Software Tools for Breast Cancer Detection in Positron Emission Mammography Images

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Abstract: Positron Emission Mammography (PEM) is a novel imaging technology utilizing a dedicated Positron Emission Breast scanner. Two detectors in a configuration that resembles a conventional mammography (MG) machine cover a 250x120x200 mm^3 volume, yielding 3D images of the breast, which is fixated between the detectors, but not compressed. The procedure depends on the administration of a radioactive contrast agent, ^{18}F FDG, as used in common whole body PET scans. Clinical studies showed the equivalent sensitivity and superior specificity of PEM regardless of hormonal status, breast density, and other factors hampering MG and MRI. Yet, due to the novelty of the imaging modality, no software support besides basic viewing and measurement capabilities exists, and common PET software is not tailored to the specific tasks in PEM image analysis. We propose algorithms and prototypical implementations for the tasks of automatic background estimation, lesion detection, lesion volumetry, and lesion measurements.

1 Introduction

Positron Emission Mammography (PEM) has been developed for the early detection of breast cancer. It's working principle sets it apart from other commonly used techniques in breast cancer detection and promises the chance for detection earlier than for example with MRI, thereby possibly improving on the state of the art imaging protocols. The measurement principle relies on the uptake of radioactive sugar – fluorinated glucose, 18F FDG – in the metabolism of cells. Uptake increases when cells need higher levels of energy supply, which is the case in most cancers of the breast. MRI contrast agents, for comparison, only make use of the vascularization of the active cell's vicinity, thereby assessing secondary effects of neoplasms. Also, PEM is acceptable to a wider population of patients, e.g. obese or claustrophobic patients, and the administration of FDG also allows for an accompanying whole body PET scan for tumor staging purposes after a single injection.

Thus, radiologists face yet another imaging modality they need to include in their work-up of patients. Since in the setting of screening for breast cancer, where PEM already plays a role in the differential diagnosis of lesions, speed in analysis and reporting is imperative, of-the-shelf solutions for PET image analysis do not suffice, because their tools are not automated, and are neither tailored to the resolution of PEM nor to mammographic reading habits.

We present methods integrated into a prototype that intends to ease common tasks, like measuring lesions, quantifying their characteristic uptake and assessing their volume. Besides, we aim at increased robustness of the lesion to background ratio (LBR) estimation and better support of efficient reporting, while providing the breast specialist radiologist with an interface that suits his needs regarding overview, side-by-side view of

projections, comparison view of contralateral side, light box view etc. This paper is meant to be a work-in-progress report that points out some obstacles and possible solutions in pursuit of an automated PEM quantification and reporting application.

2 Prior Work

Positron Emission Tomography (PET) has a history of success in patient management, disease staging, and treatment planning. Yet, for breast cancer early detection the method's spatial resolution is too poor to yield sensitivities above 50%-70% [Ber07,Fra08,LCF08]. Therefore, the search for alternatives to MRI with at least equivalent sensitivity and improved high specificity led to the development of a dedicated, breast-specific PET scanner, dubbed Positron Emission Mammography, or PEM [Adl03,Lev02,Wei05,Wei06]. The technology is now FDA approved and installed at multiple sites in the U.S. Approval for the European and other world-wide markets is ongoing. Clinical trials in the U.S. have already underlined the high sensitivity, specificity and ease of use, as well as clinical utility (integration into workflow). Newest results seem to indicate high cost efficiency, also [Ber06,Taf05,Taf07,Taf08,Sch08].

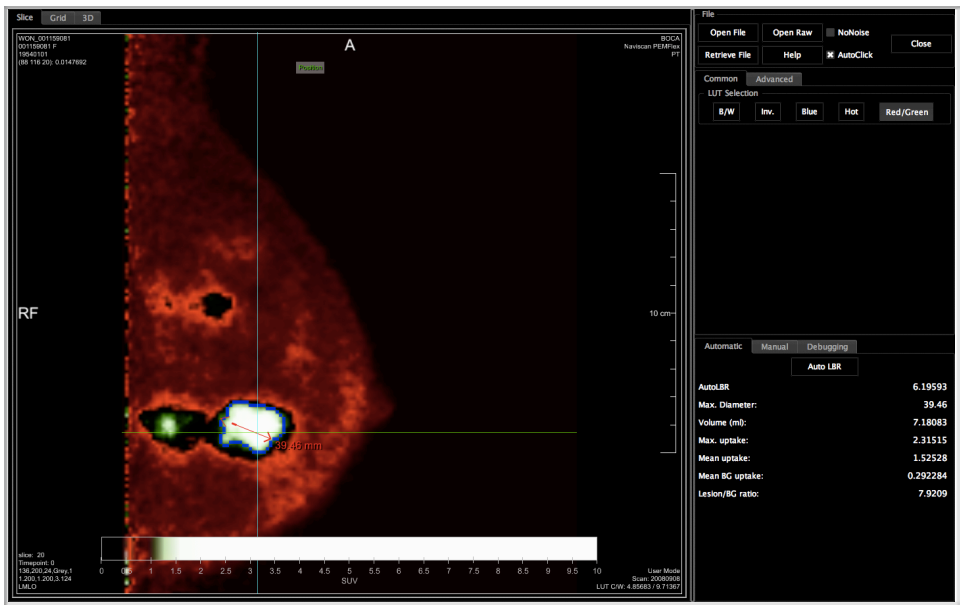

Figure 1: The PEM prototype shows a PEM image together with all estimated measurements, and a lesion segmented. The automatic lesion click point is indicated by the crosshair, its maximum diameter by an arrow and the outline in blue.

Due to the novelty of the technique, the current lack of dedicated software support is noted. PEM is in general easy to read, even for novice users, due to the high contrast be-

tween background and lesion candidates paired with reported high specificity of the modality. Therefore, the task of identifying suspicious areas in the breast does not require advanced methods. Consequently, the major contribution of dedicated software will be in the area of workflow support in the clinical setting, by providing robust, fast, and reproducible methods for quantitative evaluation and efficient reporting of findings. From the workflow perspective, employing PET software is not an option, since the viewing habits and time constraints of breast imaging specialists have to be taken into consideration. Also, most automatic tools employed in PET will fail in PEM due to its higher resolution that brings along much more detail and more subtle contrasts. Also, no standard for the quantification of background tracer uptake in PEM images exists, and no documented standard of background uptake quantification is appropriate, specifically regarding the technique of calculating the background uptake from the contralateral side. This is for the reason that a) non-attenuation corrected images are used and breasts may be unequal in size and b) that the acquisition time difference may lead to uptake differences.

To the knowledge of the authors, no prior work examined the assessment of background activity. Clinical state-of-the-art is a agreed-upon procedure that prescribes to define a background ROI on the slice that evaluates mixed fatty and dense tissue. There, a region encompassing both fatty tissue and parenchyma, but no suspicious area, shall be selected. This process is likely to yield differing results for background uptake due to individual preferences in ROI placement. Variations within and between observers is thus expected. Since the background estimation is included in the calculation of the relative uptake of a lesion, this clinically relevant measure of a lesions dignity will inherit all errors made in background selection.

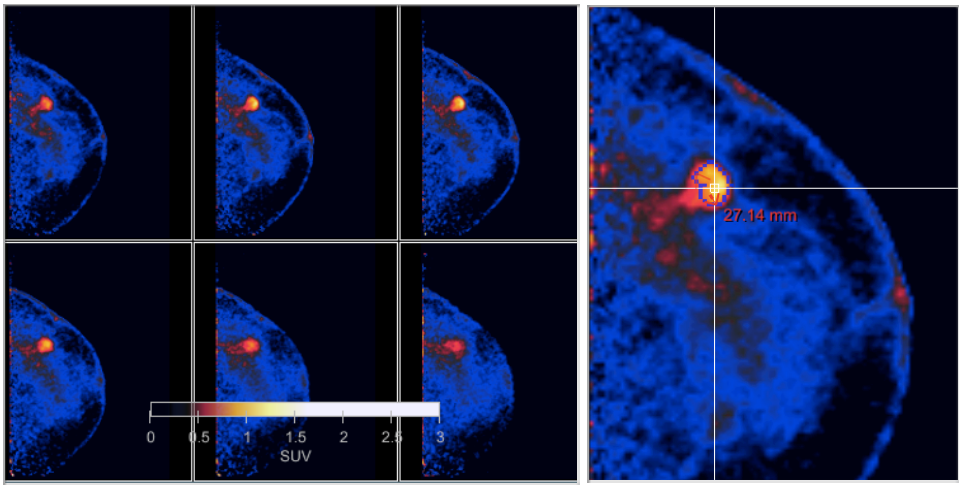

Figure 2: The application offers various color maps, a grid view (left) and a slice view (right). Overlays depict the thresholded lesion outline and the diameter measurement.

Conversely, methods for the detection and segmentation of lesions in PET images have been described before [Dai03,Gee07,Kro07]. Most of them make use of thresholds on the

uptake values, or assume other prior knowledge, as for example lesion-to-background ratios. Background enhancement is thus taken into consideration, and also locally adaptive thresholds are described. Still, the majority of approaches only calculates a locally adapted fixed threshold. In contrast, the method described by van Dalen [vDa07] additionally takes into account the size of the lesion and thus provides the ability to estimate lesions smaller than the double intrinsic scanner resolution more accurately. The method models lesions as Gaussian blurred spheres and analytically derives an optimal lesion threshold for a given size, PSF of the scanner, and background uptake. This method is extended and employed in the segmentation procedure used in this paper.

3 Material and Methods

The development of all analytical methods presented herein is based on a selection of PEM data sets with and without lesions. The data were acquired from a patient population who qualified to participate in a trial conducted in the Boca Raton Community Hospital from 2006 to 2008. In eligible patients, additionally to routine imaging, both breasts were imaged with PEM in crania-caudate (CC) and medio-lateral oblique (MLO) views if indications for MRI were given, including those according to the ACS (American Cancer Society) standard for MRI high risk screening. Images were taken with a scanning duration of 10 min per view on a Naviscan PEMFlex 1 scanner (Naviscan, San Diego, CA). The patient's glucose level and the radioactive dose delivered were recorded for later analyses. Images were reconstructed with a standard iterative MLEM algorithm to yield 250x160x24 voxel image volumes. Despite the 10 min acquisition time, due to the fixation of the breast motion artifacts rarely occur.

Background estimation is performed by thresholding the data set based on threshold levels derived from the histogram and its 2nd derivative. This approach is designed such that the parenchyma of the breast with minor contributions of the fatty tissue part is masked, and its average uptake is taken as the background signal. The details of the estimation of the two threshold levels (separating lesion candidates from parenchyma and parenchyma from fatty tissue and acquisition background) will be described elsewhere. The automatic procedure was compared with the estimation from background ROIs defined by three experienced radiologists.

Afterwards, lesions are automatically detected based on a threshold method described above. Note, that the lesion detection does not depend on the background being estimated before. Detected lesions will automatically be measured in terms of their maximum diameter across all three dimensions. To this end, the lesions need to be accurately segmented, which is also automatically performed with an adaptive optimal thresholding procedure that was proposed for lesions in PET images [vDa07]. This is especially important for the high resolution PEM breast scanner that depicts lesions earlier and at smaller sizes than conventional PET. Here, lesions are no longer seen as round blobs, but both their shaped outline and internal structure can be appreciated. This gave rise to extensions to the model described in [vDa07], by

- automatically locating the point of highest uptake in the lesion to alleviate possible operator dependence on the click point

- profiling the gray image in three directions parallel to the coordinate system intersecting in the point of highest uptake instead of only assessing a one-dimensional cross section

- averaging the three results.

After segmentation of the lesion, a profile along a cross section through the two most distant points of the lesion surface is generated. The distance of these two points is recorded.

All quantitative results are displayed in a prototypical software assistant that also allows for manual measurements and additional individualized measurements of lesion diameters or the distance to the nipple. Also, the background estimation can be manually changed to a operator-defined ROI to override or compare with the automatic results. To the best of our knowledge, none of the methods described are available in existing PET software tools.

4 Preliminary Results

We assessed the robustness and accuracy of the automated BG estimation in a study asking three experienced radiologists to draw ROIs in the fashion they used to do it. The mean uptake in the ROIs were recorded and compared to the automatic results and among each other. The variation within radiologists was found to be of the same order as the variation between radiologists and the automatic procedure, being about 10% on average and up to 50% in specific cases. Also, in general the variation between radiologists was highest where the deviation from the automatic result was the largest, indicating that there are PEM cases that are more likely to be assessed differently. Those are the cases where automatic procedures have their greatest value. To further the robustness, the automatic procedure was designed to have only two free parameters that steer robustness and background offset. These parameters were used to fine tune the method but remain fixed thereafter. The method is thus completely free of interaction, which is highly desirable in clinical routine. Details of the method and the results will be described elsewhere.

An automated procedure for lesion detection makes use of the generally extreme brightness of lesions compared to the background. Lesion center candidates are identified by thresholding the volume to the 99.85^{th} percentile and taking local bounding boxes of these clusters that extend into the background. Cross-sections of lesions so obtained are then evaluated with the Relative Threshold Level (RTL) method to find an optimal threshold to segment the lesion. This algorithm is based on the assumption of a spherical lesion convolved with a Gaussian point spread function (PSF). The maximum lesion diameter is then calculated to be the maximum distance between any two voxels from the 3D outline of the thresholded lesion. The estimated lesion extent was compared to the measurements obtained from radiologists using the vendor software, and to pathology as follows. Lesions seen with the PEM vendor provided software were measured in the x-y-plane), because no software support existed for a more thorough analysis. The same applies to the pathology results, where lesion sizes are taken to be the maximum lesion extend seen on any of the sections. A first comparison to these measurements shows deviations up to a factor of two when compared to the automatic results. Further research is

required, possibly including a different work up of histology specimen to determine more plausible 3D lesion extents.

Since no quantitative evaluation of the success of the lesion detection method has yet been performed, it may only be noted that there appear to be systematic failures of the process in lesions below a certain gray level threshold. Very tiny lesions may go unmarked by the procedure, while larger ones may appear twice. The same holds for segmental enhancement. These cases, however, are very likely the ones that pose the biggest challenge to the reading radiologist, such that a manual analysis is necessary regardless of the automatic results.

No volumetric assessment of lesions has been performed for PEM images so far, and neither pathology nor other modalities, such as MRI, assessed lesions for volume. Thus no comparison is possible. The procedure for volume estimation needs to be evaluated on phantom measurements or simulations, which is an ongoing effort jointly with the PEM Flex manufacturer, Naviscan Inc. (San Diego, CA).

Also, the emphasis in this report is on the description of methods. All work needs evaluation in the clinical setting, but since no specific and automated solutions exist that match the clinical needs in terms of PEM software support, the proposed solutions are expected to contribute to easier integration of PEM into the clinical workflow. The advantage of building the prototype on the basis of the MeVisLab platform (MeVis Medical Solutions AG, Bremen, Germany) is the possibility to rapidly change and tailor the interface layout, the way of interaction and the information provided to the specific setting. This is pursued together with both Naviscan Inc. and the Womens Center in Boca Raton Community Hospital.

5 Outlook and Conclusions

Automated quantitative procedures allow for a robust, reproducible assessment of lesion characteristics with no dependence on the radiologist. The work presented shows a tool set that goes beyond the current state of the art in this regard. Consequently, follow-up examinations may be assessed more reliably. For example in patients undergoing chemotherapy or radiation therapy, tumor growth, stagnation, or shrinkage, may be determined more confidently, and treatment decisions taken based on robust information.

The methods presented herein may be used for easier reporting of findings, including automatic generation of stub reports including all automatic results per lesion as well as screenshots for illustration. Also, lesion positions can easily stored and accessed for review or second reading. The methods, however, need further improvement and adaption to the specifics of PEM data processing. This includes the extension of the volumetry algorithm to deal with lesions more heterogeneous and morphologically different from the sphere model that is assumed in the current implementation. In a first step, a correlation with size measurements in other modalities is required. In parallel, ongoing phantom experiments elucidate the robustness and accuracy of volume estimations for the given procedure.

Also, the background uptake estimation deserves further elaboration, since especially in the least dense breasts it fails. For other densities, it systematically under- or overesti-

mates the mean uptake given by radiologist measurements. Finally, to overcome the state of a merely prototypical application, both workflow aspects and reporting need to be addressed. All this is being considered in ongoing efforts.

On the basis of the prototypical implementation, automatic generation of morphologic, textural, and further features will be explored. The objective is to test these quantitative results for their viability for an automated discrimination scheme telling true positive from false positive findings. Thus, we hope to to further decrease the already low FP rate of PEM.

In order to harvest the full potential of the PEM modality, a close integration into the clinical workflow and fusion imaging with other modalities needs to be achieved. Iin its current state the application is connected to the PEM scanner directly, retrieving the raw data for a workup. A PACS connection is currently being implemented, opening the prototype to easy daily usage. This is a prerequisite for the exploration of fusion analysis of PEM with other modalities. Particularly, mammography and tomosynthesis offer themselves to a fusion imaging approach, since the principal image acquisition directions, CC and MLO, are shared between these modalities. Due to the difference in breast shape and contrasts, image registration to MRI may be more difficult, yet less important, since PEM might replace MRI. With respect to these thoughts, we wish to emphasize that from our point of view great care has to be taken to solve existing clinical problems, especially when considering registration between specific modalities.

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