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REVIEW ARTICLE

The Demand for Quantitative Techniques in Biomedical Image Informatics

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Abstract
With recent technological advances, biomedical image informatics has become a quickly rising field. It focuses on the use of computational techniques to process and analyze biomedical images. Its goal is to obtain useful knowledge from complicated and heterogeneous images from different modalities for biomedical research. Although the advancement of imaging technologies has provided a data explosion, most biomedical images are only used by the researchers who create them. The lack of a canonical procedure, from data acquisition to data analysis, contributes to this issue. As the number of biomedical images increases, the demand for quantitative techniques rises. In order to increase awareness of the needs and importance of quantitative techniques for biomedical image informatics, this paper reviews several aspects including biomedical imaging, image repositories, and image processing. We explore the state of the art technology available in quantitative techniques for biomedical image informatics. The essential techniques for quantification, such as imaging devices, biomedical image management, and image processing, are further summarized.

Keywords Biomedical image informatics, Quantitative imaging, Bioimage informatics, Imaging informatics

INTRODUCTION

Biomedical image informatics is a rapidly growing field that focuses on the processing and analysis of images, knowledge, and data associated with images in biomedical research [1, 2]. The scale of these images is from the cellular and molecular level to organs and the whole body. The rapid growth of biomedical imaging provides huge opportunities for novel research and scientific discovery. However, the processing and analysis of biomedical images is challenging as the number of images and modalities continues to expand. Biomedical image informatics helps to overcome these challenges through computational methods to provide novel insights from the image surplus. Biomedical image informatics offers physicians and medical researchers the potential to diagnose diseases, provide optimum treatments, and predict outcomes. In addition, it offers biologists information regarding the genetic basis of diseases, sub-cellular localization, morphometrics, and metabolic activity. Eventually, biomedical image informatics will enable researchers to process and analyze the rapidly increasing amount of biomedical images.

Quantitative techniques are able to improve accuracy and reproducibility of image interpretation, reduce variation in practice, and improve quality. It will bring important scientific benefits in the form of new applications and improved performance and reproducibility [3]. Technological limitations are preventing the field of biomedical image informatics from realizing its full potential. However, many researchers are challenging these limitations. In order to increase awareness of the computational challenges in biomedical image informatics, this paper reviews quantitative techniques for biomedical image informatics. From creation to analysis of image, quantitative techniques play key role in the every stage of biomedical image informatics. However, they are more important in the stages which deal with raw image data, such as creation of image, management of data and image processing, than in image analysis which deals with preprocessed data. This is why we focus on the quantitative techniques in image acquisition, management, and processing.

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We look into the key techniques for image acquisition, management, and processing for quantification. First, we compare imaging modalities in terms of hardware and characteristics of medical imaging and microscopic imaging. Then, we look into the public biomedical image repositories and informatics solutions for image and metadata storage and analysis. After that, biomedical image processing techniques for quantification, including enhancement, segmentation, registration, and tracking are discussed. Finally, we draw conclusions based on the needs for quantitative techniques in biomedical image informatics.

BIOMEDICAL IMAGE ACQUISITION

Biomedical imaging techniques are important for biomedical informatics research since they can provide anatomical, physiological, and metabolic information. This information can be utilized not only for early diagnosis, prognosis, and treatment monitoring, but also for validation of biological scientific hypotheses. However, substantial analysis of information from images is possible only if correlated with information describing the experimental setup, image acquisition parameters, and observed object status. In fact, the needed information exists, but has not yet been provided in a common format (required for ease in collection) by medical instrument and microscope manufactures.

Each imaging modality reveals one-sided information according to the way the image is produced. In this section, imaging modalities are compared in terms of hardware and characteristics for both medical and microscopic imaging, which are sub-disciplines of biomedical imaging.

Medical imaging

Representative types of medical imaging techniques include Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Single Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET), and ultrasound. Table 1 lists several medical imaging techniques and their characteristics.

Medical imaging techniques are able to furnish morphological, structural, metabolic, and functional information of the human body [4]. In addition to diagnosis and treatment evaluation, imaging techniques are able to quantitatively extract, process, analyze, and manage the necessary data. Additionally, medical imaging can provide increasingly accurate diagnoses and treatment evaluation data non-invasively [5].

Microscopic imaging

Microscopic imaging techniques allow for the observation of structural and functional changes at the cellular level with high resolution. This technology provides cellular information, such as the growth and death of the target cells, non-invasively. The microscopic images are also used in the analysis of cell division and dynamics of cell behavior. This can include tracking drug effects in living cells and diagnosing diseases with higher precision [10]. In addition,

Table 1. Comparison of medical imaging modalities [6-9].

Medical Imaging Modality	CT	MRI	SPECT	PET	Ultrasound
Penetration level	Organ-Tissue	Organ-Tissue	Tissue-Cellular	Tissue-Cellular-Molecular	Organ-Tissue
Spatial resolution	50 ~ 200 μm	25 ~ 100 μm	1 ~ 2 mm	1 ~ 2 mm	50 ~ 500 μm
Cost	Moderate	High	High	Very high	Low
Electromagnetic radiation spectrum used in image generation	X-rays	Radio waves	Lower-energy γ rays	High-energy γ rays	High-frequency sound
Advantages	• High spatial resolution • Bone and tumor imaging • Anatomic imaging	• Highest spatial resolution • Soft-tissue contrast • Combines morphological and functional imaging	• Unlimited depth penetration • Can image multiple probes simultaneously	• High sensitivity with unlimited depth penetration • Isotopes can substitute for naturally occurring atoms	• High spatial and temporal resolution • Low cost • Real-time
Disadvantages	• No target-specific imaging • Poor soft-tissue contrast • Radiation	• Cost • Relatively low sensitivity • Long scan and post-processing time • Mass quantity of probes may be needed	• Limited spatial resolution • Radiation	• Cost • PET cyclotron or generator needed • Relatively low spatial resolution • Radiation	• Operator dependency • Targeted imaging limited to vascular compartment • Limited spatial resolution

Table 2. Comparison of optical microscopic imaging modalities [15-22].

Microscopic Imaging Modality	Optical Microscopy				
	Phase-contrast Microscopy	Wide-field Microscopy	Confocal Microscopy	Two-photon Microscopy	Optical Coherence Tomography
Principles	Refractive index differences are used to provide contrast to view unstained specimens; small phase shifts in light passing through a transparent specimen are converted into amplitude or contrast changes in the image	Fluorescence microscopy uses fluorescence instead of transmitted or reflected light.	Increases optical resolution and contrast; by using a scanning platform where the light source is imaged through a pinhole to block out-of-focus photons, it is possible to reconstruct 3D structures from images	Based on non-linear excitation of fluorophores, this mode of microscopy offers submicron depth-resolved imaging without using a pinhole	OCT enables micron scale imaging based on low coherence interferometry
Achievable resolution	Lateral ~ 200 nm Axial ~ 500 nm	Lateral ~ 200 nm Axial ~ 500 nm	Lateral ~ 200 nm Axial ~ 500 nm	Lateral ~ 300 nm Axial ~ 900 nm	Lateral ~ 1000 nm Axial ~ 900 nm
Contrast Source	Refractive index	Fluorescence	Fluorescence optical sectioning	Fluorescence optical sectioning	Scattering
Advantages	• Observe living cells/organisms in a natural/unstained state • High-contrast, high resolution images	• High contrast, high resolution images • Visualize multiple • Fluorophores simultaneously	• 3D sectioning by reducing the out-of-focus light • High resolution images • Acquired rapidly and noninvasively	• Ensures rejection of excitation light • Suitable for thick specimens • Elimination of confocal pinhole minimizes signal loss	• Observe living tissues in a natural/unstained state • Suitable for thick specimens • High-speed imaging to image 3D volume in vivo
Disadvantages	• Not ideal for thick organisms or particles • Halo effect	• Not ideal for thick organisms or particles • Needs to stain • Weak fluorescence signals	• Relatively high cost and smaller field of view • Image depth limited (a few hundreds of microns)	• Relatively low resolution • Requires introducing Fluorophores into specimens	• Relatively low molecular contrast compared to fluorescence imaging

early detection of the disease on the cellular level by anatomical structure analysis may be accomplished through these techniques. This in turn can spur the development of new drugs based on additional physiological information analysis and quantification [11]. The most commonly application of microscopic imaging is to obtain high spatial resolution cell images. Microscopic methods can be divided into two categories: optical microscopy techniques and electron microscopy techniques.

Electron microscopy can provide images with nanometer resolution. However, this imaging technique has yet to be addressed for wet environments. The images of biological samples produced by the electron microscope are inherently of very low contrast due to the organic parts of the samples. The organic elements have low electron scattering power. In addition, to capture high quality images, the samples need to be very thin (about 100 nm) at the region of interest [12]. On the other hand, optical microscopic imaging techniques provide a means of non-destructive and non-invasive in vivo tests for biomedical research [13]. Table 2 summarizes the characteristic of the leading optical microscopic imaging modalities, all providing information on the cellular level. They have different properties and, therefore, distinct characteristics of each image format exist. Therefore, with various microscopic imaging techniques, quantitative approaches are needed to efficiently handle the comprehensive image data [14].

BIOMEDICAL IMAGE REPOSITORY

Repositories for biomedical images have emerged rapidly. These repositories include spatial and temporal measurements of gene expression, macromolecule localization, and phenotypes of cells, tissues, or animals, and provide actual measurements of the distributions, dynamics, and changes in biological systems, as recorded from digital imaging systems [23]. Because of their online availability, they can be reused and shared with the other researchers. In addition, the online availability will eventually lead to the development of new analysis tools. This improves the future possibilities of the repositories and provides a benefit to the researchers who use

Table 3. Public biomedical image repositories.

	Title	Description
Medical Image	JSRT Digital Image Database	Images containing lung nodules as well as negative cases with ground truth location and diagnosis provided [24]
	SCR Database	Segmentation of the lung fields, the heart, and the clavicles in standard posterior-anterior chest radiographs [25]
	LIDC-NCIA Collection	Image database with lung lesions marked by up to four radiologists, including The Cancer Imaging Archive (TCIA)
	RIDER-NCIA Collection	Image archive of CT images from lung cancer patients followed during treatment (Reference Image Database to Evaluate Response)
	ELCAP Public Database	An image database of whole-lung, low-dose CT images of the chest with the locations of all nodules marked
	BrainWeb	Simulated Brain Database which contains simulated, 3D MR data using normal and multiple sclerosis models with different acquisition parameters
	Digital Database for Screening Mammography (DDSM)	Contains a large number of cases with both normal and abnormal findings
	Mammographic Image Analysis Society (Mini-MIAS)	Contains cases with location information of the abnormality
	DIARETDBI	Standard Diabetic Retinopathy Database
	DRIVE	Digital Retinal Images for Vessel Extraction
	NCIA Collection	ACRIN CT Colonography Collection for colonic detection from CT with XLS sheets that provide polyp descriptions and their location within the colon segments
	Standardized Evaluation Methodology for 2D-3D Registration Database	Contains multi-modality datasets, centers of rotation, evaluation criteria and starting positions for the evaluation of registration methods
	TCIA Collection	PET/CT phantom scan collection
Bio Image	Cell: An Image Library	Public repository of reviewed and annotated images, videos, and animations of cells from a variety of organisms, showcasing cell architecture, intracellular functionalities, and both normal and abnormal processes [26]
	Human Protein Atlas	Publicly available database with millions of high-resolution images showing the spatial distribution of proteins in 44 different normal human tissues and 20 different cancer types, as well as 46 different human cell lines [27]
	Allen Brain Atlas	Gene expression maps for the mouse and human brain. As of May 2012, seven brain atlases have been published: Mouse Brain Atlas, Human Brain Atlas, Developing Mouse Brain Atlas, Developing Human Brain Atlas, Mouse Connectivity Atlas, Non-Human Primate Atlas, and Mouse Spinal Cord Atlas [28]
	e-Mouse Atlas Project	Database of gene expression data in the developing mouse (*Mus musculus*) embryo with spatial annotation to a framework of 3D mouse embryo models produced by e-Mouse Atlas Project (EMAP) [29]
	Protein Subcellular Location Image Database	2D through 5D fluorescence microscope images, annotations, and derived features in a relational schema
	Worm Atlas	A database featuring behavioral and structural anatomy of *Caenorhabditis elegans* [30]
	LOCATE: Subcellular localization database	A curated database that houses data describing the membrane organization and subcellular localization of proteins from the RIKEN FANTOM4 mouse and human protein sequence set [31]

those repositories. As the size of these repositories increases, the demand for integrated data management and analysis solution also increases.

However, there is currently no standardized metadata associated with images. As shown in Table 3, there are many kinds of public biomedical image repositories. Most of them do not support the standardized metadata or provide the integrated data management environment. Of these repositories, Allen Brain Atlas is the only one that provides an integrated data management environment. They combine datasets of gene expression patterns in the mouse brain with analysis tools. Other repositories only provide access to the image data or allow searching of online journals for similarities with published images.

The growth of biomedical image data and the complexity of acquisition protocols have provided a challenge in the management and analysis of the data. Novel automation techniques for image acquisition accelerate this trend. It requires image databases that can manage, view, share, and analyze the data. These image databases provide integrated platforms to organize, search, process, analyze, share, and visualize data, including both the images and image metadata [32]. The Open Microscopy Environment (OME) is the best examples of these image databases [33].

Two examples of open-source image database projects are the Open Microscopy Environment's Remote Objects (OMERO) platform [34] and the Bio-Image Semantic Query User Environment (BISQUE) project [35]. They are web-based platforms that allow users to extend the metadata and workflow for their personal use. BISQUE and OMERO are just two examples of software systems that aid researchers in the management of the image data. Further, BISQUE and OMERO share data models. With the rapid development of analysis tools for biomedical image, this type of collaborative use of integration promises to provide very powerful tools for researchers.

BIOMEDICAL IMAGE PROCESSING

To extract quantitative information derived from images, a set of processing steps is required. However, there is no standard way of quantifying information since each processing method is designed to work for a specific purpose and associated applications. Therefore, precise understanding of image processing methods and the sequence used to extract quantitative information is a prerequisite for interpretation of results from image analysis. In this section, we briefly describe characteristics of image processing methods for enhancement, segmentation, registration, and tracking as pre-processing techniques before extracting quantitative information.

Enhancement

Biomedical images typically contain artifacts, which are generated during image acquisition: blurring, noise, and low-contrast. For example, blurring mostly occurs in fluorescence microscopy because of out-of-focus light or thicker specimens, which usually exhibit such a high degree of fluorescence emission that most of the fine detail is lost. Poisson noise, inherent in the photon emission and counting process, severely degrade SPECT images. Because of the nature and superposition of the soft tissues of the breast, mammograms have limited contrast.

Image enhancement to eliminate these artifacts requires a plethora of mathematical techniques with the aim of improving the quality of images for use not only by an operator, but also by an algorithm for subsequent processing [36]. Basic techniques for noise suppression and contrast enhancement includes histogram manipulation, mean and median filtering, Gaussian filtering, and Wiener filtering, assuming that the noise is additive with a zero-mean, constant-variance Gaussian distribution. This assumption sometimes simplifies the pre-processing resulting in poor performance. Therefore, the statistical properties of the noise in biomedical images are also studied in [37, 38] for better performance.

Deconvolution reverses a convolution of an original image with the point spread function from a blurred image. The point spread function, as an infinitely small point source of light, can be defined theoretically, by a model of diffraction, or empirically [39]. If no information about the point spread function exists, blind deconvolution can be performed. In addition, deconvolution can be combined in parallel with denoising. A more detailed review is presented in [40-42].

Segmentation

Segmentation is the process of separating interested structures, objects, or regions in an image or image sequences. Even though the same object or structure is extracted, the segmentation method is different depending on the image modality and dimensions that generate distinctive image features [43]. This technique is the most important part of image processing because it serves as the input of other image processing techniques, such as registration and tracking, and thus, influences the accuracy and efficacy of these other techniques. In the past few decades, many segmentation methods have developed and advanced in terms of accuracy, robustness, reproducibility, and automation.

Segmentation methods are classified into three categories: algorithms based on a threshold, algorithms based on artificial intelligence methods, and algorithms based on models [44, 45]. Most basic algorithms, including Otsu's method, adaptive thresholding, and the watershed algorithm, are based on a threshold. They are conceptually understandable and intuitive since they identify an interested object with discriminative features. However, noise and intensity homogeneity in biomedical images have influenced the inconsistent results from segmentation. Consequently, thresholding methods can be combined with other segmentation methods based on the specific needs. Algorithms based on artificial intelligence, such as support vector machines (SVM), neural networks, and maximum likelihood algorithms, utilize samples in the training set to extract important cues from objects of interest. The training samples should be sufficiently selected to comprise all aspects of the segmented object. Algorithms based on models, such as snake, level set methods, and active contouring, are complex

methods that can handle large shape varieties and complicated topologies. Although they usually generate the best segmentation results, they are unable to represent certain structures and are computationally expensive.

In the medical image data set, segmentation extracts the interested organs, tumors, bony structures, or blood vessels. The current trend in medical image segmentation focuses on model-based segmentation approaches with high accuracy and robustness [46]. Wesarg et al. presents 3D active shape models for the segmentation of vertebrae from dual-energy CT images [47]. In [48], 2D active shape models were also applied to extract the prostate boundary from ultrasound images, and rotation-based slicing was used to extend the segmentation method to 3D segmentation.

Cells, nuclei, lymphocytes, glands, and sub-cellular components in microscopic images are also segmented. Some commonly used segmentation algorithms for microscopic images are thresholding, voronoi-based, watershed, and the active contour method [49-52]. The watershed method is deployed to separate touching cells. However, it tends to cause an over-segmentation problem. In order to avoid over-segmentation, several techniques have proposed for pre-processing and post-processing. For example, the use of a merging technique, with compactness measurement after segmentation, is suggested in [50].

Registration

Registration is the process of transforming different images, which are acquired at different times, from respective coordinate systems into the same coordinate system. In other words, the correspondences between images of biomedical objects are determined based on measures of image similarity, and a geometric transformation is applied to align an object in one image to a fixed template object in another image. Many registration methods have been developed and can be classified by several criteria: dimensionality, nature of registration basis, nature of transformation, and optimization [53, 54].

The diversity and amount of information that can be provided from one medical imaging modality are limited, and as such, medical image registration is critical for extracting and integrating necessary information from various imaging modalities. Image registration is the enabling technique for fusion of anatomical images with functional images [55], image-guided radiation therapy [56], image-guided intervention [57], computer-aided diagnosis, disease follow-up [58], and atlas building [59].

Image registration of microscopic images on the cellular and molecular level is mainly used as a pre-processing step for image analysis. For example, translation and rotation of crawling cells in time-lapse image sequences are automatically corrected for further analysis of cell motion [60]. 2D sections of one cell nucleus that contain a variety of non-rigid deformations have been aligned for the purpose of 3D reconstruction and visualization of the tissue structure [61]. Recently, 3D multichannel microscope images of different cell nuclei have been aligned by the reference cell nucleus [62].

When microscope slides at high magnification are too large to be acquired as single images, multiple overlapping fields of view (FOVs) are acquired and assembled into a large single image. This process is known as 'mosaicing' or 'stitching' and is part of the registration technique. It consists of finding the correspondence between adjacent images and minimizing the artifacts at the seam between the stitched images [63]. In particular, serial section transmission electron microscopy (ssTEM), for mapping brain micro-circuitry, generates a set of hundreds or even thousands of overlapping image titles. Scale-invariant feature transform (SIFT) is used to detect corresponding landmarks, and then globally optimize the position of all image tiles by least square displacement [64].

Tracking

The idea of tracking objects in time-varying images provides a method to follow identical object in successive frames to analyze spatiotemporal changes of the object. Tracking in the medical field is primarily used to measure the dynamic behavior of the left ventricle (LV) from time-varying 3D cardiac images such as MR, CT, and gated SPECT sequences. A survey of tracking LV motion using deformable models is presented in [65], and a 4D polar transformation is defined to describe LV motion in [66]. Moreover, respiratory motion in radiosurgery, with or without implanted markers, has been tracked so that a beam of radiation can accurately target a tumor [67, 68].

Cell biology clearly benefits from tracking techniques to understand a range of cell behavior. In light microscopic images, intracellular structures, such as fluorescently labeled proteins, are tracked with single-particle tracking to analyze molecular dynamics [69]. In addition, cell population tracking in time-lapse images enables quantification of migration, mitosis, and apoptosis, as well as the reconstruction of cell lineages [70].

In a broad sense, tracking can be considered similar to conducting segmentations in each frame and matching identical objects in successive frames. However, basic segmentation and matching techniques do not provide satisfactory results when the objects being tracked change shape as time progresses. Since intensity and morphology of cells changes during mitosis and cell density varies, tracking by model evolution, such as active contour and deformable models, is preferred for studies of cell behavior [49].

CONCLUSION

This paper reviews the state of the art technology and available quantitative techniques for biomedical image informatics, specifically regarding biomedical imaging, management of images, and processing for quantification. As technology progresses, computational techniques and software tools will become essential to almost every researcher. Fortunately, biomedical image informatics has rapidly broadened as a research area. There are still many challenges to biomedical image informatics, such as management of large data sets with different modalities and sharing of complex biomedical images. However, all of these challenges are essential to the development of quantitative techniques and an integrated biomedical image informatics platform. The brilliant biological advances in the last decades are due to computational methods, and biomedical image informatics will continue to aid in the advances in biology in the next decades. Innovative biomedical image informatics and its quantitative solutions can serve as the foundation for new biological discoveries.

In summary, biomedical image informatics has become increasingly significant because of the increasing scale in the production of biomedical images and complexity of image data due to varying modalities, spatial and temporal information, metadata, and dimension. As the significance of biomedical image informatics increases, new challenges will arise, and an integrated biomedical image informatics platform, with solutions based on quantitative techniques, is the most promising method to overcome them.

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CONFLICT OF INTEREST STATEMENTS

Jang H-Y declares that he has no conflict of interest in relation to the work in this article. Kim H-R declares that she has no conflict of interest in relation to the work in this article. Kang M-S declares that she has no conflict of interest in relation to the work in this article. Kim M-H declares that she has no conflict of interest in relation to the work in this article. Zhang B-T declares that he has no conflict of interest in relation to the work in this article.

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