



# 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-resolved detection. Studies on 37 subjects (14 with cancer) show that tumor detection and localization is possible with high sensitivity and specificity. Validation studies (10 cancer subjects) demonstrate that the diagnostic metrics derived from analysis of the original 37 subject data correctly predict cancer status in a majority (96%) 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<sup>1</sup>. 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 group composition of the latter group was heterogeneous, that is 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 subject was performing one or more quantitative Valuable Derived Metrics (VDM). Data analysis was performed to answer three principal questions:

1. What are the diagnostic predictive values for globally derived metrics?
2. To what is the spatial 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 challenge. Three groups of metrics were defined. 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 age, tumor size and tumor location, for subjects diagnosed with breast cancer. Tumor sizes ranged from 1 cm to 27 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 3 reports the summary statistics for demographic characteristics between the two groups; they are not statistically different with respect to age or body-mass index (BMI).

#### 2) Measurement Protocol:

After giving her informed consent, each subject lay prone on the measurement gantry, with both breasts hanging pendant. The dual measuring beds were adjusted to make comfortable contact with the breasts. The instrument gantry settings appropriate to each individual breast (90° source-detector pairs' wavelength) breast were found by using an automated unit<sup>1</sup>. Dual-wavelength time-series optical tomographic data were collected during two consecutive measurement periods: baseline and provocative. Baseline data were collected for a period of 10 minutes with the subject at rest. Provocative metrics were obtained while the subject held a 40 min respiratory for a period lasting up to 30 seconds. Four QVMs, with a 4-minute recovery period after each, were attempted. In practice, only 21 subjects completed correctly at least one.

#### 3) Time-series Image Recovery:

Collected data were analyzed, using previously described software<sup>2</sup> and algorithms<sup>3</sup>, to produce a time series of volumetric images for each 10-min measurement:  $I_{0(t)}$ ,  $I_{1(t)}$ ,  $I_{2(t)}$ ,  $I_{3(t)}$ , and  $I_{4(t)}$ , via

$$I_{i(t)} = I_{0(t)} + I_{1(t)} + I_{2(t)} + I_{3(t)} + I_{4(t)}$$

#### 4) Data Analysis for Tumor Diagnosis:

4.1)  $I_{0(t)}$ - $I_{4(t)}$  Time-series-derived Metrics (Table 4):

- Group 1: Indices of resting vasomotion amplitude
  - Computed from resting vasomotion amplitude
  - Governing hypothesis is that tissue exposed to hypoxic environments have increased amplitude at vasomotion frequencies
- Group 2: Index of spatially coordinated dynamics
  - Computed from baseline measurement
  - Governing hypothesis is that blood delivery to affected breasts is less spatially coordinated than that to healthy breasts

4.2) Formulations for Intra-breast, Intra-subject Comparisons (Table 4):

- Tumor minus non-tumor for training-set cancer subjects
- Left minus right for training-set non-cancer subjects, and for validation-set subjects

4.3) Diagnostic accuracy parameters for "normalization" 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

#### 4.4) Critical Tests of Diagnostic Ability (Table 5):

- Train test metrics: Formulation: Intra-subject separation
- Unequal-variance t-test for difference between means of CA and non-CA subgroups for the training set
- Tabulate which metrics yield statistically significant differences
- Perform spot-checks with non-parameter test (Mann-Whitney), to ensure that small sample sizes are not an issue

Table 1: Tumor Characteristics in Breast Cancer Subjects

Subject No.	Age (yr)	Diagnosis <sup>a</sup>	Tumor Size <sup>b</sup> (cm)	Tumor Location <sup>c</sup>
1	32	D.Ductal CA	7.5x2.5	UOQ
2	56	R.Ductal CA	2x3	Lateral (9° clock)
3	68	R.Ductal CA	3x4	UOQ
4	40	L.Mucinous CA	7x4x3	UOQ (11° clock)
5	62	R.Inflammatory CA	3.5	Lateral (9° clock)
6	45	L.Ductal CA	3	UOQ (2° clock)
7	29	L.Metastatic CA	2.7	UOQ(2-3° clock)
8	70	R.Lobular & Ductal CA	3.0	Lateral (9° clock)
9	44	L.CA (unspecified type)	2.5	UOQ (1° clock)
10	45	L.Inflammatory CA	2.5	Lateral Breast
11	48	R.Ductal CA	2.1x1.5x1.5	UOQ
12	39	R.Ductal CA recurrence	0.7x0.8	UOQ (11° clock)
13	37	R.L.Ductal CA	8.2x1.5x1.1, 1.0x5	R.(11° clock), L.(12° clock)
14	43	R.Ductal CA	3x2x1	Inferior (8° clock)

<sup>a</sup>CA = carcinoma; <sup>b</sup>cm = centimeters; <sup>c</sup>UOQ = upper outer quadrant, LR = lower outer quadrant

Table 2: Sub-categories of Non-Cancer Subjects

Age (yr)	Subject Sub-category			
	Healthy	Prior Lymphoedema	Prior Cystectomy or Other Surgery <sup>a</sup>	Fibrocystic or Other Conditions <sup>b</sup>
31	41	63(8)	44(L.R Breast reduction)	55
33	39	1(8)	47(1)	44
36	56	1(8)	48	40
39	39	1(8)	47(1)	44
41	31	1(8)	47(1)	44
43	35	1(8)	47(1)	44
45	53	1(8)	47(1)	44
53	53	1(8)	47(1)	44
54	54	1(8)	47(1)	44
Total	8	2	2	5

Table 3: Age-matching and BMI-matching Statistical Tests

Subject Category	Demographic Parameter	Age (yr.)				BMI				
		N	Mean	SD	Range	p <sup>a</sup>	N	Mean	SD	p <sup>a</sup>
Cancer	Mean CA	14	47.5	12.7	26.70	0.39	14	24.7	5.5	0.50
	Mean non-CA	23	44.7	8.7	25.62	1.0 <sup>b</sup>	30.1	6.3	0.3	

<sup>a</sup>p by Student's T-test for the mean of the two populations are not different, from equal-variance group t-tests. If not shown that an unequal-variance test was not attempted, for both parameters.

<sup>b</sup> Fisher's exact test applied was not significant, thus the use of a non-CA BMI could not be calculated.

Table 4: Subject Parameters

Age	BMI	Cancer Sub-type	Location	Location
40	25	Right Inflammatory Ductal Carcinoma	Scan by CBE	Upper outer quadrant
65	32.9	Left Breast Invasive Ductal Carcinoma	Scan by CBE, 3x1.5cm Scan (8x5)	12 (5)clock Scan deep to areola
58	31.2	L.OV.L Breast Infiltrating Ductal CA	5x4.9x3.4cm(Scan)	Upper outer (axillary) fold
42	34	R Breast Infiltrating Ductal Carcinoma	Scan by CBE	upper part
64	36.4	Right Infiltrating Ductal Cancer	4.5x3x5y Mammo	12° clock in anterior depth
59	22.7	Right Infiltrating Ductal Cancer	10x by CBE	Anterior region
44	36.4	Right Invasive Ductal CA	7.3x1.1cm, 2.7cm by Sono	6° clock
48	25.9	Left Invasive Ductal CA	2x2.5cm by CBE	Above level of areola in UOQ
56	31.2	Right Breast Invasive Ductal CA	Scan by CBE	12 and 9° clock
56	27.4	Left Breast Invasive Ductal CA	5.5cm long 8mm by Sono	5° clock and 1° of clock
Mean	33	29.4		
SD	9.67	4.48		

Table 4: Various Metrics and Formulations

Formulation	Parameter	Group 1 (Baseline Integration) Metrics						Group 2 (Training Set) Coherence Metrics	Group 3 (Validation Set) Mammography Metrics
		TSDMS <sub>0</sub>	TMSDMS <sub>0</sub>	TSDMS <sub>1</sub>	TMSDMS <sub>1</sub>	SDFSD <sub>0</sub>	SDFSD <sub>1</sub>		
DIL/Max	$I_{0(t)}$	✓	✓	✓	✓	✓	✓	✓	✓
	$I_{1(t)}$	✓	✓	✓	✓	✓	✓	✓	✓
	$I_{2(t)}$	✓	✓	✓	✓	✓	✓	✓	✓
DIL/Min	$I_{0(t)}$	✓	✓	✓	✓	✓	✓	✓	✓
	$I_{1(t)}$	✓	✓	✓	✓	✓	✓	✓	✓
	$I_{2(t)}$	✓	✓	✓	✓	✓	✓	✓	✓
DIL/Avg	$I_{0(t)}$	✓	✓	✓	✓	✓	✓	✓	✓
	$I_{1(t)}$	✓	✓	✓	✓	✓	✓	✓	✓
	$I_{2(t)}$	✓	✓	✓	✓	✓	✓	✓	✓
DIL/Min	$I_{0(t)}$	✓	✓	✓	✓	✓	✓	✓	✓
	$I_{1(t)}$	✓	✓	✓	✓	✓	✓	✓	✓
	$I_{2(t)}$	✓	✓	✓	✓	✓	✓	✓	✓
DIL/Max	$I_{0(t)}$	✓	✓	✓	✓	✓	✓	✓	✓
	$I_{1(t)}$	✓	✓	✓	✓	✓	✓	✓	✓
	$I_{2(t)}$	✓	✓	✓	✓	✓	✓	✓	✓
DIL/Avg	$I_{0(t)}$	✓	✓	✓	✓	✓	✓	✓	✓
	$I_{1(t)}$	✓	✓	✓	✓	✓	✓	✓	✓
	$I_{2(t)}$	✓	✓	✓	✓	✓	✓	✓	✓

Legend: TSDMS<sub>0</sub> = Tumor Signal Difference Metric; TMSDMS<sub>0</sub> = Tumor Signal Difference Metric; SDFSD<sub>0</sub> = Signal Difference Metric; SDFSD<sub>1</sub> = Signal Difference Metric; TSDMS<sub>1</sub> = Tumor Signal Difference Metric; TMSDMS<sub>1</sub> = Tumor Signal Difference Metric; SDFSD<sub>1</sub> = Signal Difference Metric; TSDMS<sub>2</sub> = Tumor Signal Difference Metric; TMSDMS<sub>2</sub> = Tumor Signal Difference Metric; SDFSD<sub>2</sub> = Signal Difference Metric; TSDMS<sub>3</sub> = Tumor Signal Difference Metric; TMSDMS<sub>3</sub> = Tumor Signal Difference Metric; SDFSD<sub>3</sub> = Signal Difference Metric; TSDMS<sub>4</sub> = Tumor Signal Difference Metric; TMSDMS<sub>4</sub> = Tumor Signal Difference Metric; SDFSD<sub>4</sub> = Signal Difference Metric; TSDMS<sub>5</sub> = Tumor Signal Difference Metric; TMSDMS<sub>5</sub> = Tumor Signal Difference Metric; SDFSD<sub>5</sub> = Signal Difference Metric; TSDMS<sub>6</sub> = Tumor Signal Difference Metric; 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TMSDMS<sub>86</sub> = Tumor Signal Difference Metric; SDFSD<sub>86</sub> = Signal Difference Metric; TSDMS<sub>87</sub> = Tumor Signal Difference Metric; TMSDMS<sub>87</sub> = Tumor Signal Difference Metric; SDFSD<sub>87</sub> = Signal Difference Metric; TSDMS<sub>88</sub> = Tumor Signal Difference Metric; TMSDMS<sub>88</sub> = Tumor Signal Difference Metric; SDFSD<sub>88</sub> = Signal Difference Metric; TSDMS<sub>89</sub> = Tumor Signal Difference Metric; TMSDMS<sub>89</sub> = Tumor Signal Difference Metric; SDFSD<sub>89</sub> = Signal Difference Metric; TSDMS<sub>90</sub> = Tumor Signal Difference Metric; TMSDMS<sub>90</sub> = Tumor Signal Difference Metric; SDFSD<sub>90</sub> = Signal Difference Metric; TSDMS<sub>91</sub> = Tumor Signal Difference Metric; TMSDMS<sub>91</sub> = Tumor Signal Difference Metric; SDFSD<sub>91</sub> = Signal Difference Metric; TSDMS<sub>92</sub> = Tumor Signal Difference Metric; TMSDMS<sub>92</sub> = Tumor Signal Difference Metric; SDFSD<sub>92</sub> = Signal Difference Metric; TSDMS<sub>93</sub> = Tumor Signal Difference Metric; TMSDMS<sub>93</sub> = Tumor Signal Difference Metric; SDFSD<sub>93</sub> = Signal Difference Metric; TSDMS<sub>94</sub> = Tumor Signal Difference Metric; TMSDMS<sub>94</sub> = Tumor Signal Difference Metric; SDFSD<sub>94</sub> = Signal Difference Metric; TSDMS<sub>95</sub> =