



Derivation and validation of metrics for breast cancer screening from diffuse optical tomography imaging data

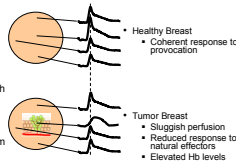
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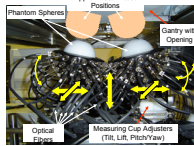


Introduction

- Dynamic Near Infrared Optical Tomography (DYNOT)
 - Provides measures of relative concentrations of hemoglobin (Hb)
 - Oxygenated, deoxygenated, total
 - Noninvasive functional imaging *in vivo*
 - Exogenous contrast agents not required
- Growth of solid tumors frequently accompanied by:
 - Marked changes in the vascular supply sustaining tumor growth
 - State of impaired perfusion
 - Relatively hypoxic environment
- To image the preceding, we developed:
 - A dual-breast diffuse optical tomography (DOT) imaging system
 - Capable of simultaneous bilateral measurements



Measuring Head (1st-Generation) for Simultaneous Dual-Breast Imaging



- DYNOT simultaneous dual-breast measuring head
 - Each optical fiber (31 per breast) is both source and detector for NIR light
 - Data collected from 124 channels (62 fibers x 2 wavelengths) in parallel
 - Sources location is time-multiplexed
- Measurement rate: 2 complete image frames (to 8x10⁶ data points) per second

Physiological Hypotheses

- There are mechanisms by which a cancerous tumor's "volume of influence" may be appreciably larger than the tumor itself
 - This is a consequence of well-characterized differences between vasculature in cancerous solid tumors, and in healthy tissue (or in non-cancer pathologies)
- A key to increasing diagnostic power is comparing detector and image data between the two simultaneously examined breasts
 - Vascular responses under automatic control should be similar in the two breasts
 - Responses under local control (e.g., autoregulation) also should be similar, if both breasts are healthy
- If one breast has a cancerous tumor, and the other doesn't, what macroscopic differences could we expect?
 - Increased amplitudes for vasomotor rhythms, in the tumor-bearing breast (TBB)
 - Owing to hypoxic environment of many solid tumors
 - Greater temporal correlation across the breast volume, and greater spatial homogeneity, in the tumor-free breast (TFB)
 - Abnormal response, in the TBB, to events that stress the microvasculature
- Therefore, three categories of diagnostic metrics will be considered in the clinical study
 - Each is devised to reveal one of the three types of expected difference between the TBB and TFB
- Group 1:** Indices of resting vasomotion amplitude
 - Computed from resting-state measurement data
 - Are sensitive to enhanced vasomotion, possibly associated with tumor angiogenesis
- Group 2:** Index of spatially coordinated dynamics
 - Computed from resting-state measurement data
 - Is sensitive to differences in timing of blood delivery within each breast
- Group 3:** Measures of pressure-induced blood volume and oxygenation shifts
 - Computed from data collected during Valsalva maneuver
 - Are sensitive to venous congestion and delayed reperfusion, which can lead to tumor hypoxia
 - In the TBB, compared to the contralateral TFB, one would expect to see:
 - Increased oxygen desaturation of Hb
 - Increased blood volume change
 - Increase in time needed for recovery

Clinical Study Design

1. Subject population

- Retrospective – subjects whose data is used for derivation of breast-cancer diagnostic metrics
- Prospective – subjects whose data is used for testing and validation

Subject Group	Breast Pathology Status	N	Age (yr) (mean ± SD)	BMI (kg-m ²) (mean ± SD)	Tumor Size (largest dimension)	Clinical Description
Retrospective	Active CA	14	47.9 ± 12.3	28.7 ± 5.3	10 × 3 cm 4 > 3 cm	10 ductal carcinoma 1 ductal & lobular carcinoma 1 mucinous carcinoma 1 metastatic CA 1 inflammatory CA 4 Grade 2/3 Grade 2: 1 had no biopsy data
	Prior CA	3	50.7 ± 9.4	30.4 ± 0.5	—	All had lumpenectomies 2-3 yr prior to NIRS study
	Pre-CA	0	—	—	—	—
Non-CA Pathology	Non-CA Pathology	11	45.7 ± 5.6	28.7 ± 5.5 (N=7)	—	3 fibrocystic disease 4 breast cyst 1 axillary cyst 2 benign breast lumps 1 breast reduction surgery
	No History of Breast Pathology	9	41.6 ± 10.0	30.3 ± 7.2	—	—
	Active CA	14	51.4 ± 10.9	30.4 ± 4.5	5 ≤ 3 cm 9 > 3 cm	13 ductal carcinoma 1 axillary adenocarcinoma with primary duct ectasia and hyperplasia 3 Grade 2, 11 Grade 3 3 prior ductal carcinoma 1 prior mucinous carcinoma All had lumpenectomies 2-6 yr prior to NIRS study
Prospective	Prior CA	4	60.8 ± 9.3	25.5 ± 1.7	—	2 DCIS 1 atypical ductal hyperplasia 1 extremely dense breasts
	Pre-CA	4	53.5 ± 3.4	29.0 ± 4.1 (N=3)	—	2 fibrocystic changes 1 benign breast lump 1 breast reduction surgery
	Non-CA Pathology	6	43.7 ± 8.4	26.6 ± 4.9 (N=4)	—	—
No History of Breast Pathology	8	44.0 ± 6.8	30.5 ± 8.9	—	—	

Subject Group	n _i	Mean	SD	Range	n _j	Mean	SD	Range	
Active Breast Cancer (CA)	Retrospective / Training Group	14	47.9	12.3	29-70	14	28.7	5.3	21.6-43.9
	Prospective / Validation Group	14	51.4	10.9	37-71	14	30.4	4.5	22.7-38.1
Non-CA	Retrospective / Training Group	23	44.7	8.6	26-62	19	30.1	6.1	18.4-44.4
	Prospective / Validation Group	22	48.7	10.0	30-69	18	28.2	6.6	21.2-48.5

2. Analysis of dual-breast DOT image time series

- 4-D (volume + time) data sets are reduced to the following scalar values:

Experimental Condition	Tumor-Associated Phenotype	Scalar Metric
Breast Density	Angiogenesis	1. $SMRSD = \sum_{i=1}^N \sqrt{\frac{1}{N} \sum_{j=1}^N r_{ij} ^2} / \sqrt{N}$
		2. $SSD7SD = \sqrt{\frac{1}{N} \sum_{i=1}^N \sum_{j=1}^N r_{ij} ^2} - SMRSD / \sqrt{N}$
		3. $TMSSD = \sum_{i=1}^N \sum_{j=1}^N r_{ij} ^2 / \sum_{i=1}^N r_i ^2$
		4. $7SDM = \sum_{i=1}^N \sum_{j=1}^N r_{ij} ^2 / \sqrt{N}$
		5. $7SDSSD = \sqrt{\frac{1}{N} \sum_{i=1}^N \sum_{j=1}^N r_{ij} ^2} - 7SDM / \sqrt{N}$
Spatial Coordination	Hypoxia	6. $SC(C_1) = 100 \frac{\sum_{i=1}^N \sum_{j=1}^N r_{ij} ^2}{\sum_{i=1}^N r_i ^2} / \sqrt{N}$
		7. $A = \frac{\sum_{i=1}^N \sum_{j=1}^N r_{ij} ^2}{\sum_{i=1}^N r_i ^2} / \sqrt{N}$
Evoked Response	Hypoxia	8. $R = \frac{\sum_{i=1}^N \sum_{j=1}^N r_{ij} ^2}{\sum_{i=1}^N r_i ^2} / \sqrt{N}$

- Differences between metric values, for each subject's two breasts, are calculated as:
 - Tumor minus non-tumor for training-set cancer subjects
 - Left minus right for training-set non-cancer subjects, and for validation-set subjects
- Each metric is converted into six candidate diagnostic parameters, by normalizing the inter-breast difference in a variety of ways:
 - Difference divided by larger, smaller, or average value of the two individual-breast values
 - Difference multiplied by larger, smaller, or average of the individual-breast values

2. Analysis of dual-breast DOT image time series (continued)

- Assessment of sensitivity, specificity, positive and negative predictive values
 - Univariate: parametric and nonparametric tests for difference between means of CA and non-CA sub-groups of the training set
 - Multivariate: binary logistic regression (BLR)
 - Use leave-out-one cross-validation (LOOCV) to determine sensitivity to idiosyncrasies of the training-set subjects
 - Validate the predictors that are most successful with respect to the retrospective group, by applying them to the data for the prospective group
- Aggregates (averages) for 1 or more multivariate predictors
 - The overall number of aggregates is $2^{C_1} + 2^{C_2} + \dots + 2^{C_{21}} + 2^{C_{22}} = 4,194,303$
 - For each subject, the aggregate breast-cancer probability is the average of the separate probabilities according to the multivariate predictors
 - For sensitivity and specificity calculations, a breast-cancer probability of 0.5 is taken as the diagnostic threshold

Results

1. Diagnostic accuracy for multivariate predictors

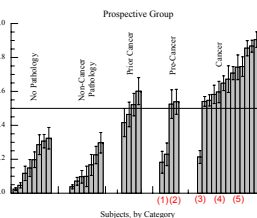
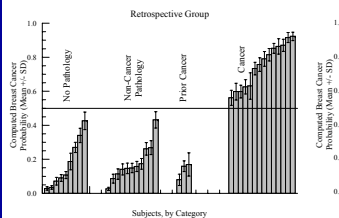
- As determined by BLR-LOOCV computations, these had statistically highly significant discriminatory ability and robustness
- Predictors 1-13 are hypothesis-based, physiological premises (above) guided the selection of which univariate metrics to include
- Predictors 14-22 are data-driven: a backward-elimination algorithm was used to determine which combinations of univariate features were the "best" multivariates, without regard to biological significance

Multivariate Predictor	Hb _{ret}	Hb _{pro}	Hb _{avg}	Sensitivity, Ret. (%)	Specificity, Ret. (%)	Sensitivity, Pro. (%)	Specificity, Pro. (%)
1	1.5	1.5	1.5	94.3	95	74.5	93.7
2	1.3	1.5	4.5	78.6	90	64.3	60
3	6	6.5	50	90	90	85.7	93.3
4	7.8	7.8	50	100	100	71.2	92.3
5	2.9	6	1	85.7	99	87.1	86.7
6	1.5	6.5	71.4	90	90	87.1	93.3
7	1.3	5.5	1.3	85.7	95	78.6	100
8	1.3	5.5	1.3	100	90	78.6	100
9	1.8	3	3	90	90	78.6	92.3
10	6.8	80	90.9	71.4	84.6	—	—
11	8	5.5	80	90.9	71.4	92.3	—
12	6	8	1	90	81.8	57.1	84.6
13	2.5	8	1.3	90	90.9	64.3	76.9
14	3	6	90	90	90	64.3	93.3
15	3	6	57.1	95	57.1	100	—
16	8	90	90.9	71.4	84.6	—	—
17	7.8	5	80	90.9	71.4	84.6	—
18	3	3	21.6	90	82.7	100	—
19	3.5	6	4	100	95	78.6	93.3
20	8	6	80	81.8	64.3	84.6	—
21	4	3	90	90.9	57.1	61.5	—
22	6	6	90	90.9	71.4	84.6	—

† The Difference/Maximum formulation is used for these predictors, and Difference/Maximum for all the others

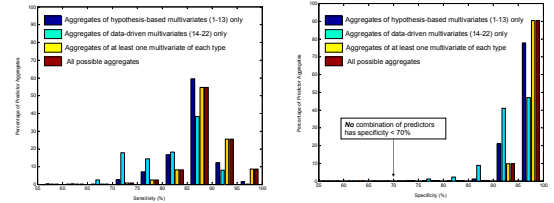
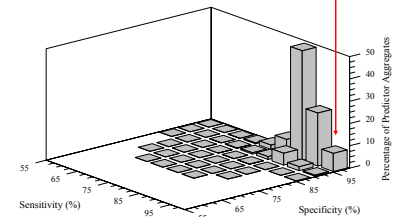
3. Average breast-CA probability, for each subject, across the 196,639 highly successful aggregates

- Low-grade DCIS, and previously diagnosed DCIS not confirmed upon re-exam
 - High-grade DCIS, and dense, cystic breasts
 - Small (< 1 cm) tumor, near the chest wall
 - Adenocarcinoma in axillary lymph node
 - Lumpectomy 8 yr. prior to NIRS exam, relapse 1 yr. after NIRS exam
4. Correlations between computed breast-CA probability and demographic variables: age and BMI
- Only the No Pathology and Non-CA Pathology sub-groups were considered here
 - Results are suggestive of a trend, in all cases, but sample size is too small for statistical significance



2. Diagnostic accuracy for aggregates of multivariate predictors

- There are more than 3x10⁶ aggregates that yield sensitivity and specificity both > 95%
- Of these, there are 196,639 that correctly identify:
 - All Non-CA Pathology and No History of Breast Pathology subjects, in both the retrospective and prospective groups
 - All Active CA subjects in the retrospective group
 - All but one Active CA subject in the prospective group



Conclusions

- Prospective-group results show that the derived multivariate metrics do operate on features of the image data that are related to breast-cancer status, and not to any idiosyncratic properties of the retrospective group.
- The observation that the inter-breast differences have the predicted directionality implies that our assumptions, regarding the effects of tumor development and growth on the dynamic properties of the vasculature, are largely correct
- The successful application of metrics derived by spatial integration of DOT image data implies that the vascular correlates of tumor growth and development are present over a volume that extends a substantial distance beyond the histological margins of the tumor.
- The preceding conclusions, plus the suggestive results from preliminary examination of the trends between breast-CA probability and age or BMI, indicate that the relationships between the DOT metrics and other data types (demographics, histology, tumor-receptor findings) should be more fully explored (NIH01-104).