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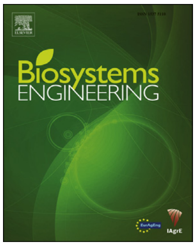

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Early classification of parotid glands shrinkage in radiotherapy patients: A comparative study

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During radiotherapy treatment of patients with head-and-neck cancer, the possibility that parotid glands shrink was evidenced, connected with increasing risk of acute toxicity. In this ambit, the early identification of patients in danger is of primary importance, in order to treat them with adaptive therapy. This work studies different approaches for classifying parotid gland samples, taking into account textural features extracted from computed tomography (CT) images of monitored patients. A real dataset is used, and accuracy, sensitivity and specificity are counted as classification performances. Therefore, firstly, different procedures to define classes are compared in terms of their physical meaning and classification performances. Then, different methods for extracting knowledge from the dataset are implemented and compared in terms of performances and model interpretability. First-rate performance was obtained by using Likelihood-Fuzzy Analysis (LFA), which is a recently developing method based on the use of statistical information by means of Fuzzy Logic. The interpretable models extracted with LFA also allow identifying among textural features those able to predict parotid shrinkage. Some of these features are already known and are confirmed here, others are new, and some of them are very early predictors. Finally, an example of textural feature monitoring and classification of a patient is presented, through a reasoning scheme similar to human reasoning, based on the interpretation of simple rule-based models using linguistic variables.

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1. Introduction

It is widely evidenced that in head-and-neck Radiotherapy (RT) most subjects experienced a loss of salivary functionality. In fact, a very frequent effect of parotid irradiation is a decrease of gland volume, which is associated with the reduction of functionality due to the loss of acinar cells, responsible for the salivary production (Robar et al., 2007). Moreover, this alteration is associated with a higher risk of acute toxicity (Dirix, Nuyts, & Van den Bogaert, 2006), due to an increased radiation dose delivered to the glands. Indeed, when parotids shrink, they also shift toward the head midline, which is typically the high dose region, thus a higher irradiation is received by the glands with respect to the planned dose (Hansen, Bucci, Quivey, Weinberg, & Xia, 2006), and the risk of acute toxicity increases.

In this context, in order to decrease these risks, supportive treatment care or adaptive RT can be provided for selected patients (Broggi et al., 2010). Therefore, it is crucial to identify patients at risk of future parotid shrinkage, during the early phase of treatment and before substantial alterations have occurred, and to contemplate for them a timely modification of the RT plan during the course of treatment, in order to warrant a low level of dose delivery to the healthy tissue of the parotids and thus preserve their functionality. In particular, two main objectives can be pursued: the first one is the individuation of subjects who most probably will be affected by a relevant parotid shrinkage during RT, since timely supportive care can be provided for these patients; the second objective is the optimisation of dose planning, taking into account the predicted parotid modifications. The scope of this work is the achievement of a classification system able to identify parotid glands at risk of a significant volume decrease.

In recent years, the analysis of Computed Tomography (CT) images has allowed monitoring of anatomical and structural modifications of parotid glands, and consequently some research (Belli et al., 2014; Fiorentino et al., 2012; Fiorino et al., 2011, 2012; Marzi et al., 2014; Obinata et al., 2013; Sanguineti, Ricchetti, Thomas, & McNutt, 2013; Scalco, Fiorino, Cattaneo, Sanguineti, & Rizzo, 2013; Teshima et al., 2012; Tomitaka et al., 2011) has dealt with the identification of measured features which show significant changes during the RT treatment. Typically, in this research, the estimated parameters were correlated with some pre-treatment anatomical and dosimetric indices, or with clinical outcomes, in order to assess possible cause–effect relations between them. The purpose of individuating subjects with a higher probability of experiencing parotid variations and toxicity after the end of RT, with respect to those who can preserve their original anatomical condition, was pursued by adopting different statistical strategies, as univariate or multivariate logistic regression (LR) (Beetz et al., 2012; Fiorino et al., 2011, 2012; Marzi et al., 2014; Sanguineti et al., 2013) or Fisher's linear discriminant analysis (LDA) (Scalco et al., 2013). In particular, Scalco et al. made an attempt to select patients affected by high parotid shrinkage at the end of treatment, by using significant early variations of textural features as predictors, dividing samples into two balanced classes, and extracting knowledge to classify new samples using LDA. However, some improvements, which could be made to the results obtained by Scalco et al., can be identified. Firstly, the LDA approach allows a “black box” model to be built, in other words the reasons why each patient is assigned to a particular class are not directly interpretable by users. Moreover, using LDA, it is not possible to measure the uncertainty associated with the classification of each patient. Finally, the accuracy of the classifier reached by Scalco et al. was not completely satisfactory.

The first two problems encountered, regarding the transparency of the model and the possibility of measuring the classification uncertainty, and both connected with the use of LDA or many other methods, are of great importance in a field like medicine. An alternative approach, by means of which it is possible to solve both problems, is based on the use of Fuzzy Logic (Zadeh, 1965), which has widely demonstrated its capability in supporting decisions for different medical classification problems (Pota, Esposito, & De Pietro, 2012, 2013a, 2013b). In particular, fuzzy rule-based systems allow at the same time: *i)* describing the model by a transparent knowledge base, satisfying the physician's need for a clearly interpretable and logical justification of the classification process (Alonso, Castiello, Lucarelli, & Mencar, 2012); *ii)* enriching the assignment of each patient to a class with the associated uncertainty, giving to the physician a measure to evaluate the confidence with which each classified case should be handled.

Regarding the accuracy of the classification, different possible reasons can be identified: *i)* the use of LDA, which linearly separates the feature space into parts associated with different classes; *ii)* the use as possible predictors of only feature variations, and among them, of only those which resulted in significant variations; *iii)* the prior assignment of class labels to the samples of the training set in such a way that the dataset was forced to be balanced.

In order to overcome the described problems, a preliminary study has been made (Pota et al., 2014). In that work, a recently developed method called Likelihood-Fuzzy Analysis (LFA), was used to build a fuzzy rule-based system using statistical information extracted from the dataset, in order to obtain an interpretable model, to allow the measure of classification uncertainty, and to reach good accuracy at the same time. Moreover, the set of possible predictors was enlarged, and the prior assignment of classes to known samples was changed.

In this work, the preliminary results of Pota et al. (2014) are extended to generate a larger number of models. Moreover, different approaches for prior class assignment are extensively described and compared. Furthermore, different methods for model construction are compared. Some new shrinkage predictors are also identified, and finally the interpretability of a chosen model is discussed.

The rest of this paper is organised as follows. The description of the dataset extracted from CT images, of the methods for assigning a class to each sample, of the approaches used to build the classifiers, and of the measures used to evaluate classification performance is given in Section 2. In Section 3, results are presented, compared, and discussed, while Section 4 concludes the work.