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MARIE SKŁODOWSKA-CURIE ACTIONS

Individual Fellowships (IF)
Call: H2020-MSCA-IF-2015

PART B

"proposal ACRONIM"

This proposal is to be evaluated as:

Standard EF

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ummary

1 SUMMARY

Breast cancer is the leading cause of cancer deaths among females worldwide.Nevertheless, death by breast cancer are highly reduced by early treatment. Thus, to run a chance of surviving breast cancer, it is uttermost important the early detection of malignant tumors. This has motivated the establishment of Breast Screening PolicyBreast Screening Policies (BSPs) to facilitate this breast cancer detection at an early stage. Despite X-ray Digital Mammography (DM) is considered the gold standard technique for BSP, other screening techniques like Ultra-Sound (US) and Magnetic Resonance Imaging (MRI) are being investigated to overcome DM limitations due to tissue superposition which can either mimic or obscure malignant pathology, and avoid X-ray radiation all together.

From the different DM alternatives, the most promising to overcome the aforementioned limitations is MRI. However, Non-mass-like enhancing (NMLE) lesions exhibit a heterogeneous appearance in breast MRI with high variations in kinetic characteristics and typical morphological parameters, and resulting in a lower reported specificity (69%) and sensitivity (75%) than mass-enhancing lesions. Combinations of morphological and temporal BI-RADS descriptors have proven to be insufficient to aid in the automated differential diagnosis of these lesions in Contrast-Enhanced MRI (CE-MRI). Newest clinical studies suggest that T2-weighted image sequences and Diffusion-Weighted Imaging (DWI) may provide additional specificity.

The aim of this fellowship is to translate these findings into a new Computer Aided Diagnosis (CAD) system. Our hypothesis is that a combination of novel descriptors extracted from multiparametric breast MRI has the potential to substantially improve the diagnostic value of the detection and classification of NMLEs.

This first and novel CAD system in multiparametric breast MRI will reduce false positive recalls and thus increase specificity. A reduction in recall of only 5% would already be clinically relevant, considering the costs and patient discomfort associated with second look ultrasound examinations and biopsies.

The experience of ViCOROB in Breast-CAD, the preliminary studies in multispectral MRI carried out in FSU at the scientific computing division, and the clinical support from UDIAT guarantee the success of this project as well as the correct transfer of knowledge from the laboratory to the clinical site. It is also planned to commercialise the output CAD tool to clinical sites through existing medical imaging companies or via a spin-off.

The specific aims of this proposed project are to:

Aim 1:

Develop an image regularization framework for multiparametric breast MRI that includes a novel simultaneous elastic registration and segmentation algorithm. ***Impact:*** *This methodology is fundamental for a correct image regularization and dramatically impacts the correct subsequent detection and diagnosis of NMLE lesions.*

Aim 2:

Develop and apply novel image descriptors for characterizing lesion heterogeneity in T2-weighted MRI and DWI. ***Impact:*** *A combination of these image descriptors may increase the diagnostic value of existing CAD systems in breast MRI.*

Aim 3:

Develop spatio-temporal feature extraction algorithms in CE-MRI. ***Impact:*** *These algorithms from Aim 2 and 3 will facilitate the categorization of NMLEs lesions.*

Aim 4:

Evaluation of the CAD system in terms of performance compared to trained readers and gold standard. ***Impact:*** *Radiologists can benefit from this system by reduced interobserver variation and improved interpretation of breast MRIs for the presence or absence of malignant non-mass-like enhancing lesions.*

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2 EXCELLENCE

2.1 Quality, innovative aspects and credibility of the research

Introduction to breast cancer and multiparametric MRI Breast cancer is the leading cause of cancer deaths among females worldwide[1]. This has motivated the establishment of BSPs to facilitate breast cancer detection at an early stage. Despite X-ray DM is considered the gold standard technique for BSP, other screening techniques like US and MRI are being investigated to overcome DM limitations due to tissue superposition which can either mimic or obscure malignant pathology, and avoid X-ray radiation all together.

Though MRI is a promising alternative to DM, NMLE lesions exhibit a heterogeneous appearance in breast MRI with high variations in kinetic characteristics and typical morphological parameters[2], and have , and resulting in a lower reported specificity (69%) and sensitivity (75%) than mass-enhancing lesions[3] in CE-MRI. The diagnosis of NMLE lesions is thus far more challenging.

Malignant lesions such as Ductal Carcinoma in Situ and Inflating Lobular Carcinoma commonly exhibit a segmental or linear enhancement pattern and benign lesions such as fibrocystic changes present as well a NMLE[4]. However, a systematic classification of NMLE lesions is not in place. A classification of such lesions would be highly beneficial since they may reduce the biopsies numbers. Recently, there have been new research initiatives to assess NMLE lesions using multiparametric MRI which combines T1-weighted contrast-enhanced MRI with DWI .

PBH + 13, YMK - 10

It was shown that the combination of morphological, functional and molecular information offered by multiparametric MRI improves the diagnostic accuracy of breast cancer diagnosis. Another study showed that T2-weighted imaging can better represent the morphological features of small lesions and combined with DWI it increased the diagnostic performance of MRI. CAD systems showed a much lower sensitivity (0.79 vs. 0.97) and specificity (0.56 vs. 0.8) for NMLE lesions compared with masses and suggested the need for more advanced algorithms for the diagnosis of NMLE[5]. Uniformity, and a clear set of imaging descriptors for the reporting of T2 and DWI features of NMLE is lacking. Furthermore, there is no quantitative technique for how to combine the morphological, functional and molecular information derived from multiparametric imaging.

WCH - 14

The bottleneck that remains for providing an improved differential diagnosis of NMLE lesions and thus contribute to advancing CAD systems beyond the current level are determining descriptors that incorporate the diagnostic information from multiparametric MRI. **Our proposal to develop advanced image analysis algorithms to improve the differential diagnosis of the challenging NMLE lesions would provide the radiologist with a fast and accurate computational diagnosis support.**

Here is missing a to state somewhere:
best career possibilities for the experiecned researcher and new collaboration opportunities for the host organization(s)

Research objectives With the aid of this fellowship, the experience in Breast-CAD of ViCOROB, the preliminary results in CE-MRI from FSU, and the clinical support from UDIAT, we aim to encode multiparametric MRI clinical findings into a new CAD with higher specificity that will reduce the costs and patient discomfort associated with second look examinations and biopsies. In order to successfully achieve this purpose, the following objectives will be pursued:

Aim 1: Develop a novel image regularization framework for NMLE lesions from multiparametric MRI.

The regularization step represents a crucial step for the subsequent feature extraction and classifica-

maybe make reference to ASURE project

[1] Ahmedin Jemal et al. "Global cancer statistics". In: *CA: A Cancer Journal for Clinicians* 61 (2011). cancerStatistics2011

[2] **skamato2008categorization**; Eric L Rosen et al. "BI-RADS MRI Enhancement Characteristics of Ductal Carcinoma In Situ". In: *The breast journal* 13.6 (2007), pp. 545–550; rosen2007birads Hidetake Yabuuchi et al. "Non-mass-like enhancement on contrast-enhanced breast MR imaging: lesion characterization using combination of dynamic contrast-enhanced and diffusion-weighted MR images". In: *European journal of radiology* 75.1 (2010), e126–e132. yabuuchi2010nmle

[3] **Vag**.

[4] **Vag**.

[5] **Newell**; **Vag**; **Jansen1**; **Jansen2**.

tion since the images stem from heterogeneous sources. A standard preprocessing step is followed by a novel joint segmentation and registration algorithm. We propose a novel joint segmentation and registration algorithm based on a variational model and level set approach which incorporates spatial as well as temporal contrast-enhanced images. The multiparametric images are registered such that all segmented images will be in the same reference frame.

maybe MRF, to link with m thesis

Aim 2: Identifying novel descriptors such as structure tensors and texture from T2-MRI and Intravoxel Incohe

The BI-RADS-based features from CE-MRI proved to be insufficient to differentiate between malignant and benign for NMLE lesions and therefore additional descriptors from multiparametric images are needed . Furthermore, the lesion heterogeneity is insufficiently described by a single ADC threshold and thus more detailed structural and functional image features have to be extracted from T2-MRI and DWI. The proposed novel descriptors include the additional information from multiparametric MRI and thus capture the structure of the breast tissue in a unique manner like no other method before.

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PBH + 13

Aim 3: Identifying novel spatio-temporal descriptors from CE-MRI as the most powerful discriminators of DCI

ADC stands for?

In the case of NMLE lesions, there is a high variance in morphological and kinetic characteristics and as a consequence a high proportion of false-positive diagnosis . The automated extracted features that have been applied to lesion characterization capture either the variations in their temporal enhancement or in spatial (morphological) structures or they are global features unable to describe local information. To address this shortcoming we propose novel mathematical spatiotemporal feature descriptors such as local velocity moments, scaling index and dynamic texture derived from geometrical multiscale decomposition that are able to capture the segmental, focal, linear, regional, and diffuse, and internal enhancement patterns (homogeneous, heterogeneous, clumped, clustered ring enhancement, dendritic), and lesion heterogeneity and will compare their performance together with the features from Aim 2 regarding lesion classification.

VBD + 13

Aim 4: Validation of the proposed system in terms of performance and direct comparison to that of the radiol

Statistical methods will evaluate its performance as a stand-alone system and in comparison with the radiologists competence. Adding novel algorithms to existing techniques will create a flexible toolbox that can be applied with minimal modifications to identifying other type of lesions or monitor response to chemotherapy.

Overview of the action The proposed 24 month fellowship will develop advanced image analysis algorithms to address the challenge of properly diagnose NMLE lesions in MRI. Multiparametric MRI information will be inserted for the first time in a new CAD system using previous experience of ViCOROB. Consequently the lesion detection in CAD systems will be improved, the false positive recalls reduced and thus a direct impact into society.

To ensure a sufficient volume of data to develop the CAD system, a database available at FSU with more than 400 patient cases of MRI-detected NMLE lesions will be used to start the project. While, the correct performance of the CAD, clinical validation and implantation, will be achieved with the support from expert radiologists from UDIAT, where 3 months secondments are planned.

The new research knowledge will be disseminated through open access journals. Finally, this feasible CAD system with potential to improve breast cancer detection will be promoted in technical exhibitions, such as European Congress of Radiology, in order to search for medical companies interested in distributing such tool in

clinical sites. Alternative, the tool can be commercialised via a new spin-off created at ViCOROB, where three spin-off companies have already been created.

Research methodology and approach

Originality and innovative aspects of the research programme The proposed research aims at developing an innovative and robust CAD system for the evaluation of NMLE lesions, based on multiparametric MRI; thus increasing specificity without compromising the sensitivity of CE-MRI. Our believe is that conventional MRI acquisition protocols are unable to capture the physical properties of NMLE lesions. Therefore, rather than trying to implement a new CAD methodology to work in regular MRI as other researcher has shown, our proposal tries to stablish new MRI acquisitions protocol to build multiparametric MRI and improve the breast cancer detection through finding new bio-markers that are not identifiable when using conventional imaging and implementing them as a new CAD system.

Furthermore, the proposed CAD system not only will be developed in a research laboratory as observed in the literature, but it will go beyond and will be tested at the clinical facilities of UDIAT to create a commercialised product.

2.2 Clarity and quality of transfer of knowledge/training for the development of the researcher in light of the research objectives

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How the Experienced Researcher will gain new knowledge The *Experienced Researcher, Dr. Joan Massich,* will be supervised principally by Dr. Anke Meyer-Baese and the *Dr. Massich*'s former PhD advisor, Dr. Joan Martí. However, they will have the support of the members in both teams: the Dept. of Scientific Computing at FSU, and ViCOROB institute at through regular meetings. This will open the possibility to open new collaboration between these teams in other medical fields like brain MRI or prostate cancer, which are medical areas currently being investigated by the two institutions with no collaboration.

Also, *Dr. Massich* will be involved in the supervision of research projects of the *Erasmus +* Master in and new PhD student. *Dr. Massich*, with the supervision and guidance of Dr. Meyer-Baese and Dr. Martí will hone his research writing skills via writing grant proposals, which will also give a continuity to his research career.

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2.3 Quality of the supervision and the hosting arrangements

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Required sub-heading:

Qualifications and experience of the supervisor(s)

Information regarding the supervisor(s) must include the level of experience on the research topic proposed and document its track record of work, including the main international collaborations. Information provided should include participation in projects, publications, patents and any other relevant results. To avoid duplication, the role and profile of the supervisor(s) should only be listed in the "Capacity of the Participating Organisations" tables (see section 6 below). The text must show that the Experienced Researcher should be well integrated within the hosting organisation(s) in order that all parties gain the maximum knowledge and skills from the fellowship. The following section of the European Charter for Researchers refers specifically to career development:

Career development Employers and/or funders of researchers should draw up, preferably within the framework of their human resources management, a specific career development strategy for researchers at all stages of their career, regardless of their contractual situation, including for researchers on fixed-term contracts. It should include the availability of mentors involved in providing support and guidance for the personal and professional development of researchers, thus motivating them and contributing to reducing any insecurity in their professional future. All researchers should be made familiar with such provisions and arrangements.

turity

2.4 Capacity of the researcher to reach and re-enforce a position of professional maturity in research

Please keep in mind that the fellowships will be awarded to the most talented researchers as shown by their ideas and their track record, where it is a fair indicator given their level of experience.

vision

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Todo list