Statistical Analysis of Tubular Structures in PET Imaging Data of Human Sarcoma

F. O'Sullivan[1], E. Wolsztynski[1], J. N. O'Sullivan[1], T. Richards[2], E. C. Conrad[2] and J. F. Eary[2]

[1] *Statistics, University College Cork*
School of Mathematical Sciences, Western Road
Cork, Ireland
E-mail: f.osullivan@ucc.ie

[2] *Center for Orthopedic and Sports Medicine and Division of Nuclear Medicine*
University of Washington
Seattle, WA, United States

Introduction

We consider the problem of representing the spatial metabolic activity of sarcomas, an infrequent form of cancer affecting soft tissue, cartilage and bone. The typical treatment protocol for sarcoma tumors is surgical resection, generally preceded by chemotherapy in advanced cases. The median survival time for patients with sarcoma is about five years after surgery. Sarcoma patients are usually followed using Positron Emission Tomography (PET) scanning with fluoro-deoxyglucose (FDG). Such imaging data are typically analysed in terms of maximum standardized uptake value (SUV_{max}) in the tumor region of interest (ROI) [4]. However, advanced spatial models for sarcoma tumors and novel quantitative descriptors of FDG-PET imaging data may enhance prognostic understanding and, ultimately, patient treatment. We previously proposed alternative measures of spatial heterogeneity of the FDG uptake pattern of sarcoma tumors [4, 8, 7]. This set of measures consisted in measuring the deviation of the uptake pattern from a simple ideal ellipsoidal form. Here we investigate a model that offers a refinement of this elliptical representation. Fitting this representation allows the derivation of novel tumor spatial features to further describe localized variations in the uptake pattern. In this model, the uptake intensity is analyzed from the central core to the boundary of the tumor. This approach yields model-derived measures of tumor core non-linearity, tumor phase of development and lack of fit of the uptake model. In particular, the phase of development measured at the tumor core is found to be significant in terms of prognosis.

Spatial uptake pattern representation

Let the array $\{(y_i, x_i), i = 1, 2, \ldots, N\}$ denote measurements of the standardized FDG-PET uptake values y_i over a set of N voxels $\{x_i = (x_{1i}, x_{2i}, x_{3i})^t,\ i = 1, \ldots, N\}$ in a 3-D region (Ω) containing tumor mass. The original data points are transformed using principal component analysis so as to obtain an objective coordinate system for modeling the uptake pattern. This results in a re-orientation of the tubular mass of the sarcoma tumor, and reduces the effect on subsequent analysis of variability related to the original field of view (FOV). This *principal axis sampling* (PAS) is based on the uptake-weighted mean and covariance of the data

$$\mu = \frac{\sum_{i=1}^N y_i x_i}{\sum_{i=1}^N y_i}\ ; \qquad \Sigma = \frac{\sum_{i=1}^N y_i (x_i - \mu)(x_i - \mu)^t}{\sum_{i=1}^N y_i} \tag{1}$$

Following spectral decomposition $\Sigma = \Gamma \Lambda \Gamma^t$ with Λ a diagonal matrix with diagonal entries $0 \leq \lambda_1 \leq$

$\lambda_2 \leq \lambda_3$ and $\Gamma = [\gamma_1, \gamma_2, \gamma_3]$, the PAS coordinates are $\tilde{x}_i = \Gamma^t(x-\mu) = (\gamma_1^t(x_i-\mu), \gamma_2^t(x_i-\mu), \gamma_3^t(x_i-\mu))^t$. This provides an array $\{(y_i, \tilde{x}_i), i = 1, 2, \ldots, N\}$. We refer to $h = \tilde{x}_3$ as the long-axis of the tumor, having values within $[a, b]$ (the tumor ends); the short-axis coordinates are $(\tilde{x}_1, \tilde{x}_2)$.

To model the spatial dynamics of the uptake pattern within the ROI, we represent the tumor mass as a set of contour surfaces arranged from the central core to boundary surface of the tumor mass. Let $c_h = (c_{1h}, c_{2h})^t$ represent the short-axis coordinates of the central core of the tumor as a function of the long-axis coordinate h. The PAS coordinates $\tilde{x} = (\tilde{x}_1, \tilde{x}_2, \tilde{x}_3)$ are transformed to a cylindrical form (r, θ, h) by

$$r = \sqrt{(\tilde{x}_1 - c_{1h})^2 + (\tilde{x}_2 - c_{2h})^2} \;\; ; \qquad \theta = \tan^{-1}\left(\frac{\tilde{x}_2 - c_{2h}}{\tilde{x}_1 - c_{1h}}\right) \;\; ; \qquad h = \tilde{x}_3 \tag{2}$$

In this representation, a star-shaped contour is given by a function specifying its polar radius as a 2π-periodic function of angle. Let us consider the collection of these contours as a function of the long-axis be denoted by $\{(\sigma_h(\theta), \theta, h)$, for $\theta \in [-\pi, \pi]$ and $h \in [a, b]\}$. Following this evaluation, we define the tumor boundary contour on each long-axis slice as the contours corresponding to a particular uptake level.

The final representation of the uptake data is obtained by a function whose contours on each short-axis PAS slice are a simple dilation or contraction of the reference contour specified $\sigma_h(\theta)$. The uptake level for the dilated or contracted contour is determined by 3-parameter adjustment of a fixed reference Gaussian radial uptake pattern $g(u) = e^{-\frac{u^2}{2}}$. Using this, the uptake at the cylindrical coordinate (r, θ, h) becomes

$$y(r, \theta, h) = \beta_h g\left(\tau_h + \phi_h \frac{r}{\sigma_h(\theta)}\right) + error \tag{3}$$

where $\beta_h \geq 0$, $\phi_h \geq 0$, and τ_h represent long-axis slice-specific adjustments of the amplitude, scale and phase of the uptake. The phase parameter τ_h varies with the shape of the radial uptake pattern, and depends in particular on whether radial uptake is monotonically decreasing or follows a more complex unimodal structure. The case $\tau_h > 0$ indicates a monotonically decreasing radial uptake, from core to boundary, while $\tau_h \leq 0$ indicates a unimodal radial uptake pattern. Note that large β_h values should be penalized within the estimation process, in order to discourage compensation by large values for τ_h. We refer to τ_h as a core-phase parameter, on the basis that early stage sarcomas typically show a monotone radial pattern and later stage ones have reduced central uptake and unimodal radial patterns. Similarly, the argument of the function g in (3) also defines a measure of the phase of development at other points. So we define the local phase at the point (r, θ, h) as

$$u = \tau_h + \phi_h \frac{r}{\sigma_h(\theta)} \tag{4}$$

Estimation of uptake pattern characteristics

In order to fit model (3), we need to estimate two subsets of parameters separately so as to ensure a faithful and meaningful description of the tumor core and boundary. We therefore devise a two-step estimation procedure for our model, where the uptake data is first binned into percentiles of the long-axis h, yielding initial parameter estimates for each bin. In a second step, this set of initial estimates is smoothed in order to provide stable output parameter estimates.

Let $h_{(j)} \in (\underline{H}, \bar{H})$ denote the $\frac{jN'}{N_h}th$ order statistic of the individual voxel long-axis coordinate values $(h_i's)$. Considering a total number N_h of bins, the j'th bin is then defined by $(h_{(j-1)}, h_{(j)}] = \text{Bin}_j$. The number of bins may be chosen so that $N_h \approx \frac{\bar{H} - \underline{H}}{\Delta_x}$, where Δ_x denotes the within-plane resolution

of the imaging data. We apply a two-pass approach for each axial bin in order to obtain initial estimates for the center and boundary contour shape. A weighted smoothing procedure across across axial bins is then applied to this set of estimates to yield final values. The weights may be chosen to be inversely proportional to the average model lack-of-it on each axial slice. Boundary contours are smoothed separately across a discretized set of angles.

Given the elliptical contour shape $\sigma_h^o(\theta) = (1 + e\cos(\theta - \varphi))$ for $\theta \in [-\pi, \pi]$ with the eccentricity (e) and orientation (φ) unknown, the uptake data within the axial bin is modeled as a non-parametric unimodal function of the elliptically adjusted radius $\rho_i = \frac{r_i}{\sigma^o_{h_i}(\theta_i)}$ where, as in equation (2), r_i and θ_i depend on an assumed axial center (c_1, c_2) for the bin. This yields

$$y_i = f(\rho_i | c_1, c_2, e, \varphi) + noise \tag{5}$$

Given data pairs (ρ_i, y_i), let f_α be the non-parametric unimodal function estimate obtained for any particular choice of the four parameters controlling the center and contour shape $\alpha = (c_1, c_2, e, \varphi)$. A simple isotonic regression [1] may be used to post-process the B-spline smooth [11] of y on ρ, after it has been divided into the components that are before and after the maximum. We can then apply a steepest descent procedure to optimize

$$RSS(\alpha) = \sum_{i \in \text{Bin}} [y_i - f_\alpha(\rho_i | c_1, c_2, e, \varphi)]^2 \tag{6}$$

w.r.t. α. In order to ensure that a minimum is picked within the interior of the convex hull of the short-axis data in the bin, we remove the outer fraction of the short axis $(\tilde{x}_1, \tilde{x}_2)$ data, using a quickhull algorithm to compute the convex hull of the set of points of interest incrementally [5] .

We select the boundary surface as the contour level corresponding to a particular uptake level (l). This value l may for instance be chosen as a certain percentile p_l of the uptake distribution, e.g. $p_l = 75\%$. Contouring of the boundary for a fixed axial bin is achieved from the initial shape $\sigma^o_{h_i}(\theta_i)$. In the polar representation (2), the data points are binned into a set of J sectorial subsets. The j'th sectorial subset consists of n_j values with angles in the interval $\left(\frac{2\pi(j-1)}{J}, \frac{2\pi j}{J}\right]$ for $j = 1, 2, ..., J$, using e.g. $J \approx 10$. The collection of scaled radii $\left(\rho_i^j = \frac{r_i}{\sigma^o_{h_i}(\theta_i)}\right)$ and uptake (y_i^j) values in the sector form a data array $\{(\rho_i^j, y_i^j)$ for $i = 1, 2, \ldots, n_j\}$. See Figure 1 for an illustration. To find the threshold radial value matching the desired uptake level, a parametric curve fitted to the noisy data is used to solve for the (largest) radius corresponding to the specified level. We choose a Gaussian function to construct the parametric fit, and use

$$\bar{\rho}_j = \frac{g^{-1}(\frac{l}{\hat{\beta}}) - \hat{\tau}}{\hat{\phi}} \tag{7}$$

where $(\hat{\beta}, \hat{\tau}, \hat{\phi})$ are found by nonlinear least squares (NLS) minimization [2, 9] of

$$RSS(\beta, \tau, \phi) = \sum_i \left[y_i^j - \beta g(\tau + \phi \rho_i^j)\right]^2 \tag{8}$$

The variance of $\bar{\rho}_j$ $(\bar{w}_j^{-1})$ is obtained by propagation of errors [2]. Repeating this process for each sector gives an array of values $\{(\bar{\theta}_j, \bar{\rho}_j, \bar{w}_j)$, for $j = 1, 2, ..., J\}$. Non-parametric spline smoothing [9, 11] of the $\bar{\rho}$-values as a function of $\bar{\theta}$ with weights $\bar{w}$ is used to produce a correction $\vartheta(\theta|h)$ to the initial elliptical contour. This yields the boundary contour $\sigma_h(\theta) = \sigma_h^o(\theta) \cdot \vartheta(\theta|h)$.

A final step in this estimation process must be taken to derive estimates for the functional amplitude, scale and phase parameters in (3). Here also we can carry out an analysis of the binned

long-axis data using NLS to obtain raw estimates, before smoothing over bins using splines to obtain the set of functional parameters. We use the penalized least squares criterion

$$RSS_\gamma(\beta,\tau,\phi) = \sum_{i\in \text{Bin}} \left[y_i - \beta g\left(\tau + \phi \frac{r_i}{\sigma_{h_i}(\theta_i)}\right)\right]^2 + \gamma\beta^2 \tag{9}$$

where $\gamma > 0$, within each axial bin. The penalty is applied to circumvent the issue occurring when larger values of core-phase τ are compensated by larger amplitudes β. A possibility is to pick γ in proportion to the squared coefficient of variation *cov* of the uptake data in the bin, e.g. $\gamma = 0.1 * cov^2$. The penalty term is entered as an additional residual so a standard NLS code [3, 9] can be directly applied for optimization. Raw NLS estimates from each axial bin are smoothed using a cubic spline [9, 11] to obtain the final set of uptake parameters.

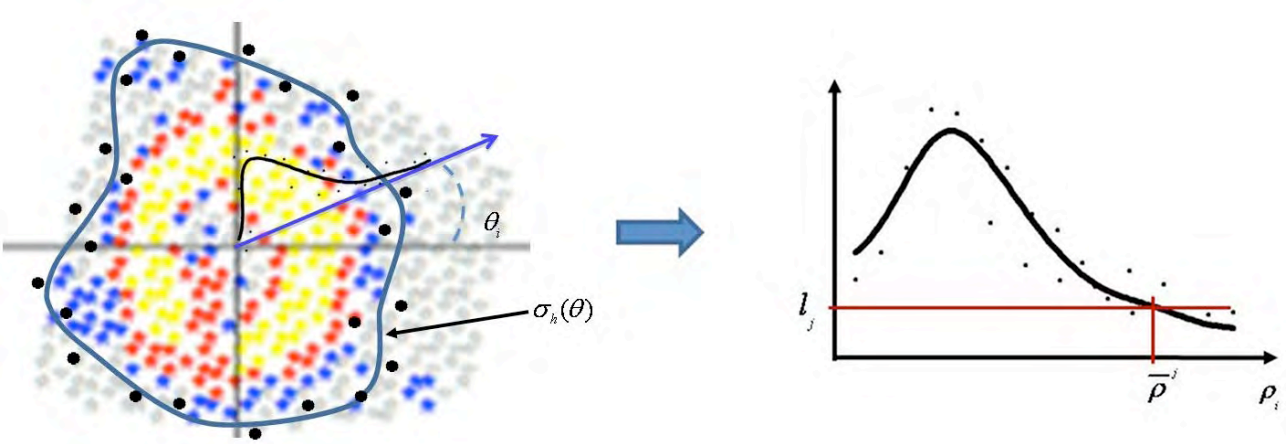

Figure 1: Schematic representation of the boundary contour estimation procedure for binned long-axis data. Left: a particular sectorial ray with fitted model-derived estimates of the boundary radius value $\bar{\rho}_j$ is used for radial analysis. Right: uptake information, represented as a function of the fitted scaled radii ρ_i, provides the collection of derived boundary points (black points) that yield the smoothed boundary contour $\sigma_h(\theta)$.

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Characterization of overall spatial tumor features

Three particular measures are of interest for the detailed characterization of uptake patterns from (3). These measures will further be examined as prognostic variables.

Nonlinearity. We define nonlinearity as a weighted deviation of the central core from a linear function of the long-axis coordinate, and write it

$$\xi = \sqrt{\frac{\sum_{i=1}^N y_i \left[(c_{1h_i} - a_1 - b_1 h_i)^2 + (c_{2h_i} - a_2 - b_2 h_i)^2\right]}{\sum_{i=1}^N y_i}} \tag{10}$$

where the intercepts (a_1, a_2) and slopes (b_1, b_2) are adjusted to minimize ξ.

Phase. Using the measure of local phase (4), we define the average uptake-weighted voxel-level phase as $\bar{u} = \sum_{i=1}^N y_i u_i / \sum_{i=1}^N y_i$. This variable allows us to derive various descriptors of the overall

spatial uptake pattern within the tumor volume. We can consider in particular the core phase, which may provide an indication of central low metabolism tissues (often observed in advanced sarcomas), and define two alternatives: the uptake-weighted core phase ($\bar{u}_c$) and the profile uptake-weighted core phase ($\tilde{u}_c$). These are defined by

$$\bar{u}_c = \frac{\sum_{i=1}^N y_i \tau_{h_i}}{\sum_{i=1}^N y_i} \quad \text{and} \quad \tilde{u}_c = \frac{\sum_{i=1}^N y_i g(\tau_{h_i})}{\sum_{i=1}^N y_i} \tag{11}$$

Model Heterogeneity (H^*). We define a measure of spatial tumor heterogeneity as the lack of fit of the ellipsoidal contoured model. Let us denote the estimated uptake by $\hat{y}_i$ and define this measure of heterogeneity as

$$H^* = 1 - \frac{\sum_{i=1}^N [y_i - \hat{y}_i]^2}{\sum_{i=1}^N [y_i - \bar{y}]^2} \tag{12}$$

where $\bar{y}$ is the mean of values in the ROI. This approach is motivated by previous definitions of heterogeneity measures from spatial ellipsoidal models, see e.g. [4].

Prognostic Evaluation

The proposed sarcoma tumor features were used to carry out a retrospective analysis of a set of 185 FDG-PET clinical studies of sarcoma patients (70 deaths and 95 disease progression events) treated at the University of Washington over a 15 year period. Each scan set was performed with a GE-Advance PET scanner and has a volume with between 35 and 105 image planes with 128×128 voxels in each image. Crude elliptical cylinder ROIs were specified using AMIDE, a free viewer for medical images [6]. Based on this data, we assess the prognostic value of two tumor characteristic features derived from the proposed model: core phase and spatial heterogeneity. We use a multivariate Cox proportional hazards regression [10, 9] for this analysis, with standard diagnostic covariates (grade, the widely used maximum standardized tumor uptake SUV_{max}, and a measure of spatial heterogeneity) along with the proposed measure of core phase. The results of this analysis, reported in Table 1, support the proposition of a prognostic model with heterogeneity based on a crude input elliptical cylinder ROI and the core-phase variables $(u_c, \tilde{u}_c)$. The latter in particular is seen to be strongly associated with risk. Two alternative measures of elliptical heterogeneity [4] as well as the measure (12) were used in place of the elliptical heterogeneity derived from the crude elliptical ROI, and proved to be strong prognostic factors also, with no significant gain observed from one measure over another. This observation suggests that it may be sufficient to use a crude geometrical ROI instead of a more finely-contoured one that would require undergoing a time-consuming and subjective protocol, or indeed to use that measure (12) directly derived from the proposed model (3). Other tumor features derived from this model also proved significant prognostic indicators in similar multivariate analyses. A considered extension of this implementation is the incorporation of a regularization procedure to fit the uptake model, in order to achieve a smoother and more controlled fit to the three-dimensional uptake pattern.

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	Death		Progression	
Variable	Hazard Ratio	95% C.I.	Hazard Ratio	95% C.I.
Grade:Intermediate vs Low	2.96	[0.68,12.9]	2.11	[0.85,5.24]
Grade:High vs Low	5.52	[1.29,23.6]*	3.54	[1.45,8.65]**
SUV_{max}	1.20	[0.93,1.56]	1.05	[0.83,1.33]
Heterogeneity (H_Ω)	1.63	[1.24,2.14]***	1.45	[1.14,1.84]**
Core Phase ($\tilde{u}_c$)	0.81	[0.66,0.99]*	0.82	[0.69,0.98]*

Table 1: Multivariate Cox regression results for death and progression for N=185 patients (70 deaths and 95 disease progression events), where hazard ratios for continuous variables account for proportional changes in risk associated with a standard deviation increase in the variables. H_Ω is the elliptical heterogeneity calculated for the simple AMIDE generated ROI. The symbols *, ** and *** correspond to p-values below 0.05, 0.01, and 0.001, respectively.

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