PhD in Information Technology and Electrical Engineering

Università degli Studi di Napoli Federico II

PhD Student: Gabriele Piantadosi

XXIX Cycle

Training and Research Activities Report – Third Year

Tutor: Carlo Sansone – co-Tutor: Mario Sansone

Student

I graduated in Computer Engineering; currently, I am attending the third year of PhD in Information Technology and Electrical Engineering - ITEE- XXIX Cycle at the University of Naples Federico II, under the supervision of Prof. Carlo Sansone and Prof. Mario Sansone. I was awarded a MIUR research grant.

Study Activity

Seminars (third year)	Type	Lecturer	Date	H	CFU
IBM Cognitive Computing	Int	Pietro Leo	17/02/2017	2	0.4
Cognitive Computing and Da Vinci Robot	Int	Paolo Maresca	17/02/2017	1	0.2

	Credits year 1								Credits year 2								Credits year 3								Total	Check
	Estimated	1 bimonth	2 bimonth	3 bimonth	4 bimonth	5 bimonth	6 bimonth	Summary	Estimated	1 bimonth	2 bimonth	3 bimonth	4 bimonth	5 bimonth	6 bimonth	Summary	Estimated	1 bimonth	2 bimonth	3 bimonth	4 bimonth	5 bimonth	6 bimonth	Summary		
Modules	26	0	3	0	3	3	11	**20**	15	3	7	0	3	0	6	**19**	5	0	0	0	0	0	0	**0**	**39**	30-70
Seminars	13	2.4	1	4.8	1	1.5	2.3	**13**	12	0.2	0.9	0	0	6.8	0	**7.9**	5	0	0	0	0	0	0.6	**0.6**	**21.5**	10-30
Research	21	7.6	6	5.2	6	5.5	0	**30.3**	33	6.8	2.1	10	7	3.2	4	**33.1**	50	10	10	10	10	10	9.4	**59.4**	**122.8**	80-140
	60	10	10	10	10	10	13.3	**63.3**	60	10	10	10	10	10	10	**60**	60	10	10	10	10	10	10	**60**	**183.3**	180

Research Activity

Breast cancer is the most common women tumour worldwide, about 2 million new cases diagnosed each year (second most common cancer overall). This disease represents about 12% of all new cancer cases and 25% of all cancers in women. Early detection of breast cancer is one of the key factors in determining the prognosis for women with malignant tumours.

In recent years, Dynamic Contrast Enhanced-Magnetic Resonance Imaging (DCE-MRI) has gained popularity as an important complementary diagnostic methodology for early detection of breast cancer, in staging newly diagnosed patients and in assessing therapy effects [1]. Due to the huge amount of data of the 4D DCE-MRI volumes, automatic detection and diagnosis of suspicious ROIs is still an open problem [2,3].

Among of the major issues in developing computer-aided detection\diagnosis (CAD) systems for breast DCE-MRI, there is the detection and the diagnosis of the suspicious region of interests (ROIs) as sensibly as possible, while simultaneously minimising the number of false alarms. This task is made harder by the peculiarity of soft tissues since any patient movements (such as involuntary due to breathing) may affect the voxel-by-voxel dynamical analysis. A therapy assessment stage should also be considered to further assist the physician in the follow-up designing.

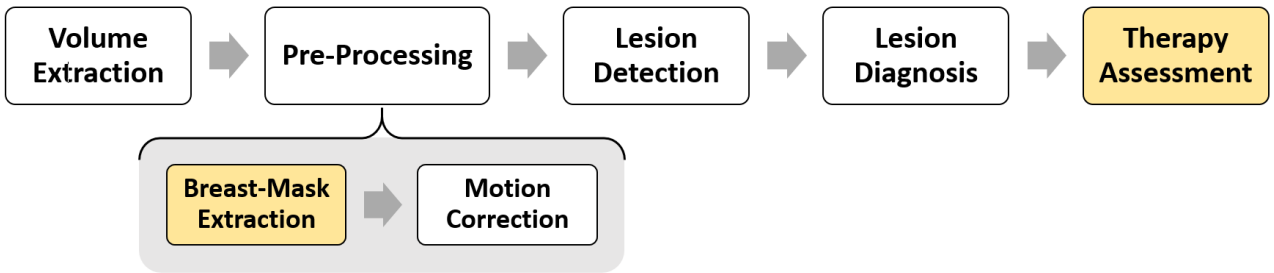

Fig.1: Block diagram of the automated proposed CAD. In yellow the stage added or improved in the last year of my PhD.

My whole research activity is mainly focused on developing a fully automated CAD system. My proposal has been modelled as a series of successive refinements (fig.1) applied to patient DCE-MRI images. The whole CAD has been designed over the three years of PhD; in the last year, I focused on the **breast-mask extraction** and **therapy assessment** stages.
To briefly summarise, the CAD proposal consists of:

- **Volume Extraction:** DCE-MRI data basically consists of a 4D volume (3 spatial dimensions + 1 temporal dimension) produced by different protocols. For each Voxel, a TIC (Time Intensity Curve) is extracted. This step prepares the data to be compatible with the next steps.
- **Breast Mask Extraction:** With the aim of reducing the computational cost of further steps and attenuate noise caused by extraneous voxel (VOlumetric piXEL) a binary mask representing only breast parenchyma and excluding background and other tissues is extracted. Segmentation of breast parenchyma has been addressed relying on fuzzy binary clustering, breast anatomical priors and morphological refinements. The breast mask extraction module combines three 2D Fuzzy C-Means clustering (executed from the three projection, axial, coronal and transversal) and geometrical breast anatomy characterization. In particular, seven well-defined key-points have been considered in order to accurately segment breast parenchyma from air and chest-wall (more details in the next paragraphs) [14].
- **Motion Correction:** It is well known [5] that some sort of motion correction technique should be performed before DCE-MRI data analysis in order to reduce movement artefacts. To diminish the effects of involuntary movement artefacts, it is usual to apply a motion correction of the DCE-MRI volumes before of any data analysis. However, there is no evidence that a single Motion Correction Technique (MCT) can handle different deformations - small or large, rigid or non-rigid - and different patients or tissues. Therefore, it would be useful to develop a quality index (QI) to evaluate the performance of different MCTs [6,11]. The existent QI might not be adequate to deal with DCE-MRI data because of the intensity variation due to contrast media. Therefore, in developing a novel QI, the underlying idea is that once DCE-MRI data have been realigned using a specific MCT, the dynamic course of the signal intensity should be as close as possible to physiological models [7], such as the currently accepted ones (e.g. Tofts-Kermode, Extended Tofts-Kermode, Hayton-Brady, Gamma Capillary Transit Time, etc.). The motion correction module ranks all the MCTs, using the QI, selects the best MCT and applies a correction before of further data analysis.
- **Lesion Detection:** Segmentation of the breast parenchyma [4] could be approached as a classification problem. The proposed lesion detection module performs the segmentation of lesions in Regions of Interest (ROIs) by means of classification at a pixel level. It is based on a Support Vector Machine (SVM) trained with dynamic features, extracted from a suitable pre-selected area by using a pixel-based approach. The pre-selection mask strongly improves the final result.
- **Lesion Diagnosis:** To perform a fully automated detection and diagnosis [12], each ROI needs to be investigated to assess the lesion aggressiveness. The lesion classification module evaluates the malignity of each ROI by means of 3D textural features. The Local Binary Patterns descriptor has been used in the Three Orthogonal Planes (LBP-TOP) configuration [8,9]. A Random Forest has been used to achieve the final classification into a benignant or malignant lesion.
- **Therapy Assessment:** It would be convenient to determine those subjects who are likely to not respond to the treatment so that a modification may be applied as soon as possible, relieving them from potentially unnecessary or toxic treatments. For each patient which has at least a malignant lesion, the recurrence of the disease has been evaluated by means of a multiple classifiers system. A set of dynamic, textural, clinicopathologic and pharmacokinetic features have been used to assess the probability of recurrence for the lesions (more details in the next paragraphs).

Finally, to improve the usability of the proposed work, a framework for tele-medicine that allows advanced medical image remote analysis in a secure and versatile client-server environment, at a low cost, was developed [10,13]. The benefits of using the proposed framework have been presented in a real-case scenario where OsiriX, a wide-spread medical image analysis software, was allowed to perform advanced remote image processing in a simple manner over a secure channel.

Third Year Activities

During the third year, I focused on investigating each step with the final aim of maximising the accuracy (with respect to a gold-standard provided by an expert radiologist). The breast mask extraction stage has been redesigned to maximise the accuracy with respect to a new gold-standard. Moreover, thanks to my six months abroad activities at the University of South Florida (USF), I added a novel therapy assessment stage to the CAD.

The **segmentation of breast parenchyma** [14] has been addressed relying on fuzzy binary clustering, breast anatomical priors and morphological refinements. In breast segmentation, the most difficult issue to address is discriminating the breast parenchyma from the pectoral muscle since signal intensities, textures and anatomical structures of these tissues are very close each other.
The proposed breast mask extraction approach overcomes the issue by mixing geometrical-based and pixel-based approaches. It relies on geometrical anatomical priors to take advance of anatomical knowledge of the breast key points and uses a pixel base segmentation to obtain the best threshold for each border.
It uses a pixel-based Fuzzy C-Means (FCM) clustering to shift the breast mask extraction from a simple grey-level based segmentation to a membership probability one. Moreover, it exploits novel geometrical consideration to weight the classes membership probability according to the breast anatomy.
The result is an automated procedure, able to extract an accurate breast mask without any prior information on the patient dataset (as in the case of atlases). The proposed procedure can be schematically depicted as composed of four main stages (fig.2).

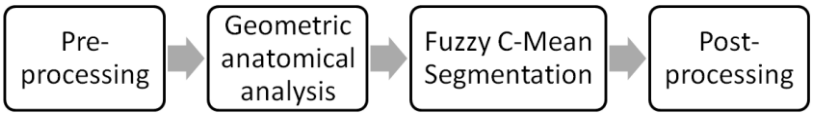

Fig.2: Block diagram of the breast mask extraction proposal.

- **Pre-processing:** The pre-processing stage lays the foundations for successive stages. The first operation consists in *reducing* the 4D DCE-MRI data to a single 3D volume, whose voxels are chosen by taking the minimal values along the time dimension for each spatial coordinate. Then, to sharpen borders of the chest wall and to smooth heart and lungs ghosts, a *flattening* process was performed. Flattening consists in applying a 2D median filter on each coronal slice, in order to attenuate brightness variations only along axial and sagittal directions, producing flat (with respect to brightness) coronal slices. The flattened 3D volume represents the data on which all successive operation will be executed.
- **Geometric anatomical analysis:** Seven anatomical key-points are automatically identified using a primal binary breast mask (fig.8 – the blue cuboid in the right image), defined by apply Otsu's Threshold on the flattened data volume. The key-points are: two nipples points (NRP and NLP), two armpits points (ARP and ALP), one chest wall point (CWP), one sternum point (SP) and one heart point (HP) (fig.3).

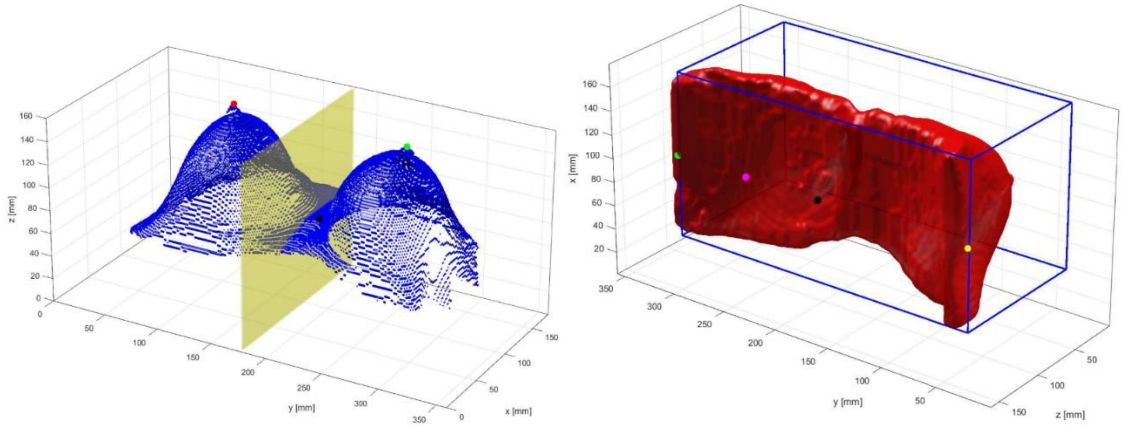

Fig.3: Anatomical characterization of the breast shape via seven key-points automatically identified. On the left image is the nipples key-points (in red and green, respectively, the right and left nipple key-points) and of the chest-wall key-point (in black). In blue the breast-air surface while in yellow the middle plane. On the right image the armpits key-points (in yellow and green, respectively, the right and left armpits key-points), of the sternum key-point (in black) and of the heart key-point (in magenta). In red the volume and in blue the detected cuboid.

The two ***nipples key-points*** are identified by finding the two highest points on the breast-air surface according to the relative position with respect to the middle plane. The ***chest wall key-point*** is identified by searching the point with the minimum height in the breast-air surface enclosed by the two nipples points. The two ***armpits key-points*** are taken in the middle of the right and left edges of the back face of the cuboid. Finally, the ***sternum key-point*** is calculated in the middle of the two armpits, and the ***heart key-point*** is calculated in the middle of the sternum point and the left armpit point.
Each key-point is provided with an action radius calculated according to the anatomy of the specific patient, defining a *pertinence sphere* for the related key-point. It follows that each key-point influence varies within the pertinence sphere, from a maximum value of 1 (reached in the centre) to a minimum value of 0 (reached on sphere surface and beyond) according to the following *key-points influence function* (kpi):

$$kpi(KP, KPr, P) = \begin{cases} 1 - \dfrac{d(KP,P)}{KPr}, & if: d(KP,P) \leq KPr \\ 0, & if: d(KP,P) > KPr \end{cases}$$

Defined over the generic point (P) in the 3D space for a generic key-point (KP) with a generic action radius (KPr) and where d(A, B) is the Euclidean distance in a 3D space between the points A and B.
Action radii are automatically calculated with the reciprocal distance of the key-points as shown in the fig.4.

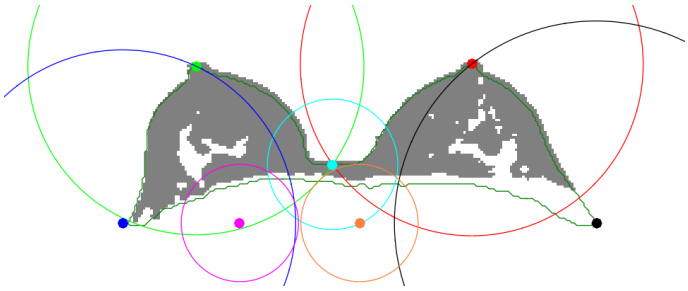

Fig.4: Action radius for each key-point. In grey the rough Otsu's segmentation, in dark green the desired breast mask and the key-points as follow: NRP (red), ARP (black), NLP (green), ALP (blue), CWP (cyan), SP (orange), HP (magenta).

- **Fuzzy C-Mean Segmentation:** For segmentation, Fuzzy C-Mean (FCM) is used. FCM is a clustering procedure very similar to the well-known K-Means algorithm, but in which the voxel class membership is not a binary condition, but a probability vector (fuzziness). In this module, FCM is calculated on two classes: the breast tissues (the class with the higher signal intensity) versus the other tissues/air (the class with the lower signal intensity). It is worth noticing that a 3D FCM clustering produces an unsuitable result since it is not able to separate all the breast tissues. On the contrary, a slice-wise 2D clustering allows exploiting local anatomical consideration to achieve a more suited segmentation. Then a slice-by-slice FCM was applied, repeating the clustering along each anatomical axis. Each of these three fuzziness volumes, taking into account brightness transitions between each slice along a given projection, highlights different characteristics of the breast anatomy. In particular (fig.5): the ***Sagittal 2D-FCM*** is able to better enhance the armpits cavities and to better reject the heart and the sternum tissues; in the ***Transversal 2D-FCM*** the pectoral muscle edges are well-defined, but fails the armpits cavities estimation (in the most of the patients the grey-levels of the armpits cavities show a significant difference between the right and the left side); the ***Coronal 2D-FCM*** can be used to easily detect the breast-air boundary, but shows a very high enhancement of pectoral muscle and heart.

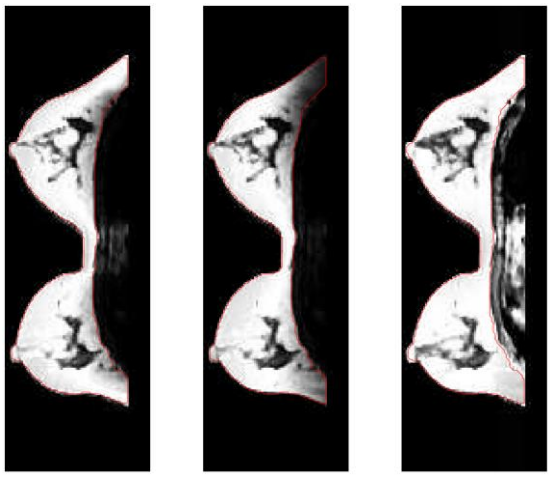

Fig.5: The three fuzziness volumes (obtained as a slice-by-slice among each projection: (a) Sagittal, (b) Transversal and (c) Coronal.

To obtain a single fuzziness volume that better attenuate the pectoral muscle and the heart anatomy while enhancing armpit cavities and breast tissues, the three FCM volumes are voxel-wise combined according to the equation:

$$\begin{aligned}\mathrm{FCM}_{\mathrm{weighted}}(\mathrm{P}) = \mathrm{FCM}_{\mathrm{sagittal}} \\ + \mathrm{FCM}_{\mathrm{frontal}} \cdot \mathrm{kpi}(\mathrm{NRP}, \mathrm{NRPr}, \mathrm{P}) \\ + \mathrm{FCM}_{\mathrm{frontal}} \cdot \mathrm{kpi}(\mathrm{NLP}, \mathrm{NLPr}, \mathrm{P}) \\ + \mathrm{FCM}_{\mathrm{sagittal}} \cdot \mathrm{kpi}(\mathrm{ARP}, \mathrm{ARPr}, \mathrm{P}) \\ + \mathrm{FCM}_{\mathrm{sagittal}} \cdot \mathrm{kpi}(\mathrm{ALP}, \mathrm{ALPr}, \mathrm{P}) \\ + \mathrm{FCM}_{\mathrm{transversal}} \cdot \mathrm{kpi}(\mathrm{CWP}, \mathrm{CWPr}, \mathrm{P}) \\ - \mathrm{FCM}_{\mathrm{frontal}} \cdot \mathrm{kpi}(\mathrm{SP}, \mathrm{SPr}, \mathrm{P}) \\ - \mathrm{FCM}_{\mathrm{frontal}} \cdot \mathrm{kpi}(\mathrm{HP}, \mathrm{HPr}, \mathrm{P})\end{aligned}$$

It is worth noticing that the first term is not weighted ensuring that each area not covered by the key-points and by their pertinence radii have, at least, a FCM sagittal contribution (the most reliable one); the last two terms are intended to attenuate the effects of the sternum and heart and, for this reason, are subtracted instead of added.

Finally, starting from the processed weighted fuzziness volume, a binary breast mask is obtained by applying a thresholding on the fuzziness values. The best threshold is automatically detected by means of the Otsu's method on the processed weighted fuzziness values.

- **Post-processing:** Post-processing is performed to refine the breast mask obtained in the previous stage. In particular, it consists in the following morphological refinements: a slice-by-slice hole-filling performed first along the frontal direction, then along the sagittal and finally along the transversal one. To be more precise, the frontal refinement fills only holes smaller than a quarter of the current mask slice area (with a maximum area of 60 mm^2, determined from the maximum diameter of a lesion in the dataset). Then a 3D smoothing (with a Gaussian filter - 3D windows = [3,3,3], σ=.65 and μ=0) is performed in order to mitigate the effects of a rough segmentation. Finally, to remove small volumes remaining from the heart or sternum, only the bigger connected volume is selected.

It would be convenient to determine those subjects who are likely to not respond to the pre-surgery treatment, and to the surgery itself, so that a modification may be applied as soon as possible, relieving them from potentially unnecessary or toxic treatments.

The **therapy assessment stage** aims to predict the patient primary tumour recurrence to support the physician in the evaluation of the therapy effects and benefits. After voxel-by-voxel lesion segmentation and then, after lesion-by-lesion aggressiveness diagnosis, only the malignant lesions have been considered at this stage. For each patient with at least a malignant lesion, the feature extraction and, consequently, the classification is performed to produce the final binary judgement about a possible recurrence of the tumour.

Different features have been used to assess the primary tumour recurrence:

- **Dynamic features:** Dynamic features (DYN) are extracted directly from the Time Intensity Curve (TIC). Since a whole lesion is analysed at this stage, the median value of the single feature is considered as representative value for that features in each ROI under examination. In addition to the features proposed in the literature and so far listed, two new features have been added. Relying on the fact that AUC and, in particular, nAUC (fig.6), brings information about the most active part of the lesion, the percentage of the most active part is considered as a new feature. By varying the approach of how to thresholding the nAUC map two different features are proposed: AUGT, AULT. In *AUGT (Area Under Global Threshold)* a global threshold, chosen with the Otsu method, within the nAUC values of all the patients. In *AULT (Area Under*

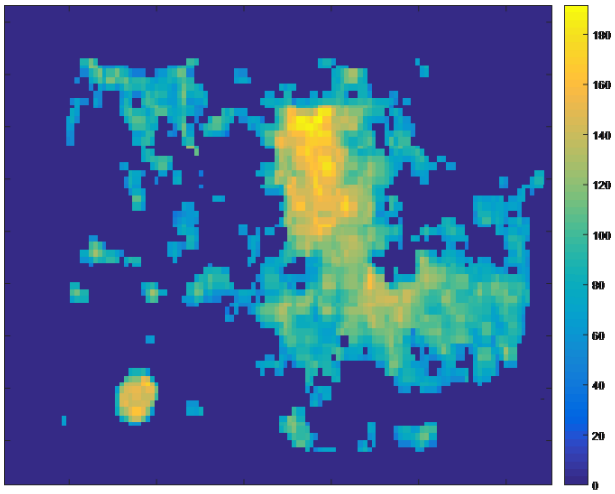

Fig.6: Normalized Area Under (nAUC) map for a single slide calculated inside the lesion ROI. It is easy to spot the most active regions of the tumour.

Local Threshold) a patient based thresholding is performed by applying Otsu only on the value of the single patient.

- **Pharmacokinetic features:** Physiologically Based Pharmacokinetic features (PBPK) extraction is performed relying on the Tofts-Kermode (TK) model [7], a simple compartmental approach in which the intra-vascular compartment can be neglected. According to this model, the time course of the contrast agent concentration $C_t(t)$ is the result of convolution between an exponential kernel and arterial input function (AIF) $C_p(t)$.
  The pharmacokinetic parameters were calculated from the mean signal intensity of the ROI over the time course of the acquisition, resulting in three pharmacokinetic parameters: The transfer constant (K^{trans}), the extracellular extra-vascular space fraction (v_e) and the Efflux rate (k_{ep}).
- **Morphological features:** In this stage, very simple geometrical features have been used, in particular volumes and the longest diameters of the lesions have been carried out. The morphological features bring information about the sizes of the lesion and, when evaluated in the different phases of the treatment, could be used to evaluate the effectiveness of a treatment. Therefore, for each geometrical measurement, the values before and after the neoadjuvant treatment are considered as features.
- **Clinicopathologic features:** The following features are directly extracted from the patient record and represent the clinical status and the pathological condition.

The proposed Multiple Classifier System (MCS) combines the results of two classifiers trained separately with dynamic and pharmacokinetic features feature on a side and on morphological and clinicopathologic feature on the other hand (fig.7). The result of each branch is the probability of disease recurrence derived from a classification of the specific feature group. The combination is obtained with a weighted Majority Voting (wMV) strategy.

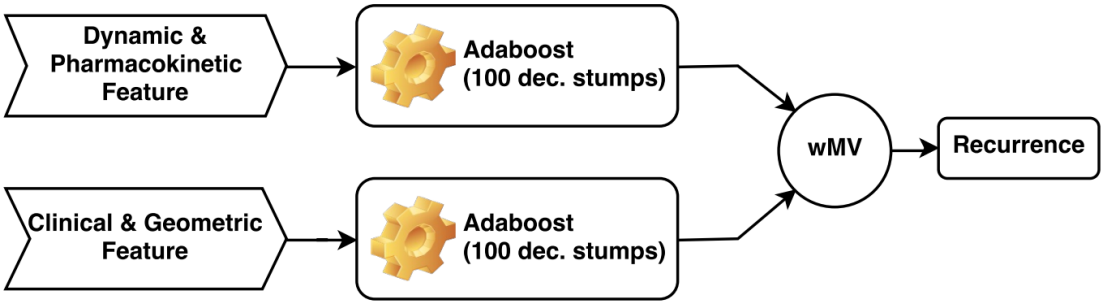

Fig.7: Block diagram of the therapy assessment Multiple Classifier System. Weighted Majority Voting (wMV) as combining strategy was used.

Activity abroad

I spent six months (from April to October 2016) at the University of South Florida under the supervision of the Prof. Lawrence O. Hall (Department of Computer Science and Engineering). This collaboration allowed me to add the therapy assessment stage to the final CAD and new results to the final PhD dissertation.
During the collaboration abroad, I was involved in a national contest for the therapy assessment with the aim of forecasting the disease-free survival time. I got the best result with respect to the other participants from the USF.

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Products

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In preparation:

journal paper on Therapy Assessment in collaboration with USF.