Biomarkers for Breast Cancer Detection in the Resting-State Dynamics of the Hemoglobin Signaling

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Abstract:
Biomarkers that are promising for breast-cancer diagnosis are identified in resting-state dynamic measures of the vascular bed. The markers also encompass a large fraction of the breast volume, which shows little dependence on tumor size.

Introduction:
Evidence of increased tissue stiffness, presence of structural malformations, and altered pulsatility of the vascular bed are known phenotypic markers for the presence of breast cancer [1,2]. Increased awareness of these phenomena has motivated our development of techniques that explore the naturally occurring dynamics of the hemoglobin signaling that accompany modulation of the vascular tree and its interactions with tissue. In particular, our group has developed several different instrumentation platforms that are suitable for exploring tissue dynamics while a simultaneous bilateral exam is performed.

In one form, and following the spirit of a clinical breast exam, our system design combines optical measures with tactile sensing and controlled artiﬁcial [3]. However, the dimensionality of the information space that could be explored in pursuit of identifying suitable biomarkers has prompted us to also consider more limited data-collection conditions. One such consideration is a simple resting-state measure, wherein time-sparse optical measures are obtained from both breasts simultaneously under defined conditions of optode contact. Our initial aim was to compare such baseline measures to responses evoked by controlled provocations, with the expectation that ﬁndings of interest would align mainly with the latter. However, as evidenced by the ﬁndings reported here, promising ﬁndings have been obtained based solely on examination of the resting-state responses.

Methods:
Measurement data considered here were obtained during an NIRIS-based pre-clinical breast imaging study that was conducted primarily to evaluate the potential of applied-pressure maneuvers to enhance discovery and characterization of breast tumors (Breast-Cancer Tumor Localization and Sizing by Functional Diffuse Optical Tomographic Imaging Combined with Controlled Compression Protocols, this conference). After research participants gave informed consent and provided a brief medical history, they were seated and the sensing heads were adjusted to make good contact with both breasts. The onset of the ﬁrst pressure maneuver was preceded by a five-minute resting baseline scan.

Optical data were analyzed ofﬁne: application of a high-pass ﬁlter with a 0.01-Hz cutoff frequency was followed by use of the Normalized Difference Method to reconstruct images of oxygenated and deoxygenated hemoglobin (HbO, HbD), tissue oxygen saturation (HbSat), and blood volume (HB) [4]. The resulting image time series (4D) were subsequently reduced to a set of ﬁve scalar metrics by: first, computing the temporal standard deviation (TSD) in each image voxel (4D → 2D) or the spatial standard (SM) or standard deviation (SSD) for each image time frame (4D → 1D); second, by computing the spatial mean and standard deviation of TSD (SMTSD, SSDTSD), temporal mean of SSD (TSSD), and temporal standard deviation of SM and SSD (TSSDSM, TSDSSD). With the same goal of probing different modulatory elements, we also have examined three additional quantities (CVSSD, CVTSD, SCV), each of which is a ratio of two metrics from the initial group of five:

\[ \text{CVSSD} = \frac{\sum x \cdot y}{\sum x \cdot \sum y}, \quad \text{CVTSD} = \frac{\sum x \cdot y}{\sum x \cdot \sum y}, \quad \text{SCV} = \frac{\sum x \cdot y}{\sum x \cdot \sum y}, \]

where \( x \) and \( y \) are component metrics.

Results:
Histograms of the TSD spatial maps for women with unilateral breast cancer, as in the examples shown in Figure 2, reveals that this metric in most cases is larger in the tumor-bearing breast. The region of elevated SSD includes a large percentage of the breast volume, which extends well beyond the known structural borders of the tumor and is largely independent of the tumor’s size. Corresponding results for women with benign breast lesions or who have known breast pathology do not show a comparable difference. When extended to group-level comparisons, all of the above-deﬁned scalar metrics are seen to have larger values in the tumor-bearing breast, and little inter-breast disparity in subjects who do not have cancer (Figure 3). In unilateral comparisons, the left/right breast group mean metric value for women with unilateral breast cancer is not signiﬁcantly different from the left/right-breast mean value for the non-cancer group. However, when bilateral comparisons are performed, by using the left/right breast ratio of metric values for all subjects (thereby minimizing inter-subject disparities that are unrelated to the presence or absence of cancer), there are highly signiﬁcant group-mean differences between the non-cancer group and either breast cancer group (Figure 4). As for the problem of predicting individual subjects’ group membership (i.e., diagnosing breast-cancer), depending on the choice of hemodynamic parameter and scalar metric, ROC analysis [6] yields area-under-curve values in the range of 74-86%, sensitivities in the range of 70-84%, and speciﬁcities in the range of 76-92% (Table 2).

Discussion:
An important aspect of the performed image reconstruction, and subsequent analysis, is that they incorporate no prior knowledge of whether a subject has breast cancer or, for ones that do have it, of the tumor size or location, or even which is the tumor-bearing breast. Some might initially suppose that the minimal assumptions made account for the observation (see Figure 2) that the increased temporal standard deviation of the TSD extends into regions far from the structural borders of the tumor. However, imaging results derived from NIRIS data collected during response to either applied pressure (“Breast-Cancer Tumor Localization and Sizing by Functional Diffuse Optical Tomographic Imaging Combined with Controlled Compression Protocols,” this conference) or respiratory-gas [7] maneuvers, which also do not presuppose any knowledge, have shown that tumor locations can be accurately extracted from those measurements. Thus, we conclude that resting baseline recordings, processed in the manner presented here, are sensitive to dynamic vascular phenomena that do in fact extend over a large percentage of the breast volume.

A corollary that potentially has substantial clinical importance is that it may be possible to conduct breast cancer screening by means of a simple bilateral NIRIS measurement involving a small number of probes distributed over the surface of both breasts. Tests of a prototype device based on this hypothesis currently are under way.

References:

Acknowledgements:
This research was supported by the National Institutes of Health (NIRIS grant RFA-BC000102, the NIH Office of Science Applications Development and Transformation Program: The Breakthrough Action Plan, the Department of Health (Empire Clinical Research Investigator Program), the New York State Foundation for Science, Technology and Innovation-Technology Transfer Incentive Program (NYSTAR-TIPP) grant C080041, and NIFx Medical Technologies).