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Brain Cancer Imaging Phenomics Toolkit (brain-CaPTk): An Interactive Platform for Quantitative Analysis of Glioblastoma

Saima Rathore, **Spyridon Bakas**, **Sarthak Pati**, **Hamed Akbari**, **Ratheesh Kalarot**, **Patmaa Sridharan**, **Martin Rozycki**, **Mark Bergman**, **Birkan Tunc**, **Ragini Verma**, **Michel Bilello**, and **Christos Davatzikos**

Department of Radiology, Perelman School of Medicine, Center for Biomedical Image Computing and Analytics (CBICA), University of Pennsylvania, Philadelphia, PA, USA

Abstract

Quantitative research, especially in the field of radio(geno)mics, has helped us understand fundamental mechanisms of neurologic diseases. Such research is integrally based on advanced algorithms to derive extensive radiomic features and integrate them into diagnostic and predictive models. To exploit the benefit of such complex algorithms, their swift translation into clinical practice is required, currently hindered by their complicated nature. brain-CaPTk is a modular platform, with components spanning across image processing, segmentation, feature extraction, and machine learning, that facilitates such translation, enabling quantitative analyses without requiring substantial computational background. Thus, brain-CaPTk can be seamlessly integrated into the typical quantification, analysis and reporting workflow of a radiologist, underscoring its clinical potential. This paper describes currently available components of brain-CaPTk and example results from their application in glioblastoma.

Keywords

Glioblastoma; Open-source software; Radiomics Radiogenomics; Computational algorithms; Image analysis; Fiber tracking

1 Introduction

Quantitative computational research has helped us gain a comprehensive understanding of fundamental mechanisms of neurologic diseases, while providing substantive insight into the biological basis of disease susceptibility and treatment response, as well as potentially leading to the identification of new therapeutic targets. During the last decade there is mounting evidence that clinically acquired radiographic imaging can reveal visual (e.g., intensity, extent) and sub-visual (e.g., morphologic, textural, kinetic) features, which when integrated via advanced computational methods can identify *in vivo* imaging signatures of clinical outcomes, as well as of underlying tumor molecular characteristics (radiogenomic signatures) [1–10]. However, despite their widespread applicability in the scientific research community and the promising findings obtained with them, the increasingly complicated

Correspondence to: Saima Rathore.

nature of advanced computational algorithms limits their accessibility in routine clinical practice. Thus, there is a rising need for relatively easy-to-use software tools that can assist the translation of such algorithms in the clinical setting. Towards this end, we present brain-Cancer imaging Phenomics Toolkit (brain-CaPTk – www.med.upenn.edu/sbia/captk.html), which can provide a bridge for quick and efficient translation between academic image analysis research and clinical application, thereby enabling translation of cutting-edge academic research into clinically practical tools.

brain-CaPTk aims to derive extensively comprehensive sets of quantitative radiomic features and integrate them via advanced multivariate machine learning methods towards providing related neuroimaging biomarkers for integrative precision diagnosis and prediction of clinical outcome, while being seamlessly integrated into the typical quantification, analysis and reporting workflow of a radiologist, underscoring its clinical potential. Existing tools offering computational algorithms have not been designed to target specific diseases [11–14] and are neither modularized nor offer specialized analysis tools [12–14]. Although the rest of this paper focuses on example applications of brain-CaPTk in glioblastoma, its incorporated components can be applied in most neurological diseases, such as meningioma, multiple sclerosis, stroke, and trauma brain injuries, with the intention of linking quantitative imaging signatures with clinical outcome and molecular characteristics.

2 Platform and Components

The hereby presented platform, brain-CaPTk, leverages well-established open-source libraries, such as the Insight ToolKit (ITK), Visualization ToolKit (VTK) and OpenCV, to perform the data input/output, preprocessing tasks, rendering and machine learning. The advantage of using these well-established community- and industry-driven software libraries is their optimized algorithmic environment, allowing for further extension, interoperability and cross-platform usability. The overall design of brain-CaPTk is adaptable, allowing for packages developed using ITK and OpenCV to be incorporated within brain-CaPTk with minimal effort, thereby providing to imaging researchers a ready-to-use graphical front-end for their computational algorithms.

Although, brain-CaPTk is a dynamically growing software platform and can consider any anatomical site and image type, it currently focuses on analyzing multimodal Magnetic Resonance Imaging (MRI), such as native (T1) and contrast-enhanced T1-weighted (T1-Gd), T2-weighted (T2), T2 Fluid Attenuated Inversion Recovery (T2-FLAIR), Diffusion Tensor Imaging (DTI), Dynamic Susceptibility Contrast (DSC), and Dynamic Contrast-Enhanced (DCE). Furthermore, brain-CaPTk also supports visualization of DTI derivative measurements such as the tensor's apparent diffusion coefficient, axial diffusivity, radial diffusivity, and fractional anisotropy, as well as parametric maps extracted from DSC of relative cerebral blood volume, peak height and percentage signal recovery.

brain-CaPTk is based on a two-tier functionality: (1) Image processing and analysis algorithms enable the extraction of extensive radiomic features; (2) Machine learning methods integrate these features into diagnostic, prognostic and predictive biomarkers.

Currently incorporated components for preprocessing, interaction, segmentation, feature extraction, and specialized diagnostic analysis, are described below.

2.1 Preprocessing

An essential component for such quantitative research is the appropriate image pre-processing. The related brain-CaPTk tools (Fig. 1) are fully-parameterizable and entail: (i) image denoising (i.e., intensity noise reduction in regions of uniform intensity profile) [15]; (ii) bias correction (i.e., correction for magnetic field inhomogeneity based on non-parametric non-uniform intensity normalization) [16]; (iii) co-registration of various modalities (i.e., for examining in tandem at the voxel level anatomically aligned signals); (iv) skull stripping; and (v) intensity normalization (scaling in a certain range, z-score, and histogram matching) [17].

2.2 Interaction

Part of brain-CaPTk's emphasis focuses in its lightweight and efficient operation without the burden of computationally expensive algorithms weighing in the interaction process. Its interaction tools include spherical approximation of abnormalities, coordinate definition, and region annotation that may be used as initialization of segmentation methods [18–20] and as region masks for further analysis (Fig. 2).

2.3 Image Segmentation

Representative applications of the interaction tools available in brain-CaPTk include two segmentation methods that require initialization, namely, GLISTRboost [18, 19] and geodesic distance transform (GDT) [20].

GLISTRboost is a hybrid generative-discriminative method developed for brain glioma segmentation and atlas registration in multimodal MRI, while incorporating tumor growth modeling via reaction-diffusion-advection [21]. The generative part creates the tumor and healthy-tissue segmentation labels based on expectation-maximization. The discriminative part refines tumor labels based on multiple patients, through a gradient boosting multi-class classification scheme [22]. A Bayesian strategy then finalizes the segmentation based on patient-specific intensity statistics from the multimodal MRI [23]. Specifically, brain-CaPTk enables the seamless initialization of GLISTRboost by (i) the definition of a sphere's center and radius that are used to initialize the growth model, and (ii) the coordinate definition on various tissue types that are used as prior knowledge to guide the segmentation process (Fig. 2). GLISTRboost, due to its complexity is not incorporated in brain-CaPTk yet, but is available for public use through the online Image Processing Portal (ipp.cbica.upenn.edu) of Center for Biomedical Image Computing and Analytics (CBICA), which allows users to perform their analyses without any software installation and whilst using CBICA's High Performance Computing resources.

The segmentation of brain structures based on the GDT [20], is a patient-based method fully incorporated in brain-CaPTk. In particular, a region is annotated to initialize the calculation of an "adaptive geodesic distance", which at a given voxel i is a joint quantification of intensity variation and spatial distance between i and the seed region. The calculation of this

distance at every voxel in the image yields an “adaptive GDT image” on which a threshold is applied to generate the final segmentation label (Fig. 3). This method is appealing as it is computationally efficient and does not need high-performance computer hardware. Moreover, it does not require any preprocessing, is highly adaptable to any imaging modality, and remains insensitive to acquisition protocols. Thus, its “simplistic” nature supports its potential applicability in ample routine clinical settings for delineation of anatomical regions.

2.4 Feature Extraction

brain-CaPTk offers extraction of an extensively comprehensive panel of radiomic features both in 3D and 2D, depending on the operator’s choice. The feature panel available in brain-CaPTk is continuously expanding, however, it currently comprises (i) intensity-based, (ii) textural, and (iii) volumetric/morphologic features (Table 1). The biological significance of the individual radiomic features remains unknown notwithstanding many related studies, and are provided to facilitate research on their association with molecular markers, clinical outcomes, treatment responses, and other endpoints. Via automated functionality provided by brain-CaPTk these features may enable clinicians and other researchers to extract feature measurements and conduct large-scale analyses in a repeatable manner.

2.5 Specialized Analysis - Imaging Signature of EGFR Mutations

The radiogenomic marker currently integrated in brain-CaPTk allows the *in vivo* determination of mutations in the Epidermal Growth Factor Receptor (EGFR) in glioblastoma, through a quantitative within-patient/self-normalized peritumoral perfusion heterogeneity measure. The specific mutations that have been assessed so far comprise the splice variant III (EGFRvIII) [6, 10] and the amplification of the wild-type EGFR [7]. This marker requires the annotation of two regions; one near and another far from the enhancing tumor, but still within the peritumoral edema depicted by the abnormal T2-FLAIR signal. Principal components of the temporal perfusion dynamics of these regions are then estimated and the Bhattacharyya coefficient is used to represent the peritumoral heterogeneity index (PHI). The discovered non-invasive personalized *in vivo* imaging marker of EGFR mutations utilizes clinically-available imaging protocols, without the need to deliver radiolabeled probes, which renders it likely for immediate translation into the clinic as a first-line pre-operative detection of this molecular target.

2.6 Neuro-Oncological Planning Tools

Some of the major challenges faced by fiber tracking in the realm of neurosurgical planning is that the reconstruction of tracts is affected by mass effect, when the tracts are displaced and distorted, and edema and infiltration, when the tracts are broken, as a result of change of diffusion parameters due to pathology. This underlines the needs for methods that can track through edema and reconstruct even partial and displaced tracts. To this end, brain-CaPTk provides tools for tractography robust to edema [32, 33] and automated tract detection based on connectivity signatures [34, 35], to extract fiber tracts, even distorted or broken, in the presence of mass effect and edema (Fig. 4). The edema invariant tractography [32, 33] is based on the multi-compartment modeling of diffusion data (a free water component representative of the edema and another component representing the underlying tissue) that

is fitted with a tensor or higher order diffusion model, based on the single/multishell acquisition. The automated tract detection framework defines a fiber bundle atlas that will emulate the expert, using white matter fibers of healthy individuals. The white matter tracts in any patient are then extracted based on the definitions encoded in the atlas, using connectivity signatures of the fibers [34, 35].

3 Results and Application

3.1 Image Segmentation

GLISTRboost is the top-performing method in the BraTS'15 challenge [18, 19, 36], thereby emphasizing the value of brain-CaPTk that allowed the initialization of numerous glioma scans in a short timeframe. The tumor regions evaluated during BraTS described the tumor part that enhances in the T1-Gd image (ET), the core of the tumor (TC) that is typically resected during surgery, and the whole tumor (WT) which comprised the TC and the peritumoral edema/invasion. Specifically, the median Dice score values with their corresponding Inter-Quartile Ranges (IQR) for the three evaluated regions, i.e. WT, TC, ET, were equal to 0.92 (IQR: 0.88–0.94), 0.88 (IQR: 0.81–0.93) and 0.88 (IQR: 0.81–0.91), respectively. Furthermore, such specialized algorithms as GLISTRboost enable the evaluation of tumor spatial distribution in standardized coordinate systems, which receive increasing attention as predictors of clinical outcome as well as markers of underlying tumor molecular characteristics [37].

The segmentation method incorporated in brain-CaPTk, based on GDT, was previously validated on T1-Gd images of 24 glioblastomas, 15 meningiomas, and 15 metastases, captured under diverse acquisition conditions, and reported Dice scores of 0.82, 0.83, and 0.69, respectively [20]. We have further evaluated GDT on 132 T2-FLAIR glioblastoma baseline images, from the BraTS'15 challenge training dataset. The optimal cut-off threshold was determined based on 10-fold cross-validation, yielding an average Dice score of 0.72 for the WT.

3.2 Feature Extraction

Extensive literature over the past decade has shown that rich panels of quantitative imaging features can result in non-invasive imaging signatures with diagnostic, prognostic and predictive value for many types of cancer, such as lung [38, 39], neck [38] and brain [2, 6–10, 40–43]. Specifically, these features have shown evidence of imaging signatures relating to underlying molecular characteristics, treatment response, patient survival, with the potential of augmenting conventional prognostic and predictive assays.

Specifically about the intensity-based features offered in brain-CaPTk, the histogram distributions capture anatomical and functional changes caused by the tumor, and have demonstrated a connection to clinical endpoints, such as survival, and molecular subtypes [8, 9]. The principal component features of temporal perfusion dynamics have been related to recurrence and infiltration [24, 42], as well as molecular characteristics [6, 7, 10, 44]. Furthermore, the textural features available in brain-CaPTk capture characteristics of the

local micro-architecture of tissue and have already demonstrated predictive and prognostic value [9, 38, 41, 44, 45].

3.3 Specialized Analysis - Imaging Signature of EGFR Mutations

The patient-based radiogenomic signature of EGFRvIII in glioblastoma integrated in brain-CaPTk was applied in independent discovery (γ) and replication (δ) cohorts, as well as their combination (ζ), and revealed highly significant distinctive results in all configurations ($p_\gamma = 1.57\ 10^{-7}$, $p_\delta = 2.8\ 10^{-4}$, $p_\zeta = 4\ 10^{-10}$) (Fig. 5). Its accuracy (89.92%), specificity (92.53%), sensitivity (83.77%), as well as its independent sample repeatability (Intra-class Correlation Coefficient (ICC) = 0.825) and reproducibility (ICC = 0.775), supports its potential routine clinical use [6, 7, 10]. Such signatures contribute to personalized medicine, and can enable non-invasive patient selection for targeted therapy, stratification into clinical trials, and repeatable monitoring of mutations during the treatment course.

3.4 Neuro-Oncological Planning Tools

The applicability, reliability and repeatability of the automated tract extraction tool integrated in brain-CaPTk, was validated in a dataset of healthy individuals acquired repeatedly [35]. Compared to the clustering of fibers for each scan independently, our framework provided better reproducibility (test-retest) results, with decreased (25%) mean intra-individual distance (i.e., disagreement of clusters between different time-points of the same individual), while preserving inter-individual differences.

Additionally, the framework was also tested in tumor patients [34] on six major fiber bundles: cingulum bundle; fornix, uncinate fasciculus (UF), arcuate fasciculus, inferior fronto-occipital fasciculus, and inferior longitudinal fasciculus (ILF). The agreement between clustering and experts as quantified by Cohen's kappa ranged between 0.6 and 0.76. Except two tracts, ILF and UF, the agreement between clustering and experts was higher than agreement between experts themselves, highlighting the reliability of the paradigm. When the tumor demonstrated significant mass effect or shift, the automated approach was useful to provide an initialization to guide the experts with the identification of the specific tract of interest.

4 Extendability

There are two mechanisms for integrating new applications into brain-CaPTk, each with its own advantages and disadvantages:

4.1 Source Level Integration

This is the tighest integration, providing memory-level access to all of brain-CaPTk interactive functionalities while allowing for maximum optimization. The external application should be written in C++ and compiled alongside brain-CaPTk.

4.2 Executable Level Integration

This level provides a graphical interface to an existing command-line application (not necessarily developed in C++), allowing users to leverage brain-CaPTk's functionality (e.g.,

interaction, feature extraction). Executable-level integration requires only minor additions to brain-CaPTk to create a menu option for the new application.

5 Conclusion and Future Work

Although, advanced computational algorithms have shown exciting clinically-significant findings in the research community, their complicated nature limits clinical applicability, revealing a need for software tools to help with translation of such complex algorithms into clinical practice, and hence to maximize their potential benefit.

brain-CaPTk describes a platform that can allow: (1) clinical use of computationally complex algorithms, (2) non-imaging experts (e.g., bioinformaticians, or clinicians who do not have sufficient computational background) to generate quantitative data useful for correlative clinical/genomic studies, and (3) imaging experts to integrate their advanced computational algorithms in an existing easy-to-use front-end, benchmark new algorithms and perform inter-institution comparisons.

Immediate future plans include the integration of various other specialized diagnostic analysis tools for glioblastoma, such as prediction of survival [9], potential recurrence [42], and characterization into distinct imaging subtypes [41], as well as application of existing brain-CaPTk components in other neurological diseases, i.e. meningioma and multiple sclerosis.

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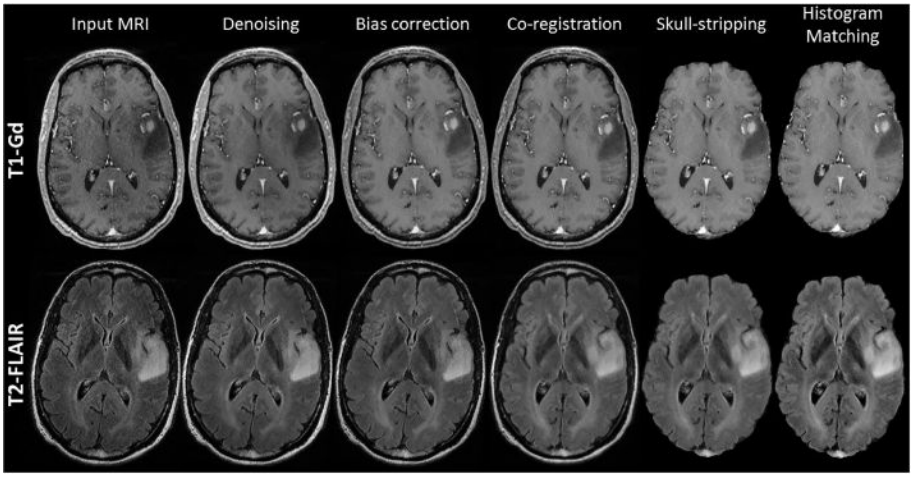

Fig. 1.
Example application of the preprocessing tools available in brain-CaPTk.

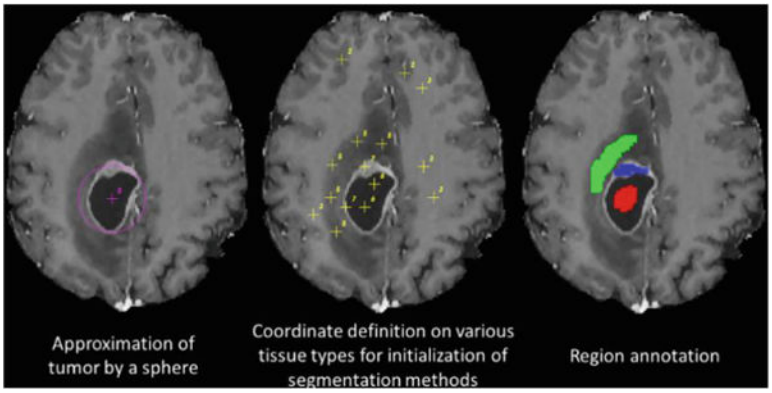

Fig. 2.
Example of brain-CaPTk's interaction tools.

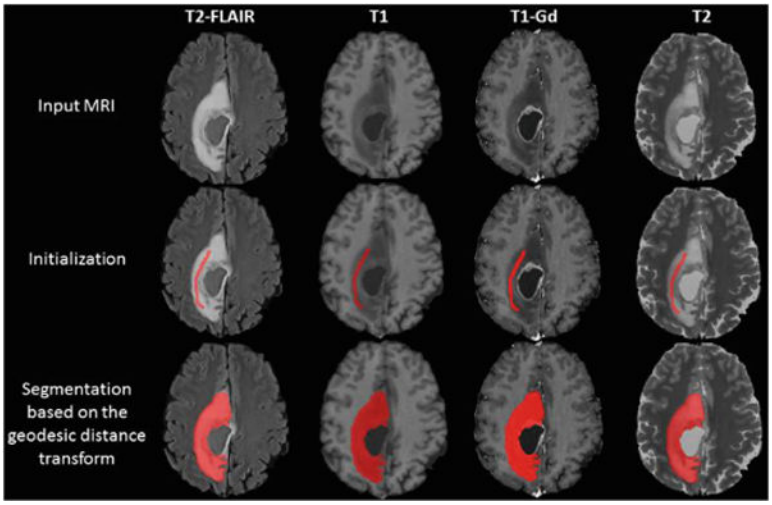

Fig. 3.

Example segmentation of a glioblastoma sub-region (i.e., edema) based on GDT. "Initialization" denotes the region annotated manually for initiating the segmentation algorithm.

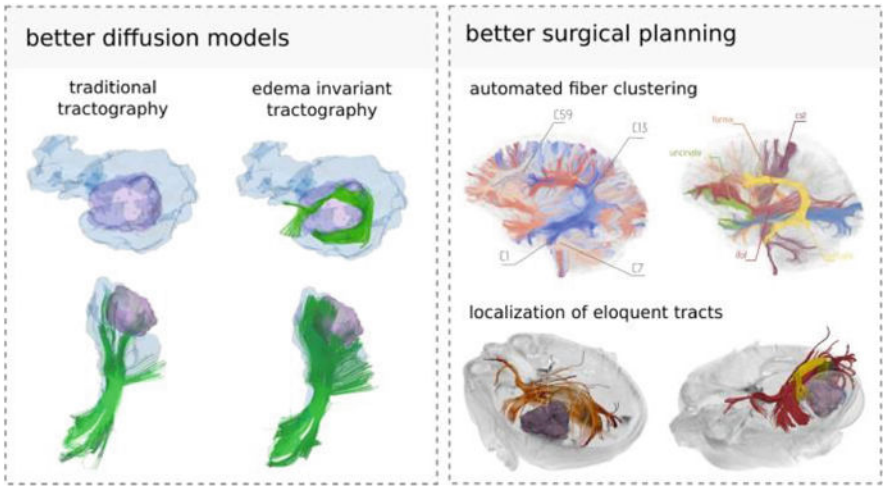

Fig. 4.

Tools for edema invariant tractography and automated tract detection. (Left panel) Tracking through edema made possible with multi-compartment modeling of diffusion data; (Right panel) Atlas-based reconstruction of tracts, resilient to mass effect induced tract distortions, and the surgical plan with the tumor and surrounding eloquent tract.

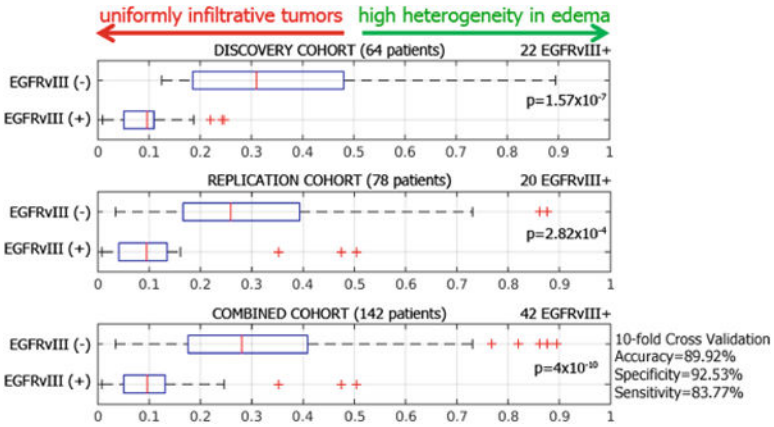

Fig. 5.
Distributions of the PHI by EGFRvIII expression status.

Table 1

Radiomic features offered by brain-CaPTk for analysis of neurological diseases.

Feature type	Description
Intensity-Based	– 1st & 2nd order statistics (mean, standard deviation, skewness, kurtosis); – range and distributions of gray-level histograms [9]; – principal components of DSC image [24]
Textural	– gray-level co-occurrence matrix [25]; – gray-level run-length matrix [26]; – gray-level size zone matrix [26, 27]; – neighborhood gray-tone difference matrix [28]; – local binary patterns [29];
Volumetric/Morphologic	– shape descriptors (i.e., area/volume, eccentricity, sphericity, solidity, perimeter, elongation) [30, 31]