Contrast Limited Adaptive Histogram Equalization Image Processing to Improve the Detection of Simulated Spiculations in Dense Mammograms

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The purpose of this project was to determine whether Contrast Limited Adaptive Histogram Equalization (CLAHE) improves detection of simulated spiculations in dense mammograms. Lines simulating the appearance of spiculations, a common marker of malignancy when visualized with masses, were embedded in dense mammograms digitized at 50 micron pixels, 12 bits deep. Film images with no CLAHE applied were compared to film images with nine different combinations of clip levels and region sizes applied. A simulated spiculation was embedded in a background of dense breast tissue, with the orientation of the spiculation varied. The key variables involved in each trial included the orientation of the spiculation, contrast level of the spiculation and the CLAHE settings applied to the image. Combining the 10 CLAHE conditions, 4 contrast levels and 4 orientations gave 160 combinations. The trials were constructed by pairing 160 combinations of key variables with 40 backgrounds. Twenty student observers were asked to detect the orientation of the spiculation in the image. There was a statistically significant improvement in detection performance for spiculations with CLAHE over unenhanced images when the region size was set at 32 with a clip level of 2, and when the region size was set at 32 with a clip level of 4. The selected CLAHE settings should be tested in the clinic with digital mammograms to determine whether detection of spiculations associated with masses detected at mammography can be improved.

KEY WORDS: mammography, image processing, contrast limited adaptive histogram equalization, observer studies, breast cancer, spiculations.

APPROXIMATELY 10% to 15% of palpable malignancies are not visible mammographically.[1] It is highly likely that many nonpalpable cancers are also not visible with current technology. Digital mammography might allow for greater contrast and improved detection of small and early tumors over standard film screen technology, especially if image processing is used to improve image contrast.[2-5]

We have previously published two articles reporting laboratory results that show improved performance by students in finding simulated masses and simulated clustered calcifications embedded in dense mammographic background when Intensity Windowing is applied compared to their performance when viewing non-windowed images.[6,7] The methods used in those experiments were based on methods reported in a previous article[8] in which we demonstrated that detection performance with the application of Contrast Limited Adaptive Equalization (CLAHE) to digitized mammograms is parallel for radiologists and student observers.[8] Using the same experimental paradigm, we report here that CLAHE can improve the detection of simulated spiculations in dense mammograms in a laboratory setting.

Many investigators have studied the use of image processing techniques in digitized mammograms. McSweeney et al attempted to improve the visibility of calcifications by using edge detection for small objects, but gave no clinical results.[9] Smathers et al improved the visibility of small objects in images by intensity band-filtering.[10] Chan et al used unsharp-masking to reduce image noise to improve detection of clustered calcifications.[11] Chan, Hale, and Yin have tested other image processing methods on digitized mammograms with variable results.[12-15] Kallergi et al have demonstrated improved radiologist performance in detecting clustered calcifications in wavelet-processed digital mammograms versus unenhanced digital mammograms.[16]

Contrast enhancement methods are not designed to increase or supplement the inherent structural information in an image, but rather to improve the image contrast and theoretically to enhance particular characteristics. CLAHE is an adaptive contrast

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enhancement method. It is based on adaptive histogram equalization (AHE),[17] where the histogram is calculated for the contextual region of a pixel. The pixel's intensity is thus transformed to a value within the display range proportional to the pixel intensity's rank in the local intensity histogram. CLAHE[18] is a refinement of AHE where the enhancement calculation is modified by imposing a user-specified maximum, ie, clip level, to the height of the local histogram, and thus on the maximum contrast enhancement factor. The enhancement is thereby reduced in very uniform areas of the image, which prevents overenhancement of noise and reduces the edge-shadowing effect of unlimited AHE. The size of the pixels' contextual region and the clip level of the histogram are the parameters of CLAHE.[18]

The experiments described in this article were performed to determine whether CLAHE could improve the detection of simulated spiculations in dense mammograms in a laboratory setting. While the scope of this article is limited to the evaluation of observer performance with respect to the contrast of the simulated spiculations to background using our established experimental paradigm, it may be interesting for follow-up work to evaluate these results with respect to measures proposed by other authors, such as the conspicuity measure proposed by Revesz and Kundel.[19-21]

MATERIALS AND METHODS

The experimental paradigm used here is based on the model we have previously described and allows for the laboratory testing of a range of parameter values (in this case, region size and clip level).[4] The experimental subject is shown a series of test images that consist of an area of a dense mammogram with a simulated spiculation embedded in the image in one of four orientations. The observer's task is to determine in which orientation the line is located. The test images are displayed in both the processed and unprocessed format, and the contrast of the object against the background is varied from quite easy to detect to impossible to detect.

A computer program randomly selected one of 40 background images and rotated that background to one of four orientations. The 40 backgrounds images of 512 × 512 pixels each were taken from actual mammograms that had been digitized using a Lumiscan digitizer (Lumisys Inc, Sunnyvale, CA) with a 50 μm sample size and 12 bits of intensity data per sample. The images were selected from relatively dense parts of the mammograms that were known to be normal by virtue of 3 years of clinical and mammographic follow-up. They were selected by a radiologist expert in breast imaging from digitized film screen craniocaudal or mediolateral oblique mammograms.

A grey scale value for each pixel of the digitized mammographic background is assigned a value recorded by the Lumisys digitizer. The digitizer assigns digital values in the range 495 to 4095 representing an optical density (OD) range of 3.43 to 0.08. The digitizer produces digitized grey values that map one to one with OD values, ie, the same OD value on film will produce the same grey level.

The 40 different dense backgrounds were utilized. A phantom feature, the simulated spiculation, was then added into the background. The image was then processed with CLAHE to yield the test stimulus.

A spiculation was simulated using a 13 to 18 mm. long line, 160 μm wide. Simulated spiculations were used instead of real features so that we could have precise control over the structure location, orientation and structure to background contrast of the pseudolesions. To more realistically simulate spiculated masses would have required using multiple pixels per spiculation, for instance a 2 pixel wide or 3 pixel wide matrix. Because of limitations of our printer which had a spot size of 160 μm per pixel, the use of a wider spiculation would have unrealistically enlarged the simulated spiculations. Thus we limited our simulated lesions to single pixel wide areas, and varied only the contrast of the spiculation. As a result, the simulated spiculations were not entirely realistic, but they did possess the same scale and similar spatial characteristics to actual spiculations seen at mammography.

The intensity difference of the spiculations from background was defined as the grey level of the digital spiculations before addition to the background. The spiculations were then embedded at four different orientations with four different intensity levels equally spaced in perceived brightness relative to background by pixel-wise addition of the structure and background images. Figures 1 and 2B show an example of a simulated spiculation. Figure 2A shows a set of real spiculations within a specimen radiograph for comparison.

A three-by-three grid of appropriate region size and clip level parameter settings was selected based on the results of pilot preference studies done with two radiologists who specialize in breast imaging (EDP and MPB). In these pilot studies, the two radiologists reviewed dense mammograms with real clinical lesions that were judged to be difficult to visualize using standard screen film mammography. There were 7 cases of this type reviewed with 70 combinations of region size and clip level applied. The radiologists scored each combination of values as showing no change over standard image, improved visibility of the lesion, or worsened visibility of the lesion. The grid of CLAHE values tested spanned all the likely optimal settings as determined by the pilot work. The CLAHE settings tested were the following: region size 2 with clip levels 2, 4 and 16; region size 4, with clip levels 2, 4 and 16; and region size 32 with clip levels 2, 4 and 16. The default or "unprocessed" settings correspond to the background image not undergoing CLAHE processing at all, which is equivalent to CLAHE processing with a clip of 0 and a region size of 512 (ie, a single region covering the entire background). There were thus a total of 10 CLAHE settings tested in this experiment.

The digital images were printed onto standard 14 × 17 inch single emulsion film (3M HNC Laser Film; 3M, St Paul, MN) using a Lumisys Lumicam film printer. Each original 50 μm pixel was printed at a spot size of 160 μm, which produced film images 4 × 4 centimeters, resulting in an enlargement by a factor of three. The radiologist observers in the pilot experiment reported that the magnification did not make the backgrounds

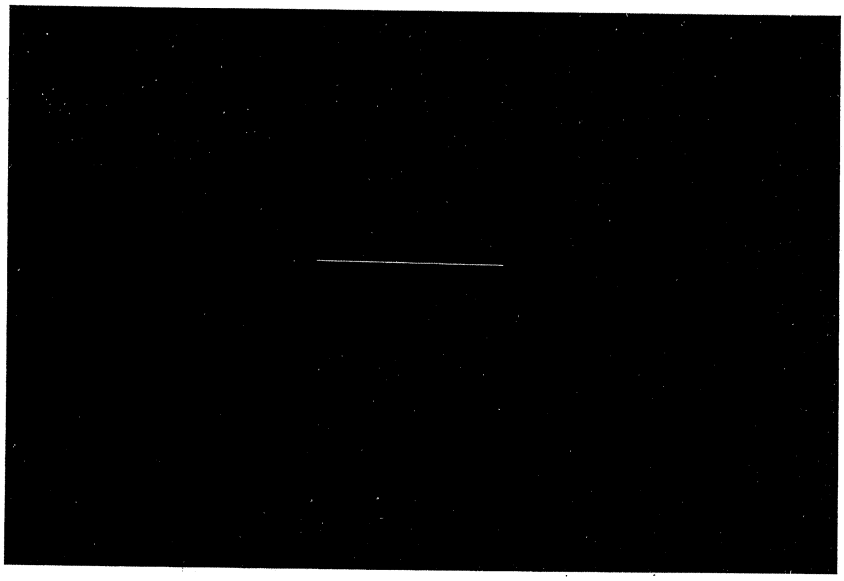

Fig 1. An example of a simulated spiculation used in the experiment.

unrealistic. Forty images were printed per sheet of film. The images were randomly ordered and printed into thirty-two 8 × 5 grids on film. Both the film digitizer and film printer were calibrated, and measurements of the relationship between optical density on film and digital units on the computer were determined in order to generate transfer functions describing the digitizer and film printer. To maintain a linear relationship between the optical densities on the original analogue film and the digitally printed film, we calculated a standardization function that provided a linear matching between the digital and printer transfer functions. This standardization function was applied when printing the films to maintain consistency between the original optical densities of the original mammography film and those reproduced on the digitally printed films. The film printer produces films with a constant relationship between an optical density range of 3.35 OD to 0.13 OD, corresponding to a digital input range of 0 to 4,095, respectively.

There were 20 observers for the experiment. They were medical students and graduate students from the biomedical engineering and computer science departments. Performance bonus pay was provided. Observers selected the orientation of the spiculation within the image. All images contained a simulated spiculation in one of four orientations, for a four alternative-forced choice design. Observers were instructed to make their best guess if they could not see the spiculation or determine its orientation in a particular image.

Films were displayed in a dark room on a standard mammography viewbox that was masked to exclude excess light. Observers could move closer to the image, and could use a magnifying glass, if desired. A standard script was read to each observer prior to their participation, describing the goals of the research and the role of the observers in the study. Before actually starting the experiment, the observers were trained for the task through the use of three sets of images, including images in which the simulated object was very easy to detect. Thus the observers were quite familiar with the object that they were attempting to detect.

The order of presentation of stimuli was counterbalanced so as to eliminate any effects of learning and fatigue. All 160 possible combinations of processing conditions (10 CLAHE combinations of region size and clip level), contrast level (4 contrasts) and orientation of the simulated spiculations (4 orientations) were used in the experiment. The experiment was divided into 4 blocks, in which all 160 combinations appeared. Each observer saw all combinations in each block. All observers completed the experiment. There were 40 backgrounds. In each block, the 40 backgrounds are each paired with 160 possible processing condition combinations. The assignment was different for each block. Each observer examined 1280 images, for a total of 25,600 total observations across all observers in the experiment. Each observer was assigned a different randomization of film order for the purpose of counterbalancing.

The experimental design can be thought of as a 3 × 3 factorial plus one additional condition. The factorial involves 3 clip levels (2, 4, 16) crossed with 3 region sizes (2, 8, 32). In each of the 9 conditions in the factorial, the observer made 32 decisions at each of 4 contrast levels (10, 25, 40, 55). In addition, each observer made 32 judgments at each of the 4 contrast levels with unenhanced images (clip = 0, region = 0). Therefore, each observer judged 3 × 3 × 4 × 32 plus 1 × 4 × 32 decisions, for a total of 1,280 observations.

A total of 40 distinct background images from dense mammograms were used to create the stimuli. A phantom feature, the simulated spiculation, was added into the background. The image was then processed with CLAHE to yield the test stimulus. Each image was used in each of 4 orientations to create 160 distinct backgrounds. Each background was used five times in a random order. Of the 32 decisions within each clip-region-contrast combination, 8 were made at each of 4 distinct spiculation orientations (Table 1).

Observers took breaks after each block of images, and more often if necessary. No time limit was imposed on the observation of the images. Typically, the experiment took no more than 4 hours for each observer, divided into two sessions of 2 hours each. The two sessions were always scheduled on two different days within a week of each other.

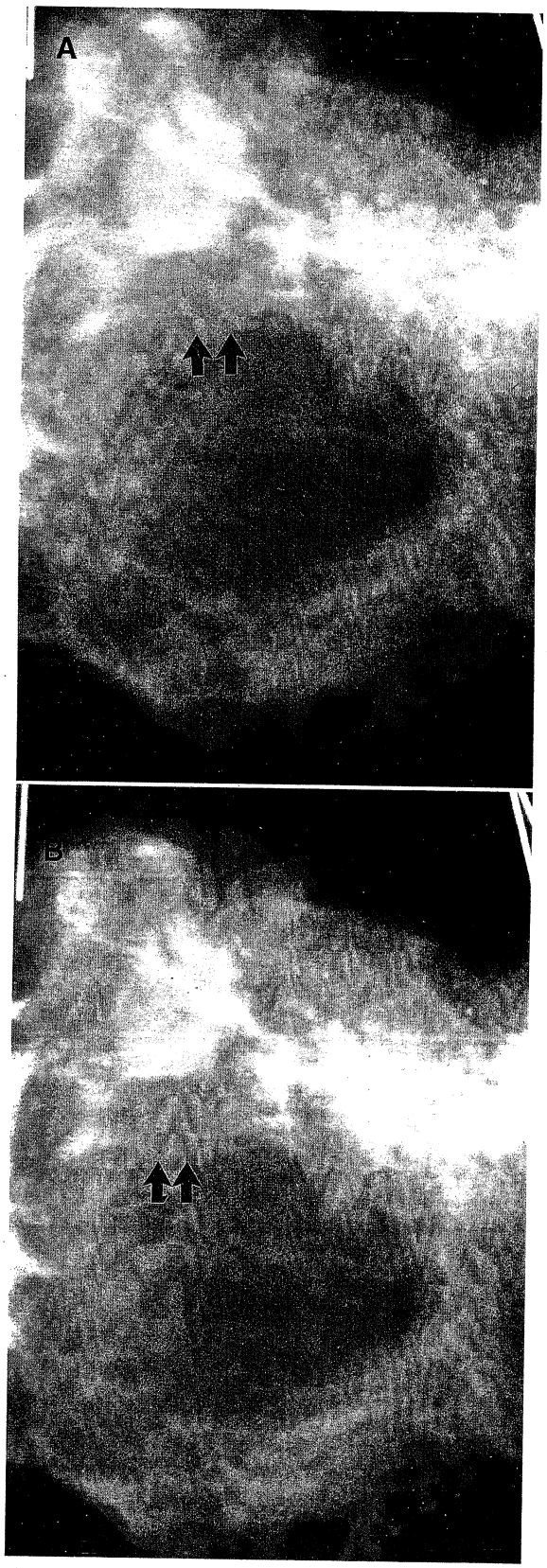

Table 1. Number of Observations per Observer

Region Size	Contrast	Clip Level 2	Clip Level 4	Clip Level 16	Total
2	10	32	32	32	96
	25	32	32	32	96
	40	32	32	32	96
	55	32	32	32	96
8	10	32	32	32	96
	25	32	32	32	96
	40	32	32	32	96
	55	32	32	32	96
32	10	32	32	32	96
	25	32	32	32	96
	40	32	32	32	96
	55	32	32	32	96
Unenhanced	10		32		32
	25		32		32
	40		32		32
	55		32		32
					1,280

Data Analysis Overview

Probit models were fit for each subject and enhancement condition using LOG10 contrast as the predictor. The probability that a subject gets a correct answer is assumed to be given by the following equation:

$$\Pr[\text{correct}] = \tfrac{1}{4} + (1 - \tfrac{1}{4})\Phi[(x - \mu_{ij})\sigma_i^{-1}]$$

where i indexes subject, and j indexes CLAHE settings. Here Φ indicates the cumulative Gaussian distribution function. For each subject, this gave a separate location parameter estimate for each CLAHE setting, and a common spread parameter estimate. Assuming a common spread parameter makes sense biologically, as it corresponds to an equal change in log contrast producing an equal change in perception, throughout the visual range. Also, the $\frac{1}{4}$ arises from the 4 choice task.

The location parameter, μ_{ij}, is the mean of the corresponding Gaussian distribution for the ith subject and jth CLAHE setting. Processing conditions that improve detection performance will cause this parameter to be smaller, and the curve will shift to the left. This occurs because lower contrast levels are required to spot the object. When the processing of the image makes detection harder, higher contrast levels are needed to determine the orientation of the spiculation, and the curve shifts to the right. The values of σ_i, the spread parameter for the ith subject correspond to the slope of the curve. Larger values of σ_i correspond to steep slopes, or greater increase in detection rates per log contrast.

To compare the processing conditions and to examine the effect of window width and level, further analysis was needed. We defined an overall measure to be $\theta_{ij} = \mu_{ij} + \sigma_i$, which corresponds to the log contrast level at which the ith subject

Fig 2. (A) A specimen radiograph of a carcinoma showing spiculations (arrows). (B) The same carcinoma with a pseudospiculation inserted adjacent to the real spiculations (arrows) in the image. Note the extra linear structure running parallel to the 3 linear structures seen in Fig 2A.

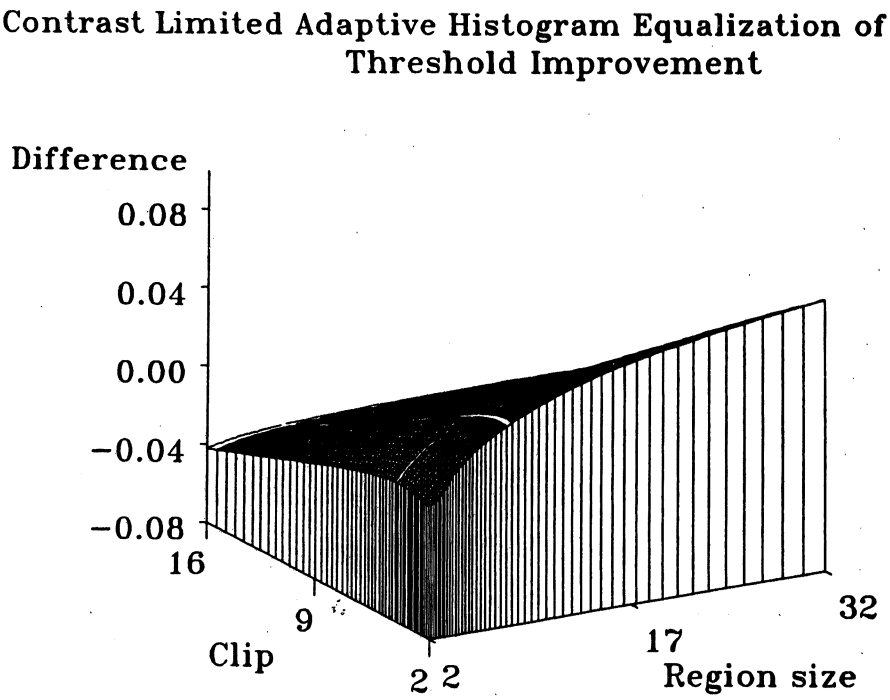

Fig 3. Interpolated predicted values from repeated measures ANOVA: difference in θ value versus region size and clip level. The peak shows the improved performance due to region size 32 with clip level 2.

viewing the jth CLAHE condition scored 88% correct. We measured the "success" of a processing condition by calculating the difference between the θ score for the unprocessed image and the θ score for the condition for each subject, say $\delta j = \theta u - \theta j$, where u is unprocessed. A large positive δj score reflects improved performance. It indicates better detection with processed images than with unprocessed images.

Two analyses were performed using this outcome measure. To keep an overall nominal experiment-wise type 1 error rate of .05, a repeated measures analysis of variance (ANOVA) was done at the .04 level, with a set of 9 *t*-tests at a .01/9 nominal level for each, and hence a .01 level for the whole set.

Repeated measures ANOVA allows one to examine the effect of processing conditions and the interactions between region size and clip level, while accounting for the dependence of measurements taken on the same observer. The Geisser-Greenhouse corrected test was used throughout. The repeated measures ANOVA model was fitted, with the δj scores as the outcome. The LOG2 transformation of region size and clip level (LOG2reg and LOG2clip) are the predictors in this model.

RESULTS

The repeated measures analysis of variance revealed that the interaction between region size and clip level was significant at the .04 level (*P* value = .0004, $G - G\Sigma = 0.6987$). Hence a series of (planned) step-down tests was implemented to investigate the nature of the interaction. The test of a linear-by-linear interaction was significant (*P* value = .0002) as seen in Fig 3.

At the nominal level of .01/9 = .0011, the differences between the default unprocessed condition and the CLAHE conditions were examined. Three settings of CLAHE processing conditions made finding the spiculations significantly easier and six made no significant difference. The settings that made detection easier were region size 32, with clip levels 2 and 4. There was one setting that significantly worsened detection performance (region size 2 with clip level 16; Table 2).

Table 2. Mean Difference Between CLAHE-Processed and Unprocessed Theta Scores

Enhancement	Region Size	Clip Level	Difference Score	Standard Deviation	*P* Value
1	2	2	−0.002	0.044	.8087
2	8	2	−0.007	0.047	.5226
3	32	2	0.061	0.038	.0001*
4	2	4	−0.019	0.045	.0736
5	8	4	0.008	0.055	.5076
6	32	4	0.053	0.045	.0001*
7	2	16	−0.039	0.040	.0004*
8	8	16	−0.036	0.058	.0122
9	32	16	−0.031	0.062	.0374

Note: Larger difference scores correspond to better performance; average μij, ij and i parameters from the best processing condition and the unprocessed condition.

* Indicates significance at the .0011 level.

Average μij and σi parameters from the best processing condition and the unprocessed condition were used to calculate a typical probit curve. Of the parameter values tested, the greatest improvement occurred for CLAHE processing with settings of region size = 32 and clip level = 2 (LOG2reg = 5, LOG2clip = 1). These values increased the correct detection of spiculations by 9 percent. This is shown in Fig 4.

DISCUSSION

These results suggest that CLAHE can improve the detection of spiculations on dense mammographic backgrounds, if used properly. Our results also indicate that significant lesion visibility degradation can occur if the region size and clip levels are not chosen carefully. We believe that it is important to select the parameters to be applied in the testing of this tool in the clinic based on these types of careful analyses of laboratory studies. Preset parameter values might then be selected to apply to printed digital mammograms or to mammographic work stations where radiologists might interpret images "on line." Many radiologists who view CLAHE-enhanced mammograms have commented on the unpleasantness of the "image noise" that is rendered more visible when this algorithm is applied, and how it might cause worsening of their clinical performance. Our laboratory results support those concerns. If chosen poorly, CLAHE can degrade performance.

This work may not predict how this tool will function in a clinical setting. Specifically, graduate student observers and the use of simulated lesions might incorrectly predict the performance of radiologists in detecting real spiculations associated with real masses in real patients. We have demonstrated previously that graduate student performance at this task parallels the performance of experienced mammographers.[4] The signal-to-noise ratio and the type of image noise present in digital images might vary substantially from digitized mammograms when real full field digital images are used as the stimuli. Because we have used real clinical images and we have simulated lesions using relatively realistic stimuli, we are optimistic that this image processing algorithm will improve clinical performance. If so, radiologists might use CLAHE in the clinic as an adjunct to screening mammography whenever a mass is detected, much the way compression magnification views are used now. If the border characteristics, including the detection of subtle spiculation, is improved, radiologists might use this type of image processing to decide which lesions require further work-up.

Digital mammography is already available in a number of clinics in the United States and Canada, including our own. It is highly likely that radiologists will want to apply image processing in an attempt to improve their performance in interpreting mammograms. The work reported here is intended to help radiologists narrow their choices regarding what might be clinically helpful before expensive clinical tests are undertaken. This project

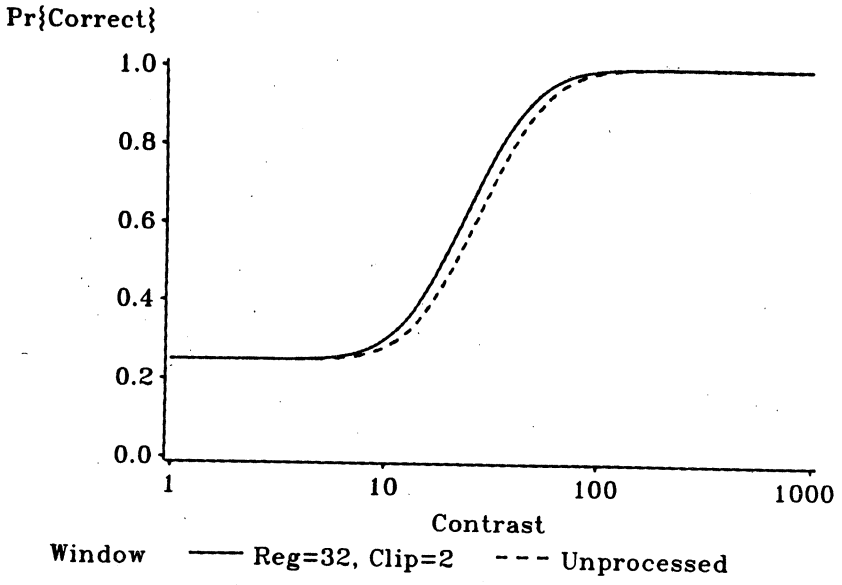

Fig 4. Estimated detection probability for region size of 32 and clip level of 2. The shift in the curve to the left for the processed image reflects improved detection.

was intended to be a more rigorous exploration of the CLAHE parameters that might be used clinically in the most challenging areas in the breast, namely the dense parts.

This experiment does not address how CLAHE would affect the appearance of fatty areas of the breast, and the detection of spiculations in those parts. We would not want to view a mammogram solely with an algorithm applied that degrades performance in areas where sensitivity is currently quite high. By enhancing the visibility of image noise in fatty areas of the breast, CLAHE might degrade performance in these areas. It is possible that with effective training, radiologists might become used to improved visibility of background structures so that performance would not be degraded. However, if this algorithm is ultimately useful in dense areas only, it could potentially be applied selectively to only the dense parts of the breast. This could be accomplished by automatically segmenting the image to select for the densest parts and applying CLAHE only to those parts where it might provide benefit. Alternatively, it could be used as an adjunct with the image viewed in a standard format, and then with CLAHE applied to selected areas. In fact, we believe that CLAHE might be useful in this setting because it enhances the visibility of structures that extend across pixel boundaries, an apt description for the type of linear structure that a spiculation represents. Our results do not give us information about the performance of this algorithm in purely fatty areas of the breast, but the backgrounds used were relatively inhomogeneous in density, just as normal breast tissue is, and we expect these results to hold for all areas of the breast containing any soft-tissue density.

Our experiments to date cannot estimate the frequency of false positives when CLAHE would be used clinically. As discussed in our previous papers that explored the same issues, alternate forced choice tests yield proportion correct as the primary outcome. Methods for converting proportion correct in this setting to a value for d′, the sensitivity parameter of an ROC analysis, have been developed by Macmillan and Creelman.[22] With this study design, and with the types of subjects and the amount of training used in this experiment, we believe that superior proportion correct will translate into superior d′. Of course, this must be proven in a true clinical setting with ROC analysis before these methods can be embraced for clinical purposes by practicing radiologists.

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