

Tumor Detection by Simultaneous Bilateral DOT Breast Imaging

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ABSTRACT

We have constructed a 64 channel dual breast imager for simultaneous bilateral time-series detection. Studies on 37 subjects (14 with cancer) shows that tumor detection and localization is possible with high sensitivity and specificity. Validation studies (10 concer subjects) demonstrate that the diagnostic metrics derived from analysis of the original 37subject data correctly predict cancer status in a majority (60-90%) of cases.

OVERVIEW

Here we present results of a systematic examination of data obtained from 37 subjects who comprise a cancer group and a control group, each of whom underwent a simultaneous bilateral breast scan using the NIRx dynamic mammographic imager.1 The two groups were matched in terms of age and body mass index. The cancer group contained 14 subjects, while the control group included 23 subjects. The composition of the latter group was heterogeneous, in that it included both healthy subjects and subjects who had other breast pathologies (non-cancers). Data collection involved two contiguous measurement periods: baseline measurements, and measurements taken while the subjects were performing one or more quantitative Valsalva maneuvers (QVM). Data analysis was performed to answer three principal questions

- 1. What are the diagnostic predictor values for globally derived metrics?
- 2. To within the statial scale of a breast quadrant, how accurately can tumors be located? 3. How accurate are estimates of tumor size for subjects whose quadrant localization is correct?

The selection of diagnostic metrics was motivated by knowledge of differences between the vasculature of tumors and healthy tissue, and of the responses that can be expected, from each to a vascular challence. Three groups of metrics were devised. Multiple parameters were evaluated for each group, in many cases using several alternative formulations for the differences between the responses of each subject's left and right breasts

METHODS

1) Subjects

Table 1 lists the and tumor size and tumor location, for subjects disappend with baset cancer. Tumor sizes ranged from <1 cm to >7 cm; of these 6 were in the left breast 7 in the right and 1 bilateral (the last case folded into the right-breast tumor group, as her right-breast tumor was larger). Table 2 lists the age and health status of the heterogeneous control group (N = 23), who had a variety of lesions and prior surgical procedures on the breast. Table a reports the summary statistics for demographic comparisons between the two groups: they are not statistically different with respect to age or body mass index (DMD)

After giving her informed consent, each subject law more on the measurement eartry, with both breasts hanging pendent. The dual measuring heads were adjusted to make comfortable contact with the breasts. The instrument gain settings appropriate to each individual breast (961 source-detector pairs/ wavelength/ breast) were found by using an automated mutine¹. Dual-wavelength time-series ontical tomographic data were collected during two consecutive measurement periods; baseline and provocation. Baseline data were collected for a period of 10 minutes with the subject at rest. Provocation results were obtained while the subject held a 40 mm resistance for a neriod lasting up to 30 seconds. Four OVMs, with a 4-minute recovery period after each, were attempted. In practice, only 21 subjects correctly performed at least one

3) Time-series Image Recovery

Collected data were analyzed, using previously described software² and algorithms³, to produce a time series of volumetric images for each Hb state parameter: Hb, and Hb, Sat.

4) Data Analysis for Tumor Diagnosi

- 4.1) Hb-State Time-series-derived Metrics [Table 4].
- · Group 1: Indices of resting vasomotion amplitude
- · Computed from baseline measurement data
- · Governing hypothesis is that tissues exposed to hypoxic environments have increased amplitude at vasomotor frequencies

· Group 2: Index of spatially coordinated dynamics

- · Computed from baseline measurement data
- · Governing hypothesis is that blood delivery to affected breasts is less spatially coordinated than that to healthy breasts
- · Group 3: Measures of pressure-induced blood volume and oxygenation shifts
- Computed from data collected during OVM
- · Governing hypothesis is that a tumor will increase a breast's hemoglobin oxygen desaturation in response to QVM, increase the blood volume change, and introduce a response time lag.

4-2) Formulations for Inter-breast Intro-subject Commarisons (Table 4) Compute difference between metric values for each subject's two breasts

- · Tumor minus non-tumor for training-set cancer subjects
- · Left minus right for training-set non-cancer subjects, and for validation-set subjects
- · Compute diagnostic accuracy parameters for six "normalizations" of the difference
- Difference divided by larger smaller, or average of the two individual-breast values.
- · Difference multiplied by larger, smaller, or average of the two individual-breast values

4.3) Univariate Tests of Diagnostic Ability (Tables 4.5):

- · Treat each metric/formulation/Hb-state permutation separately
- Unequal-variance t-test for difference between means of CA and non-CA subgroups of the training set · Tabulate which metrics yield statistically significant differences
- · Perform spot-checks with non-parametric test (Mann-Whitney), to ensure that small sample sizes is not an issue

Subject No.	Age (yr.)	Diagnosis ^{(a}	Tumor Size ^(b) (cm)	Tumor Location/*
1	32	I. Ductal CA	7×5×2.5	UOQ
2	56	R Ductal CA	2×3	Lateral (9 o'clock)
3	60	R Ductal CA	3×4	UOQ
4	40	L Mucinous CA	7×4×3	UIQ (11 o'clock)
5	62	R Inflammatory CA	3.5	Lateral (9 o'clock)
6	45	I. Ductal CA	3	UOQ (2 o'clock)
7	29	L Metastatic CA	2.7	UOQ(2-3 o'clock)
8	70	R Lobular & Ductal CA	3.0	Lateral (9 o'clock)
9	44	L CA (unspecified type)	2.5	UOQ (1 o'clock)
10	65	L Inflammatory CA	Entire Breast	Entire Breast
11	48	R Ductal CA	2×1.5×1.5	UOQ
12	39	R Ductal CA recurrence	0.7×0.8	UOQ (11 o'clock)
13	37	R/L Ductal CA	R 2×1.5×1, L 0.5	R (11 o'clock), L (12 o'clock)
14	43	R Ductal CA	3×2×1	Inferior (6 o'clock)

others only two or only one. c) UOQ = upper outer quadrant, UIQ = upper inner quadrant

Table 2: Sub-categories of Non-Canoer, Subjects

	Subject Sub-category									
	Healthy	Prior Lumpectomy	Prior Cystectomy or Other Surgery	Fibrocystic Disease	Other Conditions					
	43	62 (R)	44 (L,R breast reduction)	55	44 (R galactorrhea)					
	33	39 (L,R)	47 (L)	44	40 (L fibroadenoma					
	26			38	56 (L cyst)					
Age (yr.)	31			46	40 (R cyst)					
(97.)	35			46	49 (R cyst)					
	53				50 (L cyst)					
	53									
	54									
Total	8	2	2	5	6					

Demographic Parameter			Age (y	r.)		BMI			
Subject Category		Mean		Range			Mean		
Cancer	14	47.9	12.7	29-70	0.39	14	28.7	5.5	0.50
Non-CA	23	44.7	8.7	26-62	1	19 th	30.1	6.3	1



			Group 1 (Ba	seline Integrat	(Temporal Coherence) Metrics		(Valsalva Maneuver) Metrics			
Formulation	Parameter	TSDSMts	TMSSDts	TSDSSDts	SMTSDi	SSDTSDi		$\operatorname{High} f$		Range
	Hboxy	1				- 11	11			1
Diff./Min.	Hbbeery		~	~	1	1	1	1		~
	Hb _{Tetel}	~	~		-	-				
	Hboxy		111		111	11	~		1	11
Diff/Max.	Hbbeery	1	~	11	1	1	11	1		~
	Bhild I III I III Bhild I III III III III									
	Hboy		111		111	11	11			~
Diff./Avg.	Hbbeery		*		1	1	11	1		~
	Hb _{febl}	1	11	~	11	11				-
	Hboxy		44		11	1	11		1	~
Diff.*Min.	Hbbeery						111			
	Hb _{Tetal}		*		1					
	Hboy		11		11	1	1			~
Diff.*Max.	Hbbony						11			~
	Hb _{fetel}				1					
	Hboy		11		11	1	1		1	~
Diff.ºAvg.	Hbbeery						11			~
			~		-					
autoregulation), Aminton time a	Mts (amplitude of r temporal mean of tries; SMTSDN (am on of temporal stan 61.	spatial standard of	lociation time set	ies; TSDSSDss (st	ariance of autors	gulation), tempor	al standard di	relation of sp	stal stands	4

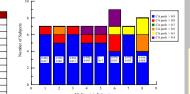
Table 5 Diagnostic Measures for Group 1 - 3 Data Minimum - Maximum (Mean)

	Sensitivity	Specificity		
Composite Group 1 Data	50.0-85.7(72.5)	56.5-84.2(72.7)	50.0-78.6(62.0)	70.8-90.0(81.5)
Composite Group 2 Data	42.9-78.6 (59.8)	56.5-95.7 (82.6)	44.4-88.9 (69.8)	68.4-82.4 (77.1)
Composite Group 3 Data	70.0-90.0 (83.3)	72.7-100 (86.4)	75.0-100 (85.7)	76.9-91.7 (85.2)
Average Composite For Groups 1-3	42.9-90.0 (70.7)	56.5-100 (78.6)	44.4-100 (69.0)	68.4-91.7 (80.7)

Table 6: Summary of Multivariate Analysis Results

Table 4 Various Metrics and Formulations

Formulation	$N_{\rm enlytes}$	$N_{\rm metrics}$	Hb States Included	Data Groups Included	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)														
					100	90.9	90.1	100	All Subjects													
Diff./Max.	21	3	Oxy (2), Total (1)	1, 3	87.5	90.0	87.5	90.0	LOOCV ⁹													
Diff.*Max	21		Oxy (1), Deoxy (1), Total (1)	1.2.3	100	81.8	83.3	100	All Subjects													
Diff-Max	21	3		Total (1)	Total (1)	Total (1)	Total (1)	Total (1)	Total (1)	Total (1)	Total (1)	Total (1)	Total (1)	Total (1)	Total (1)	Total (1)	Total (1)	Total (1)	70.0	90.0	87.5	75.0
Diff.*Max.	37	5	Oxy (3), Deoxy (1),	1.2	100	87.0	82.4	100	All Subjects													
Dur-Max	37	3	Total (1)		85.7	73.9	66.7	89.5	LOOCV													



Multivariate Estimator

Figure 3. Probability of disease for indicated number of subjects as a function of multivariat estimator. Inset in bar graph is the mean and SD probability for the >90% decile

Table 7 Summary of Breast-quadrant Tumor Localization Result

ata		Hbosy		Hb _{Doosy}		Hb _{fet}	Avg.	
oup	Parameter	Quadrant Score		Quadrant Score		Quadrant Score		Incorrect Breast (%)
	SMTSD	0.68	4.4e-5	0.43	0.052	0.68	4.4e-5	16
	SSDTSD	0.50	0.011	0.43	0.052	0.50	0.011	29
	TSDSM	0.39	0.098	0.36	0.17	0.43	0.052	33
	TSDSSD _{IN}	0.46	0.025	0.32	0.28	0.39	0.098	36
	TMSSD ₁₈	0.64	1.6e-4	0.46	0.025	0.54	0.0044	19
	Temporal Coherence (0.045-0.065 Hz)	0.50	0.011	0.61	5.4e-4			21
	Multi-parameter	0.68	2.7c-4	0.68	2.7e-4			5
	Range					0.73	6.3e-5	9

Table 8 Summary of Turnor Sixing Paculty

		Actual tumor size							
Subject	E	h _{ory}	Hb _{Deexy}		HbO ₂ S	aturation	Estimated		
	Volume (cm ³)	Diameter ^{(a} (cm)	Volume (cm ³)	Diameter ^{(a} (cm)	Volume (cm ³)	Diameter ^{(a} (cm)	volume th (cm ³)	Size (cm)	
2	3.64	1.91	4.65	2.07	7.07	2.38	14.1	2×3	
4	2.42	1.67					84.0	7×4×3	
8	3.23	1.83	3.43	1.87	5.86	2.24	14.1	3.0	
9	0.20	0.73			0.61	1.05	8.18	2.5	
11			3.64	1.91	2.63	1.71	4.50	2×1.5×1.5	
12	1.62	1.46	1.62	1.46			0.27	0.7×0.8	
13			1.82	1.51	3.84	1.94	3.00	$2 \times 1.5 \times 1$	
14	3.64	1.91	2.02	1.57	4.24	2.01	6.00	3×2×1	

Finure 1 Thresholded Valsalva Maneuver Resnonses Cancer Subject 14

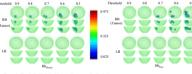
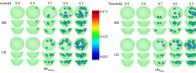


Figure 2. Thresholded Valsalva Maneuver Responses. Healthy Subject



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4-3) Multivariate Texts of Diagnostic Ability (Table 6)

- For each difference formulation
 - · Postulate a multivariate predictive model, consisting of an unknown linear combination of all univariate pradictory that yield statistically significant differences between the sub-group means
 - Use a basistic represented (LP) algorithm to find the optimal coefficients for the multivariate model.
- · Eliminate least significant metric from the model and repeat LR computation, until performance of the reduced multivariate model begins to degrade (i.e., remove redundant metrics)
 - · Combine metrics for different Hb states, but not (set) for different difference formulations
 - · Use leave-out-one cross-validation⁴ to determine sensitivity of multivariate predictive models to idiosynerasies of the training out subjects
 - Predictive models including Group 3 metrics can consider only 21 subjects: models including only Group 1 and/or 2 metrics consider all 37 subject

5) Data Analysis for Tumor Localization (Resect-Oundrant Level) (Table 7):

- Pa commuta universita disancetia matrice, for each subject's eight breast quadrants constrability
- Datamina which sundrast has the largest (Groups 1 and 2) or smallast (Group 2) matrix value
- Tabulate the number of subjects for which each matrix identifies the correct subdrast, and the number of matrices that correctly localize each subject's tumor

6) Data Analysis for Tumor Sizing (Table 8: Figures 1.2)

- Tumor, volume estimates computed for only those CA subjects whose tumors were correctly localized Volume estimation based on Group-3 data
- 50% of maximum OVM response amplitude chosen as a threshold value · Count the number of voxels in tumor, quadrant volume that have OVM amplitudes exceeding the threshold

7) Data Analysis for Validation Study [Table 9; Figure 3];

- · Compute values of previously employed inter-breast, intra-subject univariate metrics for the subjects in the validation set
- · Combine new metric values with multivariate-medictor coefficients derived from the training-set subjects to compute an estimated probability of CA for each validation-set subject

FINDINGS/CONCLUSIONS

- Diagnostic sensitivity, specificity, PPV, and NPV all vary over a range of 43-100%, depending on the particular combination of metric and inter-breast difference formulation, and whether the computations are based on individual or combined metrics
- · Univariate data analysis: Clinical predictive values, over the complete set of available metrics and formulations. range from 57 to 91%. Mean values for these diagnostic accuracy indices range from 60% to 86% Corresponding values averaged over all data groups, parameters and formulations range from 69% to 81%.
- · Multivariate data analyzie: In many instances the composite clinical predictive values increase markedly ranging from 87% to 100%, with the best-case composite having minimum values >40% for all measures
- · Cross-validation more dury: Predictive values declined only modestly in most cases. The best-case cross validation result, encompassing all three data groups, yields values of 100%, 70%, 73% and 100% for diagnostic sensitivity, specificity, PPV and NPV, respectively.

Ouestion 2:

- · With group 1 data, localization accuracy ranged from 32% to 68%. For group 2 data, values ranged from 50-61% and for group 3 data values ranged from 68,77%
- The preceding values were obtained without prior knowledge of which breast contained a tumor
- when a similar analysis was expanded to consider multiple parameters simultaneously and used to distinguish

· Predictive nower of previously defined metrics for cancer detection was confirmed

· Not presently warranted, given the size of the data sets so far considered

Given that only subjects with cancer were tested here, the overall false negative rate was ~30%.

extends considerably beyond the boarders of the tumor

considered simultaneously

- which breast contained a tumor (i.e., a global analysis), assignment accuracy improved to a range of 91-100%.
- · These findings strongly argue for the value of imposing a maneuver that can alter the tissue oxygen supplydemand balance

Onestion 3:

- · For those subjects having the best quadrant-level tumor accuracy (N = 6), we estimated tumor volume by computing the fraction of image volume wherein the contrast level exceeds a 50% threshold value for one or all of countral different matrice
- · The functional tumor volumes thus obtained underestimate the anatomical volume by approximately a factor of two in most cases Validation Study · The finding that rather crude measures are nevertheless canable of accurately detecting cancer speaks to the

inherent sensitivity of the method and strongly indicates that the biological processes underlying the measures

· Predictive power of the multivariate estimators would likely increase should more that one estimator group be