Cancer Image Analysis

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Welcome to the first in a series of articles that will highlight the role of image analysis in oncology. Cancer Image Analysis (CIA) is concerned with the extraction and manipulation of useful information from oncological images, and therefore it is closely related to Cancer Imaging per se and can be seen as complementary step in the process towards diagnosis, screening, drug testing or assessing treatments. CIA is a very wide field of research, not only due to the wide range of cancer-related images, from MRI to histology to optical images, but also because image analysis has inherited many techniques from the fields of Statistics, Pattern Recognition and Computer Vision. This series will show the potential of image analysis as applied to cancer with the ultimate objective of fostering an interdisciplinary cross-fertilization that will bring benefits to clinicians, scientists and ultimately the patient.

Introduction

Technological advances in imaging and computers are seen in everyday life. Digital cameras are widely used as they have become cheaper and smaller, yet offer very high quality. Computers have also become more powerful, less expensive and easier to handle. The advances in storage technology in the form of optical disks (CDs and DVDs), magnetic disks (Internal and External Hard Disk Drives), flash memory data storage device (USB drives) and even the availability of some of these technologies through the internet (storage area networks) have grown accordingly. Large files can be transmitted around the globe through the internet without the need for specialised equipment or skills.

In the life sciences and medicine, conjunction of imaging technology with computers that control cameras, microscopes and other equipment have resulted in new technological setups that generate very large amounts of images or videos at a speed that was unimaginable a few years ago. However, once the imaging has been completed, there is sometimes a lack of resources to process, quantify, analyse and interpret the wealth of the information contained in them. In many cases data is acquired at a faster rate than the processing rate of human experts; this situation has increased the workload of pathologists and radiologists in both clinical [1,2] and experimental settings [3], for instance, in biomarker discovery. This situation has led great opportunities in the field of Biomedical Image Analysis (BIA).

The research in BIA is intrinsically interdisciplinary as the expertise required for processing images is largely computational and mathematical. However, all the algorithms or methodologies are tailored to the physical characteristics that form an image in a biomedical or clinical study, and these characteristics are in turn related to anatomy, physiology, chemistry and their underlying biology. Therefore, imaging and image analysis are linked by the data, the images themselves, and the nature of the data. The fields diverge once the data has been acquired; traditionally, specialists like pathologists or radiologists observe the images to reach a conclusion, based on the superb capabilities of human vision and highly specialised training. Image analysis uses computers and digital image processing techniques.

Image analysis methodologies can assist experts in three ways. First, computers are highly efficient at processing large amounts of data; when a study requires the comparison of two sets, each with hundreds of images, a computer shortens the time required to detect any possible difference. Second, algorithms may not be as good as a visual examination by an expert, but they are consistent and therefore avoid the well-known problem of inter- and intra-observer variability. Third, and probably most important, there may be information not immediately apparent to a human eye that can be extracted through computer algorithms, patterns or texture that, for instance, can help an expert reach a conclusion.

Elements of Image Analysis

There are many ways in which image analysis work can be classified, one of the most common being to group into organ-specific topics, as the techniques applied to the heart or the brain will share anatomy, physiology, and sometimes imaging technique. Another way to classify research is through acquisition technology used to take images: Microscopy, Computed Tomography, Magnetic Resonance Imaging or Spectroscopy, etc. Yet another possibility is through the underlying algorithms or techniques used to process the images, like Fractals, Texture or Registration. These divisions are naturally not clear-cut; mammography, for instance, is related to an organ and an acquisition technique.

When a cancer-related image is analysed, one or more steps can follow each other. The steps are related to what is done with the images, regardless of the acquisition technique, organ or disease. Some common steps are described below and illustrated in Figure 1.

The analysis generally starts with an enhancement step. Biomedical images can be noisy, with low contrast or complicated due to artefacts such as caused by motion [4] or uneven intensities [5]. It should be noted that enhancement is done on the images, and is not related to the enhancement that can be achieved by modifying the acquisition itself, like using contrast materials [6]. Enhancement techniques modify an image in such a way that it is easier to interpret or analyse. Some of the techniques may be relatively simple, such as stretching a histogram to boost contrast, removing noise through filtering, and correcting shading or uneven intensities. However, in some cases, enhancement may become rather involved, as in compensating for cardiac or respiratory motion that causes errors when planning and delivering radiotherapy treatment for lung [7] or colon cancer [8]. Enhancement should therefore be understood beyond the transformations that create a visually improved image from a human perspective. It is also important to consider that the enhancement of the visibility of features – calcifications for instance – may distort the shapes of these or other features that ultimately could lead to an incorrect diagnosis if the variations are not taken into account [9].

A segmentation step aims to partition an image into regions or classes that are homogeneous according to certain criteria. Thus, an image can be separated into one or more objects and a background. The objects may or may not correspond directly to an anatomically-relevant structure (an organ), a subset of a structure (a tumour), or a feature of a structure (the cell membrane). There are many segmentation techniques,

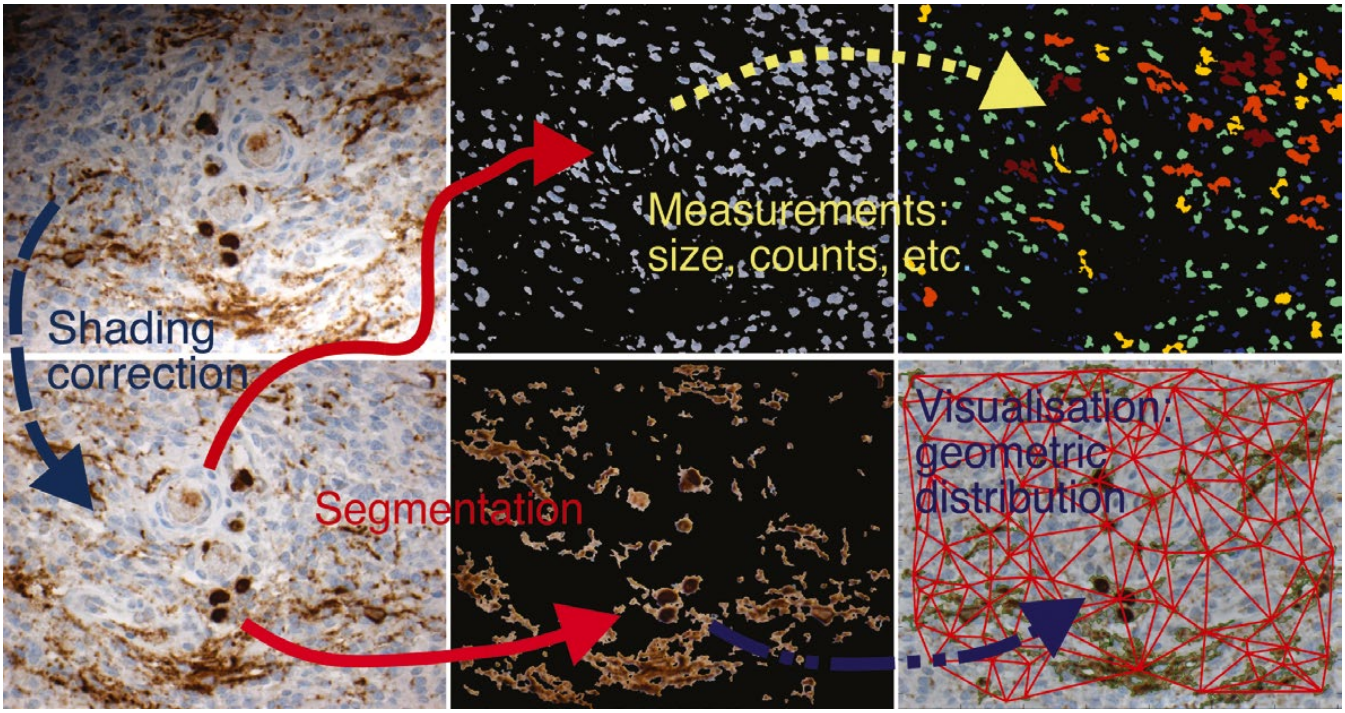

Figure 1: Illustration of several image-processing steps. An image obtained by immunohistochemistry is first enhanced to remove inhomogeneous shading seen in the upper part of the image. The corrected image is then segmented into two types of cells using chromatic information. Once the cells have been segmented into objects at this stage, numerous measurements can be made - size, elongation, density, variation of intensity, etc. In this example, blue cells are colour-coded according to their size: brown > orange > yellow > green > blue. Some measurements, e.g. the geometric distribution of the brown cells, can be used for visualisation purposes.

one of the most traditional segmentation techniques being to assign pixels to different classes by comparing their intensities against a value or a threshold (referred to as thresholding). Even when thresholding is very simple, it can be effective in the analysis of prostate malignancies [10]. Other techniques can: look for edges on images, for instance to delineate the breasts as areas of interest in thermal imaging [11], compare structures, like spiculated lesions, against pre-defined models in mammography [12], or perform regional analysis of the intensities of the pixels, in terms of their texture to segment cancerous and normal regions of colon biopsies [13], or lesions and normal brain tissue [14]. In some cases, a combination of different algorithms is necessary to obtain satisfactory segmentation; this is common in immunohistochemistry [15,16]. In PET, it is of particular interest to delineate tumour volumes, which can be achieved by setting thresholds based on the SUVmax, measuring the local contrast or measuring the gradient of the intensity [17].

At the measurement step, a series of rules are applied to extract numerical values from the images, which may have previously been processed with other steps. It is possible to apply a very large number of rules, with a filter bank for instance, and create a large measurement space (sometimes called pattern representation) with the result of all the rules. Some of these measurements may be directly related to a cancer condition - the irregular border shape of a melanoma [18] or the effect of a drug. The length of microvessels and their characteristic colours are related to the influence of vascular disrupting agents [19]. In the histology of cancer, the number of cells or nuclei can sometimes have diagnostic significance [20], for instance, the number of tumour infiltrating lymphocytes from thresholded images [21]. Common measurements in sections can include area, size, colour, elongation, and sphericity [16]. The measurements may come from different acquisition modes; the combination of data from MR spectroscopy with textural measurements from MRI has been used to discriminate meningiomas from metastatic brain tumours [22]. However, it is important to note that many measurements may not be of interest and therefore might be discarded in a process called feature selection, or combined among themselves to create new measurements, which is called feature extraction.

At the classification step, the information obtained from the segmentation and measurement steps is integrated in some way, and rules are applied to reach decisions that have clinically or biologically relevant criteria in a particular context. In some cases this step is called computer-aided-diagnosis as it provides information that can be used to reach a diagnosis. For instance, Loeffler [10] presented an algorithm that differentiates Gleason grade 3 from grade 4/5 histology. Rojas-Domínguez [23] analysed breast-mass contours as a step toward breast cancer diagnosis, and Chen [24] presented a method for automated mammographic risk classification based on estimation of breast density.

There is a very fine line between segmentation and classification; indeed the terms are sometimes interchanged. In this review, we consider that the segmentation step is at the level of the pixels and their characteristics: there are 10 regions with pixels above the value of 100, and classification on the other hand, reaches a higher level; e.g. a higher than normal density of cells may indicate the presence of a tumour.

Another step, not necessarily after classification is a visualisation step, where information from different sources may be combined or merged. The most common application of a merging of information in a cancer context is probably the registration between PET and CT modalities [25]. CT provides anatomical information whereas PET provides functional information. The visualisation can be formed with extracted features from a single source; for instance, Ganeshan [26-28] developed an interesting technique that combines texture features with CT scans in the analysis of liver, colorectal and oesophageal cancer.

Image Analysis Tools

Image analysis relies on the use of suitable software tools and ever more powerful computers. Software packages developed specifically for image analysis consist of a basic platform to which modules, sometimes called plug-ins, are added (ImageJ, ICY, Imaris, AxioVision, Volocity, etc.). There are some general purpose scientific platforms that are highly flexible and powerful, offering high-level programming with a wide variety of toolboxes, thus being capable of processing images in a very efficient way (Matlab, Scilab, Octave, Mathematica, etc.). These platforms provide many advantages over lower level programming languages like C and FORTRAN, especially in terms of visualisation, functions and toolboxes, at the expense of slower processing times. There is even the possi-

bility of using graphically-oriented packages (Photoshop, Corel, etc.) to analyse biomedical images; however, this option does not provide the power of the previous cases. Some of these tools are open-source and freely available, but a certain level of software expertise is required to use them effectively in obtaining quantitative results.

With the development of the internet, new possibilities have emerged in which web-based tools are available, for example, in: virtual slide analysis in diagnostic pathology [29], the analysis of microarray gene expression [30], and the online automatic processing of images of several cancer-related experiments [31].

Conclusion

This article briefly describes some elements of image analysis mostly related to oncology. In future issues, different techniques will be described in the context of clinical applications and pre-clinical research. ■

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