An Integrated Visual Analysis System for Fusing MR Spectroscopy and Multi-Modal Radiology Imaging

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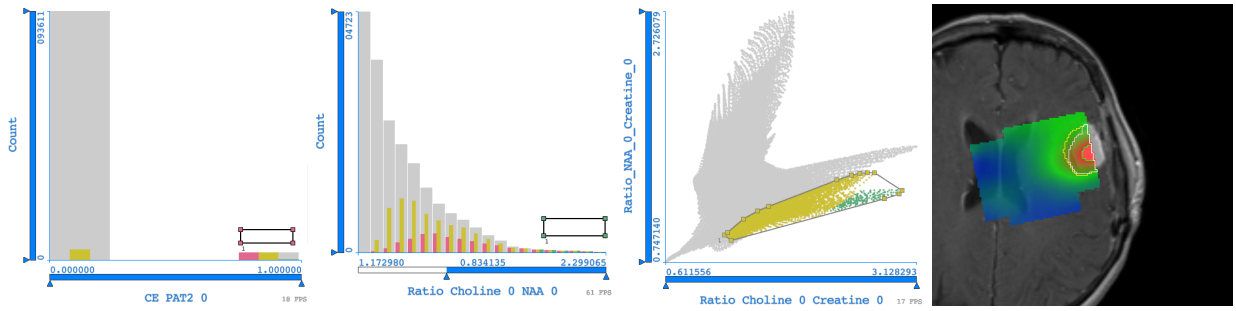

(a) (b) (c) (d)

Fig. 1: Analysing and visualizing MRSI data in our system. Red brush selecting the originally drawn CE region by a user in a histogram (a). Green brush selecting voxels with $CNR \geq 2$ depicting high tumour intensity (b). Yellow convex hull brush gathering similar voxels in a scatter plot relating NAA/Creatine and Choline/Creatine ratios (c). Multi-modal rendering of Axial view of MR T1 Gado with manually thresholded $CNR \geq 2$, FLAIR, CNR color map and yellow, red and green segmentations obtained from the respective brushes (d).

Abstract— For cancers such as glioblastoma multiforme, there is an increasing interest in defining "biological target volumes" (BTV), high tumour-burden regions which may be targeted with dose boosts in radiotherapy. The definition of a BTV requires insight into tumour characteristics going beyond conventionally defined radiological abnormalities and anatomical features. Molecular and biochemical imaging techniques, like positron emission tomography, the use of Magnetic Resonance (MR) Imaging contrast agents or MR Spectroscopy deliver this information and support BTV delineation. MR Spectroscopy Imaging (MRSI) is the only non-invasive technique in this list. Studies with MRSI have shown that voxels with certain metabolic signatures are more susceptible to predict the site of relapse. Nevertheless, the discovery of complex relationships between a high number of different metabolites, anatomical, molecular and functional features is an ongoing topic of research - still lacking appropriate tools supporting a smooth workflow by providing data integration and fusion of MRSI data with other imaging modalities. We present a solution bridging this gap which gives fast and flexible access to all data at once. By integrating a customized visualization of the multi-modal and multi-variate image data with a highly flexible visual analytics (VA) framework, it is for the first time possible to interactively fuse, visualize and explore user defined metabolite relations derived from MRSI in combination with markers delivered by other imaging modalities. Real-world medical cases demonstrate the utility of our solution. By making MRSI data available both in a VA tool and in a multi-modal visualization renderer we can combine insights from each side to arrive at a superior BTV delineation. We also report feedback from domain experts indicating significant positive impact in how this work can improve the understanding of MRSI data and its integration into radiotherapy planning.

Index Terms—MR spectroscopy, cancer, brain, visualization, multi-modality data, radiotherapy planning, medical decision support systems

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1 Introduction

Radiotherapy is an important method of treating many cancers. Its planning enables physicians to identify key areas and organs at risk of the human body that should be managed in different ways while treating cancerous tissue. According to the calculated Radiotherapy Treatment (RT) plan, pre-determined areas are targeted for conventional or higher doses of radiation while others have to be protected from such intensities. For a good RT plan, multiple imaging modalities should be employed to understand the different aspects of the disease. The most common modalities include Computed Tomography (CT), Contrast Enhanced (CE) T1-weighted Magnetic Resonance (MR) images, Fluid Attenuated Inversion Recovery (FLAIR) T2-weighted MR images, Positron Emission Tomography (PET) and other MR images such as diffusion or perfusion. In addition to the planning images acquired before RT, most patients will undergo repeated follow up exams after RT to evaluate their response to the treatment, generating enormous amounts of information. The success of the treatment depends most on the type and grade of the cancer, but having the right imaging modalities available can significantly improve the treatment decision and the outcome for the patient, increasing survival probability and

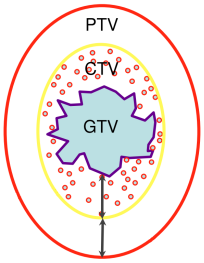
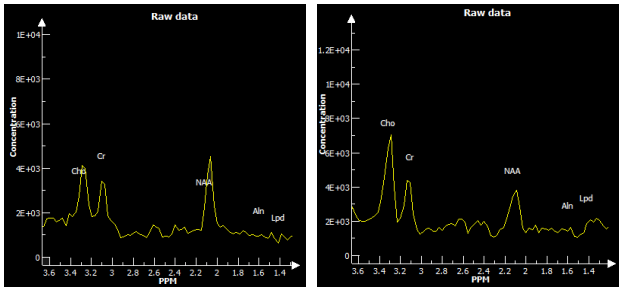


Fig. 2: An illustration of GTV, CTV, PTV.



(a) (b)

Fig. 3: Examples of MRSI raw voxels showing (a) healthy tissue with high NAA, intermediate Choline and Creatine, compared to (b) tumour tissue with enhanced Choline and reduced NAA.

reducing side effects.

During the initial step of the RT plan, delineations of volumes of interest must be performed compromising suspected regions where tumour tissue can be found. For this reason it is necessary for physicians to identify where healthy and cancerous tissues are located, allowing a better definition of the tumour volume and to deliver the dose for a better radiotherapy plan. For RT treatment planning, three contours are created: gross tumour volume (GTV), clinical target volume (CTV) and planning target volume (PTV) [1]. GTV is the segmentation that corresponds to the imaged tumour that can clearly be seen in anatomical images, as they define the macroscopic disease area. The CTV includes the GTV with a margin corresponding to the spread of the microscopic disease which cannot be clearly seen in anatomical images. The last segmentation, PTV, takes into account the positioning uncertainties in the different sessions of treatment delivery (Fig. 2).

Unfortunately, for some types of cancer, including glioblastoma multiforme (GBM), existing dose targeting strategies are insufficient. Relapses still occur very frequently within the the irradiated volumes. This has lead to widespread interest in using additional "functional" imaging modalities to identify regions of high tumour burden or radioresistance. These regions, known as Biological Target Volumes (BTV) [2, 3], can then be targeted with radiation dose boosts, either integrated into standard therapy or added at the end of a treatment. In GBM treatment, one modality which has garnered a lot of interest for its predictive potential is Magnetic Resonance Spectroscopy Imaging (MRSI).

MRSI is a non-invasive molecular imaging modality which permits the concentrations of multiple brain metabolites to be quantified in each spectroscopy voxel. It is used as an effective tool to find malignant gliomas, assessment of treatment response and therapy monitoring [4]. Its spectra information regarding cell activity is highly complex and is mainly visualized in a voxel by voxel basis (Figures 3a and 3b), and requires pre-processing analysis steps, limiting its application to RT planning. In addition to this, MR imaging is known for not producing standardized image values, thus making it difficult to understand what normal concentration values are for any given patient [5]. MRSI has been present in the clinical world since the 1980s and since then, important findings about the relation between certain metabolites have been identified [3, 6]. However, until now, MRSI has not yet been generally integrated as a part of the radiotherapy treatment planning due to its highly complex data and lack of tools to produce information that can be accessed in an easy and flexible fashion.

Plotting MRSI data in connected views that enable relating metabolites with one another can enhance the understanding of this data. Furthermore, having a system which enables the comparison between MRSI data and other medical data opens the possibility to create more precise signatures of voxels from different characteristics present in each modality. Such a system has to meet certain requirements:

R1: Metabolic data should be easily accessed and visualized so users can study metabolic properties.

R2: A method to select and relate any given set of properties must be included to facilitate the process of analysis.

R3: Introduction of other medical data in order to gain more insights over tissue properties.

R4: Allow users to produce new values on the fly from the original data, using mathematical operations.

R5: Instant visual feedback of selected values in spatial views.

R6: Facilitate the introduction of MRSI visualization into current radiotherapy treatment protocols.

R7: Allow analysis and visualization of uncertainty present in MRSI data.

R8: Intuitive to use with straightforward interaction.

This work proposes an interactive prototype composed of a partnership between the visual analysis framework ComVis [7] and the medical image processing and visualization framework MITK [8]. This system enables MRSI data analysis and visualization together with other kinds of medical images which mitigates the challenges previously noted. By making use of ComVis' multiple views and brushes, together with the addition of minor plugins, we are able to provide physicians with a new way to investigate this data. In ComVis, data can be plotted and related according to the respective concentrations or intensities. As a main objective, accessing all the power of MRSI and allowing the understanding of relations between a wide range of medical images should be enabled by fast generation of new values and distribution of the multi-modal medical data across connected views. Through ComVis-MITK partnership, the system supports an interactive BTV finding process consisting of brushing values (Figures 1a and 1b), studying the possible relations and patterns (Fig. 1c), and instant rendering of generated BTV (Fig. 1d) in MITK.

Figures present in this paper illustrate the use-cases in Sections 6.1 to 6.5 that were developed respecting medical requirements. The MRSI quantified metabolites Creatine, Choline and N-Acetyl-Aspartate (NAA) are shown as these are the most well known metabolites for high grade tumour detection in brain cases. Choline is a marker of membrane cells so its increase reflects cellular proliferation. NAA is a marker of functional neurons, indicating healthy brain tissue and Creatine is a marker of cellular metabolism. The proposed system is not limited to MRSI data, or the radiotherapy field. Other areas of science working with multivariate and multivoxel data would also potentially be able to benefit. The contributions of this paper include:

- Integration of MRSI data analysis and visualization into RT treatment planning (supporting R6, R8).
- Promoting the introduction of Visual Analytics (VA) into clinical environment (supporting R1, R2, R5, R6, R7, R8).
- Allowing users to flexibly combine any dataset through ratios (supporting R4, R8).

- Automatic generation of BTV which is ready to export into radiotherapy dose planing systems (supporting R1, R5, R6, R8).
- Brushing method allowing uncertainty visualization (supporting R1, R2, R3, R7, R8).
- Allowing a better understanding of the characteristics of tissues by defining complex voxel signatures, allowing other clinical research such as studying the origin of patients' relapses (supporting R1, R4, R6).
- Individualization of MRSI analysis (supporting R1, R4, R6).
- Evaluation of use-cases gathering the opinion of expert users (supporting R6, R8).

2 Related Work

Analysis and visualization of MRSI data is a key issue to better understand the biological characteristics of tumours. Research in both topics has been active for several years, resulting in medical and visualization methods on which the basis of this work relies on.

2.1 Current Tools

Commercial software accompanying MR scanners like Syngo MR [9] and SpectroView (provided with the Intera Achieva 3.0 T MRI system) respectively, allow only the visualization of integral or ratio map over anatomical images. Other third party research tools are used to obtain more specific information or results, depending on the clinical case. Open-source tools for MRSI pre-processing and quantification, such as TARQUIN [10] and AQSES [11] suffer from the same visualization limitations as the two previously cited commercial tools. Also, the inspection of metabolites concentrations can only be done on a voxel-by-voxel basis, which does not allow a general inspection over the multiplicity of data present in MRSI. This results in medical staff having to judge each voxel by a single value at a time. Sivic [12] is an open source framework that processes and visualizes MRSI data with an overlayed anatomical image that can be a CE T1 or FLAIR. None of the mentioned tools allow any integration of spectroscopy values with manual contours. This means that assigning labels differentiating regions of the tumour and healthy tissues to spectroscopy voxels has to be done manually and in separated software packages, which makes the planning of radiotherapy a long and complicated process [13]. Details on the current workflow process are stated in section 3.

2.2 Studies and Systems Involving Multi-modal Medical Data

Analysis of complex medical data has been performed for many years. In one recent work [14], an effort to gain insight of neurodegenerative diseases was made by fusing information from structural, perfusion weighted, and diffusion-weighted MRI data. This study proved how observations of multivariate data enables the detection of anatomical brain changes that would not have been easily achieved by a univariate analysis.

A recent survey [15] focusing on segmentation and registration of MR images, lists several important missing points in medical imaging analysis and lack of powerful tools. For instance, current performance of automatic algorithms for segmentation and registration of brain and tumour areas is still to be investigated. Also, missing fusion of modalities limits the robustness of algorithms. It is pointed out that new MR-based data and integration of other modalities like PET have the potential to provide better prognostics by separating radiation necrosis from recurrent tumour. Finally, it is stated that individualized treatments for patients should be enhanced with personalized image-based modelling of the brain.

The majority of studies involving visualization of MR images focus on how to deliver a meaningful result considering the highly complex data and fusion of different modalities. A survey on current techniques [16] analyses and compares different approaches, in order to reach a guideline on how to visualize such data. One important point that was not taken in consideration is the fact that highly complex data, such as MRSI, is not well described in medical literature. There is a lack of profound studies on the relationship among metabolites and other types of data, making it an hazardous task to actually generate a meaningful visualization of metabolites and provide the respective correct information to users.

Visualization of multi parametric data for prostate cancer [17] fusing three modalities into difference maps and segmentations achieved good results in detecting treatment related changes. T2w MRI, MRSI and Diffusion Weighted Imaging markers are weighted to create these difference maps. Results show that this is more efficient in detecting changes in tissues between pre- and post-radiotherapy when a multivalued comparison approach is taken compared to an individual imaging markers approach. However, only Choline and Creatine metabolites were taken into account and only their ratio map was used, ignoring the relation to other metabolic markers. Also, there is no other way of comparing values in this work besides a visual inspection over multiplanar reconstruction.

An approach using VA in combination with automatic outliers detection and dimensionality reduction [18] was applied to identify and characterize spectroscopy data that corresponded to different brain tumour pathologies. The discoveries made by the authors raise the question for the possibility of using the complex characteristics of voxels for automated tumour detection.

In another work, brushing and linking techniques allowed exploration of breast perfusion data [19], which gathers information that characterize regional blood flow. Each voxel of this data is composed of a time-intensity curve depicting the enhancement of a contrast agent. Dimension reduction is achieved by correlation analysis and Principal Component Analysis, in order to achieve understanding of the relation between different parameters. On the account of data limitation, with only one dataset being used per patient, it becomes complicated to produce a correct distinction between very similar voxels. Our approach is similar to this one, however we allow multiple datasets with different configurations to be studied in ComVis and rendered in MITK.

Glaßer et al. [20] also proposed a VA approach to characterize and correctly localize malignant tissues in breast cancer with Dynamic Contrast-Enhanced MRI. Based on 4D feature vectors, similar characteristics among voxels were found and used to subdivide tumours into different regions. Visualization of data is made through linked views and rendering of glyphs and maps of a single dataset are also implemented. This approach granted a faster way to evaluate suspicious tumour by avoiding manual segmentations. Again, only single datasets were used to analyse properties of voxels, and all extra information was derived from the same dataset in no relation to other medical data.

Feng's work on visualization of MRSI data [21, 22, 23] provides both rendering and analysis of MRSI data and its uncertainty. Initially, by extending a 2D multivariate visualization technique, Feng used sphere sizes to map the expression level and colors to differentiate metabolites. These are then visualized together with gray-scaled anatomical images to help radiologists see spectroscopy values in the anatomical space. In his first work [23], he made use of complex visualization relating colors, thickness and roundness to each property of the metabolites glyphs displayed in a 3D scene where users had to perform MRSI value estimation and relationship identification with stereo goggles. Later, Feng was able to link his previous work of MRSI data visualization with parallel coordinates data plotting and a slice based visualization for accurate fit of MRSI data with anatomical images [21]. Feng's parallel coordinates were designed to incorporate brushing and uncertainty. Uncertainty is represented directly as Gaussian curves distributions along the different variables in parallel coordinates view. The creation of relationships between variables is allowed depicting a difference between two variables or a ratio calculation. Feng then enhances the visualization in parallel coordinates and scatter plots [22] by incorporating statistically modelled uncertainty. This visualization approach together with brushing generated good tumour segmentations.

However, no state of the art work presents a solution which enables

doctors to quickly access all the power of MRSI, by allowing the analysis of all its metabolites together with accompanying medical data. Generation of ratios, or other values, is never flexible enough to allow multiple combinations of data. The characteristics of voxels are still accessed as ratio values or metabolite concentrations, and never in combination of more metabolites concentrations or anatomical voxel intensities.

This work expands the current state of the art by enabling the comparison of any given dataset value with MRSI data. By making use of ComVis, we plot data in different linked views such as scatter plots or histograms. We introduce a range of brushes that help on better defining BTV and allows fast relationship analysis of MRSI metabolites and other molecular or anatomical data. We are able to effortlessly fuse any kind of data in ComVis to enhance analysis and we then support the visualization of segmentations representing the synchronized brushing of those values in a MITK plugin.

3 Clinical Workflow

Current workflow in the radiotherapy context of our partner, as show in Fig. 4a, is a tedious process. Preparation of RT treatment plan is usually done by gathering MR, MRSI and FLAIR images of the patient after surgery or biopsy and thorough co-registration of these data a is necessary step to define contours for irradiation. However, the analysis and visualization of gathered data are the tasks which take the majority of the time and which we focus upon.

Firstly, MRSI data is extracted through a meticulous pre-processing workflow including water subtraction, low-pass filtering, frequency-shift correction, baseline correction, phase correction and curve fitting in the frequency domain. Then, by using the Siemens Syngo MR B17 Spectroscopy application (Erlang, Germany), computation of ratio maps are performed. Throughout this process, each MRSI voxel is meticulously reviewed to assess for artifacts, poor signal-to-noise ratio, bad spectral resolution and other issues which may result in such voxels to be excluded. Out of each data slice, 8-bit RGB snapshots of metabolic ratio color maps are taken from co-registered MR anatomical images, which are later converted to hue-saturation-value colorspace. These are then normalized across the MRSI volume according to maximum values of metabolite ratios. Finally, segmentations are created to represent the thresholds of ratio maps. Usually, the threshold of Choline/NAA ratio (CNR) ≥ 2 is used. These thresholded areas are re-mapped onto the respective MR images with smooth linear interpolation, resulting in anatomic-metabolic images that can be fused with CT images and incorporated into the planning system. To achieve this incorporation of data, Brainlab iPlan RT image 3.0.1 software is used.

Secondly, for each patient, a number of regions of interest (ROIs) are manually delineated for spatial analysis from anatomical and metabolic data. In case of the MRSI field of view does not cover the anatomical region of interest, only the portion inside the MRSI data of the lesion is taken in for analysis. Next, the generated contours are linked to the planning CT-scan and exported as RTStruct files, which can later be loaded by dose painting software tools.

Finally, extracted contours from the RTStruct files are rasterized to voxels using a Python script for the spatial analysis. This is performed in two ways: volumetric comparison of pre-RT ratio maps with ROIs and a voxel-by-voxel evaluation of pre-RT metabolic abnormalities as predictors for local relapses. Each of this voxels gets classified as "positive" or "negative" either they are inside or outside the ROIs, respectively. All resulting information is then used for radiotherapy dose planning and other studies such as evaluating the probability of relapse in patients [24].

These tasks are spread over a number of software tools that are not compatible among themselves. Clearly the current process to incorporate information from MRSI data is far from being straight forward (Fig. 4a), making doctors use different software packages and scripts to combine and extract data. These tasks and respective challenges are tackled in our solution, resulting in a simpler and more flexible workflow (Fig. 4b). Section 4 explains decisions made over why our software system was built the way it was. Section 5 depicts how this system was implemented for users to test it with real-world RT data.

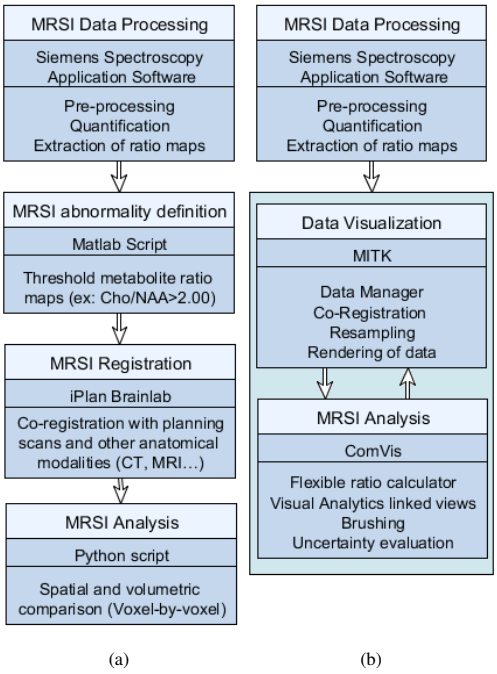


Fig. 4: Workflows of clinical partner (a) and ComVis-MITK (b).

4 System Design

Feng et al. [22] demonstrated the benefit of using VA tools and rendering of anatomical images with metabolic information. In addition, a study from our clinical partner used scatter plots showing advantages for better evaluating metabolic ratios [25]. VA grants users the opportunity to analyse a large number of variables in views depicting statistical and numerical information which are connected, giving visual and intuitive cues of how variables relate with themselves. However, it does not give spatial localization of voxels. Even though the rendering of multivariate datasets for a low number of components is giving its first steps [16, 26], the association of both approaches grants users to correctly analyse and locate MRSI data at the same time. For these reasons, we decided to use existing tools that would grant us management, visualization and VA methods for both anatomical and multivariate data, alternatively to develop a completely new system which is not the purpose of this work.

In order to overcome current challenges and respect the initial requirements, we made several decisions of what the envisioned system should include and how it should behave. For the selected tools, these must already been reported to the scientific community with proven utility and usability (requirement R8), to which we would have to make appropriate changes. To support requirement R1, metabolic values should be plotted in a way so users can intuitively understand the relationships between variables, through VA. From the wide range of possibilities given by VA, together with the users we decided to use 2D scatter plots, histograms and parallel coordinates. For the visualization of multivariate data such as MRSI data, this topic is still an open challenge, for which we decided to render metabolic maps and ratios as the users are accustomed to: red-green-blue colors to represent high-medium-low values in orthogonal views. These maps should be rendered together with accompanying anatomical data and delineations.

To solve requirement R2, the intuitive way of selecting values in VA views is to gather them inside user-defined regions. This is usually done by brushing around desired values. In this matter, the VA tool has to support brushing and be able to be easily extendable to support doctors' needs. Also, this tool should be able to support the handling of an undetermined number of medical datasets doctors would like

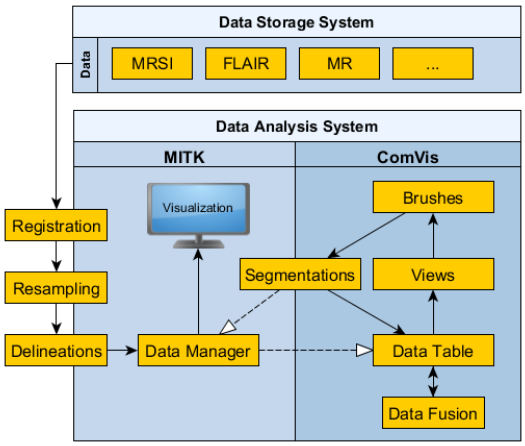


Fig. 5: Workflow of the ComVis-MITK system.

to evaluate (requirement R3). From these datasets, doctors need to derive information, which currently is very limited and inflexible in commercial tools, such as ratios between metabolites. We decided that our system must be able to instantly generates values for any desired combination of datasets (requirement R4). In that way, the system has to provide, at least, the generation of metabolite ratios, leaving to the user the responsibility of choosing which datasets to fuse.

The selection of values in the VA side of our system should be clearly visualized in anatomical context. In this way, any brushing technique or combination of brushes should be spatially identified though segmentations that can be instantly rendered on top of the orthogonal rendering (requirement R5). Furthermore, physicians want to be able to visualize and study uncertainties present in MRSI data (requirement R7), so our system has to support a mechanism that adds uncertainty to analysed data. Also, uncertainty values should be passed to the renderer so uncertainties of metabolites relationships can be spatially located.

After analysing the requirements and understanding the time and effort of implementing such solution, it was chosen the MITK framework to manage medical data and render the respective images, and ComVis to support us with the VA side of the envisioned system. Other VA systems could have been chosen, but the decision to use ComVis was determined by its availability and knowing that time and effort for implementations in it would be rather low, for it already covered the majority of the requirements associated with brushing and analysis of data. The combination of necessary implementations and functionalities should ultimately support the introduction of MRSI data analysis and visualization in RT treatment planning workflows (requirement R6). Also, general studies over MRSI data will be facilitated by making use of this system.

5 Implementation

ComVis and MITK were expanded and adapted to meet the requirements discussed in Section 4. Here, we start by introducing MITK and ComVis in Section 5.1 and the system's workflow in Section 5.2. Next, we state how information is exchanged between the two applications in Section 5.3. In Section 5.4, we specify how MITK is extended to answer the need for a multi-model rendering of radiotherapy planning inputs. Lastly, Sections 5.5, 5.6 and 5.7 refer to how ComVis was adapted to visualize and analyse multi-modal datasets in linked views.

5.1 MITK - ComVis System

MITK is a framework mainly designed for medical image processing. MITK includes basic VTK [27] rendering of datasets, multiple plugins to support a wide range of medical applications and provides a collection of widgets for fast user interface generation, allowing it to be extended with new plugins. The data manager in MITK is responsible for holding all datasets, and through its event system, changes in datasets are instantly reported to all running plugins.

ComVis is a tool for multi-purpose visualization of tabular and time dependent data. It includes a number of plugins that plot data in various statistical ways, allowing better understanding of highly complex data and its variables relationships. ComVis relies on tabular data which is stored in a data table, where each row represents an item and each column a property of the respective item. Each view is connected to the data table in order to query information in columns and generate the respective data plot visualization. Data is usually shown as plotted points, lines or bars and they can be selectively brushed in order to focus on certain properties of these items. Brushed data in one view also gets color painted in the other views, allowing an instant observation over related variables. A selection of brushes is present in ComVis and each view makes use of the necessary types of brushes. Histograms and parallel coordinate views only allow one-dimensional brushing to select data, but the 2D scatter plot employs other brushes allowing a two-dimensional brushing over the data. Synchronized brushes are organized as composite brushes giving users room to create several brushes that may or may not interfere among them. Combinations such as AND, OR, XOR and DIFF give liberty to how brushes should select data. An example of this interaction is Fig. 1 where multiple brushes of different colors and in different views, are depicted in all the other views.

5.2 System Workflow

The workflow of our system can be seen in Fig. 5. After images are acquired by scanners, they are processed and later stored in radiotherapy centres' Data Storage Systems. Images are retrieved from a Data Storage System and are registered to a common coordinate system. As shown in Fig. 5, registration can be done independently by using available commercial software or using MITK's registration plugin. Resampling is performed if images have different resolutions or dimensions. This can also be done by third party software packages or MITK plugins. Likewise, delineations of regions of interest can be done either inside or outside MITK.

MRSI data format is not interpreted by MITK, so we decided MRSI metabolites values would be separeted in a pre-processing step to single values 3D datasets compatible with MITK. Then, all pre-processed data is loaded into MITK's Data Manager and can immediately be visualized. MITK is responsible for interpreting and sending the data to ComVis via socket communication in its own format. ComVis places each image voxel in a row and fills the respective columns with metabolites concentrations and other modalities' intensities. Next, by selecting a view and choosing which values to plot, users can instantly gain access to statistics and relations between different characteristics of the data. Since datasets transmitted into the data table of ComVis are resampled to a common grid, each voxel can be associated to a long list of values.

As long as ComVis is connected to MITK, brushed data is sent back to the latter as segmentations (Section 5.3). Because of how the MITK data manager is implemented, any changes detected in datasets causes the whole framework to update its running plugins. This results in interactive visualization of brushing voxels in ComVis. It is also possible to generate values on the fly by assessing a data table's columns values and applying a combination of these. This enables fusion on data level by combining different datasets together in user defined ways. During the entire process, users can change what is being rendered in MITK, by enabling or disabling datasets, changing transfer functions or segmentations' colors or adding multiple side-by-side rendering windows with different appearances of datasets (Section 5.4).

5.3 Data Exchange

To realize the envisioned system, MITK and ComVis have been linked together via a TCP/IP socket connection. Both halves of the system were upgraded with plugins supporting this link for data exchange. A MITK plugin specifically developed for this is responsible for creating the socket server and translating medical data into a ComVis format.

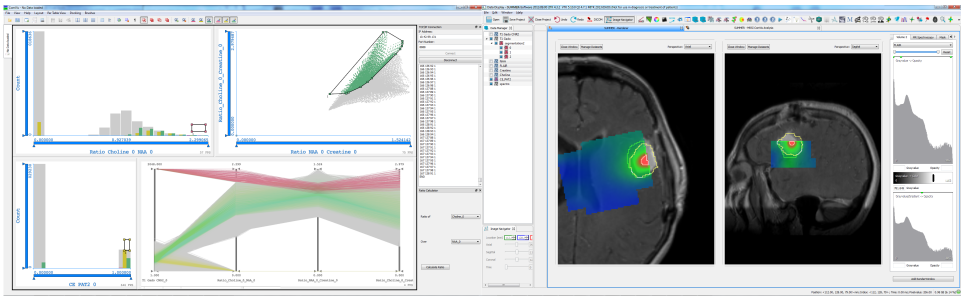


Fig. 6: Screen-shot of our system: ComVis (Left) and MITK (Right) running side-by-side in dual screen.

This plugin is also responsible for creating and maintaining segmentations sent from ComVis in MITK's data manager. When receiving new data, the socket plugin updates the correspondent mask's values in the data manager.

On the other side, the communication plugin interprets the received information and populates its data table with voxels' position indexes and respective values of datasets for each column. Later, ComVis transmits any change of brushed voxels by sending a message with a segmentation identifier, the 3D index position of each selected voxel and a smoothness value (Section 5.7) associated to each voxel. ComVis can be updated with more columns/datasets sent by MITK at any given time.

5.4 Visualization Module

We have developed a plugin for MITK providing multi-modality rendering to answer the need of visualizing BTV and metabolite ratio data together with related datasets. Our plugin (Fig. 6 right) is built using transfer functions, render windows, color palettes and other minor user interface implementations. We allow modifying ratio color maps by manually setting red, blue and green respectively to maximum, minimum and median values, helping users differentiate higher or lower ratios of metabolites. Segmentations can be visualized with any desired color.

Since MITK uses VTK for rendering, we implemented a VTK interface for our multi-modal renderer backend, so we could include it in the MITK rendering pipeline. The backend is implemented in CUDA [28] which holds a storage structure where multiple datasets are stored and later accessed during rendering.

For the actual rendering of images, a kernel designed to access data and perform the necessary operations to produce an orthogonal image (axial, sagittal or coronal) also runs in the backend. To produce the images shown in this work, we use a data fusion algorithm based on linear combinations. We render anatomical images together with an on-demand ratio map generator and segmentations masks containing probability values ranging between 0 and 1. First, anatomical images are fused using the arithmetic mean of the intensity values. Then, ratio maps are calculated and color painted in the following manner: two scalar values corresponding to the two given metabolites in the same 3D position, are subject to a ratio calculation. Next, the obtained value is colored according to the minimum, medium and maximum values passed by the user in the plugin's user interface. Simultaneous rendering of diverse ratio maps was not a requirement, but its implementation could be achieved by inserting a fusion algorithm step at this point. The fused anatomical images are then combined with the ratio color map, based on linear combination. This linear fusion is set to 30%-70% weight, respectively, giving more emphasis to the ratio map. Lastly, segmentations are generated out of the masks obtained from ComVis. These are shown as lines or as fading areas, depending on if the mask is set as maximum probability or as a value between 1 and 0, respectively. When two or more segmentations overlap, they get depicted in white. Fig. 1d is an example of all datasets being rendered together.

5.5 Analysis Module

We extended ComVis with new types of brushes giving room to explore specific use-cases desired by the clinical staff (Section 6). Triangle, polygonal, convex hull brushes generation and smooth brushing were added to ComVis 2D scatter plot's view. A triangle brush holds 3 handles and can be designed in any fashion as format of triangles goes. Polygonal brushes allow the creation of brushes with three or more handles, allowing the creation of complex geometrical compositions. It is possible to create a convex hull (which translates as a polygonal brush) from brushed voxels in other views (Fig. 9). Advantages of this functionality are described in Section 6.2. Smooth brushing was also added to box, triangle and circle brushes (Section 5.7). Another functionality added to ComVis is the calculation of new values by applying mathematical operations to data already present in ComVis's data table. Section 5.6 is a clear example of how this simple functionality positively impacts the system.

5.6 On-the-fly Fusion of Datasets

Absolute metabolite concentrations are difficult to calculate from MRSI, largely due to variations in measurement sensitivity across the volume. This means that signals from different voxels will be subject to an arbitrary scaling factor. The standard solution to this problem is to take ratios of the metabolite values, to cancel out this scaling factor.

Rather than requiring that these ratio values are precomputed before loading the data, we added support within ComVis to directly calculate the ratio between two existing columns as a new value in the existing data table. This gives users more flexibility to choose which ratios users are interested in, and reduces the amount of data which needs to be transferred back and forth.

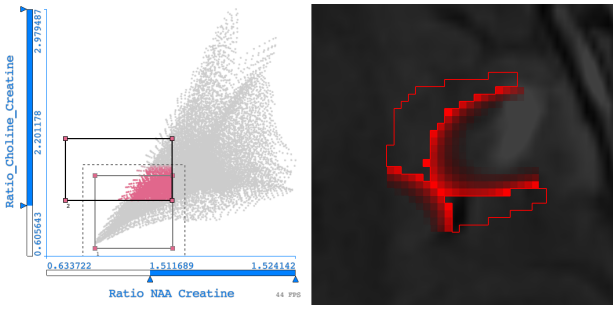
5.7 Smooth Brushing

In order to allow users to assess values of uncertainty depicted by neighbouring voxels present in the vicinity of brushes in scatter plot views, we decided to extend the range of the brushes by drawing an area around the selected brush. Voxels contained inside this new area are awarded a probability between 1 and 0, depending on the distance between the brush line and the smoothness line. The closer a point is to the brush, the higher is the probability. Naturally, voxels inside brushes are awarded probability 1 and voxels outside both regions have a probability of 0 as they are not selected. We are applying fuzzy set theory [29] to calculate sets of overlapping fuzzy brushes: if a AND operation relates the brushes, then the minimum probability is chosen, but if an OR operation is set, then the maximum probability is picked.

The interpretation of voxel probabilities help with the visualization of uncertainty in medical data. Voxels inside a smoothed region are color painted in the respective segmentation color, with an opacity equal to the respective probability value, originating a fading effect in our renderer (Fig. 7). This margin of probabilities around a segmentation can help expert users to visualize voxels which have similar signatures to the ones inside the original brush.

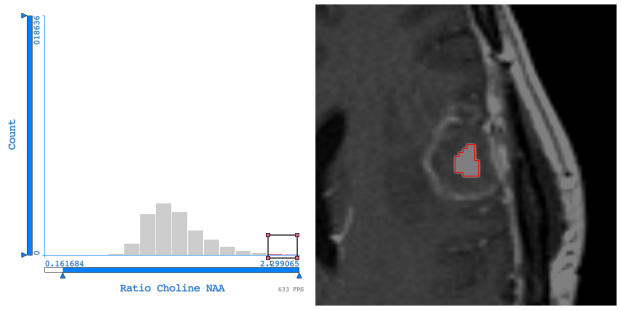
6 Evaluation

For evaluating our solution, five experienced medical doctors and physicists from a public cancer hospital were using our system on



(a) (b)

Fig. 7: Smooth brushing in ComVis (a) and respective visualization in MITK (red contour with different intensity related to membership probability) (b).



(a) (b)

Fig. 8: Brushed values of CNR in a histogram (a) and its visualization in MITK red contour matches perfectly the currently used method (b).

data of six patients from a multi-centre phase III clinical trial called Spectro-Glio. This trial uses the metabolite ratio CNR, thresholded at 2, to guide an integrated radiotherapy dose boost in patients with GBM. Their current workflow is both inflexible and time-consuming, making it difficult to keep up with the arrival of new patient data.

During this evaluation we used CE T1 Gadolinium, FLAIR and 1H MRSI with a weighted, elliptically sampled, $10 \times 10 \times 8$ 3D CSI grid and PRESS for localised excitation. The MRSI acquisition time is 512 ms with a dwell time of 1 ms, and a long echo time of 135 ms is used to suppress the macromolecular baseline. Hardware water suppression is performed with the CHESS sequence and additional spatial saturation bands are used to suppress out-of-volume lipid signals. All acquisitions are done on Siemens 1.5 T scanners. The raw MRSI data is upsampled to $16 \times 16 \times 10$ and then each voxel is automatically processed individually. Further software water suppression is performed, then the data is filtered to improve the signal to noise ratio, zero-filled to improve the spectral resolution and Fourier transformed to the spectral domain. Frequency and phase errors are corrected and any residual baseline removed, then finally the signal peaks are integrated to arrive at concentration estimates for each metabolite. For this trial the metabolites Choline, Creatine and NAA are quantified. Once automatic processing is complete each voxel is manually examined to check for artefacts or processing errors which may require the voxel to be discarded. To allow its loading into MITK, metabolites were separately processed into single scalar volumes. There was no need of registering datasets as they are already aligned during acquisition. Volumes were resampled inside MITK to the respective T1 Gadolinium dataset. A delineation of a volume of interest was made around each patient's tumour tissue, which bounded the amount of data sent to ComVis.

While closely working with the users, five use-cases were developed and are presented in Sections 6.1 to 6.5. These five use-cases demonstrate how we allow an interactive analysis of MRSI Brain together with other MRI and CE datasets. Each section reports the respective user feedback from the five clinical specialists who explored the possibilities offered by our system at their radiotherapy centre. All tasks were performed in the same machine.

6.1 Analysis and BTV computation

In the work environment of our collaborators, with their currently available commercial software, the only way to obtain correctly registered MRSI data is to generate a color map of the CNR, which is then fused to the co-registered anatomical images. This must then be manually exported as color images slice by slice. Once the complete volume is exported, a MATLAB script is used to recompute the CNR value at each voxel, which is then thresholded at 2.0, then a greyscale DICOM series is generated with the thresholded CNR region embedded in the anatomical scan. This DICOM is then imported into the contouring software, where it can be registered to other modalities using the anatomical component of the image and the BTV is manually contoured using the CNR threshold component. Working from already quantified MRSI values, this process to generate the BTV takes around 100 minutes.

Using our system, the MRSI data may be imported directly into MITK in the coordinate system of the companion MRI and the data shared with ComVis. The CNR data column is calculated inside ComVis and displayed as a histogram, then simply by brushing the histogram above the desired threshold (2.0 in this case) the correct BTV contour is generated inside MITK, ready for export to the dose calculation software. Fig. 8 shows an example of the resulting contour, superimposed on the thresholded DICOM series produced by the current method for comparison. The time taken to generate the BTV in our system is around 2 minutes, representing an enormous reduction in time required for this essential step in the workflow.

Although our user panel were extremely pleased at the reduction in their data processing burden for the clinical trial, their primary interest in our tool was to explore more complicated relationships in the MRSI data. They told us "with our current software we can only see the MRSI data as a color map, but with MITK and ComVis we can visualize all the different aspects of the data simultaneously, and see the numerical values too". Working with these medical experts, we have enhanced our system to support several new use-cases for MRSI data which they have already developed, and some of these will be presented in the next sections.

6.2 Tumour Signature

The system allows users to easily delineate, for example, the enhancing region on a post contrast T1 MRI image in MITK, and immediately see in ComVis which other values from other modalities are present in that region. Examining the relevant MRSI data views for those voxels in ComVis will show how the voxels are grouped, defining a metabolic "signature" indicative of the tumour voxels. Brushing around this region, or using the automatic convex hull tool, will select the other regions which are not contrast enhancing, but which share the metabolic properties of the voxels which are in their vicinity. An example of this can be seen in Fig. 9.

The anatomical region which is generated by this technique can be validated using previously acquired data from patients who have subsequently relapsed. In this case the manually delineated contrast enhancement which is visible after the patient has relapsed can be compared to the ComVis BTV to evaluate whether this volume is more predictive of future disease than other biomarkers. Such evaluation will be realized in the future during a medical study involving a large number of patients who will clearly present site of relapse on radiological point of view .

By combining different linked views and synchronized brushes in ComVis, expert users were allowed to take measurements of different tissues for each patient, in a very short period of time, where it was confirmed that each patient has their own set of metabolite ratios values. This helped redefining the BTV by adapting ComVis brushes to these new ratio values. With this in mind, we can say that the intro-

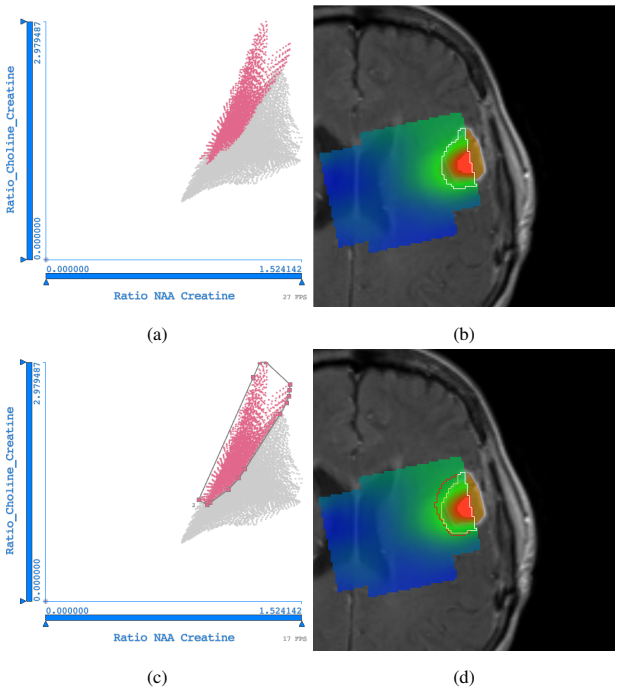


Fig. 9: Brushed values from a CE T1 segmentation of tumour tissue and respective colored values in a scatter plot relating Choline/Creatine and NAA/Creatine ratios (a). Rendering of both ComVis generated and CE T1 overlapping segmentations in white in Axial view (b). Generation of convex hull around previously selected values (c) depicting the selection of extra voxels and render of updated ComVis segmentation, in red, including newly selected voxels (d). MR T1 in gray values and FLAIR showing infiltration in orange.

duction of individualized treatments with MRSI metabolites in radiotherapy treatment planning has been facilitated with this work. Furthermore, users regarded as one of the most powerful features in our system the ease of interaction between the anatomical and functional image data (mainly displayed in MITK) and the metabolic MRSI data (mainly shown in ComVis).

6.3 Personalised Analysis

Although in most cases MRSI analysis focuses on fixed ratio thresholds for simplicity, it has already been demonstrated that there is a large degree of variation in healthy tissue properties between subjects, and values which might be considered anomalous for one patient are entirely normal for another. In Fig. 10, it is possible to compare the variety of distributions presented by different patients, which points for the necessity of having a personalised analysis when evaluating MRSI data in RT planning.

Expanding the concept of the previous section, in MITK it is also possible to draw additional contours using the anatomical reference images, for example to delineate the oedema, necrosis and "healthy tissue" (ideally taken from the contralateral hemisphere). The regions and extents of these anatomical regions can be examined in ComVis and the statistical distributions of each class of tissue compared. This will allow a much clearer determination of what constitutes "anomalous" spectral properties.

Allowing a detailed study of tumour and healthy tissue from each patient by creating and relating values from a multiplicity of datasets was noted as one of the major contributions of this work.

6.4 Tissue classification

The anatomically delineated contours described in section 6.3 provide labels for certain regions of metabolite space. By combining these regions with smooth brushes, the voxels in between these regions can

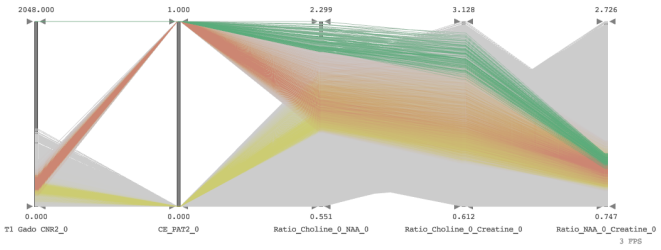


Fig. 11: Parallel coordinates in ComVis displaying the relations between different datasets: Voxels T1 Gadolinium with manual threshold of $CNR \geq 2$ correctly correspond to CE in green in the second axis, and respectively higher values of CNR in the third axis. The three colored sets of lines create a visual pattern between ratios on the three last axes. Color painted lines correspond to brushes from Fig. 1.

also be assigned a probability of membership for each region. For example the probability that a voxel should be classified as either healthy tissue or tumour can be computed. These probabilities can then be compared with the relapse volumes as described in section 6.2.

Users forecast this to be a first step to allow the creation of models for automatic cancer detection according to voxels' signatures. This conclusion goes in line with what has been previously reported [18].

6.5 Longitudinal Studies

In parallel coordinates views, for each axis a variable is plotted and enables visualization of relations between selected variables. Parallel Coordinates allows the comparison between metabolites concentrations, metabolite ratios and other data such as CE or anatomical images. Since every view is connected, it is possible to instantly realize which variables are in relation when a certain range of values are selected in a parallel coordinate axis (Fig. 11).

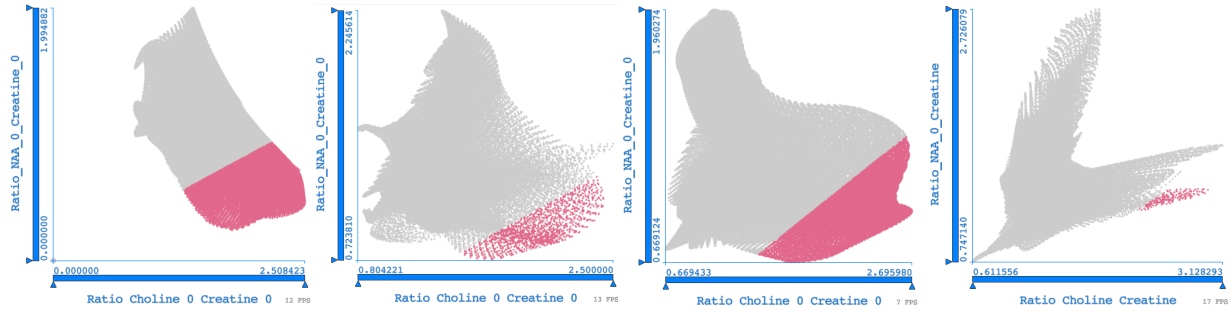
One relevant use-case for the use of parallel coordinates is the opportunity to longitudinally compare a given ratio across different exams. Given that the images are aligned and correctly resampled, it is possible to follow the evolution of ratio concentrations after treatment. Studying MRSI data of relapsing patients across different exams has the power to enlighten the behaviour of metabolite ratios after radiotherapy. By tracking lines of the parallel coordinates plot (which corresponds to spatial voxels) it is possible to register if metabolite ratios drop, rise or remain stable over the different follow-up time points.

It was noted by the expert users that such analysis with many patients' data opens up the possibility to better understand the different imaging biomarkers evolution and changing in order to predict the tumour mechanism of relapse. To validate this theory, a medical study with a large number of patients' data is scheduled (22 patients).

7 Discussion

Extensions implemented in ComVis and MITK were closely accompanied by clinical staff in order to detect changes in the requirements. Discussion with physicians lead to the development of five use-cases that would enhance their workflow and understanding of MRSI data. The system was tested by these users with real-world medical data from six patients, leading to an evaluation of how well our system respected initial requirements. During the evaluation with expert users, we noted the time using our MITK plugin was lower compared to the time spent in ComVis analysing and brushing metabolites' values. This is due to the fact that analysing data in ComVis brings much more meaning to such complex data compared to approaches on pure complex visualizations of the same data in a multiplanar reconstruction view. Expert users obtained much better information from this kind of approach, for the quantity of information being rendered usually results in clutter of information.

In one patient, it was possible to observe an interesting feature related to metabolic concentrations behaviour around vessels and ventricles. Because of its activity, voxels around these structures present



(a) (b) (c) (d)

Fig. 10: Scatter plots with different Choline/Creatine and NAA/Creatine ratios distributions from four patients with $CNR \geq 2$ brushed, in red.

metabolic values similar to the ones labelled as cancer (Fig. 12). Experts know that these situations can occur and BTV have to be manually adapted using this prior knowledge. What expert users were able to do with our system was to easily separate tumour tissue from these distant regions using ComVis brushes.

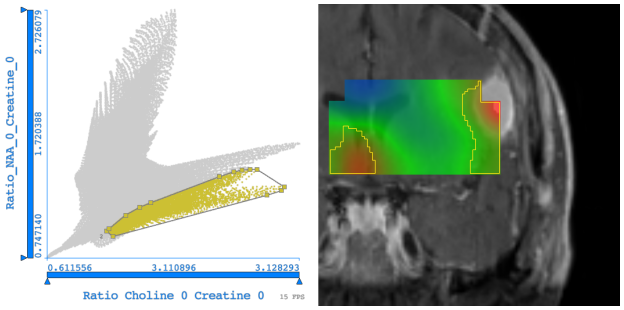
Negative aspects of how this system was implemented includes the necessity of using two independent software tools which contributes to an unsatisfying user experience (requirement R8) in single monitor machines. Ideally, the development of a VA plugin for MITK could contribute to a smoother and faster workflow, including better memory management for the reason that loading data into ComVis is merely a replication of data in memory.

Our system was able to change our clinical partner's workflow by speeding up the process of analysing metabolites and introducing flexibility in creating ratios. Fig. 4 depicts how the workflow changed, introducing a two way communication between the VA tool and MITK. Through the use of VA, MRSI data analysis and visualization together with other medical data can be straightforwardly achieved. Also, calculating metabolites ratios can be instantly done and plotted in VA linked views for further studies, such as understanding that different patients present different metabolites characteristics. Achieving a correct BTV is done in proximately 2 minutes as stated in Section 6.1. Furthermore, VA methods allow physicians to gain access to new ways of understanding medical data, bringing individualized treatment of patients closer to reality. Even thought requirement R8 was not totally met, we can state that all other requirements were met.

Expert users expressed a very positive opinion of this work with special focus on the possibility of fusing values on the fly, the opportunity of studying voxels' signatures in depth and the fast and better delineation of BTV with the help of convex hull generation over CE segmentations. They foresee a fast growing understanding of MRSI data in the radiotherapy field by using systems like the one presented in this work. It was also agreed that our system has the power to accelerate the treatment workflow for GBM cases.

8 Conclusion and Future Work

To answer the need for better understanding magnetic resonance spectroscopy imaging found in the radiotherapy field, this paper presented a system to enhance the analysis of such data. This was achieved by connecting the medical imaging framework MITK to the general purpose data exploration and visualization tool ComVis. Regarded as the key benefit of our system, we provide medical staff with the opportunity to analyse, relate and visualize MRSI data together with already studied multi-modality images in a new light. Linking both applications answers the current medical requirements, bringing, in one case, the same results obtained with current commercial software but in a much shorter time. We described real-world medical cases of how this system can introduce flexibility and novelty in future radiology MRSI studies by permitting the discovery of new MRSI metabolites' relationships and tumour tissues' signatures. The feedback received by expert users motivates us to introduce new functionalities and to investigate the impact of this system with other kinds of data and even



(a) (b)

Fig. 12: A case where brushing the voxel signature relating Choline/Creatine and NAA/Creatine similar to the CE area initially drawn by the user (a) selects a region with no detectable tumour corresponding to high activity near vessels and ventricles located in the middle of the brain (b). Image rendered composed of T1 Gado, FLAIR, ratio map and one segmentation.

in other scientific fields facing similar challenges.

Regarding future work, it is planned to extend the on the fly generation of values functionality (Section 5.6) to create a list of mathematical relation between datasets' voxel values. An example of this could be the computation of a ratio between the sum of two metabolites with a third metabolite. For the purpose of this work, and limited literature about more complex relationships among metabolites in GBM cases, we decided to leave the implementation of more complex computations for future work while respecting medical requirements. Another point we envision with great potential in better defining radiotherapy target volumes is the introduction of other modalities. fMRI brings information about functional areas of the brain which could impose adaptations in the planning treatment. PET and other multi-modality data can improve the quality of voxels' signatures (Section 6.2) by granting even more information to tumour localization and activity. Since our rendering system is flexible and may be extended to support more datasets as well as other visualization and fusion algorithms, the integration of more datasets should be easily achieved. Finally, a study gathering 22 patients' data who registered relapses is scheduled. It is our intention to perform an extensive evaluation of this system by reporting on medical findings, usefulness of this system and future implemented features both in ComVis and in our MITK plugin.

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