DELTAMap: A web enabled multi-parameter-multi-time-point analysis tool for imaging biomarker discovery

Chandan Kumar Aladahalli[1], Dattesh D Shanbhag[2], Venkata Veerendranadh Chebrolu[2], Patrice Hervo[3], Sandeep N Gupta[4], and Rakesh Mullick[5]

[1]Biomedical Signal Analysis Laboratory, GE Global Research, Bangalore, Karnataka, India, [2]Medical Image Analysis Laboratory, GE Global Research, Bangalore, Karnataka, India, [3]GEHC, Buc, France, [4]Clinical Systems and Signal Processing, GE Global Research, Niskayuna, NY, India, [5]Diagnostics & Biomedical Technologies, GE Global Research, Bangalore, Karnataka, India

Introduction: Disease, its progression and treatment response is increasingly being assessed using multi-parametric biomarkers obtained from different modalities [1]. Some of the biomarkers (such as RECIST in oncology, perfusion-diffusion mismatch in stroke, SUV from PET imaging) are well established and in use clinically [2, 3]; while newer ones are being continuously discovered by researchers (PERSIST to incorporate dynamic and functional information, DEFUSE criteria in stroke). Clinicians (which includes: pathologist, oncologist, radiologist, radiation planning, surgeon) face challenges in accessing, visualizing and collaborating on the multi-parametric data. The specific tasks which can be cumbersome include: **a**. Registration of the multi-parameter volumes, **b.** marking out parameter ranges of interest, **c.** manually combining the parameters to generate the established / promising biomarkers, and **d.** visualization over time of aggregate statistics corresponding to the integrated biomarker. Previously, software applications were presented for registration, segmentation and visualization of oncology data across time-points [4, 5, 6]. These approaches were primarily based on dedicated workstations and therefore reduce mobility of data visualization and subsequent analytics or guidance for planning management of diseases. To address these limitations, we have conceptualized and are currently building a web-enabled tool to allow generic collaborative exploration of longitudinal multi-parameter data for disease assessment. The tool allows clinicians to quickly apply existing biomarkers definitions using prior data and offers pre-set visualization templates for broad based diagnostics and therapeutic evaluation of longitudinal studies.

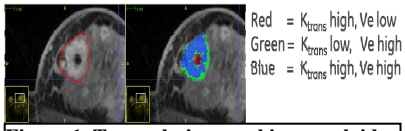

Figure 1. Tumor lesion marking overlaid on DCE data. The K_{trans} and Ve regions merged using their thresholds & can indicate tissue functional information.

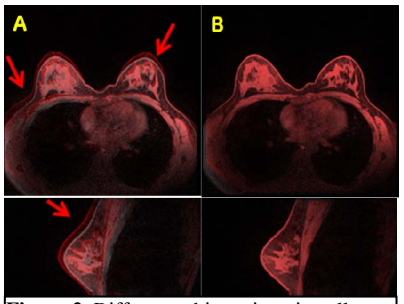

Figure 2. Diffeomorphic registration allows for anatomy variations to be captured across visits (A: Before, B. after NRR)

Methods and Materials: ***Patient Data:*** The data presented was obtained from the Quantitative Imaging Network (*QIN-BREAST DCE Challenge*) [7, 8]. We used multi-time point data from four patient cases (QIN-Breast-DCE-MRI-BC01 – Non responder, QIN-Breast-DCE-MRI-BC05-complete responder, QIN-Breast-DCE-MRI-BC15-complete responder, QIN-Breast-DCE-MRI-BC16-partial responder) from the available challenge data. The AIM challenge data also identified the tumor regions (i.e. mask provided), both before and after treatment. ***DCE data analysis:*** The entire analysis was performed using completely automated in-house tool developed for DCE analysis within the ITK framework [7, 9]. The data were analyzed using the methodology (AIF, T1) provided in [7] to obtain area under curve (AUC), max-slope , and three parameter Tofts' parameter (**fPV**, $\mathbf{K_{trans}}$ and $\mathbf{V_e}$). ***Registration:*** The multi treatment data were registered to the baseline volume using 3D symmetric diffeomorphic based non-rigid registration (NRR) scheme [10, 11]. Before the NRR, data were normalized for intensity variations using N4 algorithm available in ITK [8].The diffeomorphic transforms were also applied on the mask. The use of symmetric diffeomorphic transform guarantees invertibility and allows bidirectional navigation. ***Multi-parameter-multi-time-point analysis:*** An in-house web based tool developed allows user to load multiple volumes of different parameters at different time points. For example, as a representative case, we choose QIN-Breast-DCE-MRI-BC01 pK data (K_{trans} and Ve). Next we choose to mark the areas of high/low K_{trans} and high/low Ve using their histograms within in a lesion at baseline. ***Statistical Analysis of biomarkers***: Aggregate statistics of any of the loaded parameters can be visualized by the user using standard visualization techniques which include bar charts, spider charts, and histograms. A novel polar chart is also introduced where multiple parameters are plotted in the angular direction and the radial direction shows the progression of the parameters in time. ***Visualization:*** The biomarkers created above can be assigned colors chosen by the user and displayed one or more of the loaded volumes. They are preferably visualized on volume containing structural information. Multiple biomarkers can be added as masks to the volume which can then be turned on/off by the user. This allows for quick estimation of the tumor/pathology response to treatment.

Results and Discussion: Figure 1 shows the multi-parametric data with areas marked based on their thresholds in K_{trans} and Ve maps. Since high K_{trans} can be indicative of contrast/vascular leakage and low Ve of aggressiveness of tumors, this can be used to ascertain the vascular or angiogenesis status of the underlying tissue (benign, malignant, and normal). Figure 2 demonstrates the effectiveness of non-rigid registration algorithms in allowing seamless navigation over longitudinal data. This allows for regions of interest (ROIs) to be transferred across longitudinal datasets for studying the change in morphological and functional parameters Figure 3 gives a sample snapshot of how the progression of the disease can be easily visualized, both for individual time–points as well as for any time-point in longitudinal series to be tracked over other time-points. (For e.g. baseline over following treatment cycles or second time-point over all other first to last treatment cycle). For e.g, for the case BC15 (complete responder) was similarly identified based on imaging parameters: reduced K_{trans} and increase in Ve over treatment cycle (Figure 3). Similarly patient BC-01 (non-responder) could also be deduced from increase in Ktrans and decrease in Ve data over time. The advantage of the current tool is that this status can be immediately ascertained visually without need for scrolling through huge volume of multi-parametric data, thus simplifying the lesion management workflow. Figure 4 shows the snapshot of the tool we have developed that allows for manipulation and visualization of multi-parameter-multi-time-point data without being tied to a particular modality, pathology or biomarker. The tool is generic enough to aid in new biomarker discovery by allowing users to track their own parameters that they find interesting and useful. At the same time the tool can be used by clinicians to quickly apply existing biomarkers for quick estimation of treatment response.

Acknowledgement: The breast DCE-MRI data were collected at Oregon Health & Science University with the support of NCI Quantitative Imaging Network consortium grant (U01 CA154602).

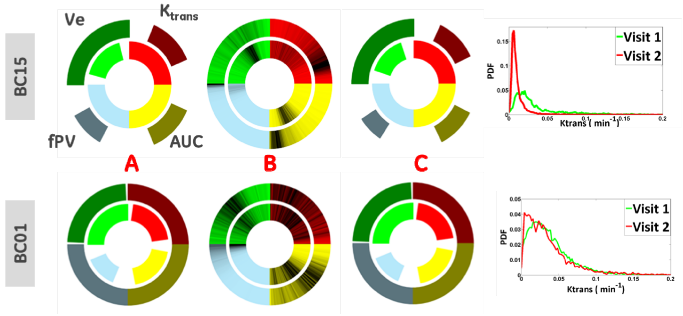

Figure 3. Polar charts depicting four DCE parameters in four sectors (K_{trans}, Ve, fPV, AUC from top-right) and the ***longitudinal progression are arranged radially outwards***. **A.** The individual parameters within the tumor mask for each visit are depicted and indicate the change over time. For..eg. Ktrans has changed more in patient BC-15, compare to patient BC-01**. B.** The histogram spread for each parameter within the respective visit tumor mask. It quickly indicates the heterogeneity of tumor K_{trans} in BC01 (non-responder) compared to BC15 (complete responder) **C.** Same as A, but tumor mask at baseline is followed for the longitudinal series.

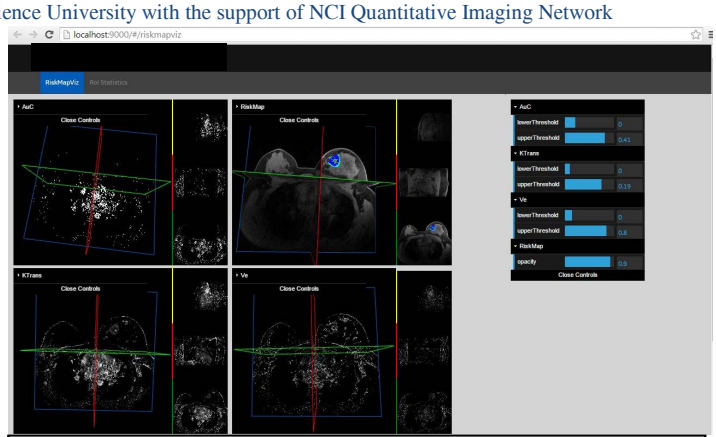

Figure 4. A snapshot of the web-enabled tool for longitudinal data analysis

References:

[1]. Phys Med Biol. 2010; 55(9): **[2].** Stroke 2005;36;980-985, **[3].** Semin Oncol. 2011; 38(1): **[4].** Proc Natl Acad Sci USA 102, 5524 – 5529;2005. **[5].** Int J CARS (2007) 1:231–242 **[6].** ESMRMB 2009 , e-poster no. 280 **[7].** Transl Oncol. ,2014 pp. 7(1): 153–166 **[8].** J, Transl Oncol. 2014; 7(1): 147–152 **[9].** http://www.itk.org **[10].** Penn Img Comp and Sci Lab. 2009.**[11]** Neuroimage 2009;46(3):786–802.