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14. ABSTRACT

Although screening for breast cancer has been effective in detecting cancers, it is not clear that the diagnostic information present in sequences of screening exams is currently being utilized. This project has integrated several novel technologies into a system for providing mammographers with information about changing tissue patterns derived from temporal sequences of images. Our hypotheses are: 1) Sequences of screening mammograms contain information about tissue changes that is not otherwise being exploited in the diagnosis of breast cancer; and, 2) Changing tissue patterns can automatically be identified, and correlated with diagnostic questions. To date, the tasks described in the statement of work have been completed, but unexpected issues arising from that work are being addressed in a 1-year extension of the project. This involves defining additional time-dependent features, and having the system subjectively evaluated by radiologists.

15. SUBJECT TERMS
screening mammography, mammography, computer-aided diagnosis, image registration and subtraction, electronic mammography display

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Walter F. Good, Ph.D.

Introduction

Considerable attention has been paid to methods for improving the diagnostic accuracy and efficiency of mammographic screening procedures, including: Assessments of the importance of age of patients to be screened [1]; Appropriate screening intervals [2]; Appropriate screening techniques [3,4]; Recommended number of views per examination [5]; Single vs. double reading [6]; and, Use of prior examinations for comparison [7].

Customarily, in screening programs mammographers only compare the current exam to one previous exam (e.g., one year prior or two years prior). This is partly for efficiency but also because there is a lack of compelling evidence on how changing tissue patterns relate to the likelihood of developing a malignancy. Retrospective inspection of exams taken in years prior to the detection of a malignancy often indicates the presence of an abnormality. Such anecdotal evidence suggests that it is at least possible that series of screening exams contain additional information that could improve the accuracy of the diagnostic process.

There is also evidence that difference images in certain procedures can contain diagnostically useful information, despite the presence of substantial subtraction artifact. In the diagnosis of chest radiography, it has been demonstrated that adding temporally subtracted images to the diagnostic process can, in many situations, significantly improve diagnostic accuracy and reduce mean interpretation time [8]. Difference images obtained by temporal subtraction methods in mammography have properties somewhat similar to images obtained with bilateral subtraction images used in CAD, where it can be shown that differences contain diagnostic information [9-13]. However, like the subtraction of chest images, temporal image subtraction of mammograms is a difficult task due to tissue changes over time, inconsistencies in breast compression, skewing of the three-dimensional breast relative to the image projection during compression and lack of easy landmarks on the breast that can be used to facilitate optimal image registration. Previous attempts to develop acceptable subtraction methods for mammograms, including methods for both bilateral subtraction [9-12] and temporal subtraction [14-16], have had only partial success. As a result, the temporal subtraction of mammograms has not been employed clinically.

In an attempt to improve diagnostic accuracy of screening mammography, this project is adapting and integrating several novel technologies, under development in our laboratory, into a system for providing mammographers with information about changing tissue patterns, and the corresponding likelihood of malignancy, derived from temporal sequences of images. Specifically, these technologies include: 1) A method for locally deforming and registering mammograms [17,18]; 2) Multi-image CAD, which we have previously used to identify corresponding features in ipsilateral views [19]; and, 3) Adjustment of digitized mammograms to account nonuniform tissue thickness due to breast compression, to enhance soft display of mammograms and to enable more accurate computerized estimation of tissue composition [20]. Our hypotheses are: 1) Sequences of screening mammograms contain information about tissue changes that is not otherwise being exploited in the diagnosis of breast cancer; 2) Changing tissue patterns can automatically be identified, and correlated with diagnostic questions; and, 3) Such information can be made available to mammographers, in an efficient manner, through displays specifically designed for these image sequences.

The main objectives of this project are to provide a system, which can be employed at the discretion of mammographers, to: 1) Normalize images to facilitate comparisons; 2) Apply our previously developed multi-image CAD methods to identify corresponding features between images, and evaluate possible trends for any such features; 3) Detect and classify trends in temporal sequences (e.g., distinguish between normal and abnormal age-dependent changes, and identify those patterns of change that are associated with the development of malignancies); 4) Calculate and present various kinds of parameter images; and, 5) Develop a display system for efficiently presenting sequences of exams to mammographers, with the optional ability to emphasize trends by correcting images for differences in exposure, compression, and local misregistration. Our expectation is that this display will improve the diagnostic performance of mammographers for these cases.

Body

Progress on this project closely followed the schedule and methods outlined in the original proposal. All tasks described in the statement of work have been undertaken and completed successfully. The tasks that were completed during the past year include:

Task 4: Image analysis software development (Months 6 – 30).
k. Detection and classification of trends.
Task 7: Final training and testing of classifier (Months 24-30).
Task 8: Final processing of all cases (Months 30 – 34).
Task 9: Data analysis and final report (Months 30-36).

Throughout the project certain technical issues arose and these are being addressed in the one-year extension that has been granted. The following paragraphs summarize the work that has been completed to date.

***Task 1*: Select, verify and digitize cases (Months 1 – 30)**
a. A set of 240 sequences of screening mammograms will be selected and verified
b. All verified cases will be digitized

A total of 240 cases, have been collected since this project was funded. Some of these were collected from other institutions. Of these, 125 are negative and 115 contain malignancies. All cases have been verified, digitized, and assembled into a database. The database has been anonymized by use of an honest broker system, to comply with the requirements of HIPPA. This completes the active acquisition of cases within this project.

Case selection was based on a historical prospective approach, in which we examined cases that had at least two prior screening examinations. We only considered cases for which, prior to the latest examination in which a positive abnormality may have been detected, all the mammograms for these patients had been interpreted as negative. Each case consists of two views of a single breast. Originally, we had expected to select all cases from routine mammographic examinations performed at the UPMC and Magee health care systems, but to find a sufficient quantity of positive cases having the appropriate historical sequence, we have included images from other institutions. Positive cases were drawn from cases that have undergone biopsy. Negative cases, for the most part, are cases that have not been recommended for biopsy, but in some instances, subtle negative cases, which have had biopsies that were negative for the presence of a mass or microcalcification cluster, have been selected.

Each selected film has been digitized with a 12 bit modified film digitizer (Lumisys) having an MTF of 27 and 24% at the Nyquist frequency (10 lp/mm) in the X and Y directions, respectively. The digitizer is routinely evaluated and adjusted to maintain spot size, linearity, geometric fidelity, stability and acceptable spatial noise characteristics, and to maintain a linear relationship between pixel value and optical density, as part of our quality assurance procedures.

***Task 2*: Modification of workstation for this project (Months 1 – 12)**

An existing 4-monitor display, which was developed in our laboratory, has been adapted for this study. The individual monitors (Clinton Electronics, Model DS5000) are 21 inch portrait monitors, having a resolution of 2048 x 2560 pixels, 150 ftL light output and P45 phosphor. The displays are driven by a display controller (Dome Imaging Systems, Model Md5/PCX-2) specifically designed for these monitors, and calibrated with a Barten lookup table to accommodate the contrast sensitivity of the human eye. The system has been designed to display four images of a single exam at a time, or a single image and its associated parameter images, or to display sequences of exams sequentially, at a rate determined by viewers. This task was completed in year one.

***Task 3*: Develop display software (Months 3 – 15)**

a. Display difference images

b. Display trends

The ability to deform sequentially acquired mammograms so that they can be placed in reasonable registration is a central aspect of this project. While image subtraction was addressed somewhat in year one, we continued the development of the image deformation and subtraction software in the second year. In the originally proposed method, which is described in more detail under section g of Task 4 below, we used intersections of nipple axis lines with chest walls as origins of polar coordinate systems for performing mappings between mammograms. We have demonstrated that a modification of this approach is preferable. Specifically, the origin is now defined as the midpoint of the chest wall. The line from this point, passing through the nipple serves as the base for measuring angles. But because this line is not generally perpendicular to the chest wall, a nonlinear monotonic function is used to find corresponding angles between images. Viewers, at their discretion, have the option of either subtracting consecutive images in sequence or subtracting each previous image from a specific (e.g., the most recent) image. Prior to actually performing the subtraction, images are first normalized to correct for tissue thickness, and then geometrically deformed to match a common template. The details of this procedure, and a comparison of the various techniques, have been submitted for presentation at SPIE Medical Imaging 2005.

Because the parameter images are at a much lower effective resolution that the original mammographic data, these can be displayed side-by-side. The display software has been appropriately modified to allow for alternative display formats. A cine mode has also been implemented on the display system as one means of displaying temporal sequences of image data. This can be used to display either the original mammographic data or the parameter images being generated from each mammographic image. The optimal arrangement of the displayed information will depend to a great extent on the importance of the various kinds of parameter and trend summary images being generated.

***Task 4*: Image analysis software development (Months 6 – 30)**

a. Correct for characteristic curve

b. Correct for breast compression

c. Skin line detection

d. Breast compression adjustment

e. Local and global composition

f. Global composition from 2 views
g. Local geometric registration
h. Histogram equalization between images
i. Modify Multi-View CAD for this project
j. Create parameter images
k. Detect and classify trends

Subtasks **a-e** and **g** were largely completed during year one.

a. Correct for characteristic curve – The characteristic curve for each particular film was obtained from the manufacturer. Although these curves are generic, they are sufficiently accurate for this application, given other imperfections in the overall imaging chain. Our routine quality assurance process on the digitizer maintains a linear relationship between pixel value and optical density. The characteristic curve correction algorithm is written to use the inverse of the digitizer characteristic curve to convert pixel values to optical density values, and then us the inverse of the film's characteristic curve to convert optical density to film exposure.

b,d. Correct for breast compression – The wide dynamic range of mammograms is caused in part by the non-uniformity of breast thickness during breast compression. To correct for this, at each pixel in a mammogram, we determine the relative thickness of the compressed breast as a function of the distance of the pixel from the skin line. Although there are computationally more efficient methods, we measure the distance of each pixel to the skin line with a simple exhaustive search. We divide the range of possible distances into a small number of intervals (typically 32 to 64 depending on image size) and for each interval, all of the tissue pixels whose distance falls within that interval are grouped. For each such group the mean and standard deviation are calculated, and an appropriate function is fitted, with constraints, to the means plus one standard deviation. This "correction" function represents the change in pixel value with respect to distance from the skin line, and actually indicates tissue thickness relative to this distance. For each pixel, the correction function is used to calculate a correction value from the pixel's distance value, and this correction value is used to normalize the pixel value. In the central regions of the breast area, the correction values are 1 and these pixels are left unchanged.

c. Skin line detection – In this project it is necessary to make geometric measurements that are referenced to the skin line and nipple. We first produce a low-resolution version of the image by averaging pixel values over a 16□16 block and then apply the Sobel gradient to the reduced-resolution image. At each point in the image, the original pixel value, the magnitude of the gradient, the direction of the gradient, the radial distance of the pixel from the center of the left edge of the film and a direction value for the surrounding neighborhood are all combined to produce a value which is proportional to the likelihood that the pixel falls on the skin line. These likelihood values are thresholded and then placed in an image where they are processed with morphological operators to eliminate isolated points. The points that remain, which are invariably on the skin line, are mapped back to the high-resolution image and used to fit a Bezier Curve to define a smooth skin line. Although failure is rather uncommon, it can happen when the tissue thickness adjustment process fails to correctly identify the skin line. This can occur for images where the skin line on the film was so dense (i.e., over an optical density of about 4.2) that the digitizer was unable to distinguish between the skin line and the image background. In this event, we do not include the case in this study.

Detection of pectoral muscle – To detect the pectoral muscle, we employ a template matching with the mammographic image, which is a standard approach, and effective in cases such as this where structures are relatively well defined. The chest wall is not normally visible in the CC view so we assume, in these cases, that it is parallel to, and 0.5 cm beyond the edge of the image.

e. Local and global composition – After correcting images for characteristic curves of film and then correcting them for nonuniformities due to breast compression, at each point in a view, we estimate % fibroglandular tissue, by deriving certain features directly from a local histogram and using a neural network, trained with values from breast MRI, to obtain a local estimate of composition. An initial global value is determined for the image by integrating over the tissue area. Tissue composition is calculated independently from CC and MLO views, and averaged to obtain the global value for the breast. The local values in each of the two views are then scaled appropriately.

f. Global composition from two views – As implemented, calculating a global composition for a breast from two views simply involves averaging the values from the CC and MLO views and then adjusting the local values in each of the individual views so that they match the averaged value. Values for individual views are found by the following procedure: 1) Correct images for characteristic curve of film; 2) Detect skin line; 3) Detect pectoral muscle; 4) Correct for breast compression; 5) Calculate fraction of fibroglandular tissue at each pixel; 6) Multiply this fraction by the breast thickness at the pixel to obtain absolute amount of fibroglandular tissue at pixel; and, 7) Integrate this over the projected area of the breast.

g. Local geometric registration – To make comparisons between sequentially acquired images more feasible, we adjust the geometry of all images being compared, so that the images can be placed in accurate registration, and we normalize grayscales so that they reflect equivalent exposure conditions. In brief, the subtraction method uses a fully automatic nonlinear transformation that can map any mammographic image onto a template or reference image while assuring concurrent and accurate registration of skin lines, nipples, pectoral muscles and nipple axis lines.

The geometric transformation is diagramed in Figure 1. The technique begins by automatically detecting pectoral muscles on MLO views (e.g., *OL* and *O'L'* in Figure 1), skin lines and nipple locations, *N* and *N'*, in Figure 1. Polar coordinate systems are established with the origins, *O* and *O'*, at the intersection of the nipple axes lines (NALs), *ON* and *O'N'*, and lines indicating the pectoral muscles, on MLO views or with lines parallel to, and *0.5 cm* beyond, the edge of the film on CC views. Tissue pixels within a mammogram are identified by a relative polar coordinate, which we define to be the angle, α, of their position vector relative to the NAL and their fractional distance between the origin and the skin line. For each pixel *P* in a reference template (e.g., left image in Figure 1), a point *P'*, having the same relative polar coordinate, is found in the image to be deformed. The pixel at location *P* in the template is then given the value of the point at *P'*, as determined by the nearest pixel or through interpolation, after adjusting for the local Jacobian of the transformation at the particular point. Clearly, this transformation maps nipples onto nipples, skin pixels onto skin pixels and chest wall pixels onto chest wall pixels, while interior pixels are deformed correspondingly.

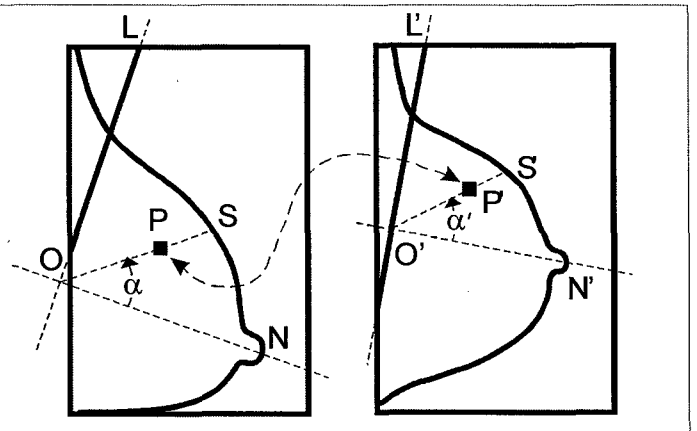

Figure 1: Relative radius polar coordinate transformation.

Grayscale adjustment – Once images have been deformed so that a reasonable correlation between pixels can be assumed, grayscales are corrected by applying a standard linear or nonlinear regression (e.g., using low degree polynomials) to pixel value pairs for the corresponding image points. Pixel values

of the deformed image are then adjusted by the regression equation, to minimize the sum-of-squares difference, with respect to admissible grayscale changes.

As stated above, the geometric registration method described above has been modified somewhat to improve performance. In the originally proposed method, we used the intersection of the nipple axis line with the chest wall as the origin of a polar coordinate system for performing a mapping between mammograms. We now have demonstrated that a modification of this approach is preferable. Specifically, the origin is now defined as the midpoint of the chest wall. The line from this point, passing through the nipple now serves as the base for measuring angles. But because this line is not generally perpendicular to the chest wall, a nonlinear monotonic function is used to find corresponding angles between images.

h. Histogram equalization between images – Once images have been deformed so that a reasonable correlation between pixels can be assumed, grayscales are corrected by fitting all pixel value pairs for corresponding image points with a 3-segment spline function consisting of two quadratic polynomials smoothly joined by a linear segment. Pixel values of the deformed image are then adjusted by the regression equation, to minimize the sum-of-squares difference, with respect to admissible grayscale changes.

i. Modify multi-view CAD for this project – Our multi-view CAD program, much of which is being adapted for use in this project, contains methods for comparing features taken at the same time from multiple views. For this project, these methods have been modified to permit their use on images taken at different times. Specifically, we included methods for applying linear regression to measure changes in features with respect to time. The main difficulty we have encountered in doing this is that our ability to find corresponding features in a sequence of images depends on our ability to deform the images so that they can be put in geometric registration.

j. Create parameter images – A general method for creating parameter images has been implemented. For temporal sequences of images, all images are deformed to the shape of the most recent image. A local feature filter is applied to each image to produce a corresponding image in which pixel values reflect the local magnitude of the particular feature in the original image.

Local features – We have defined a number of local features that could potentially be of value in identifying changing patterns in temporal sequences of mammograms. These include: local breast density, local variance, and, various measures of image texture.

k. Detect and classify trends – For each sequence of parameter files as described above, we have attempted to identify both local and global trends. Direct information about local trends, such as correlation coefficients, is displayable. To create the trend summary image for a feature, at each pixel we calculate a correlation coefficient and the slope of the best-fit line to the sequence of parameter values. In summary images we are currently using hue to represent slope and brightness to represent correlation (with black corresponding to $r^2 = 0$).

As a prototype for developing these methods we used the local breast density filter that produces images somewhat similar in appearance to the original mammograms, but at a lower resolution. In summary images, locations are assigned values from a scale that ranges from cyan (falling density) to red (increasing density), where brightness indicates the degree of correlation (uncorrelated sequences of pixel values are shown in black). Other filters (e.g., local variance, local fractal dimension) have also been implemented and behave in a similar manner. The results of these methods were presented at the Era of Hope Meeting in 2005.

Task 5: Initial training and testing of classifier (Months 16 – 18)

In addition to creating parameter images corresponding to individual features, we have trained a classifier to predict the likelihood of developing a malignancy based on actual features as well as on changes in features. Effectively, this has been accomplished by adding temporal changes in features, averaged over images, to the feature vector already used in our CAD algorithms. This classification mechanism has been implemented as a neural network, and trained using the training subset of our dataset. This is performed locally for sequences of ipsilateral exams, and the results of these classifications are displayable. The feature set used as input to the classifier includeds:

- Local density
- Local trend of changes in density
- Local variance
- Local trend of changes in variance
- Probability of malignancy from multi-view CAD

The system has been designed to allow additional features to be easily incorporated, once they are defined and implemented.

An intense value in one of these images corresponds to a high probability of the existence of a malignancy at the particular location.

Task 6: Interim testing and analysis (Months 18 – 22)

We have developed methods and software to measure the contribution of each of the temporal features to the overall performance of the classifier defined above. The neural network classifier is trained and tested on the training set of cases using a jackknife procedure, both with and without a feature of interest. Performance is measured by ROC analysis, with the A_z value being used as a figure-of merit. The difference in performance, with or without the feature, is taken as a measure of the importance of the particular feature.

Task 7: Final training and testing of classifier (Months 24-30)

Our method for selecting an optimal feature set by using genetic algorithms has been adapted for this project. But because the set of features implemented to date is small, and we have paid particular attention to insure that they are independent, the method is not actually useful at this point. It will become more important during the one-year extension of the project as texture features are added that are not expected to be independent.

The main significant difference between the final version (to date) and the interim version of the classification mechanism is that we have now included age as a feature. This was necessary because trends in other parameters, such as breast density, tend to be age dependent.

Task 8: Final processing of all cases (Months 30 – 34)

Within the past year, all cases in the available dataset have been processed by the finalized methods described above and the images have been placed on the workstation developed for this project. While evaluation in terms of efficacy was not described in the original Statement of Work, we are currently soliciting subjective opinions of radiologists.

Task 9: **Data analysis and final report (Months 30-36)**

The project was intended to be primarily of a developmental nature, and no quantitative evaluation of overall performance has been performed to date. However, the methods that have been developed were displayed at the Era of Hope Meeting in 2005. Other manuscripts summarizing the work have been prepared and are in the process of being reviewed. These documents will provide details on the relative contributions of each of the local features studied in this project

One-Year Extension – This project was intended to be primarily of a developmental nature, and no meaningful evaluation of the work has been performed to date. However, prior to testing the system we believe it is desirable to implement certain other features that should be included in the evaluation.

Within the scope of the project we implemented several filters, as specified in the original Statement of Work, that measure characteristics of mammograms that can be followed throughout a woman's mammographic history. While doing this, it became apparent that there were many other features that could turn out to be important, but which were not within the aims of the project. Nevertheless, some of these should be implemented before a quantitative evaluation of the system is performed. The main example of such features would be measures of image texture (e.g., fractal dimension), which have been receiving increasing attention for their potential relevance in predicting risk of malignancy. In any event, the filters developed within the project can serve as templates to make the task of creating new filters much easier.

A thorough evaluation of the project, such as by an ROC study, is not feasible at this time because of limitations of our current dataset, and the cost and effort required. However, it will be possible to have the system evaluated subjectively by radiologists within the coming year. Such an evaluation will provide the kind of preliminary results that will make it possible for us to propose a more formal ROC evaluation in the future.

We acquired the image dataset as proposed, though the number of long sequences of screening mammograms, ending with a positive biopsy, was somewhat less than expected. It has turned out that finding biopsy proven positive cases, having long mammographic histories, has been very difficult. This is mainly due to the fact that recommendations for mammographic screening of younger women have historically been ambiguous, and until recently relatively few women routinely have had annual mammographic examinations. The cases we acquired were sufficient for the work proposed in the contract, but this left few positive cases that are available for testing the system. (It is not meaningful to test the system with cases used in its development and optimization.) Discovering generalizable trends by using the methods developed in this project requires these longer exam histories. With this in mind, database acquisition is an ongoing activity in our facility, and will continue with funding from this and other projects. We are presently trying to collect a sufficient set of these long image sequences for us to perform a more rigorous analysis of the relationship between mammographic trends and risk of malignancy. These additional cases will also increase the power of any evaluation study. This work will be completed during the coming year.

Key Research Accomplishments

- Selected, verified and digitized 240 cases, and entered them into database.
- Modified workstation for this project.

- Developed display software.
- Developed an innovative registration method for mammograms.
- Developed Image analysis software including software to:
    - Correct for characteristic curve.
    - Correct for breast compression.
    - Detect Skin line.
    - Adjust for breast compression.
    - Calculate local and global composition.
    - Global composition from two views.
    - Perform local geometric registration.
    - Perform histogram equalization between multiple images.
- Identified local and global temporal features.
- Used temporal features to create parameter images.
- Derived trend summary images from the sequences of parameter images.
- Developed a classification mechanism for predicting risk from temporal features.
- Provided a mechanism for ROC analysis of the performance of individual features.
- Provided a mechanism for optimization of feature sets.
- Processed and installed the dataset of cases on the workstation, for subjective evaluation by radiologists.

Reportable Outcomes

Manuscripts

Chang YH, Good WF, Wang XH, Glenn S. Maitz GS, Zheng B, Hardesty LA, Hakim CM, Gur D. Integrated Density of a Lesion: A Quantitative, Mammographically-derived, Invariable Measure. Med. Phys. 2003; 30(7):1805-11.

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Wang XH, Good WF, Fuhrman CR, Sumkin JH, Britton CA, Warfel TE, Gur D. Projection Models for Stereo Display of Chest CT. SPIE Medical Imaging 2004; 5367: *In Press*

Wang XH, Good WF, Fuhrman CR, Sumkin JH, Britton CA, Warfel TE, Gur D. Stereo Display for Chest CT. RSNA Dec 2003;

Good WF, Wang XH, Maitz G. Automated Analysis and Display of Temporal Sequences of Mammograms. Era of Hope 2005; Philadelphia, PA.

Databases

We have established a database of verified cases, where each case consists of a sequence of screening mammography exams. While we will continue to accrue cases to this database, it is currently in a form that can be used for analysis.

Proposals applied for

US Army MRMC 2003	Assessing the Interdependence of Tumor Risk, Conspicuity and Breast Tissue Characteristics Derived from Mammography
US Army MRMC 2003	Computerized Analysis and Display of Contralateral Breast Asymmetry
US Army MRMC 2003	Improving Breast Cancer Assessment Through More Accurate Measurement of Mass Size and Growth Rate
Komen 2002	Integrated Density – A Quantitative Measure of Breast Lesion
NIH 2004	Improving Early Detection of Breast Cancer
NIH 2004	Integrated Density – A Quantitative Measure of Breast Lesion

Conclusions

Progress on this project closely followed the schedule and methods outlined in the original proposal. All tasks described in the statement of work have been undertaken and completed successfully. The tasks that were completed during the past year include:

Task 4: Image analysis software development (Months 6 – 30).
k. Detection and classification of trends.
Task 7: Final training and testing of classifier (Months 24-30).
Task 8: Final processing of all cases (Months 30 – 34).
Task 9: Data analysis and final report (Months 30-36).

Throughout the project certain technical issues arose and these are being addressed in the one-year extension that has been granted. We expect to be able to complete this extra work during the coming year.

We remain optimistic about the prospects for the methods developed in this project to have a positive impact on Radiology. The workstation we have developed will make it possible for radiologists to efficiently view a woman's entire mammographic history, as well as view summarized presentations of that history. We expect that the viewing of this additional data will increase radiologists' understanding of the kinds of changes that are occurring in breasts, and the rapidity with which these changes are occurring. Ultimate, this will likely result in increased efficacy for screening mammography. During the coming year, the work will be published and presented at meetings, in an effort to introduce some of the concepts to a wider range of potential researchers.

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Appendices

1. Good WF, Wang XH, Maitz G. Automated Analysis and Display of Temporal Sequences of Mammograms. Era of Hope 2005; Philadelphia, PA.

In reading screening mammography, radiologists customarily only compare current exams to most recent prior exams. Based on the hypothesis that longer sequences of screening exams contain information that is not currently being exploited in the diagnostic process, we have developed a display system for efficiently presenting information about changing tissue patterns, derived from longer mammographic histories.

The system provides for: 1) Deforming mammograms so that all images geometrically match the form of the corresponding view in the most recent exam; 2) Correcting for differences in exposure between exams; 3) Measuring local trends in various parameters over time and representing these trends in summary images; and, 4) Displaying the normalized mammographic images in a cine mode, along with

summary images. The parameters that have been implemented to date are local breast density and local variance of pixel values, which provide a general prototype mechanism for other parameters to be added in the future.

The fully automatic geometric transform can map any mammographic image onto a reference image while guaranteeing registration of specific features and maintaining grayscale equivalence. A polar coordinate system is established with its origin at the intersection of the nipple axis with the pectoral muscle. A tissue pixel is identified by coordinates consisting of: 1) a relative distance between the origin and skin line; and 2) its angle relative to the nipple axis. Pixels are mapped onto a position in a reference image determined by these relative coordinates. This transformation guarantees that pectoral lines, nipples and skin lines are all placed in complete registration. Images are then adjusted by converting film density to log-exposure and dividing by the Jacobian of the geometric transformation to correct for local expansion factors. Relative exposures are equalized with respect to the reference image by applying linear regression to adjust corresponding pixel value pairs.

After this normalization process, each image in a sequence is processed by two feature-detection filters that measure local tissue density and local variance at each point. To measure local density, the fraction of fibroglandular tissue projected onto each pixel is determined and represented in an image, which is then convolved with a Gaussian kernel. At each location, trends over time in parameters are calculated and represented in summary images. For each parameter, the slope of its regression line, and its variance with respect to its regression line, are mapped onto a 2D color scale.

For subjective evaluation by radiologists, the system has been loaded with 240 verified cases for which we have at least three screening exams, however an overall objective evaluation of the system is not within the scope of the current project.