Measuring contour functions deformation by Principal Differential Analysis:a distance based approach for the analysis of Gioblastoma Multiform

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Abstract. *This paper introduces an explorative functional data analysis approach for the analysis of brain tumor contour functions deformation. A dataset of* 15 *patients affected by Gioblastoma multiform related to two different stages is analyzed. The purpose is to study the dynamic of a sequence of two sets of tumor contour functions related to the two stages, thus Principal Differential Analysis has been performed into the two steps. The estimated proposed operator approximates efficiently the observed functions not only taking into account the observed functions, but also their derivatives. A distance among the coefficients of the differential equation is proposed to define the degree of the contour functions changes.*

Keywords. *Contour functions; Registration; Tumor growth; Distance; Principal Differential Analysis*

1 Introduction

Gioblastoma multiform is the most aggressive of the gliomas, tumors arising from glia within the central nervous system. Because most patients with this pathologies die in less than a year and essentially none has long-term survival, these tumors have drawn significant attention. Several mathematical models for studying the dynamics of the cancer progression have been proposed (see[1], for example). These models give a mathematical expression of the dependence of tumor size on time. Most of them show that any type of tumor developing has most of its proliferation constrained to the border [3]. We thus aim at studying the relation which affect the measured countours into different steps of observation. In particular we focus on the problem of monitoring the dynamic of the tumor contour growth. This study is part of joint research program involving the Department of Mathematics (Campus Riu Sec, University Jaume I, University Jaume I). The tumor contour functions extracted by a registration algorithm [7] from Functional Magnetic Resonance Images (FMRI) are treated like a two-dimensional functional data. The dataset is composed by 15 brain tumor contour functions. Let's note that the tomography of the images we are dealing with, has been done in the same conditions for both the steps of the observations and for all the patients. Moreover the position of each patient is the same in order to have an image collected

with the same cartesian benchmarks (Figure1 shows two contour for one patient).

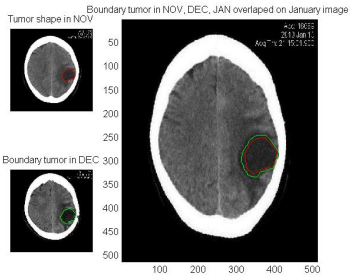
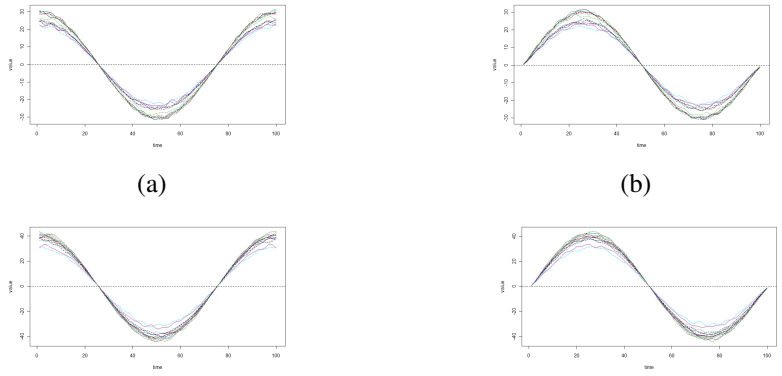


Figure 1: Contour functions for one patient. The red curve identifies the contour in a first stage and the green one the contour in a second stage.

We perform an explorative functional analysis of the dataset. Thus, we first fit the raw data and then we define a global registration criterion for finding an optimal warping function for aligning the two set of contours. These data have already been analyzed but with different approaches in two previous exploratory works ([5] [6]) with the aim to explore only the dynamic evolution from the first step to the second step. Here, functional variability of the two set of contours is assessed by including the derivatives and their relationship in a Principal Differential Model. Quantitative information about the degree of local similarity among contour functions and their evolution, observed into the two phases, is found by defining a distance among the coefficients of the two Principal Differential Models.

2 Parametric contour functions of Gioblastoma Multiform: the problem of registration by FDA

Let n be a set of individuals on which we monitor the brain tumor boundary evolution in two different steps of observation. Tumor boundary contours are extracted by an automatic procedure for tumor image segmentation ([7]). Brain tumor outline can be seen as a sampled closed contour of a figure in an Euclidean space. Let the perimeter of the figures be S. Every point p_s of the contours can thus be defined with coordinate $(X_i(s),Y_i(s)), i = 1,\ldots,n$ in a first visit and $(X_i^*(s),Y_i^*(s)), i = 1,\ldots,n$ in a second visit. The data structure observed for longitudinal studies in which functional data are obtained at each of two visits is shown in Fig.2. As in shape analysis, several problems arise when comparing tumor contour functions. The starting point are not the same from an observation to another (the classic registration problem in FDA), the sense of rotation can be different, however the objects are not aligned and of the same size. Thus, in order to overcome these problems, we at first, consider that sampled functional data $(X_i(s),Y_i(s)),i = 1,\ldots,n$ and $(X_i^*(s),Y_i^*(s)), i = 1,\ldots,n$ in the two steps can be expressed in terms of K known basis functions, especially we chose Fourier basis. Thus K couple of vectors of parameters respectively α and β and α^* and β^* are estimated by least squares fitting. The fit of the basis function is not penalized since the differences among the contours depend on the curvature. Welch's T test on the mean curvature of the first set of curves ($p-value = 0.0004$) underline that the mean curvature in a first stage is significantly smaller than that of the second step. Then, we need to scale the object to the same surface, to center each profile function, to define a global registration criterion for finding the shift δi for each curve in both the two steps. We scale the shape contour to the same surface S_T. We fix an anticlockwise direction of rotation and standardize the profiles so that we can avoid fictitious variability. Visual inspection of the first derivative shows that data present amplitude variability into the



(a) (b)

(c) (d)

Figure 2: Functional approximations of the tumor contour functions: a) $x(s)$, $i = 1,\ldots,15$ in a first stage; b) $y(s)$, $i = 1,\ldots,15$ in a first stage; c) $x^*(s)$, $i = 1,\ldots,15$ in a second stage; d)$y^*(s)$, $i = 1,\ldots,15$ in a second stage

two steps and phase variability among the two steps. This phase variability must be removed in order to have a meaningful comparison among the two steps [4]. We thus look for the optimal warping functions maximizing the similarity between the curves in both the two steps and a target curve. The mean curve of the first set of curves (the " not deformed" curves) is used as target curve for the registration. Then we define the following global registration criterion in order to search for a shift δi for each curve i respect to the target curve.

$$\Delta = \sum_{i=1}^{N} \int_S [(x_i(s+\delta i) - \bar{x*}(s))^2 + (y_i(s+\delta i) - \bar{y*}(s))^2 ds] \tag{1}$$

Each curve is then shifted so as to minimize the Δ. The estimated mean are then updated by re-estimating them from the registred objects. The derivatives of functional observations play a strong rule for this kind of data as shown in this first explorative step. Now we look how velocity of $(X_i(s), Y_i(s)), i = 1,\ldots,n$ may be employed in describing changes of contour functions in the two steps of observation by Principal Differential Analysis (Ramsay, 2005).

2.1 Principal Differential Analysis and Tumor Growth

Principal differential Analysis extends the concept of differential equation in the framework of functional data. A differential equation describes a process with changing dynamics by specifying relationships among the function and its derivatives. In the context of tumor growth we view the contour functions as a dynamic system described by the linear relations among the derivatives. Because the structure of our data is sinusoidal it seems appropriate to set out a second order differential equation model that can capture contour function dynamics. We define the following non homogenous differential operator for the couple of functional contour in the two steps (for simplicity we report only the ones related to the first step):

$$\begin{aligned} LX(s) &= \alpha_x(s) + \varepsilon_x(s) \\ LY(s) &= \alpha_y(s) + \varepsilon_y(s) \end{aligned} \tag{2}$$

where $LX(s)$ and $LY(s)$ are defined as

$$\begin{aligned} LX(s) &= \beta_{1x}(s)DX(s) + \beta_{2x}(s)D^2X(s) + D^3X(s) \\ LY(s) &= \beta_{1y}(s)DY(s) + \beta_{2y}(s)D^2Y(s) + D^3Y(s) \end{aligned} \tag{3}$$

The two set of contours modeled by a linear differential operator are respectively characterized by six functions $\alpha_x(s)$,$\alpha_y(s)$,$\beta_{1x}(s)$, $\beta_{2x}(s)$, $\beta_{1y}(s)$, $\beta_{2y}(s)$ for the first step and $\alpha_{x*}(s)$,$\alpha_{y*}(s)$,$\beta_{1x*}(s)$, $\beta_{2x*}(s)$, $\beta_{1y*}(s)$, $\beta_{2y*}(s)$ for the second step. The covariates $\alpha_x(s)$,$\alpha_y(s)$, $\alpha_{x*}(s)$,$\alpha_{y*}(s)$ are the forcing functions and $\beta_{1x}(s)$, $\beta_{2x}(s)$, $\beta_{1y}(s)$, β_{2y},$\beta_{1x*}(s)$, $\beta_{2x*}(s)$, $\beta_{1y*}(s)$, $\beta_{2y*}(s)$ are the weight functions with $s \in S = [0,100]$. A least square criterion is used for estimating these functions,especially 34 B-Spline basis function of order 6 are used to estimate the functional form. From the figure it can be seen that the forcing function is the major source of variation rather than the second derivative for both the step. The problem we try to solve is how we can compare these dynamics? Can we monitor the degree of the evolution of the two steps? The twelve functions obtained by estimating the Principal Differential Equation give indication on the dynamic variability, thus we define the following distance among the two models. Let us consider two models Pde_j, $Pde_{j'}$ defined on the same support S. Each of them can be defined by a compound of six functions, respectively $Pde_j = \{\alpha_x(s), \alpha_y(s), \beta_{1x}(s), \beta_{2x}(s), \beta_{1y}(s), \beta_{2y}(s)\}$, $Pde_{j'} = \{\alpha_{x*}(s), \alpha_{y*}(s), \beta_{1x*}(s), \beta_{2x*}(s), \beta_{1y*}(s), \beta_{2y*}(s)\}$. The distance between Pde_j, $Pde_{j'}$ is

$$\begin{aligned} d(Pde_j, Pde_{j'}) \quad = \quad & \sqrt{\int_{s\in S}(\alpha_x(s) - \alpha_{x*}(s))^2 ds} + \sqrt{\int_{s\in S}(\alpha_y(s) - \alpha_{y*}(s))^2 ds} + \\ & + \sqrt{\int_{s\in S}(\beta_{1x}(s) - \beta_{1x*}(s))^2 ds} + \sqrt{\int_{s\in S}(\beta_{2x}(s) - \beta_{2x*}(s))^2 ds} + \\ & + \sqrt{\int_{s\in S}(\beta_{1y}(s) - \beta_{1y*}(s))^2 ds} + \sqrt{\int_{s\in S}(\beta_{2y}(s) - \beta_{2y*}(s))^2 ds} \end{aligned}$$

This distance allows to quantify the diversity among two consecutive steps. If more than two images are available it takes the dynamic evolution of the distance among the contours. Results on the application of this distance seems encouraging. More details can be found in [6].

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