Translating cancer research into clinical practice: A framework for analyzing and modeling cancer from imaging data

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Abstract

This paper presents the work of our group concerning cancer image analysis and modeling. The adopted strategy aims to build a complete system for analysis and visualization of DICOM tomographic data, offering a variety of annotation or automatic segmentation tools as well as tools for tumor growth simulation and visualization.

1. Introduction

One of the major concerns in clinical practice and treatment of cancer is the fastest possible transform of scientific discoveries arising from laboratory, clinical or population studies into clinical applications, to reduce cancer incidence, morbidity and mortality. This is the scope of translational research (illustrated in Fig. 1), which in turn can be further resolved in early and later states [1]. Towards this direction this paper refers to a concrete and practical framework of applying state of the art image analysis algorithms to facilitate tumor delineation and further estimate tumor growth dynamics and treatment response "in silico"; in a dedicated easy to use computer platform. To state its applicability and potential use, the presented framework is specialized in highly aggressive and malignant cancer cases, like the Glioblastoma multiforme (GBM). It is the most common and most aggressive type of primary brain tumor in humans, accounting for 52% of all primary brain tumor cases and 20% of all intracranial tumors. Unfortunately, even with complete surgical resection of the tumor, combined with the best to date available treatment, the survival rate for GBM remains very low [2].

The paper proceeds as follows: Section 2 provides an overview of the platform that forms the cornerstone of the presented framework. Details on the implemented delineation algorithms are given in section 3. Section 4 details the 3D model of heterogeneous anisotropic glioma evolution and presents some initial results using the platform, whereas section 5 concludes the paper.

2. Integration Platform

The different technologies concerning cancer image analysis and modeling developed by our group are currently being integrated in 'DoctorEye' (available at http://biomodeling.ics.forth.gr/) [3], a novel, open access and easy to use platform, for intuitive annotation and/ or segmentation, visualization and growth simulation of tumors. Its development is clinically driven and follows an open modular architecture focusing on plug-in components. The main advantage of the proposed platform is that the user can quickly and accurately delineate complex areas in medical images in contrast with other platforms that do not facilitate the delineation of areas with complicated shapes. Additionally, multiple labels can be set to allow the user to annotate and manage many different

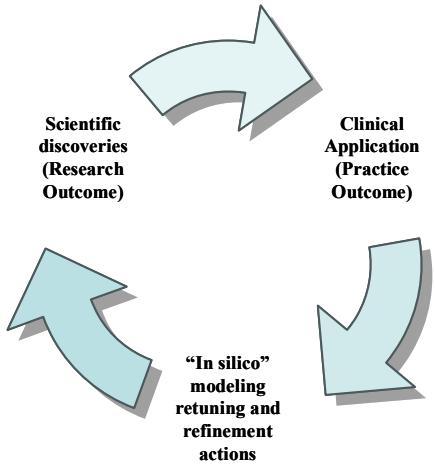

Fig. 1: Translating research into cancer care can greatly benefit the diseased patient. A practical easy to use "in-silico modeling" application can advance discoveries more effectively toward early human testing for a new therapeutic, diagnostic and preventative intervention scheme.

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areas of interest in each selected slide. The close collaboration with clinicians in designing the platform has ensured that it can be effectively used in the clinical setting.

Another feature that adds value to the platform is that it allows computational "in-silico" models of cancer growth and simulation of therapy response to be easily plugged in, providing a future integrated platform for modeling assisted therapy decision making. Currently, our group is working towards incorporating such models in the platform and the new version will also be freely available. In this context, the platform could also serve as a validation environment where the simulation predictions could be compared with the actual therapy outcome in order to achieve a global optimization of the modeling modules. This tool is part of the "Contra Cancrum" EU-ICT research project [4] and in its first stage serves as an intuitive 3D annotation system.

3. Tumor delineation

Medical image segmentation and specifically tumor delineation has been a subject of vast research in the past years. The region of a tumor is typically heterogeneous, containing different tissue structures and fuzzy boundaries. For this reason, accurate segmentation for both the automatic and semiautomatic case is a very challenging task. The platform currently invests on different segmentation approaches that mostly focus on MRI tomographic images since this modality has been extensively used by the clinicians in the glioma case.

Two different, in terms of underlying theoretical concepts, segmentation algorithms are currently available in the platform: namely the "Magic Wand" (described in section 3.1), mainly designed for the clinician to annotate ROIs as well as improvements of the "Active Contours" (described in section 3.2), algorithm for semi-automated segmentation for the non-expert user aiming at saving time and reducing intra/ inter-observer variability among radiologists. The first is based on image intensity, whereas the second is a model-based method. However, supported algorithms can easily be extended using external plug-ins.

In case of errors in the segmentation process the clinician can adjust the tolerance level (when using the Magic Wand option), in order to achieve a more precise delineation of the tumor region. This can be done in real time by the user adjusting a slider in the GUI as illustrated in Fig. 2.

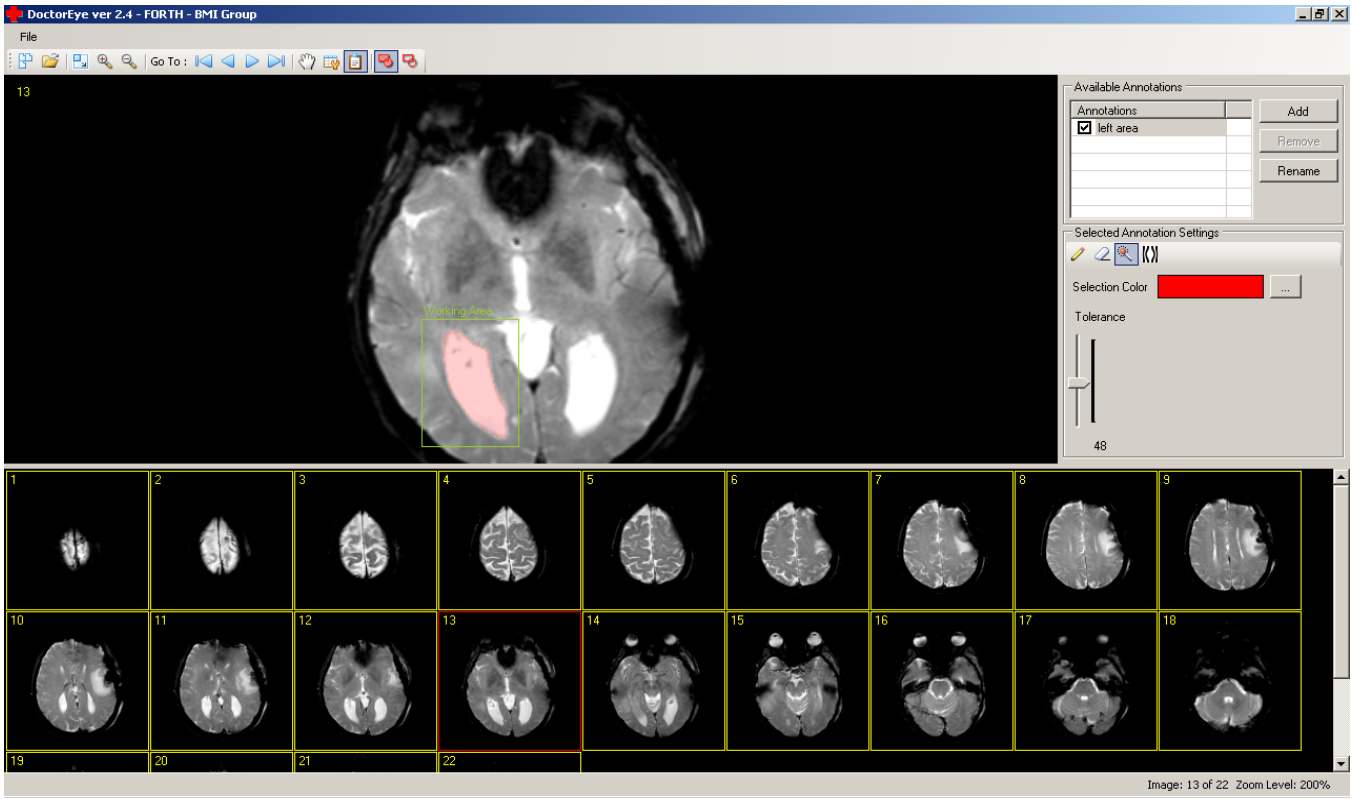

Fig. 2: A single slide is selected for further processing. A working area has been set (green rectangle) and the segmentation algorithm has been applied. The selected area is labeled with a pink alpha-channel transparency.

3.1. The Magic Wand Algorithm

The function of the Magic Wand algorithm is based on finding and selecting all the pixels around a pre-specified user-selected initial point that are similar in gray intensity. A tolerance value can be specified by the user to determine how closely to match colors (higher tolerance ends up in a larger selection).

All the points selected by the algorithm are automatically stored in an image mask of the same size as the original image. Each pixel in the image mask represents the position of the selected pixels in the original image and is used to label the delineated tumors. Moreover, to enhance its effectiveness, we implemented a faster version of this algorithm which excludes all the pixels that have already been examined, to ensure that the algorithm does not check them again.

3.2. The Active Contours Algorithm

An alternative method to perform segmentation in two-dimensional images is based on iterative evolution methods such as the discrete active contours algorithm. A number of evolution methods are available to evolve active contours. A traditional snake is a curve $\mathbf{v}(s) = [x(s), y(s)], s \in [0,1]$, that evolves through time in order to minimize its energy functional, which has the following form:

$$E_{snake}(\mathbf{v}) = \int_0^1 (E_{internal}(\mathbf{v}(s)) + E_{image}(\mathbf{v}(s)))ds \qquad (1)$$

The internal contour energy is defined as:

$$E_{internal} = (\alpha(s)\left|\mathbf{v}'(s)\right|^2 + \beta(s)\left|\mathbf{v}''(s)\right|^2)/2 \qquad (2)$$

where $\mathbf{v}'(s)$ and $\mathbf{v}''(s)$ denote the first and second derivatives of $\mathbf{v}(s)$ with respect to s.The parameters α and β are weighting parameters that control the snake's rigidity and curvature, respectively: high values discourage stretching and bending of the contour, imposing it to be more rigid, while low values let the snake be more elastic and develop corners. The image energy term E_{image} depends on the gradient of the image and is associated to the external forces that pull the snake towards the desired image boundaries.

The external energy is supposed to be minimal when the snake is at the object boundary position. The user is required only to add points in order to define the initial boundary approximation step. The following parameters can also be defined in order to achieve optimal segmentation results: Continuity, Curvature, Gradient and Pressure (or balloon).

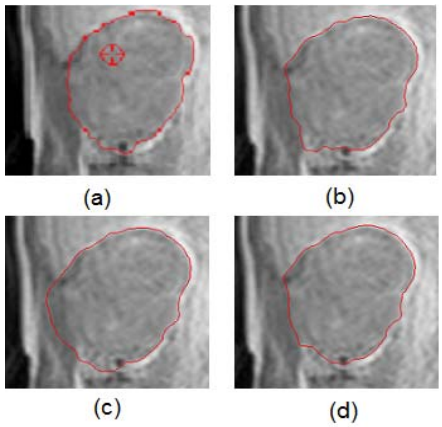

Fig. 3: (a) Clinician's manual annotation, (b, c) Traditional snake's results, (d) Results applying our proposed method.

Recently, our group introduced an improved method, the key point of which is the use of adaptable parameters for the snake evolution [5]. Instead of using constant parameters for every pixel, we group the pixels according to their gradient magnitude and the corner strength, and assign to each group a different set of parameters. Thus, we are able to geographically adapt the snake's behavior in the image and include, or not, small high-contrast regions by simply adjusting two user-defined thresholds. The method follows very closely the annotation of the clinician and as shown in Fig. 3 it can be locally adaptive to include small details near the boundary (probably a necrotic center that the clinician has included in his ROI annotation), while the traditional active contours fail.

4. Glioma Growth Simulation

Several mathematical models have been developed towards simulating the mechanism of glioma growth. The most successful models have used variations of the diffusion-reaction equation, with the recent ones taking into account brain tissue heterogeneity and anisotropy. Our group has implemented continuous models by studying in detail the mathematical solution and implementation of the 3D diffusion equation, addressing related heterogeneity and anisotropy issues [6]. The model developed are in essence a fast realization and solution of the diffusion-reaction equation using different numerical approximation of finite differences. It can simulate either glioma growth or other diffusive phenomena, with the vectorization operator giving anyone the ability to adjust the model to a preferred proliferation rate. Moreover, a performance study of different numerical schemes, based on finite differences concluded that the Backward Euler (BE) method yields the best results when tested in a theoretical framework. This study was

Fig. 4: 3D representation of tumor state as extracted from MRI images: Initial real data (left column), after 112 simulated days using the BE method (central column), by using BE, and actual growth on 112th day (right column).

testing the performance of different numerical schemes in a simplified test case of the pure diffusion equation, for which there is a known analytical continuous expression of the solution [6]. Fig. 4 illustrates the results of the BE when applied on real dataset; initial tumor state (left column showing different views) and after 112 simulated days (central column). Finally, the actual tumor growth is depicted in the last column and was found to correspond very well to the model-based simulation [6].

The platform developed focuses on the implementation and inherent features of the later approximations and points out how an efficient model could help clinicians to better visualize the exact tumor boundaries, predict tumor expansion and, thus, accustom therapy.

5. Conclusion

This paper presented the work of our group towards a complete system for cancer image analysis, annotation, visualization and modeling. The system is being developed in close collaboration with clinicians and the ultimate goal is to include as many state of the art technologies as possible in order to become a useful interface that could help the clinical translation of in-silico technologies.

6. References

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