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A Decision Support System for the assisted diagnosis of brain tumors: a feasibility study for ^{18}F-FDG PET preclinical studies

E. Grosso, M. López, C. Salvatore, F. Gallivanone, G. Di Grigoli, S. Valtorta, R. Moresco, M.C. Gilardi, J. Ramírez, J. M Górriz and I. Castiglioni

Abstract— **Decision support systems for the assisted medical diagnosis offer the main feature of giving assessments which are poorly affected from arbitrary clinical reasoning. Aim of this work was to assess the feasibility of a decision support system for the assisted diagnosis of brain cancer, such approach presenting potential for early diagnosis of tumors and for the classification of the degree of the disease progression. For this purpose, a supervised learning algorithm combined with a pattern recognition method was developed and cross-validated in ^{18}F-FDG PET studies of a model of a brain tumour implantation.**

I. Introduction

Decision support systems for medical diagnosis are computer-based information systems which are designed to assist physicians with decision-making tasks by automatically determining diagnosis [e.g. 1]. Such active-knowledge systems are recently coming clinically available, offering the main feature of giving assessments which are poorly affected from arbitrary clinical reasoning.

Supervised Machine Learning algorithms, such as Support Vector Machines (SVM) have been applied to *in-vivo* functional imaging studies (e.g. Magnetic Resonance Imaging, MRI, and Positron Emission Tomography, PET), in particular for the classification of functional brain images by means of pattern recognition techniques [2] [3].

The development of SVM in pre-clinical imaging studies is an interesting approach due to the increasingly availability of animal models for a variety of human diseases. Furthermore, animal studies allow better validation of these systems with respect to human studies, due to a more objective a-priori knowledge of the disease under study.

E. Grosso, C. Salvatore, S. Valtorta, and M.R. Moresco are with the University of Milan-Bicocca, Milan, Italy (e-mail: grosso.eleonora@ hsr.it).

G. Di Grigoli and S. Valtorta are with Fondazione Tecnomed, Milan, Italy (email: digrigoli.giuseppe@hsr.it).

F. Gallivanone, M.C. Gilardi and I. Castiglioni are with the Institute of Molecular Bioimaging and Physiology of the National Research Council (IBFM-CNR), Milan, Italy (corresponding author to provide phone: 0039-02-26432715; fax: 0039-02-26415202, e-mail: castiglioni.isabella@ibfm.cnr.it).

M. LÓpez, J. RamÍrez and J. M GÓrriz are with the Department of Signal Theory, Networking and Communications, University of Granada, Spain (e-mail: miriamlp@ugr.es).

Aim of this work was to assess the feasibility of a SVM algorithm for the assisted diagnosis of cancer in preclinical studies, such approach presenting potential for early diagnosis, in classifying the degree of disease progression and in monitoring the early efficacy of new therapies. For this purpose a decision support system based on Principal Component Analysis (PCA) as feature extraction technique [4][5] and on Support Vector Machines (SVM) as classification algorithm was developed, implemented and cross-validated in PET studies of a model of a brain tumour implantation.

II. Materials

A. The animal model of brain tumor

An animal model of brain glioma tumor implantation was implemented [6] [7]. The onset of glioma was induced to a cohort of rats by injection of F98 cells. The cohort was composed of 12 Fischer 344 male rats (age: 8 weeks, weight: 215-226 g).

B. MRI and PET animal studies

All rats (anesthetized with isoflurane) underwent a MRI study after 7 days from cell inoculation (stage I). All MRI studies were performed with a 3T MRI system (Achieva 3T, Philips Medical System, The Netherlands) with a spatial resolution of 0.078x0.078x0.741mm^3 (FOV=40x40mm^2, 512x512 matrix size, 54 slices, 0.741mm slice thickness). Before MRI studies, rats were injected with [^{64}Gd]Gadolinium (23.6mg/200g in 150 µl of Gadovist), that enhanced MR signal in T1-weighted sequences and reduced T1 relaxation time.

All rats (anesthetized with isoflurane) underwent a PET study the day after the MRI study (stage I) but two rats moved during the PET acquisitions. Four rats (anesthetized with isoflurane) underwent also a second PET study after 14 days from cell inoculation (stage II).

All PET studies were performed with a PET animal system (YAP-S-PETII, ISE, Italy) with a spatial resolution of 0.3125x0.3125x1.48mm^3 (FOV=40x40mm^2, 127x127 matrix size, 27 slices, 1.48mm slice thickness). Before PET studies, rats were injected with ([^{18}F]fluorodeoxiglucouse [^{18}F]FDG) (1mCu/200gr in 100 µl of saline solution) to study the glyclolysis of the tumors. The [^{18}F]FDG PET studies started after 60min from injection).

III. METHODS

A. Image pre-processing

PET studies were coregistered to MRI studies. This allowed the coregistration procedure of PET studies to be optimized (coregistration of PET to MRI image volumes has a better accuracy than coregistration of [^{18}F]FDG PET to [^{18}F]FDG PET image volumes, due to the reference of anatomical markers).

All MRI images were limited within a bounding box of 19.5x25.5x15mm^3. All MRI images were coregistered using SPM normalization routines for MRI modality [8]. The first step of the normalization was to determine the optimum 12-parameter affine transformation. A Bayesian framework was used, in order to obtain the solution that maximizes the a posteriori probability.. The affine registration was followed by estimating nonlinear deformations, whereby the deformations were defined by a linear combination of three dimensional discrete cosine transform (DCT) basis functions. Normalization was achieved by using 7x8x7 basis functions, 12 nonlinear iterations.

Each [^{18}F]FDG PET study was normalized to the corresponding MRI study using PMOD software tool [9]. Thus, the coregistered [^{18}F]FDG PET image volume was within the bounding box of 19.5x25.5x15mm^3.

The final brain volume of both MRI and [^{18}F]FDG PET consisted of 251x35x199 voxels (0.078x0.741x0.078mm^3). MRI studies coregistered to PET studies allowed to confirm the classification of PET stage I images also on the basis of the tumor presence, localization and size.

In order to reduce inter-subjects anatomical differences, a smoothing Gaussian kernel of 2x5x2mm^3 with was applied to the coregistered [^{18}F]FDGPET images, using SPM smoothing routine.

A mask was applied on the images in order to discard voxels of no interest for the disease under study. The mask intensity threshold was assessed from 0 to 0.27.

B. The Decision Support System

The decision support system was based on Principal Component Analysis (PCA) as feature extraction technique and on Support Vector Machines (SVM) as classification algorithm [10].

- *PCA analysis*

PCA transformation was applied on the images in order to reduce the dimension of the image space without loosing relevant information. The resultant PCA coefficients obtained by the projection of the [^{18}F]FDG PET images at stage I onto the PCA subspace were used as features of early disease class, while the coefficients corresponding to the [^{18}F]FDG PET images at stage II were gathered into the advanced class, labeled as "0" and "1", respectively.

- *SVM Training*

The PCA features and the associated labels were used to train a SVM classifier with linear kernel, which designed a decision boundary (hyperplane) able to distinguish between the two stages of the cancer disease (the two classes). The classifier was trained on a number of PCA coefficients ranging from 1 to 13. For each number of PCA coefficients, the classifier was trained 14 times, excluding each time one different image from the 14 images of the two classes (stage I and stage II) and using this image as testing element for the SVM classifier (see Section C. *Leave-One-Out cross-validation of the SVM classifier)*

C. *Leave-One-Out cross-validation of the SVM classifier*

A Leave-One-Out (LOO) cross-validation strategy was carried out on the SVM classifier for the different values of the mask intensity threshold and for the different number of PCA coefficients.

The mean accuracy rate (<A>) was calculated for each mask threshold value as in (1).

$$< A >= \sum_{i=1}^{N} \frac{\text{Accuracy}_i}{N} \quad (1)$$

where N is the number of PCA coefficients (13 in this work) and Accuracy_i is the Accuracy of the i-th PCA coefficient computed as in (2)

$$Accuracy_i = \frac{S - S_{WC}}{S} = \frac{S_{RC}}{S} \quad (2)$$

where S is the total number of classified images, S_{WC} is the number of classified images that underwent Wrong Classification (WC); S_{RC} is the number of classified images that underwent Right Classification (RC).

The mask threshold value for which the mean accuracy rate was maximum was chosen as the optimal mask intensity threshold for the SVM classification analysis.

Fixed the optimal mask intensity threshold, a Leave-One-Out (LOO) cross-validation of the classifier was performed by varying only the number of PCA coefficients.

Accuracy was calculated as Accuracy_i, with i=1,..N, while Sensitivity and Specificity were calculated as in (3) and (4)

$$Sensitivity = \frac{P_{RC}}{P_{RC} + N_{WC}} \quad (3)$$

$$Specificity = \frac{N_{RC}}{N_{RC} + P_{WC}} \quad (4)$$

where P_{RC} is the number of images in the class '1' and RC to classification; N_{RC} is the number of images that were in the class '0' and RC to classification; P_{WC} is the number of images in the class '1' and WC to classification; N_{WC} is the number of images in the class '0' and WC to classification.

IV. RESULTS

A. Image pre-processing

As representative example, Fig. 1 shows a slice of a [^{18}F]FDG PET study (transaxial, sagittal, coronal) of a rat brain coregistered and overlapped to the corresponding slice of the MRI study.

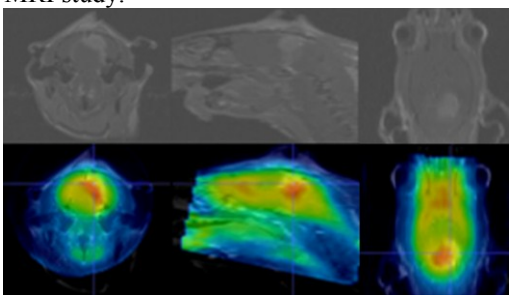

Figure 1. Transaxial, sagittal, coronal [^{18}F]FDG PET and MRI coregistred images of a rat brain.

B. The Decision Support System

- *PCA analysis*

The resultant PCA coefficients are shown in Fig. 2 for a representative [^{18}F]FDG PET image study.

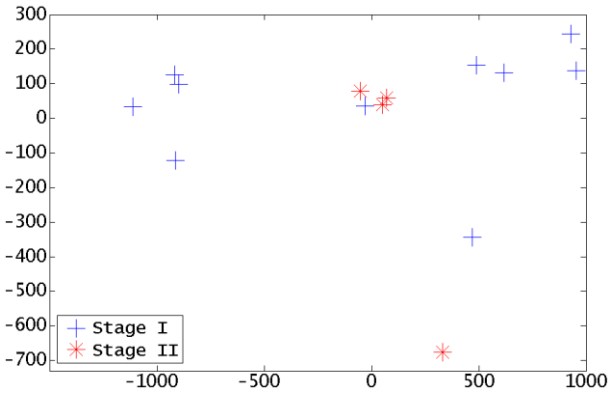

Figure 2. PCA coefficients (1st and 2nd coefficients, MIT=0.19).

- *SVM Training*

As representative example of the SVM Training procedure, Fig. 3 and Fig. 4 show the results of one SVM training on 13 images and the optimal hyper-planes separating the two classes of images ('0','1'), for two different number of PCA components (5 and 8, respectively).

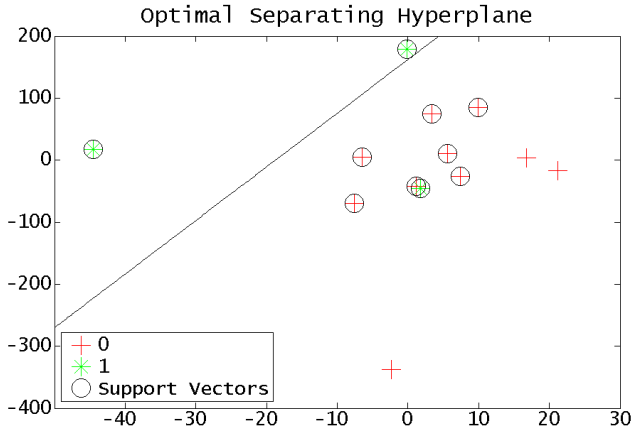

Figure 3. Optimal separating hyper-plane with 5 PCA coefficients, MIT=0.19 (Stage II study of Rat 7excluded)

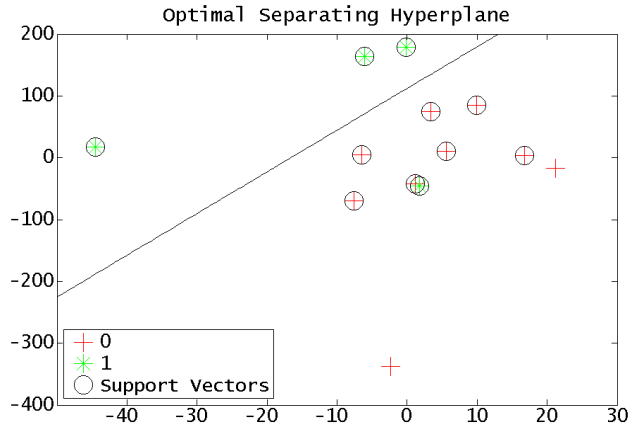

Figure 4. Optimal separating hyper-plane with 8 PCA coefficients, MIT=0.19 (Stage I study of Rat 12 excluded).

C. LOO cross-validation

The results of mean accuracy rate (<A>) as a function of the mask intensity threshold are summarized in Table I.

TABLE I. MEAN ACCURACY RATE OF SVM

Mask intensity threshold	Mean accuracy rate (<A>) (%)
No mask	89.01 ± 6.91
0.10	84.06 ± 12.42
0.15	86.26 ± 17.61
0.17	85.16 ± 10.29
0.18	87.91 ± 10.67
0.19	90.66 ± 9.40
0.20	90.11 ± 8.52
0.21	90.11 ± 9.01
0.23	89.56 ± 9.94
0.27	84.07 ± 10.17

The mask threshold value for which the mean accuracy rate was maximum (optimal mask intensity threshold) was 0.19; it corresponded to a mean accuracy rate value of 90.66% ± 9.40%. The results of the Accuracy, Sensitivity and Specificity of the SVM classifier (optimal mask intensity threshold, MIT =0.19) for the different number of PCA

components, are presented in Table II. All the imaging studies in the dataset were correctly classified by the SVM for a number of PCA coefficient = 4, 5, 6, 8 and 9 (Accuracy = 100%). When using 1, 2, 3, 7, 10, 11, 12 and 13 PCA coefficients, the Accuracy decreased, up to 71.43% for 13 PCA coefficients. The results show that for 4, 5, 6, 8 and 9 PCA coefficients, also the sensitivity and the specificity rates reach a value of 100%.

TABLE II. ACCURACY RATE OF SVM (MIT=0.19)

PCA coefficients	Accuracy (%)	Sensitivity (%)	Specificity (%)
1	78.57	100	76.92
2	85.71	100	83.33
3	92.86	100	90.91
4	100	100	100
5	100	100	100
6	100	100	100
7	92.86	100	90.91
8	100	100	100
9	100	100	100
10	85.71	100	83.33
11	85.71	75	90
12	85.71	100	83.33
13	71.43	50	75

The output results obtained by the SVM classifier under the LOO validation strategy for all the considered image studies (10 [^{18}F]FDG PET images at stage I and 4 [^{18}F]FDG PET images at stage II) for 4,5,6,8 and 9 PCA components is presented in Table III.

TABLE III. SVM CLASSIFICATION, 4 PCA, MIT=0.19

Rat	Stage	SVM classification
1	I	0
2	I	0
3	I	0
4	I	0
	II	1
5	II	1
6	I	0
	II	1
7	II	1
8	I	0
9	I	0
10	I	0
11	I	0
12	I	0

V. CONCLUSIONS

A Decision Support System for the early diagnosis and staging of brain tumors has been developed and applied to PET studies in a model of a brain tumour implantation.

Although both the SVM training and validation were limited by the poor number of samples, the application of SVM to the considered rat brain-glioma model returned an Accuracy, Specificity and Sensitivity of 100% by means of LOO validation. These results encourage the use of SVM methods in PET oncological studies with the purpose of the early diagnosis and classification of the progression of the disease, but this experiment should be repeated with more samples and with a more fair distribution between classes for a significant validation and in order to avoid overtraining for one class.

Since SVM does not return any spatial information, a joint of this methodology at another one that includes spatial pattern recognition, such as Statistical Parametric Mapping, could represent an effective way of merging the high accuracy of SVM to regional characteristics of the diseases, increasing the potential of the systems (e.g. toward a differential diagnosis).

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