AN EVALUATION OF A NEW OBJECTIVE METHOD

FOR EARLY BREAST CANCER SCREENING

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This study is supported by a grant from Ohio's Thomas Edison Program for Innovative Research and by ChronoDynamics, Ltd., Dayton, Ohio.

BACKGROUND:

Self-breast exam, examination by a health-care provider, and mammography continue to be the mainstays of early breast cancer detection although none of these methods is fail safe. Increasing rates of breast cancer mandate that additional safe, early, painless, and inexpensive methods of detection be discovered. One potential method involves evaluation of circadian temperature patterns of breast tissue which in the presence of a malignancy have been shown to become asynchronous from patterns of normal tissue.

Increases in temperature associated with tumor formation have been attributed to neovascularization of the tumor secondary to angiogenesis. Further, some neovasculature of malignancies lack smooth muscle, rendering it unreceptive to control by epinephrine. This lack of receptivity produces more constant blood flow and tumor temperature with less circadian temperature variation than is evident in healthy breast tissue. Identification of such "high risk" pattems should alert the practitioner to the need for further patient evaluation.

OBJECTIVES:

1. To evaluate circadian patterns of breast temperature as an objective method of breast cancer screening.

2. To compare circadian pattem behavior analysis to mammography and physical examination for breast cancer screening.

METHODS:

Clinical

138 subjects who had been scheduled for open-breast biopsies as a result of physical examination and mammography were recruited from the population of patients at a surgical oncology clinic at the Ohio State University Hospitals. Each subject wore a portable breast monitor which consisted of a microprocessor with sixteen thermistors that automatically recorded temperatures every five minutes for forty-eight hours. Each subject recorded her daily activities for the entire time the monitor was worn.

Data Analysis

Data for the 138 subjects were first analyzed using statistical software developed to evaluate the approximately 9000 data points recorded per patient. A Gaussian distribution of the data was assumed to allow calculation of the mean and variance of data points so that a best-fit line was established to represent the structure of the data. Temperature points from contralateral breast sensors were plotted against each other, forming a cluster of data points. Classification boundaries which had been previously established in a preliminary study were used to determine whether a subject was classified as high or low risk. In addition, the data were subjected to a least square spectral analysis. Predominant periodicities were identified, and a modified cosine vector analysis was performed to represent an approximation of circadian temperature rhythm.

Subsequently, the same data were analyzed retrospectively using a neural net. Neural network paradigms use no assumptions about the data; feature segmentation is automati cally performed. The network itself selects features of the input vector sets. These features are weighted based on truth; and, in the case of the breast monitor, only pathology is truth. Ideally, any neural network requires data from 100 exemplar cases (in this instance 100 confirmed cancers) before it will be totally functional. The architecture of the present neural network utilizes a Multi-Layer Back Propagation (MLBP) algorithm which seems well-suited for circadian temperature pattern recognition. (For further description of Neural Network Mechanics, see Appendix.)

RESULTS:

Total biopsies:	138
Positive for cancer:	23 of 138 (17%)
Cancers found on mammogram:	19 of 23 (83%)
*Cancers found by monitor (Stat. anal.):	20 of 23 (87%)
Cancers found by monitor (Neural net anal.):	21 of 23 (91%)
Palpable cancers:	17 of 23 (74%)
Needle localization:	6 of 23 (26%)

*3 cancers were found by the monitor that were missed by mammography. The subjects' ages were 36, 38, and 44; the tumor sizes were 0.5, 0.7 and 2 cms; all had dense parenchyma.

False positives: 30% by statistical analysis; reduced to 18% wit neural-net analysis.

DISCUSSION:

138 patients, all of whom wore the monitor, were biopsied. Twenty-three (17%) of these patients were diagnosed by pathology as having breast cancer. Twenty (87%) of the twenty-three were correctly identified by the breast monitor as

Selected Characteristics of Breast Carcinomas (n=23)

Indicator (n=3)	Identified by monitor (n=20)	Not identified by monitor
Tumor size range	mic.-4.5 cms	0.8-2.8 cms
Mean tumor size	1.91 cms	1.87 cms
Patient age range	34-69 years	30-57 years
Mean patient age	53.2 years	51 years
Node neg. patients	14	1*
Aneuploid tumors	12	1
Diploid tumors	7	2
ER negative	9	0
ER positive	9	3
ER unknown	2	0
Ductal carcinoma	15	3
Other carcinoma	5	0

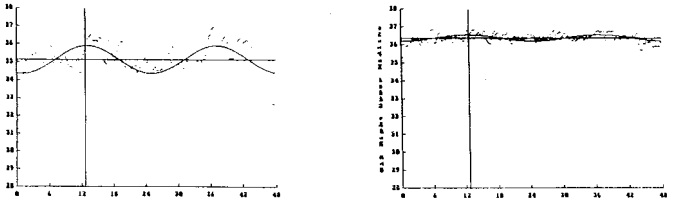
*complete data not available

high risk for cancer. (The monitor missed three ductal carcinomas.) Of these twenty-three patients only nineteen (83%) mammograms were read as suspicious or positive for carcinoma. Of he four cancers missed by mammography, three were in premenopausal women with ductal carcinomas, tumor sizes of 0.5 cms, 0.7cms and a 2 cms medullary carcinoma. The final cancer missed by mammography was a microscopic intraductal carcinoma in a sixty-eight-year-old woman. The monitor correctly identified three of the four cancers missed by mammography. (It may be significant that these women were either pre- or perimenopausal.) One patient had a tumor which was not evident on either the mammogram or the monitor reading but was located by physical exam alone. Only seventeen (74%) of the twenty-three carcinomas were identifiable by palpation.

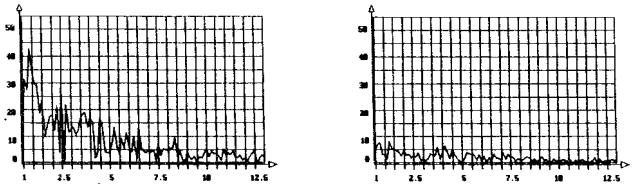
The neural-net algorithm was developed and evaluated because this newer methodology offers theoretical advantages when analyzing non-linear data such as those generated by the breast monitor. This initial retrospective analysis seems to confirm its advantage over statistical analysis in terms of improved diagnosis, i.e., 91% vs. 87%, and a reduction in "false positives," i.e., 18% vs. 30%.

Three Different Computer Displays of Non-linear Data from the Same Subject

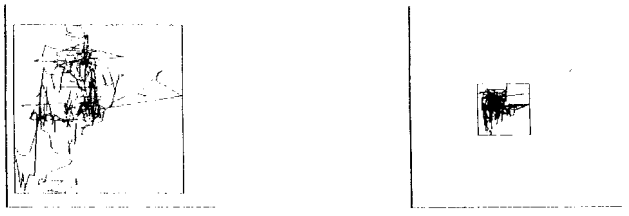
Normal Left Breast **Cancerous Right Breast**



Best cosinor fit of time series plots



Fourier spectra analysis by neural net



Phase space attractors (chaos analysis)

Some of the data were also analyzed retrospectively by chaos analysis which employs phase space attractors, another alternative analysis algorithm. It is based on the fact that normal tissue exhibits an apparant chaotic behavior whereas diseased tissue shows increased regularity. (Computer display examples of the three types of analysis are shown above.) Both Fourier spectra analysis and phase space attractor analysis will be pursued further, but the major emphasis will be on the former because of its superior capability of handling multiple variables.

CONCLUSIONS:

The quantity of data collected to date in this ongoing pilot study is inadequate for firm conclusions. However, these very preliminary data suggest that the monitor may be useful for screening those women with difficult mammographic interpretation. The term "false positive" should be used with caution since the monitor was positive for three cancers missed by mammography which were either premenopausal or perimenopausal, with tumor sizes as small as 0.5 as well as micro-calcifications. Patient data which are positive on the monitor in the absence of mammographic or physical evidence of cancer does not preclude the presence of cancer at its earliest stages. These patients may be considered at "high risk" for the disease which may become clinically evident at a future date.

IMPLICATIONS FOR FUTURE RESEARCH:

1. Prospective study with long-term follow-up of patients with high-risk readings.
2. Complete the development of neural-net analysis for interpretation of results.
3. Follow up the patients now classified as false positives to determine the true sensitivity and accuracy of the monitor in early detection.
4. Determine the minimum number of hours the monitor must be worn to promote maximum patient convenience and compliance.

APPENDIX

Neural Network Mechanics

Neural nets are modelled after their biological counterparts, specifically living neurons; and they are structured similarly to systems found in living organisms such as the human brain. The human brain is a massive parallel computer capable of extraordinary feats of information processing with its essential strength being that it can do things digital computers cannot. The opposite is also true, however; digital computers can perform mathematical operations at a greater rate and with better accuracy than the human brain. Digital computers do not generalize well and certainly have difficulties with pattern recognition tasks such as handwritten numeral recognition and speech recognition. In addition, digital computer architecture is drastically different than the networks within our brains and is limited by a paradigm of single instruction serial execution.

To create a neural net, one models the biological processing components (neurons) and interconnects them to form a system (network) of simple efficient "nodes" that communicate simultaneously with each other. These models are usually implemented with a serial processor so the advantages of the parallel structure are somewhat diminished. Each of these simple proc-

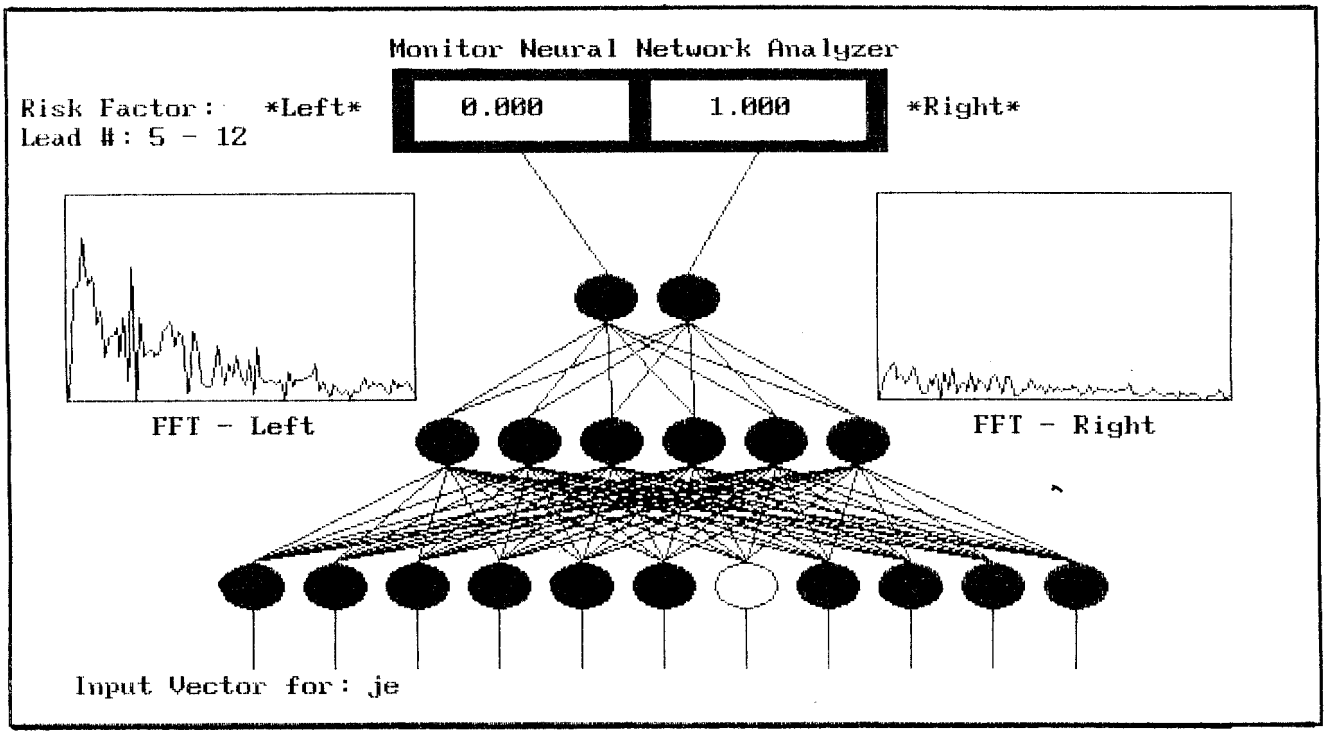
essors is connected to its counterparts via a weighting factor. This weight serves to modulate inputs to the node and is analogous to the living neural synapse. Training of the network is accomplished by modifying these weights systematically through an iterative algorithm. The weights as a whole (after training) represent the global knowledge that the network possesses, with each part contributing to the whole. This distributed data accounts for the network's resistance to induced failures.

In addition to the weighted interconnects, the node also performs some simple mathematical manipulations of input signals. The node first computes the weighted sum over all of the inputs and then utilizes a transfer function called the "activation function" to generate an output. Throughout the training and operation of the network, the transfer function and the process for summing over the inputs remain unchanged. Only the weights and "thresholds" change.

The objective of the training algorithm is to cause changes in the weight values within the network that minimize error between the expected level of network performance and actual level of performance. Training paradigms are of two general types: Supervised and Unsupervised. With Supervised training, an operator presents the network with a given input vector and then provides the network with the correct answer. The network then adjusts its parameters to minimize error generated by its own original answer in comparison to the correct answer. Unsupervised learning occurs in the absence of an operator. Networks utilizing this type of learning create decision boundaries by themselves. They usually perform tasks such as data clustering, that is, grouping similar data together based on segmented features.

As one can well imagine, networks can also be created using different architectures. The structure of a network is denoted as its type. There are dozens of different network types: Simple Perceptron, Multi-Layer Back Propagation, Adaptive Resonance, Neocognitron, Kohonen, etc. Essentially, however, all the networks usually fall into one of the two groups, namely Supervised or Unsupervised. Two very popular network types are the Multi-Layer Back Prop (MLBP) and the Kohonen. The MLBP is a Supervised net that is extremely well-suited for pattern recognition/identification applications. The Kohonen is a shining example of a self-learning or Unsupervised architecture. For the purposes of this study, the MLBP and the Kohonen networks were chosen due to their effectiveness and flexibility.

Statistical analysis of the non-linear data generated by the breast monitor requires the operator to make certain a priori assumptions about the data. In order to calculate the mean and variance of a given set of data and thereby establish parameters for it, one must assume that the data are distributed normally; for example, one might assume a Gaussian distribution. In addition, important features in the data set must be identified along with a classification rule in order to generate the categories that the information will hopefully fall into. With neural network paradigms, no assumptions about the data are made and feature segmentation is performed automatically. The network selects by itself which features of the input vector set are important. These features are then weighted more heavily in its analysis of the data. The neural network models learning and, in so doing, creates a knowledge base about input relationships without the aid of external influence.



Computer display of neural network analysis, demonstrating parallel node interconnections, fast Fourier transform of the input data and resulting confidence index of risk. This is the complete printout of the Fourier Spectra analysis shown in the **DISCUSSION.**