Extracting Biomarkers from Dynamic Images
Approaches and Challenges

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Abstract: Imaging technologies have developed rapidly over the past decade proving to be valuable and effective tools for diagnosis, evaluation and treatment of many conditions, especially cancer. Dynamic contrast enhanced imaging using computed tomography or magnetic resonance has been shown particularly effective and has been intensively studied to allow for assessing the vascular support of various tumours and other tissues. In this paper, we discuss current approaches and most important challenges in extracting markers from such dynamic images. These difficulties have to be resolved in order to ultimately improve patient care.

1 INTRODUCTION

Imaging technologies have developed extremely rapidly over the past decade proving to be valuable and effective tools for diagnosis, evaluation and treatment of many conditions, especially cancer. Cross-sectional imaging such as magnetic resonance (MR) and computed tomography (CT) have been shown particularly effective. The pixel data in these images holds significant information which can be uncovered by post-processing analytical software. This is currently not widely done due to the complexity of this process. It results in many conditions being undetected and miss-diagnosed leading to incorrect or prolonged treatment, increased costs and unnecessary emotional upset.

Therefore, there is need of early diagnostic and predictive factors to refine the management of patients with various types of cancer, e.g., in order to differentiate between benign and malignant, guide the use of surgical adjuncts, response evaluation and help determine patients that are at risk of early reoccurrence, requiring intense monitoring and follow-up.

Dynamic contrast enhanced (DCE) biomarkers were proven to be correlated with physiological and molecular processes which can be observed in tumour angiogenesis (these processes are morphologically characterised by an increased number of microvessels, which are extremely difficult to image directly using well-known imaging techniques (Miles, 2002)). Therefore, DCE biomarkers can robustly assess tumour characteristics and stage, and provide an independent indicator of prognosis, enabling risk stratification for patients with various types of cancer.

The first description of the application of multislice DCE computed tomography (DCE-CT) for measuring tumour perfusion dates back to early 90's (Miles et al., 1993). The process of the DCE analysis involves acquiring time series images and investigating temporal changes of injected contrast material (very often referred to as tracer) attenuation in vessels and tissues. Such biomarkers extracted from dynamic images have been investigated in several clinical trials (Coenegrachts et al., 2012). They were also used for determining the drug effects in various cancers (thus monitoring the therapy progress and treatment response), which include glioma (Ford et al., 1996), rectal, renal (Fournier et al., 2010), lung (Ng et al., 2007) cancers, carcinoids, and numerous others (Miles, 2002). Importantly, DCE imaging produces reproducible measurements which have been validated against many reference methods—this reproducibility of results is extremely important in clinical applications which are aimed at helping in di-

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agnosis. It is a non-invasive technique and can be easily incorporated into standard protocols, thus does not require an additional imaging modality. Finally, the linear relationship between the contrast medium concentration and CT attenuation value implies an easier quantification compared with MRI (Miles, 2002).

Quantitative imaging—according to the Quantitative Imaging Biomarkers Alliance (which is the initiative of the Radiological Society of North America, looking into improving the practicality of quantitative biomarkers by reducing variability across devices, patients, time, and sites[1])—is the process of extraction of *quantifiable* features from medical images (e.g., dynamic contrast enhanced images). These image-derived features should allow for assessing the status of a disease, injury, or chronic conditions relative to normal. The field of quantitative imaging encompasses additional activities, including data analysis, along with the display and reporting methods. Importantly, these procedures should directly lead to extracting accurate, precise and reproducible metrics, which can be coupled with additional, physiologically relevant patient parameters to improve the treatment outcome and prognostic efficiency of imaging.

A *quantitative imaging biomarker* is then an objective characteristic derived from an in vivo image. This characteristic is *measured* on a ratio or interval scale as indicators of biological/pathogenic processes or a response to the intervention and/or treatment. The biomarkers may be extracted from a plethora of currently available image modalities (e.g., computed tomography, magnetic resonance or positron emission tomography), and coupling them may further boost their prognostic efficiency. Optimising the performance of the derived biomarkers can directly affect the patient treatment pathway.

This paper is structured as follows. In Section 2, we discuss the procedure of extracting biomarkers from dynamic images. It is interleaved with the references to the literature, which highlight the current advances in this field. Section 3 concludes the paper and serves as an outlook to our future research.

2 EXTRACTING BIOMARKERS FROM DYNAMIC IMAGES

The process of extracting biomarkers from dynamic images is visualised in Figure 1. The flowchart presents the standard steps in the processing pipeline—the images (e.g., DCE-CT or DCE-MR) are acquired using an appropriate acquisition protocol. It is worth noting that novel volumetric acquisition techniques allow for decreasing the radiation dose as pointed out by Miles et al. (Miles et al., 2012). Then, the acquired images are registered (in order to minimise the impact of e.g., the patient motion on the DCE results) and segmented (at a minimum, an arterial blood vessel must be identified to enable analysis).

The DCE processing involves generating time/density curves for volumes of interest (VOIs) along with the parametric maps, which are later analysed for extracting useful (quantifiable) metrics. Finally, these results should be safely stored since they will be re-investigated in the future. This investigation will help understand how the current treatment affects the patient condition, and will allow for choosing the best care pathway.

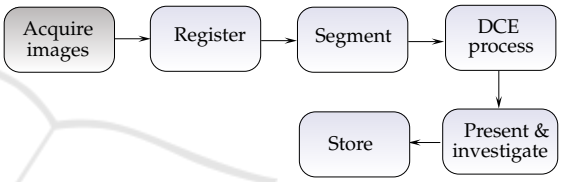

Figure 1: Extracting biomarkers from dynamic images.

In the following subsections, we discuss in more detail the pivotal steps of deriving biomarkers from dynamic images. Although we focus on the DCE-CT imaging, this processing strategy is quite generic and can be easily tailored to other modalities too.

2.1 Image Registration

4D acquisition (3D image stack acquired in time, which becomes the fourth dimension) techniques suffer from motion artifacts which may be caused by irregularities in patient breathing or heartbeat. These differences between images should be corrected before any curve analysis since they are of the non-pathological origin and can easily jeopardise the investigation (Hachama et al., 2010). This issue is tackled by the image registration process which maps images to a common space to correct geometric differences. On the one hand, rigid transformations allow for overcoming translational and rotational displacements, whereas non-rigid transformations can account for deformable changes in tissue shape.

The registration is crucial for an accurate DCE analysis since it can influence the shape of resulting enhancement curves (obtained either for segmented automatically or manually annotated tissues of interest). Importantly, some peaks in these curves can be attenuated by the registration process, as shown

[1]For more details on QIBA see: http://www.rsna.org/qiba/

in (Hachama et al., 2010). These peaks correspond to the patient breathing periods which occur after periods of apnea. If these peaks were not removed during the registration process, then they could be mistakenly interpreted during the further curve analysis (either by an automated algorithm or by the operator).

Incorporating advanced registration techniques to minimise the impact of motion artifacts on time-attenuation curve analysis is a pivotal task—it became a vital research topic and some registration techniques emerged during the years (Hou et al., 2014). Nonetheless, there is a need for fast and efficient algorithms (both rigid and non-rigid) which will help mitigate the risk of inaccurate analysis (which, in turn, affects the biomarker extraction process).

Speeding up the registration process may be accomplished by designing and implementing parallel algorithms which may possibly run either on modern multi-core processor or graphics processing unit architectures, which are widely available nowadays. We already showed that co-operative parallel algorithms are extremely efficient in solving a variety of complex optimisation problems (Nalepa and Błocho, 2015). Investigating the possibility of fusing the results of various registration algorithms run in parallel (so that the execution time of this processing step is not increased) to retrieve higher quality results is of high research interest.

The recent advances and trends in medical image registration are gathered in a number of interesting surveys and reviews (Hill et al., 2001; Oliveira and Tavares, 2014). These papers also highlight the potential future research directions.

2.2 Image Segmentation

Automatic image segmentation (very often referred to as the image labelling) algorithms identify particular structures (or tissues) in the input medical image. It has been recently shown that this step is crucial for the 4-dimensional CT (3D stack of images along the temporal dimension) and can significantly affect the image-guided therapy (Martin et al., 2015). This issue is especially challenging for target volumes which are subject to motion (e.g., the lung cancers are subject to varying magnitudes of respiratory motion). Discrepancies (in the annotated region's shape and/or area) between the automatic and manual segmentation (or even the manual segmentation undertaken by two or more experienced radiology experts) may lead to differences in treatment planning. Therefore, there is a need for accurate (and robust against low-quality data) 4D image segmentation techniques.

In recent segmentation algorithms, images are

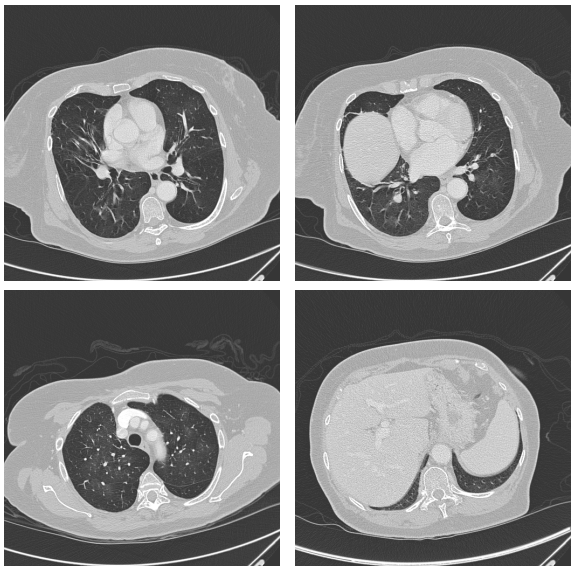

Figure 2: Example CT images containing lungs of various shapes and characteristics.

very often denoised at first, and then the tissue of interest is manually outlined to provide a seed point for further analysis (Hou et al., 2014). Then, the image is segmented into the foreground (tissue) and background (usually air) parts, and undergoes the morphological processing (although images can provide a lot of information, only some—usually one or two within the image—tissue areas are of interest). The 3D spatial and temporal domains are exploited with the shape encoding, propagation and refinement techniques. Since the consecutive images most probably share the similarities between tissues and their shapes, these similarities can be used to increase the quality of the initial segmentation (the third dimension is utilised). The contour information (which may be represented e.g., as the control points of the B-spline corresponding to a given image segment) of one image is therefore used for refining the control points in the following image. Although it is a relatively easy way of propagating the information between frames, this approach helps boost the segmentation accuracy. Such propagation is commonly used in segmentation techniques which analyse the neighbouring frames in stacks of images.

Segmenting medical images has been summarised in numerous interesting surveys (Vitulano et al., 1997; Wei and Li, 2014). A very recent paper by Smistad et al. (Smistad et al., 2015) indicates that exploiting parallel architectures (which are easily accessible at the moment) is an important issue. Combining the information reflecting various image features, including intensity, texture and spatial characteristics appears as a very promising research direction. This combined

feature domain can be utilised for new 2D segmentation (for individual images) techniques, and can be coupled with the 3D spatial and temporal image relations to provide accurate segmentation into organs (i.e., to classify the organs in the input images properly). Also, weakly supervised segmentation techniques are gaining attention too (Jia et al., 2017).

Four example images containing lungs of various characteristics, positions and shapes are given in Figure 2, along with the example volumetric rendering of segmented lungs presented in Figure 3. These examples show how difficult the segmentation task is—a well-performing algorithm should deal well with collapsed or malformed lung structures. Also, it is possible that a tumour appears on the lung edge, hence it influences its shape. These images come from the Cancer Imaging Archive[2] repository (Clark et al., 2013), and it was used during the 2015 SPIE Medical Imaging Conference (the LUNGx Segmentation Challenge (Armato et al., 2015)). Organs are very often segmented from whole-body scans which imposes the additional difficulty of locating the frames containing these organs in the first step (other frames can be pruned and removed from further analysis).

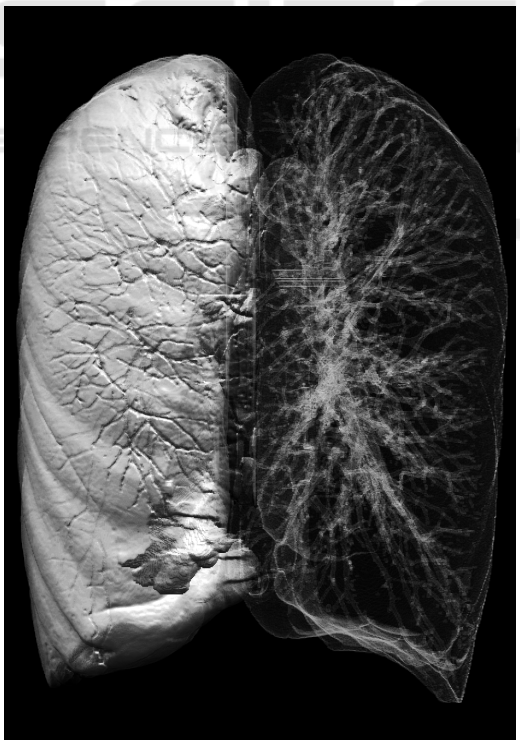

Figure 3: Lungs segmented from a whole-body CT scan using our lung segmentation algorithm (Walczak et al., 2017).

[2]See https://wiki.cancerimagingarchive.net; Last access: November 11, 2017.

2.3 DCE Processing

DCE biomarkers are derived from analysing the movement of contrast dye into and out of soft tissue in the human body following injection of a bolus of dye. The semi-quantitative parameters which can be derived from DCE imaging with the use of time-attenuation curves reflect and quantify tumour vascularity (O'Connor et al., 2011). These measures encompass (but are not limited to):

- Peak enhancement—the maximum contrast concentration.
- Perfusion normalised to cardiac output—the peak enhancement corrected for dose of contrast medium and contrast sensitivity.
- Standardised perfusion value—the peak enhancement corrected for the patient weight and iodine calibration factor.
- Area under the time-attenuation curve.
- Maximum upslope.

Derived values (quantifying physiological parameters) also require the time-attenuation curve from the supplying artery, referred to as the arterial input function (AIF). These additional DCE parameters include:

- Perfusion (regional tumour blood flow)—the amount of blood (contrast) flowing through the unit volume of tissue.
- Permeability—the amount of contrast leaving the blood stream.
- Blood volume—the fraction of the tissue which is blood.
- Mean transit time—the time indicating how long the contrast takes to pass through the given tissue vasculature.
- Time to peak—the time taken to reach the maximum contrast concentration.

The extracted features are depicted as parametric maps (for better visualisation and easier interpretation). Although comparing DCE results for various images obtained using software delivered by one manufacturer (e.g., GE Healthcare or Siemens Healthcare) is quite intuitive, such comparisons are extremely challenging (or even impossible) if different DCE analysis approaches are exploited.

As discussed by Miles et al. (Miles et al., 2012), there are three tracer kinetics models currently in use: the Fick's principle (implemented by e.g., Philips and Toshiba), the Patlak model (Siemens), and the Johnson and Wilson model (GE Healthcare). Because of differences in the underlying physics of these models, the results cannot be compared directly. This is

an important real-life issue—it is not possible to compare DCE results retrieved for the same patient e.g., at different sites.

3 CONCLUSIONS AND OUTLOOK

Although DCE is widely used and accepted in clinical practice, there are a number of technical issues (including the interoperability of medical systems (Chmielewski and Stapor, 2016)) which remain unresolved and should be tackled to provide robust and efficient personalised medical care. The guidelines and recommendations (concerning the system requirements, quality assurance, radiation dosimetry, patient preparation and many others which may influence the examination) which help optimise the use of the DCE imaging in a day-to-day oncology care, along with the current status of DCE have been summarised in a survey by Miles et al. (Miles et al., 2012).

DCE biomarkers have been available for some 25 years, but the improvements in acquisition technology have accelerated the adoption recently. Modern CT and MR scanners are able to acquire time series images of 3D volumes routinely and most equipment manufacturers offer a DCE analysis package. However, though a number of analysis algorithms have been already published, each manufacturer applies different analysis techniques leading to difficulties in comparing results. Therefore, there is a need for a more generally available analysis system for clinical and research use. This issue was raised by Miles et al. as the most important research direction, which should be undertaken as fast as possible.

Our current research is focused on incorporating machine learning and evolutionary (e.g., memetic (Nalepa and Blocho, 2016), being the hybrid approaches coupling evolutionary algorithms with various local-search procedures) approaches at various steps of the DCE processing pipeline. We plan to incorporate support vector machines, which are a supervised classifier applied successfully in a range of pattern recognition tasks (Nalepa and Kawulok, 2014; Nalepa and Kawulok, 2016). Interestingly, segmenting medical images resembles the problem of detecting and segmenting skin in colour images, which was the topic of our earlier research (Kawulok et al., 2014a; Kawulok et al., 2014b). The results obtained in our previous works on skin detection can be beneficial to implement in emerging medical image segmentation techniques. Finally, deep neural networks (DNNs) are being intensively developed to segment various image modalities (Liskowski and Krawiec, 2016). Such classification engines can be provided with annotated images and are aimed at extracting features automatically. Since the medical data sets are very often extremely imbalanced (the majority class examples represent healthy tissue), the data augmentation step is critical and was shown to dramatically affect the performance od the deep convolutional layers. Also, determining the appropriate deep architecture is an important problem which attracted research attention (Lorenzo et al., 2017). Tailoring the DNN architecture can allow for exploiting the additional knowledge about the medical data (e.g., the 3D relationships) which has not been extensively investigated in the literature so far.

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