digital representation of chest and abdominal abnormalities, were set as primary targets. This project ended in March, 2007. The resulting technologies for analysis of medical images were improved, but had not achieved the level of sophistication of CAD technologies for the brain, which had been a priority for a longer period of time and involved an organ with less inter-individual variability. This provided strong motivation for us to organize a new research project. The 5-year research project on "Computational Anatomy for Computer-Aided Diagnosis and Therapy: Frontiers of Medical Image Sciences" (CA project) was initiated in October, 2009. It was supported by a Grant-in-Aid for Scientific Research on Innovative Areas from MEXT, Japan. The CA project employed a mathematical approach to provide a computational framework to deal with human anatomy in the chest and abdomen. The challenges consisted of (1) development of models for representation of anatomy that cover inter-individual variability in shape and topology and their construction through statistical analysis of population data, (2) investigation of methodologies for precise and robust retrieval of anatomical information from medical images, virtually equivalent to real human body dissection, and (3) development of innovative technologies to assist medical diagnosis and interventions based on computational anatomy. Details of the CA project are shown on the website: http://www.comp-anatomy.org/

The CA project completed its work at the end of March 2014. It greatly contributed to the development of advanced computational anatomy for the chest and abdomen and its applications to CAD and surgery. The purpose of this book is to introduce the basics and the state-of-the-art of this technology and its applications in the chest and abdomen. It contains not only the cutting-edge technologies produced by the CA project but also the basic mathematics and fundamentals. This book will be helpful and informative for researchers wishing to systematically survey the state-of-the-art in computational anatomy. We still have a long way to the final goal, that is, to realize perfect understanding of anatomical structures of patients from medical imageanalysis and intelligent assistance in medical diagnosis and interventions. I believe that this book will help to accelerate computational anatomy research.

Tokyo, Japan Hidefumi Kobatake
July 31, 2015

Acknowledgments

This book is a review of the state of the art of the basics of computational anatomy focused primarily on the trunk area and its application to computer-aided diagnosis and surgery. As I mentioned in the preface, computational anatomy primarily focused on the brain came first and developed rapidly. The research project "Computational Anatomy for Computer-Aided Diagnosis and Therapy: Frontiers of Medical Image Sciences," which was supported by the Ministry of Education, Culture, Sports, Science and Technology, Japan (MEXT, Japan), was a challenge to establish computational anatomy on the modeling and analysis of the biological variability of organs in the chest and abdomen. About half the contents of this book are a compilation of the results of that project. As leader of the project, I am grateful to MEXT, Japan for the special support of our research. We will be very happy if this book is used as a standard textbook on computational anatomy for young researchers and as a result it contributes to accelerating the advance of computational anatomy not only on the trunk area but also on the whole body.

On behalf of the organizing committee of the research project, I would like to express sincere thanks to all the contributors, especially to the leaders of eight primary planned research groups who promoted the project successfully. And I also would like to express my great appreciation to the advisory committee members:

Dr. Karl Heinz Hoehne, Professor Emeritus, University of Hamburg, Germany,
Dr. Nicholas Ayache, Research Director, INRIA, France,
Dr. Takahiro Kozuka, Professor Emeritus, Osaka University, Japan,
Dr. Takeshi Iinuma, Honorary Research Fellow, National Institute of Radiological Sciences, Japan,
Dr. Koichiro Deguchi, Professor, Tohoku University, Japan,
and
Dr. Yoshimasa Kurumi, Professor, Shiga University of Medical Science, Japan.

They provided helpful directions for our research policy and gave us invaluable advice on our research activities. The role they played was essential for the success of our project.

The final goal of computational anatomy is the perfect understanding of human anatomy through the analysis of medical images and its application to intelligent assistance in diagnosis and surgery. There is still a long way to that goal, but I hope that this book will serve as a guideline for further work in this field and will mark a new era of computational anatomy research.

Tokyo University of Agriculture and Technology Hidefumi Kobatake
Tokyo, Japan

Contents

Chapter 1
Introduction

Yoshitaka Masutani, Sakon Noriki, Shoji Kido, Hidetaka Arimura, Morimasa Tomikawa, Hidekata Hontani, and Yoshinobu Sato

Abstract This chapter presents the background and purpose of the computational anatomy research field from medical (needs) and technical (seeds) perspectives. We begin with a historical overview of the emergence of the discipline of computational anatomy (Sect. 1.1). Then, overviews of existing fields and the potential impact of computational anatomy on them are described (Sect. 1.2). To clarify the value of computational anatomy from the clinical viewpoint, medical education, diagnostic imaging, surgery, and radiation therapy are discussed, including situations that

Y. Masutani
Faculty of Information Science, Hiroshima City University, Hiroshima, 731-3194, Japan
e-mail: masutani@hiroshima-cu.ac.jp

S. Noriki
Faculty of Medical Sciences, University of Fukui, Eiheiji-cho, Fukui, 910-1193, Japan
e-mail: noriki@u-fukui.ac.jp

S. Kido
Department of Information Science and Engineering, Yamaguchi University, Ube-shi, Yamaguchi, 755-8611, Japan
e-mail: kido@ai.csse.yamaguchi-u.ac.jp

H. Arimura
Department of Health Sciences, Kyushu University, Fukuoka, 812-8582, Japan
e-mail: arimurah@med.kyushu-u.ac.jp

M. Tomikawa
Department of Surgery, Fukuoka City Hospital, Fukuoka, 812-0046, Japan
e-mail: mtomikaw@surg2.med.kyushu-u.ac.jp

H. Hontani
Department of Computer Science, Nagoya Institute of Technology, Aichi, 466-8555, Japan
e-mail: hontani@nitech.ac.jp

Y. Sato (✉)
Graduate School of Information Science, Nara Institute of Science and Technology, Ikoma-shi, Nara, 630-0192, Japan
e-mail: yoshi@is.naist.jp

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motivated the emergence of computational anatomy (Sect. 1.2.1). Similarly, from the technical (computer science) viewpoint, important technological developments providing the theoretical and algorithmic basis of computational anatomy are explored (Sect. 1.2.2). This book mainly addresses the development of whole-body computational anatomy, which is supported by the rapid progress of whole-body 3D imaging technologies. Thus, the impact of whole-body imaging (Sect. 1.3.1) and its utilization (Sect. 1.3.2) are discussed. Finally, the structure of this book is outlined (Sect. 1.4).

Keywords Medical education • Autopsy imaging • Computer-aided diagnosis • Radiation therapy • Computer-assisted surgery • Computer vision • Whole-body imaging

1.1 What Is Computational Anatomy?

Yoshitaka Masutani
Faculty of Information Science, Hiroshima City University, Hiroshima, 731-3194, Japan
e-mail: masutani@hiroshima-cu.ac.jp

Computational anatomy is an emerging discipline deriving from medical anatomy and several other sciences and technologies, including medical imaging, computer vision, and applied mathematics. The main focus of the discipline covers the quantitative analysis and modeling of variability of biological shapes in human anatomy in health and disease.

Beyond just adding numerical and quantitative information to the conventional anatomy describing human body structures, a wide spectrum of research topics are involved including simulation of average anatomies and normal variations, discovery of structural differences between healthy and diseased populations, detection and classification of pathologies from structural anomalies, and so on.

Disciplines such as morphometrics and anthropology have long been involved with analyzing biological shapes. Among them, the book *On Shape and Growth* by Thompson published a century ago [1] is regarded as the Bible for morphometrics. It focuses on the importance of the roles of physical laws and mechanics as the fundamental determinants of the form and structure of living organisms.

From the technical viewpoint, statistical analysis of shapes in pattern recognition [2], computer vision [3], and artificial intelligence [4] can be regarded as one of the origins. In the development of medical imaging research, digitizing data, including spatial and functional relationships of anatomical structures based on high-resolution images of a cadaver [5], was an essential step. It allowed creation of a digital atlas, which has been widely used in medical education. In the medical imaging research field, one of the pioneer works for computational anatomy was initiated by a so-called digital atlas of human anatomy created from high-resolution optical cross-sectional images of a cadaver [5], in which systematically organized knowledge was implemented. The digital atlas is now widely used in medical education.

An important role of computational anatomy in the clinical setting is in computer-assisted diagnosis (CAD) and computer-assisted surgery (CAS). In such application-oriented aspects of the discipline, one of the key demands is computational understanding of medical images with high accuracy and robustness. In other words, reliable and automated segmentation schemes for all organs in medical images are necessary for detecting abnormal structures and surgical planning. It has been a long-term challenge in medical imaging researches and still has been exhaustively studied over time.

Before the 1990s, various automated segmentation techniques based on data-driven approaches using simple techniques such as thresholding and voxel connectivity analysis were developed and were proven to be useful within limited clinical imaging situations.

In the 1990s, shape model-based approaches initiated by SNAKES [6] were intensively used to overcome the drawbacks of data-driven approaches. The concept uses parameter optimization to fit the model to the correct boundary of target organs. Those approaches attained some success. The key to improvement is acquiring statistics of inter-patient variations in representing shapes and image intensities of target organs.

Recent advances in medical image segmentation have mainly been based on using computational models based on a number of organ shape samples. The models are statistical representations of shapes/intensity patterns, called active shape/appearance models (ASM/AAM) [7], which are also known as statistical shape/intensity models. Recently, several mathematical tools, such as the Riemannian framework, have been successfully introduced [8], especially for statistical analysis of anatomical structures based on medical images at the population level. Those statistical approaches are effectively combined with machine learning methodologies [9] to obtain more reliable results based on a vast amount of samples.

So far, one of the most successful areas for statistical analysis of image-based anatomy is neuroimaging because of the intensive demand in this field. One of the reasons for this success is related to the challenges involved in investigating brain function. Free software for image analysis such as statistical parameter mapping (SPM) [10] has pushed research in this area forward. In brain image analysis tools, a standard brain atlas, which includes pre-segmented regions, is used. A new dataset is registered to the template and then the pre-segmented regions can be reflected in the data. Such atlas registration techniques can be regarded as another mainstream method in addition to statistical shape/intensity models.

Anatomical structures with nonpathological variations, "anomalies," can pose problems. For example, the number of the vertebrae is frequently more or less than the normal. That is, there is a discrete variation in the number of the vertebrae. In addition to continuous shape variations, these noncontinuous or discrete organ variations must also be considered in modeling anatomical structures.

Recent achievements based on analysis of a huge number of clinical image samples (so-called big data), including healthy volunteers and real patients, throw new questions at us, such as "What is the definition of abnormality?", "What is the border between normal and abnormal?", and "Is a given abnormality significant, or might its workup cause more morbidity without eliminating an important disease?". The keys to the answers are naturally in the statistical analysis.

In an attempt to answer these questions, a computational anatomy project in Japan was initiated in 2009, supported by a Grant-in-Aid for Scientific Research on Innovative Areas from the Ministry of Education, Culture, Sports, Science, and Technology, Japan [11]. As the project name "Computational Anatomy for Computer-Aided Diagnosis and Therapy: Frontiers of Medical Image Sciences ("Computational Anatomy" (CA) in short)" shows, it was aimed at establishing a mathematical framework to deal with human anatomy and diseases, primarily focused on the chest and abdomen, based on medical images with certain application-oriented aspects such as CAD and surgery.

Several related research projects are found all over the world, such as the Human Connectome Project (HCP) [12] and the Physiome Project [13]. The HCP is intended to construct a human brain map describing the complete neural connections of both structures and functions of intra- and intersubjects (over time). It is a long-term project, begun in 2011, involving the collection and sharing of multimodality images, including magnetic resonance imaging (MRI), among multiple centers. Similarly, the Physiome ("physio-" meaning "life" and the suffix "-ome" meaning "as a whole") Project is aimed at providing a quantitative description of physiological dynamics and functional behavior of the organism within anatomical structures.

Thus, computational anatomy is a developing research field involving a wide array of sciences and technologies aimed at improving human health.

1.2 Needs, Seeds, and Solutions Around Medical Imaging: History and Perspectives

1.2.1 Needs in Medical Education and Clinical Practice

1.2.1.1 From the Viewpoint of Medical Education

Sakon Noriki
Faculty of Medical Sciences, University of Fukui, Eiheiji-cho, Fukui, 910-1193, Japan
e-mail: noriki@u-fukui.ac.jp

Medical education needs to be highly structured to impart the enormous amount of information necessary just to go on to further clinical training. The basic framework is similar all over the world. It consists of basic sciences (e.g., anatomy, physiology, and biochemistry) and clinical training (e.g., internal medicine, surgery) where skills are mastered. Anatomy is considered to be basic science but is strongly related to and interwoven with clinical medicine [14, 15]. In fact, clinical instructors often interact with students taking anatomy. The educational method called “image anatomy” emphasizes the inclusion of medical imaging [16]. Image anatomy is a method for studying anatomy, in which the nondestructively visualized human body structures are used.

We describe the practice of human anatomy using cadaver imaging, which was inspired by autopsy imaging (Ai), in our facility, and then review history of anatomy education. Finally, we describe the present problems of teaching human anatomy and the future of the relationship between anatomy education and computational anatomy.

In Japan, the application of cadaver computed tomography (CT) imaging to educational anatomy training is becoming a big current, and its trials are carried out at several medical schools, where CT scanners only for the dead body are introduced.

CT images of cadavers have been used for anatomy practice by the Faculty of Medicine at Fukui University since 2010 [17–20]. Imaging data are acquired over 128 cm and reconstructed at 5-mm section thickness. The medical students can refer to the CT images as well as MRI images of cadavers under dissection in the anatomy department (Fig. 1.1). iPads connected with wireless LAN and desktop PCs connected with school LAN are used to refer to the images (Fig. 1.2).

In Japan, this is carried out at several medical schools including Fukui, Chiba, and Gunma Universities and is becoming more widespread with the growing installation of computed tomography (CT) scanners in pathology departments for postmortem examinations. An Ai conference, in which radiologists, pathologists, and forensic specialists participate, is held so that the anatomy teaching staff can understand the interpretation of the images. Then, the anatomy teaching staff pass on the CT images to the students.

Human anatomy was first described by the ancient Egyptians approximately 3500 years BCE. Minute descriptions of the cranial sutures and the brain surface are found in the Edwin Smith Papyrus, an ancient Egyptian medical text

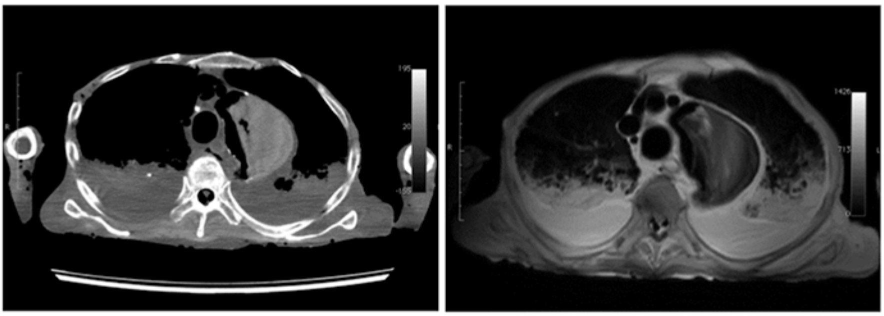

Fig. 1.1 CT image (*left*) and MR image (*right*) of a cadaver chest for anatomical study

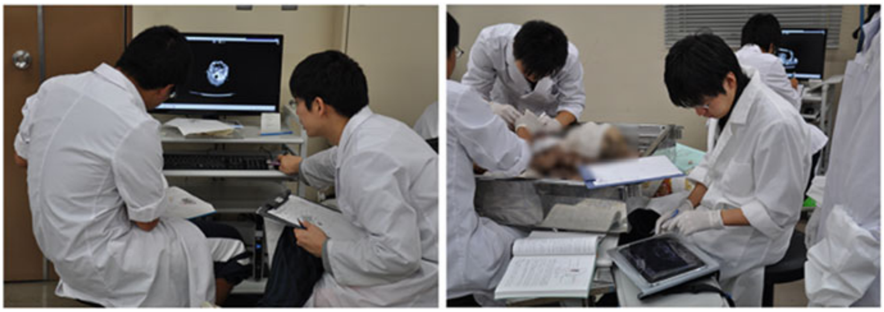

Fig. 1.2 Students can refer to CT images on the monitor, which is put adjacent to the cadaver

from approximately 1700 BCE [21]. Hippocrates, an ancient Greek physician, investigated the goat brain. Various findings about anatomy are described in the *Corpus Hippocraticum*, which the pupils of Hippocrates edited. Though it is told that Herophilos (335–280 BCE) and Erasistratus (304–250 BCE) dissected the human body in ancient Alexandria, their writings have vanished. After that, Alexandria prohibited human dissection for religious reasons, and new knowledge about anatomy did not arise for 1000 years or more. During this period, Galen (129–216 CE) dissected animals energetically [22]. He left inclusive and detailed anatomy books, mostly based on dissections of apes.

There was a revival of interest in anatomy during the Renaissance. Leonard da Vinci created human anatomical drawings, although his notebook was not published during his lifetime [23]. In the early 1500s, the study of anatomy commenced at the University of Bologna, and Andreas Vesalius (1514–1564) of the University of Padua published *De humani corporis fabrica* (*Structure of the Human Body*) based on dissections performed in 1543. This became the basis of modern anatomy.

After this, research in human anatomy advanced, and cadaver dissection became part of medical education. At the present time, physical dissection is partly replaced with image-based dissection, that is, image anatomy, such as Ai. The history of Ai is described in the other section (Chapter 4.4.1) of this book. Especially "Virtopsy" in Switzerland is actively used in the forensic field [24]. The purpose of Virtopsy is not the education of anatomy to medical students but the investigation of the cause of death. That is, there is little collaboration between experts in the Ai and educational anatomy fields in countries other than Japan. Ai and its related research areas including Virtopsy are also called "postmortem imaging (PMI)." Medical educational reform is leading to more concentration on clinical studies and less on basic science. In some areas, obtaining cadavers for dissection is difficult [25]. Human anatomy is considered a fundamental subject in medical education [26]. Adding imaging techniques, such as X-rays, CT, MRI, and new technologies (e.g., web-based learning), is becoming more common.

The "Visible Human Project," which provides cross-sectional human body imaging data including high-resolution optical, CT, and MR images [27–29], has