Quantitative image analysis: software systems in drug development trials

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Multi-dimensional image analysis is being used increasingly to arrive at surrogate end-points for drug development trials. Various imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and ultrasound are used to analyze treatments for diseases such as cancer, multiple sclerosis, osteoarthritis, and Alzheimer's disease. However, extracting information from images can be tedious and is prone to high user variability. The medical image analysis community is moving towards advanced software systems specifically designed for drug development trials. These systems can automatically identify the anatomy of interest in medical images (segmentation methods), can compare the anatomy over time or between patients (registration methods) and allow the quantitative extraction of anatomical features and the integration of the data and results into a database management system, automatically tracking the changes made to the data (audit trail generation). In this article, we present a case study using a prototype system that is used for quantifying multiple sclerosis lesions from multivariate MRI.

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▼ Medical images are being used increasingly to extract quantitative end-points in clinical trials of drugs and devices. High-resolution medical imaging techniques such as X-ray computed tomography (CT), magnetic resonance (MR), positron emission tomography (PET) and ultrasound can provide unique views of anatomy and pathology and enable quantitative measurements to be made that are not otherwise possible. Furthermore, the quantitative nature and the relatively low variability in computing these end-points make images very attractive tools to use in clinical trials. For example, reducing the variability of an end-point allows the reduction in the cohort size required, resulting in significantly cheaper and faster randomized clinical trials.

In all phases of drug development, from drug discovery to animal studies, and from preclinical to late-phase clinical trials, medical images are being used increasingly to test the efficacy of new drugs [1–5]. Quantitative features extracted from medical images have been used as surrogate endpoints in clinical trials and include (1) the tumor volume and the tumor cross-sectional diameter measured from MR or CT images in clinical trials for cancer drugs [6]; (2) the total number of lesions and lesion volume measured from multi-echo MR images of the brain in multiple sclerosis (MS) drug trials [7]; the cartilage thickness and cartilage volume measured from MR images of the knees for osteoarthritis drugs [8–12]; and (4) the total brain volume and total hippocampus volume measured from MR images of the brain are used as indicators of Alzheimer's disease progression [13,14].

Current state and motivation

Although the use of picture, archiving and communication systems (PACS) [15] is becoming more pervasive, at present, measurements from medical images are performed mostly by manual means. Most studies that require morphological patient-specific information use crude methods to calculate areas and volumes of structures. Most methods that are used widely involve the measurement of the minor and major axes of the structure, followed by simple geometric calculations [16]. Such measurements are error-prone and are only used as a rough guideline for making clinical decisions. Physicians who require more accurate measures typically resort to manual delineation of the structure. Manual delineation, particularly on a 3D image series, is painstakingly slow and expensive. Moreover,

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these manual delineation approaches suffer from a lack of consistency and reproducibility [17]. Therefore, there is a need for automatic and semi-automatic 2D and 3D image tools to segment out structures of interest and to extract shape and intensity features from these segmented regions. However, in a few situations in which the images are 'noisy', a human expert with knowledge of the subject might achieve a better performance than the automated methods, albeit at the cost of increased time and effort.

In pharmaceutical clinical trials involving images, a subject is typically scanned at different time points, resulting in longitudinal image datasets. The ability to consistently interpret data across the scans is one of the most important requirements in clinical trials. Image alignment using registration algorithms simplifies the interpretation and correlation of findings between such studies by removing the effect differences in patient placement.

Most imaging clinical trials collect large amounts of image and patient data. Although there are electronic systems available for the management of case report forms (CRFs), the management of patient data and the potentially giga- or tera-bytes of image data are not adequately addressed. Furthermore, recent regulations [21 code of federal regulations (CFR) Part 11] from the FDA [18] require the maintenance of audit trails and electronic signatures for digital data management. Managing this data manually can be tedious. Therefore, the integration of automated data management and reporting tools with image analysis tools is essential.

Since the early 1980s the scientific community has developed a wide variety of tools directed towards solving problems in medical imaging [19]. To date, these technologies have not been widely used clinically. However, the push towards computed-aided quantitative analysis is emerging owing to several factors, including: (1) the increased access to digital data; (2) progressively increasing dataset sizes; (3) increased pressure for improved efficiency in healthcare systems; and (4) increased use of image data as the underlying evidence for drug discovery studies.

This article presents the algorithmic and system management concepts, in addition to the software and regulatory requirements involved in using image information and computed-aided image analysis for clinical drug trials. A short case study on MS lesion quantification will also be described.

Software requirements for computed-aided image analysis

An image analysis platform for drug discovery must support the transfer and reading of images stored in the DICOM (Digital Image Communications in Medicine) format [20]. It is important that the system enables image analysis experts with varying degrees of computer expertise to review the images via an easy-to-use radiology-oriented graphical user interface (GUI) and supports the standard image manipulation features available in PACS workstations [15].

In drug trials, there is a particular need to quantify results from the images. Thus, a variety of segmentation methods are needed to identify structures of interest [21] and to extract information such as volume, surface area and mean pixel intensity. Because clinical trials require statistical information across the studies, the ability to consistently and accurately quantify, correlate, report and store this information is extremely important.

Imaging during clinical trials places additional emphasis on the examination of longitudinal data. Thus, the software must enable tracking and registration of longitudinal data, allow the quantification of differences between datasets and allow the analysis of trends across patient groups [22]. The ability to store quantified results in a database and to perform cross-subject queries and to create quantitative reports is essential for statistical analysis.

Another system design issue is to find an appropriate balance between the amount of user interaction and full automation. Therefore, the popular approach often taken is to adopt the philosophy of using 'just-enough interaction' [23]. This approach permits semi-automation of image processing tasks, which improves the consistency, reduces the time to completion and enables a clinical expert to bring their patient- and domain-specific expertise into the analysis procedure.

Regulatory requirements for computed-aided image analysis

In addition to the technical design, medical devices such as medical image processing workstations must follow the governing federal regulations. In this article, we consider only the US regulations and discuss the relevant regulations concerning the use of electronic records during a trial.

Quality system regulations

The FDA closely regulates the drug discovery and development process. To obtain regulatory approval in the USA, any medical device, including software, must follow the Quality System Regulation (QSR) process [24] to ensure that proper controls are in place to guarantee a quality product from concept through to field support. These controls cover design, documentation, purchasing, traceability, production and processes, acceptance activities, handling of non-conforming products, corrective and preventive action, labeling and packaging control, distribution and installation, records and servicing, and are

similar to the guidelines for software development, such as the Institute of Electrical and Electronics Engineers (IEEE) or International Standard Organization (ISO) standards [25]. Implementation of these controls must begin before the first line of code is written. Consequently, it is difficult to retroactively implement a QSR process on an existing code.

Electronic records regulations

Another important regulatory aspect of conducting a clinical trial with imaging involves ensuring the integrity of the electronic data. The primary aspects of this regulation with respect to the analysis of medical images are the use of audit trails and electronic security [26].

An audit trail is a secure, computer-generated, time-stamped electronic record that enables the reconstruction of the course of events relating to the creation, modification and deletion of an electronic record [26]. Although, the images themselves must not be altered during the trial, the analysis of the images and, in particular, the segmentations, are considered electronic records, which are typically generated and modified by one or more users. Security is required to protect patient records and maintain the integrity of the data. Although access to the data is controlled primarily through the users' system passwords, any event that creates an audit trail item must be from a registered and verified user.

Software system design

A high-level architecture of an imaging analysis and management platform for drug discovery trials is shown in Figure 1. The three main components are: (1) medical image processing modules; (2) a database for storing the images and features extracted from the images; and (3) a GUI. The medical image processing modules typically consist of segmentation, registration and feature extraction tools and methods. The database serves as a warehouse for the original images, processed images and the extracted results. The user interface is the link to the outside world, enabling the image analysis experts to perform the drug trial studies. The interface allows image display and manipulation, invokes the image processing functions and facilitates the storage and retrieval of results to and from the database.

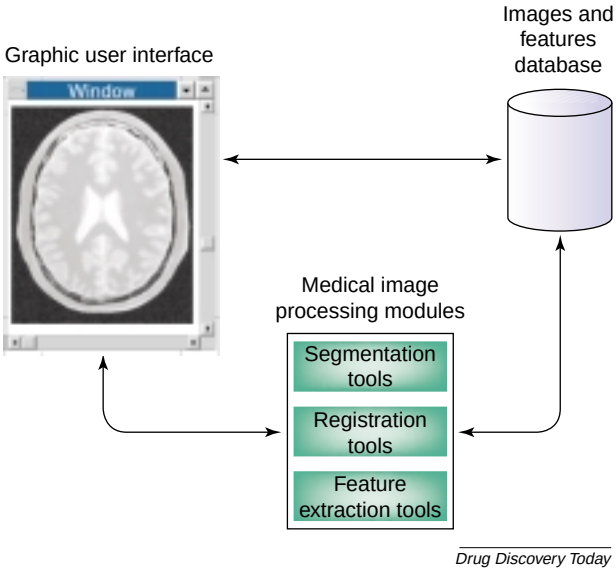

Figure 1. Schematic of the software system design, illustrating the key components and their interactions. The arrows indicate the bi-directional nature of the interactions between the three primary components in an imaging platform for drug discovery trials.

Image processing module

Image segmentation

The delineation of structures of interest is perhaps the most important component of an imaging software system used in drug discovery trials. Typically, the manual outlining of complex structures is a difficult and tedious task that suffers from poor reproducibility. The incorporation of automatic and semi-automatic segmentation tools is essential to aid this process. In this section, we outline a few 'just-enough interaction' delineation methods applicable to drug trials.

Seeded region-growing

The seeded region-growing algorithm [27,28] permits the user to place a seed point within the regions to be segmented. This simple but effective algorithm segments all the connected pixels within the range of pixel intensities around the mean of the seed point in both 2D and 3D.

Live-wire delineation

Live-wire is an interactive tracing tool [29,30] used for the precise delineation of structure boundaries with minimal user effort. The user starts tracing with live-wire by clicking on any point on a structure boundary. Then, as the mouse is moved around the image, an active polygon connects the current cursor location with the last-clicked mouse point along the strong gradient edges in the image. As the user moves the mouse near the boundary of the structure, the algorithm traces the precise boundary of the structure.

Shape-based interpolation

A shape-based interpolation algorithm [31] is used to rapidly create, by interpolation, a 3D segmentation from a few 2D segmentations. One can delineate the 2D boundary

of a structure on a few intermediate slices and then the shape-based interpolation algorithm can be used to interpolate the segmentation on all the other image slices. A deformable model [32,33] or Snakes-based [34,35] intelligent interpolation has shown promise in the effective segmentation of structures where the shape change between several image slices is gradual and can be well-approximated using intelligent shape-based interpolation.

Multi-channel tissue segmentation

Although the seeded region-growing algorithm finds regions that are spatially limited and connected to the seed point, the tissue segmentation algorithm is useful for delineating tissues that are distributed throughout the image set, particularly in large 3D datasets [36–38]. This tool uses multivariate statistics to combine multiple channels of information, such as T1 and T2-weighted MR series. Combining multiple channels of data can increase the discrimination between different tissue types, thus leading to improved segmentation.

The first step in multi-channel tissue segmentation is to provide training data, in the form of annotations of the regions of interest for one or more tissue types present on the image. Based on these training data, multi-dimensional probability models are generated for each tissue type [39]. The user can either specify a probability threshold value on a single Gaussian model or apply a maximum likelihood (ML) classifier. An optional Markov random field (MRF) filter is often used to further refine the ML results [37].

Image registration

When imaging is used during the drug discovery or development process, the images are almost always acquired at different time points and are often acquired using more than one imaging modality. Image registration tools have two primary uses. First, registration can be used to align images acquired using different imaging modalities. Each modality can give rise to different information regarding anatomy, pathology or function. Aligning this information assists the user in visualizing and interpreting the results. Second, registration can be used for aligning images acquired at different time points. Aligning the images enables easier visualization and correlation of the changes.

Registration techniques can be categorized by the permissible transformation and the features used to match one image to another. Rigid registration permits translation in any direction and rotation around any axis, resulting in six degrees of freedom in 3D imaging. Affine registration adds skew and scaling to the rigid transformations, permitting 12 degrees of freedom for 3D image sets [40]. Rigid and affine registration methods have been shown to be effective in aligning PET, CT and MR images of the brain where the rigidity of the skull prevents arbitrary deformation [41]. However, in more general cases, rigid and affine approaches cannot sufficiently model the image differences. Deformable registration algorithms (for example [42–45]) enables non-rigid free-form transformation. Deformable registration is a much more complex task than rigid and affine registration and is currently the topic of ongoing research. In addition, the difficulties in validating the technology means that such tools are not widely available commercially and it will probably be several years before the technology is introduced to the drug discovery system software.

Registration algorithms can also be grouped as either feature based or voxel based [46]. Feature based methods require the preprocessing of the images to extract features such as edges, landmarks, segmented structures and texture. Voxel-based methods work directly on the image gray values without any preceding feature extraction. Although both approaches have their advantages, voxel-based methods are more flexible and less reliant on the success of the processing steps. The ability to register images from different image modalities is also important to fuse the information from each mode, enabling better clinical decisions to be made. In the literature, information theory-based techniques such as mutual information [47–49] have been widely used for fusing various imaging modalities and images of various body parts. Figure 2 shows an example of rigid multi-modality registration of MRI images of the brain.

Quantitative feature extraction

After the user has finished delineating the different regions and tissue types on the images, different shape and intensity features associated with the segmentations can be extracted. Image analysis systems can typically compute the following quantitative features: (1) the total volume of each labeled region or area of a region in 2D; (2) the coordinates of the centroid of each labeled region; (3) the coordinates of the bounding cube around the labeled region; (4) the row, column and slice extent of each labeled region; (5) the cross-product diameters of each labeled region. A principal-component transform is used to determine these cross-product diameters; (6) the coordinates of the end points of the principal axes diameters; and (7) the mean, standard deviation, minimum and maximum image pixel intensities within the labeled region. Saving these computed values to the database will enable the creation of reports for statistical analysis or for cross-subject queries.

Database management system

There are several available choices for the database sub-system, and each is equally useful. A standard 'off-the-shelf' database management system (DBMS) would be used to store all the audit trails, image data, segmented images and the extracted features, such as the volumes of structures. A standard DBMS offers many built-in advantages, such as backups, redundancy, security, multi-user support and client-server accessibility. If the open database connectivity (ODBC) protocol is used to communicate between the GUI and the database, then any database management system, such as SQL Server (Microsoft; http://www.microsoft.com) or Oracle (Oracle; http://www.oracle.com) can be used to store the data. The structured query language (SQL) is often used to store and retrieve data from the database. The results of an SQL query forms a report, which can be displayed within the GUI or exported to other statistical analysis packages such as S-PLUS (Insightful; http://www.insightful.com) or SAS (SAS Institute; http://www.sas.com).

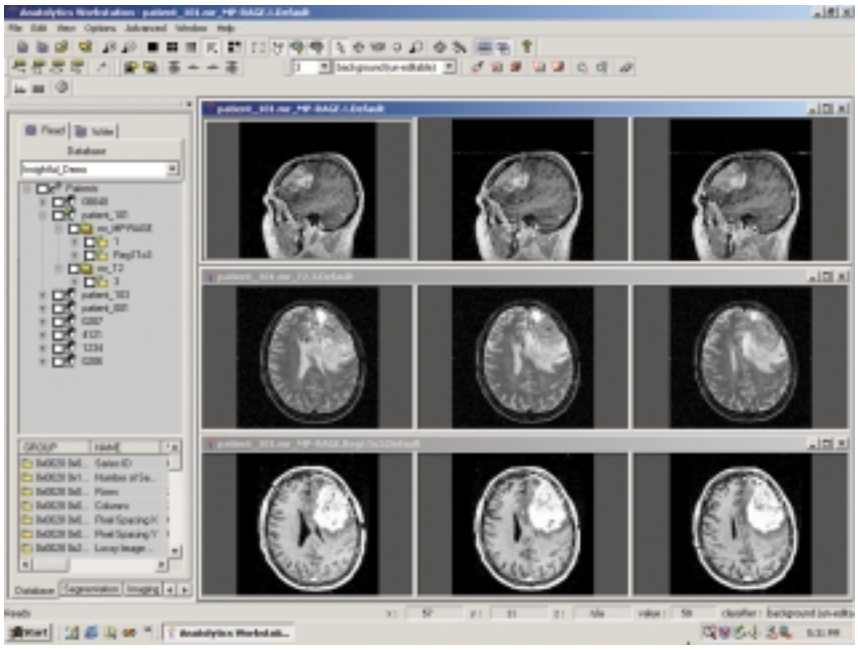

Figure 2. Screen shot demonstrating multi-modality registration results. Images in the top row show three consecutive sagittal slices of an aggressive brain tumor acquired with a T1-weighted 3D magnetic resonance image (MRI). The images in the middle row show a T2-weighted axial MRI acquisition of the same patient. It is difficult to correlate features between these two sequences The bottom row shows the results of registering the sagittal T1 images with the axial T2 images. The images derived after registration permit a direct comparison between the two sequences.

Graphical user interface

An effective and easy-to-use user interface is as crucial a feature as the image processing algorithms. Similar to a standard radiology workstation, the GUI should provide navigation capabilities for paging through image sequences. Other desirable tools include the facility to link sequences, enabling a user to page through several sequences in unison or a Cine-mode feature, allowing the user to rapidly scan through all the slices of sequence in one position. 3D reconstruction of the data is also needed to provide different views of the image data that are more suitable to performing particular tasks. For example, the reconstructed data can be displayed in a multi-planar rendering (MPR) view where sagittal, axial and coronal views of the same region are displayed together.

The provision of manual drawing and/or outline tools is also fundamental. The minimum tools required include the drawing of simple shapes (e.g. lines, rectangles and ellipses) and free-from drawing. These tools can also be used to train or initialize segmentation algorithms or to correct the results generated by the segmentation tools.

Database navigation and management tools are also requirements, allowing a user to select images, annotation and other associated patient information. Typically, images of one particular patient would be grouped together. One scenario involves using a tree structure similar to the prototype system shown in Fig. 2.

Potential applications

The system described would be useful in a variety of pharmaceutical and patient-care applications. Some potential uses for the system include: (1) the measurement of tumor volume and tumor cross-sectional diameters from CT and MR images of brain, head, neck and chest; (2) MS lesion load measurement from MR images of the brain; (3) articular cartilage volume and thickness measurement from MR images of the knee; (4) delineation of abdominal aortic aneurysm (AAA) from thoracic CT images; (5) delineation of brain structures for neurodegenerative diseases on MR images; (6) delineation of prostate from trans-rectal ultrasound images; and (7) delineation of the heart wall (endocardial and epicardial contours) from cardiac MR images. In the following section, we demonstrate a prototype system for the application of measuring MS lesion load from MR images of the brain.

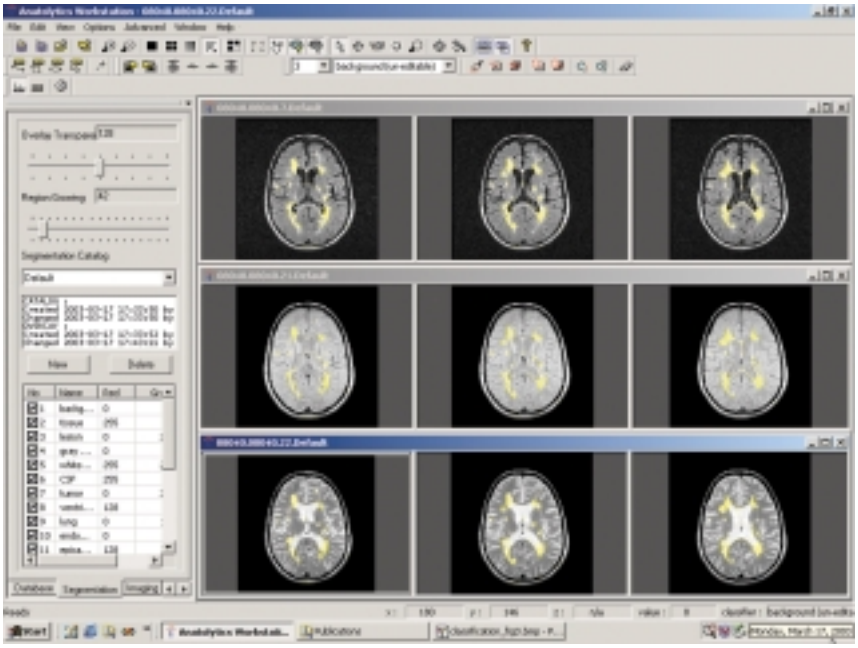

Figure 3. Screen shot demonstrating multi-channel segmentation of multiple sclerosis (MS) lesions. Images in the top, middle and bottom row show three consecutive sagittal slices of fluid-attenuated inversion recovery (FLAIR), proton density (PD)-weighted, and T2-weighted images of a patient with MS lesions, with the segmented lesions overlaid on top in cyan.

Case study: multiple sclerosis lesion detection

MS is an acquired disease of the central nervous system (CNS) characterized primarily by multifocal inflammation and the destruction of myelin. Drug trials often use the lesion load as a biomarker to quantitatively monitor disease progression [7,50]. Manual determination of the lesion load from MRI data is subjective [51] and extremely time and labor intensive, particularly when a physician needs to combine information from multiple channels, such as proton density (PD), T2-weighted imaging (T2) and fluid-attenuated inversion recovery (FLAIR), to perform lesion classification. Several studies have detected MS from brain MRI sequences [51,52]. In the following section, we present a case study on MS lesion quantitation using a simple interactive computer-assisted tool that significantly reduces the time, effort and variability of quantifying total lesion load.

Procedure

The multi-channel tissue classification method was tested on a phantom (designed at the University of Washington to mimic the MR brain tissue properties such as CSF, white matter tissue and MS lesions) and several patient datasets. For training, the seeded region-growing was used to delineate sample lesions on the FLAIR images. The segmentation algorithm was then run using the T2-weighted, PD-weighted and FLAIR sequences. From the final segmentations (after expert editing) the total lesion load was calculated.

In the phantom study, the measured lesion volume after segmentation was 26.3 ml, which increased slightly to 27 ml after user editing, compared with the actual volume of 29 ml. The under-detection was a result of a partial voluming artefact [53]. Figure 3 is an example of the MS segmentation, shown as overlays on a multi-channel MR dataset. Minimal training (typically a couple of lesions in different parts of the brain) was required. It took less than a minute to provide all the training data using the seeded region-growing tool. The automatic segmentation took typically <10 s. Following the segmentation, the user manually edited the results, requiring ~20–40 s per slice. The total time of 20–25 min per case using the semi-automatic approach was lower by a factor of 2–3 compared with the manual approach, which took ~60 min. Although this study was not a part of a drug trial, it did demonstrate the use of an image analysis system as it might be applied towards the testing of an MS drug.

Lesion identification in MR images is often more of an art than a science. There can be different interpretations of the subtle lesions by individuals, resulting in personal biases. However, the inter-observer and the intra-observer coefficient of variability in this study of 4.5% and 4.7% compare favorably with the inter-observer variability reported for manual segmentation of MS studies from MRI [54]. The intra-observer correlation coefficient was 99.2%, which, as expected, was higher than the inter-observer correlation coefficient. The high correlation coefficient suggests that it is possible to have rapid, easy-to-use, interactive and reliable lesion segmentation using multi-channel image data. In a real clinical situation, this is very important, particularly where a single expert is segmenting serial patient scans over time.

Conclusions

Image processing for drug discovery and development requires a different set of tools from those developed for the typical clinical setting, which generally places an emphasis on visualization capabilities. For drug discovery and development, there is a greater need to reliably quantify

results and to make comparisons between different time points and different populations. The general requirements of a software system specifically designed for this application include tools for registration, segmentation, feature extraction, audit-trails, data management and reporting. Our experience with a prototype software system has shown that using semi-automated segmentation, registration and feature extraction tools results in low measurement variability and an increase in confidence in the quantitative end results. Reducing the variability often results in a reduced cohort size, which favorably impacts on the time and cost of conducting a trial.

Application of image processing to medical images is an active area of research with new algorithms and new biomarkers continually being developed. Therefore, software systems for drug discovery must also be designed to be agile and extensible, allowing the incorporation of new methods and the performance of new tasks without extensive architectural redesign.

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