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PRINCIPAL INVESTIGATOR: Etta D. Pisano, M.D., Dean Chapman, Ph.D., Dale Sayers, Ph.D., Kuruvilla Verghese, Ph.D., Michael Doster, Ph.D., Mohamed Bourham, Ph.D., Zhong Zhong, Ph.D., R. Eugene Johnston, Ph.D., Elodia Cole, Christopher Parham, Yuanshui Zheng, Ph.D., Martin Yaffe, Ph.D., Keith Muller

CONTRACTING ORGANIZATION: University of North Carolina
Chapel Hill, North Carolina 27599-7510

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Etta D. Pisano, M.D., Dean Chapman, Ph.D., Dale Sayers, Ph.D., Kuruvilla Verghese, Ph.D., Michael Doster, Ph.D., Mohamed Bourham, Ph.D., Zhong Zhong, Ph.D., R. Eugene Johnston, Ph.D., Elodia Cole, Christopher Parham, Yuanshui Zheng, Ph.D., Martin Yaffe, Ph.D., Keith Muller

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of North Carolina
Chapel Hill, North Carolina 27599-7510

E-Mail: etpisano@med.unc.edu

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13. ABSTRACT (Maximum 200 Words)

The purpose of this study is to determine the potential utility of a new imaging modality, Diffraction Enhanced Imaging, DEI. The long-term goal of this program is to develop a clinically-based DEI system for breast imaging. The first step is to identify the optimal DEI parameters for visualization of breast tissue structures and use these parameters to develop a conceptual design for a clinical DEI system. In order to standardize the statistical analysis, mammography phantoms were used to simulate breast tissue.

Breast imaging requires a high degree of spatial resolution to visualize abnormalities in the breast, such as calcifications, which can often be as small as 20-50 microns in diameter when clinically important. Two challenging phantoms designed to test the resolving ability of an imaging system were chosen for this study. The following parameters were varied in the acquisition process: beam energy, analyzer crystal configuration, and crystal lattice plane. The specific parameter values must be known before a "compact" machine can be designed. To determine which parameter values provide images of most use to readers, a reader study was performed where readers score images taken at each of the parameter values according to which images yield the image information.

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INTRODUCTION:

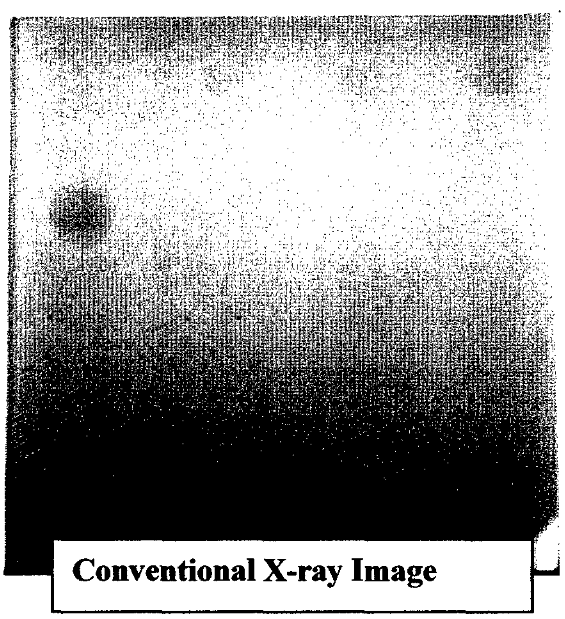
Screening mammography has proven to be an effective procedure for the detection of early breast cancer. However, a significant fraction of cancer escapes detection due to dense glandular tissue which obscures the underlying pathology. Diffraction Enhanced x-ray Imaging (DEI) is a new imaging modality that has the potential to dramatically change mammography and radiography in general. This is a method of imaging that utilizes single energy x-rays from a synchrotron source and has produced images of test objects and tissue whose contrast and information content far exceeds conventional techniques. Preliminary work with human breast cancer specimens suggests that DEI images include information regarding specific physical characteristics of the lesion including border detail and associated features that are not detected by conventional imaging.

The long term goal of this program is to develop a clinical based DEI system for mammography. However, the DEI Development Group must first identify the optimal DEI parameters for visualization of lesions of the breast and then use these parameters to develop a conceptual design of a clinical DEI system. Specifically, an observer study of human breast tissue samples with cancer was performed in which the DEI parameters were systematically assessed in regards to the visibility of structures suggestive of breast cancer. This study will include the assessment of a wide variety of DEI parameters such as the x-ray energy, x-ray optical geometry and several other factors that affect the resulting image. The intent of this study is to optimize DEI for the clinical task. This will allow us to specify the x-ray source, x-ray optics, and detection method requirements for a clinical based system. The results of this work will give us the information that we need to develop a conceptual design for a clinical system for mammography using DEI.

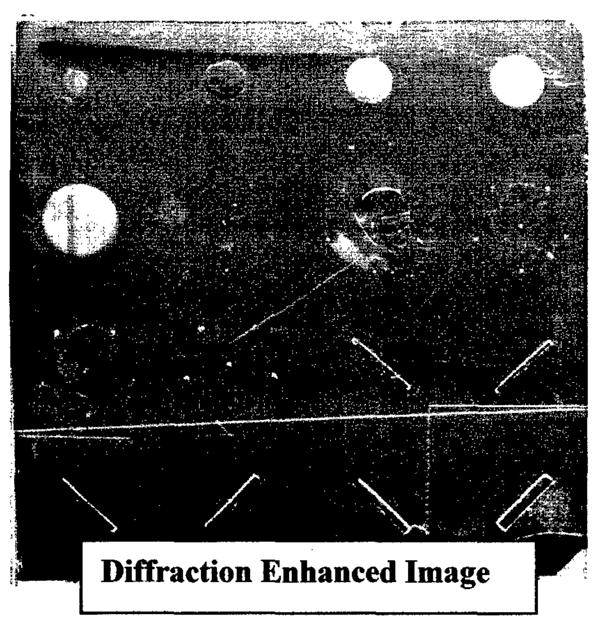
BODY:

Breast cancer continues to rank as one of the leading causes of death in women, with an estimated 182,000 new cases and 44,000 deaths each year.[1] Screen-film mammography is the standard for breast cancer detection, and numerous large randomized screen trials show that screen-film mammography reduces breast cancer mortality by approximately 18-30%.[2,3] The performance of screen-film mammography is admirable, but it is still far from perfect. The technique is limited both by its low predictive value, leading to a considerable number of biopsies revealing benign lesions, and by its insensitivity, missing up to 20% of palpable cancers. Significant improvements have been made in mammography over the past two decades, including the introduction of digital mammography, which is currently being introduced into clinical use[4]. However, all current existing radiographic systems are based on x-ray absorption to define the differences between normal and abnormal tissues. Given the complexity of imaging breast tissue, there are characteristics and findings that are difficult to interpret or missed entirely by conventional methods. A new radiographic imaging method, Diffraction Enhanced Imaging (DEI), has been proposed to extend the capabilities of the current standard and increase detection of occult disease.

In conventional mammography, differences in tissue densities and composition are shown, due to absorption, as contrasting areas in the image allowing visualization of tumors or changes in tissue. The problem is that differences between healthy and cancerous tissues are very small and scattering of x-rays can lead to blurring and lower contrast, making it difficult to detect small tumors. As currently implemented, using synchrotron radiation, the DEI method uses a single-energy (monochromatic) fan beam of x-rays—instead of the broad polychromatic energy beam of conventional imaging. The object or tissue is scanned through the beam and the data is recorded on a detector. This method of line scan imaging reduces scatter and helps us visualize low-contrast areas that otherwise would be lost.



Conventional X-ray Image



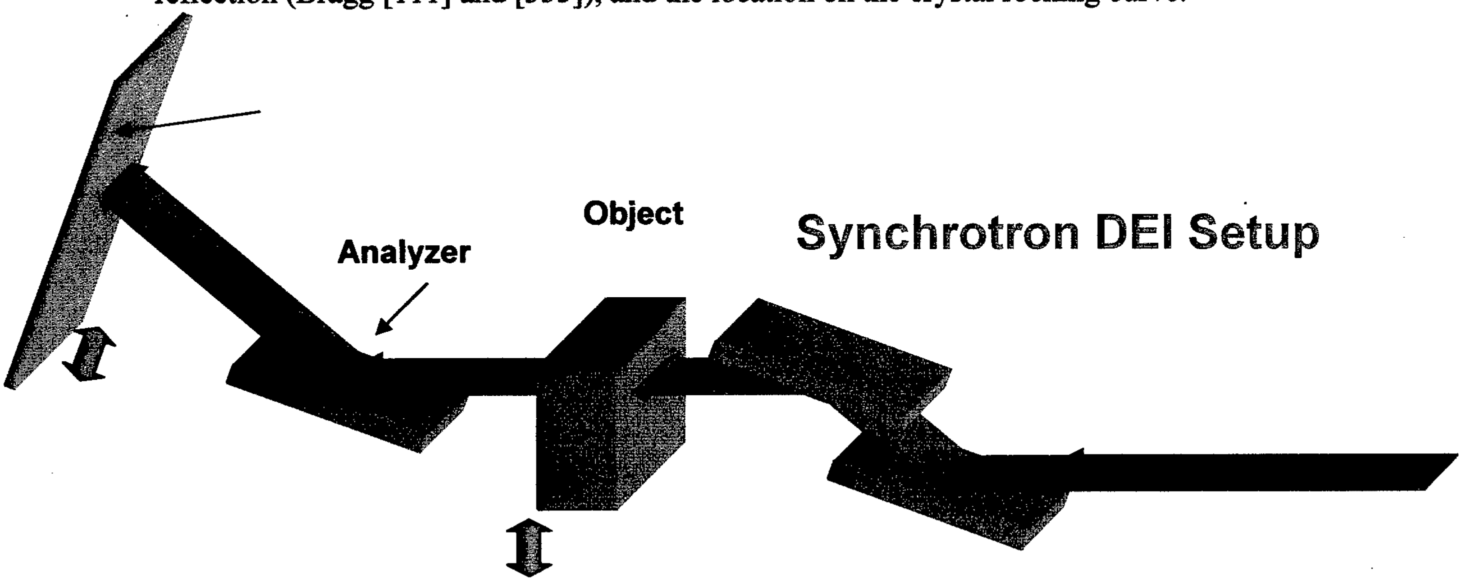
Diffraction Enhanced Image

DEI also produces images of the refraction and apparent absorption of an object. The refraction image shows the changes in x-ray refractive index and highlights the edges of structures in the object. Obtaining refraction images is one of the unique aspects of DEI, because this physical component can detect fine structural architecture that is normally not detected with conventional systems that rely entirely on x-ray absorption. Objects which have very little absorption contrast may have strong refraction properties which this image will highlight. An example is the fine, thread-like fibers that characterize some malignant tumors. Normally difficult to see in radiography, they are clearly visible in the refraction image.

Preliminary studies of DEI have been promising, suggesting that there is potential for improved visualization of breast cancer lesions. Seven breast cancer specimens were examined with DEI and compared with digital radiographs of the specimen. Six of the seven cases (86%) showed enhanced visibility of surface spiculations that correlated with histopathologic information, including extension of tumor into surrounding tissue[5]. These initial studies have prompted further investigation into the detection ability of DEI and its application in a clinical setting. The major overall research goal of the development team is to move DEI from the synchrotron to a clinical setting.

Objectives of the DEI Parameter Study

The primary aim of this study is to determine the optimal imaging parameters for Diffraction Enhanced Imaging. Numerous images of tissue samples and phantoms have been taken using the DEI technique, but the optimal imaging parameters have not been determined. Determining these parameters is a necessary step in the characterization of DEI and the future development of a clinically based system. The imaging parameters being studied are: the imaging energy (18keV, 25keV, 30keV, and 40 keV) the crystal reflection (Bragg [111] and [333]), and the location on the crystal rocking curve.



Data obtained from this experiment will be used to determine the optimal imaging parameters for subsequent DEI experiments. The hypothesis of this experiment is that there is a set of operating characteristics that will provide optimal visibility of the mammographic features of breast cancer.

Description of Research Accomplishments

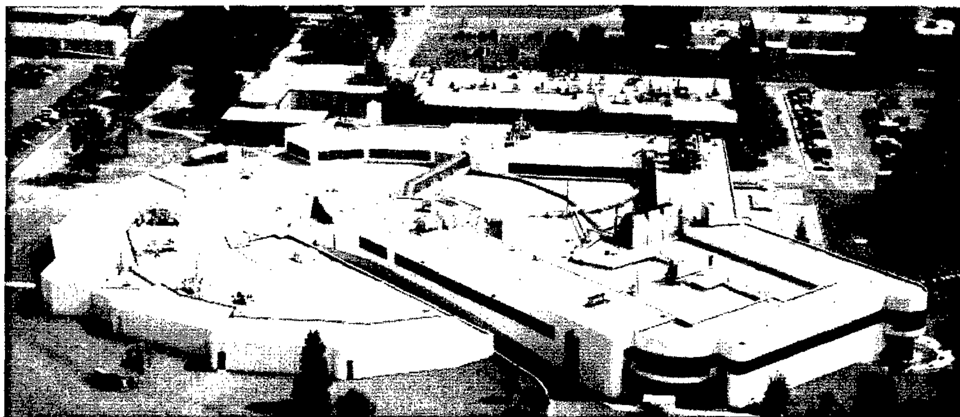
Initial Experiments Using Tissue Images

The first two sections of this project were completed using breast tissue samples. These images were processed and prepared for a reader study to determine the optimal parameters for DEI. However, further analysis of these images revealed that breast tissue specimens did not provide the consistent data necessary to fully characterize the effect of the parameters on image quality. This initial attempt demonstrated that the information needed could be more accurately quantified using breast imaging phantoms. Imaging phantoms have been used to test and evaluate all of the major imaging modalities. Two phantoms were selected for imaging at the National Synchrotron Light Source (NSLS) at Brookhaven National Laboratory. Utilizing breast imaging phantoms was helpful in that it reduced the statistical variance invariably present in human specimens.

The phantoms being used for the experiment are the International Digital Mammography Development Group phantom (Misty) and the Contrast-Detail (CD) phantom. The level of detail in these phantoms make them well suited for DEI and provide the statistical data necessary to determine the optimal imaging parameters. The Misty phantom contains several regions of interest that help to demonstrate the spatial and density resolution of DEI. For example, one of the regions includes a series of 14 clusters each containing 6 specs. Close inspection of the specs demonstrates they are actually stars. These details are difficult to observe in conventional radiography, but they can be resolved using DEI. One of the problems encountered in testing the DEI system is that most phantoms are not "challenging" enough, in that level of detail is not sufficient to determine the resolving ability of the different configurations. The Misty phantom has the regions of interest imbedded in a film, which means that the absorption component of DEI will be predominate. The CD phantom, which has strong refractive properties, was chosen to investigate this component of DEI image acquisition. This Contrast-Detail (CD) phantom contains a 9 x 10 grid of circles that gradually decrease in size and contrast. Statistically, the phantom is scored based on a volume analysis. The reader views the image and marks on a separate sheet the number of circles that can be seen. For example, if the reader can only see three circles in the upper right hand corner, then they would circle those points on a separate sheet of paper. On a volume basis, this configuration represents 3/90 or 3%. This phantom is well suited for determining the optimal imaging parameters because it is a standardized grid that provides valuable information on both decreasing size and contrast. The CD phantom provides a defined scale for determining the full resolving capability of the modality, a characteristic that available breast tissue samples lack.

Acquisition of Breast Phantom Images at Brookhaven National Laboratory

A second trip to Brookhaven National Laboratory was required to obtain the DEI phantom images. At this point in the research, it was believed that the optimal beam energy would be between the range of 18-30keV. Ongoing research in the DEI Development Group indicated that the optimal signal to noise ratio might occur between 30keV and 40keV, which led to a third trip to Brookhaven and a delay in completing the study.



National Synchrotron Light Source, Brookhaven National Laboratory

Image Processing of DEI Raw Images

Once the raw images were obtained, the next step was to crop and process each of the images, totaling 128. A UNIX workstation was used to perform the task using a custom image editing program called Xim. Image processing in a parameter analysis is a key area of concern, because any major processing filters and algorithms will alter the image on a pixel by pixel basis. Most imaging modalities use a well defined image processing algorithm to smooth and enhance images, but this is not appropriate in this case. The purpose of the study was to determine the optimal hardware and system parameters, any significant image processing alterations would introduce a non-uniform statistical variation in the images that could complicate the analysis. One image artifact that is often present in DEI images is a series of horizontal streaks that are artifacts of the diffraction process. These can be easily removed for display purposes, but they were not removed for this study.

Given these restrictions, the only change in the raw images was to use Manual Intensity Windowing (MIW) to optimize the contrast levels. Dr. Etta Pisano, M.D., an expert radiologist, initially windowed the images to what was believed to be the optimal contrast setting. After consulting with the study statisticians on the revised reader study design, it was decided to allow the reader to manually control the window settings. It was believed that this would allow for the optimal visualization on the images based on the reader's preference. Although this does introduce some statistical variation among the readers, the overall benefit of individual reader control outweighed this.

Reader Study Design

The use of phantoms instead of tissues made the reader study design significantly more challenging and difficult. However, the use of phantoms dramatically reduced the statistical variance of the images. Upon consultation with Dr. Keith Muller, Ph.D. and the other members of the statistical team, it was determined that fewer readers were needed in a study with phantoms. Based on their recommendation, two readers were chosen for the study. An experienced breast imaging radiologist and a medical physicist were selected based on their experience with reading phantoms.

A description of the phantoms, including proposed scoring methods, will help to explain how the data that was collected. The Misty phantom was cropped into three separate regions of interest (ROI). The first Misty ROI is referred to as the "calcification simulation". This ROI contains a series of calcification simulations on the left side of the phantom. There are 4 columns containing 7 clusters each. Each cluster is a group of 6 stars, with one star in each cluster missing a point. The ACRIN scoring system was felt to be geared more towards clinical quality control than research, so the following set of rules, proposed by Dr. Pisano were utilized:

1) Count and record the number of stars that can be seen in each group
2) Starting at the bottom of the sheet, record the last cluster where all 29 points can be seen (6 stars per cluster, each with 5 points except one star with one missing point equals 29 points)
3) Record the number of specks that can been seen in each cluster

Therefore three outcomes were reported for each calcification simulation ROI viewed. The questions were carefully chosen to provide a varying degree of complexity, which will help differentiate the parameter configurations at the upper limits of visualization.

The second Misty ROI is a line pair simulation. Looking at the center of the phantom, two sets of line pairs appear (one horizontal, one vertical). Because the x-ray beam for DEI is collimated in the vertical direction, objects that are perfectly vertical will not show up well, especially when relying on absorption to obtain contrast. Therefore, only the horizontal lines were used for this study. This is a condition only seen with perfectly engineered structure of phantoms and should not be a complicating factor with later tissue imaging. There are 12 clusters, each containing 4 lines. The number of line pairs per mm increases from cluster to cluster, until one can no longer resolve the lines visually. The use of a magnifying glass, mimicking clinical practice, was allowed. The highest pairing in the series in which any part of all 4 lines can be resolved were scored. Therefore one outcome was reported for each line pair ROI image viewed.

The third Misty ROI is a contrast gradient referred to as a grayscale series. On the left side of the phantom, two pairs of dark lines are visible. There are 7 distinct regions in the series. With some DEI configurations, only a few distinct regions can be distinguished. All of the sections can be seen with the other configurations. Each line separating the regions that can be seen will be checked and the number of checks were tallied. Therefore one outcome was reported for each line pair ROI image viewed. Since the window settings have a strong impact on the visualization of these sections, the readers were allowed to change the settings (manual windowing) as desired.

The CD phantom is a 9x10 grid of right circular cylinders drilled to varying depth and diameter in plexiglass, which are visualized as circles. The cylinders decrease in diameter in one direction, and depth in the other, with smaller diameter and smaller depth decreasing salience, which corresponds to moving from the upper right corner to the lower left of the phantom. The exact specs for the phantom are: 7.071, 5.000, 3.536, 2.500, 1.768, 1.250, 0.884, 0.625, 0.442, 0.312 mm diameter and; 1.000, 0.707, 0.500, 0.354, 0.250, 0.177, 0.125, 0.088, 0.062 mm thickness (depth). The reader circled their response on a drawing of the phantom on a separate sheet of paper with a graphical representation of the phantom. Three definitions of what constitutes "visible" were utilized:

1) A circle is deemed visible if the entire circumference of the circle can be seen.
2) A circle is deemed visible if at least half of the circumference can be seen.
3) A circle is deemed visible if any part of the circumference is visible.

Therefore three outcomes were reported for each CD phantom ROI viewed.

Statistical Analysis of Reader Study Data

Once the reader study was completed, the data was codified and submitted for analysis by Dr. Keith Muller, Ph.D. and Dr. Donglin Zeng, Ph.D. in the UNC Department of Biostatistics. The reader sheets used for the study are included in this document as Appendix A. The following is a summary of the reader study.

Statistical Analysis

In this full factorial design, three factors including beam energy (18, 25, 30,40 KeV), crystal reflection (Bragg[111], Bragg[333]) and rocking curve position (n, p, peak, rad), are of the main interest. The block factor is Reader 1 and Reader 2. In determining which level of each factor gives the highest performance, eight performance measurements are collected and they are

1. The volume of the circles for which the entire circumference can be seen in the CD phantom;
2. The volume of the circles for which at least half of the circumference can be seen in the CD phantom;
3. The volume of the circles for which any part of the circumference is visible in the CD phantom;
4. The number of line pair groups observed in the Region 1 in the Misty;
5. The number of stars that are visible in Region 2 in the Misty;
6. The last cluster number with all points seen in Region in the Misty;
7. The number of specks seen in the Region 2 in the Misty;
8. The number of sections in the grayscale series in the Misty.

Each of the following table gives the summary information of each observed outcome within all the levels of all the factors.

Table 1. Marginal statistics for volume of circles (mm^3) with entire circumference visible in CD phantom

Beam energy	# obs	Mean	Std dev	Range
18	16	127.96	109.58	(0,255.56)
25	16	185.63	73.62	(39.27,256.02)
30	16	169.36	96.80	(0,256.03)
40	16	134.24	107.30	(0,253.04)
Crystal reflection	#obs	Mean	Std dev	Range
111	32	150.96	95.99	(0,253.07)
333	32	157.64	102.42	(0,256.03)
Curve position	#obs	Mean	Std dev	Range
N	16	162.24	104.75	(0,253.57)
P	16	165.51	102.42	(0,255.72)
Peak	16	178.83	95.13	(0,256.03)
Rad	16	110.61	85.90	(0,211.73)
Reader	#obs	Mean	Std dev	Range
Reader1	32	231.90	27.95	(164.24,256.03)
Reader2	32	76.70	80.71	(0,243.49)

Table 2. Marginal statistics for volume of circles (mm^3) with at least half circumference visible in CD phantom

Beam energy	# obs	Mean	Std dev	Range
18	16	210.49	68.98	(0,255.96)
25	16	232.04	39.16	(125.90,256.03)
30	16	227.56	48.73	(100.55,256.03)
40	16	198.31	67.93	(0,255.61)
Crystal reflection	#obs	Mean	Std dev	Range
111	32	214.98	46.73	(96.49,254.59)
333	32	219.22	67.90	(0,256.03)
Curve position	#obs	Mean	Std dev	Range
N	16	241.13	21.21	(172.52,255.61)
P	16	238.35	32.28	(122.22,255.90)
Peak	16	241.82	18.43	(189.39,256.03)
Rad	16	147.10	72.48	(0,228.11)
Reader	#obs	Mean	Std dev	Range
Reader1	32	238.75	22.99	(174.17,256.03)
Reader2	32	195.46	72.85	(0,255.96)

Table 3. Marginal statistics for volume (mm^3) of circles with any part of circumference visible in CD phantom

Beam energy	# obs	Mean	Std dev	Range
18	16	241.43	19.76	(185.58,256.03)
25	16	247.96	9.66	(229.68,256.03)
30	16	245.16	13.87	(212.81,256.03)
40	16	237.85	23.65	(187.65,256.03)
Crystal reflection	#obs	Mean	Std dev	Range
111	32	242.89	10.74	(207.56,254.72)
333	32	243.31	22.64	(185.58,256.03)
Curve position	#obs	Mean	Std dev	Range
N	16	251.24	5.32	(238.94,255.95)
P	16	252.28	3.80	(246.34,256.03)
Peak	16	250.67	5.60	(235.42,256.03)
Rad	16	218.21	18.46	(185.58,239.22)
Reader	#obs	Mean	Std dev	Range
Reader1	32	243.41	18.84	(185.58,256.03)
Reader2	32	242.79	16.51	(187.65,256.03)

Table 4. Marginal statistics for the number of line pair groups seen in Misty

Beam energy	# obs	Mean	Std dev	Range
18	16	1.625	1.147	(0,4)
25	16	1.937	1.181	(0,4)
30	16	1.812	1.223	(0,4)
40	16	0.375	0.619	(0,2)
Crystal reflection	#obs	Mean	Std dev	Range
111	32	0.969	0.897	(0,3)
333	32	1.906	1.328	(0,4)
Curve position	#obs	Mean	Std dev	Range
N	16	1.687	1.078	(0,3)
P	16	1.687	1.250	(0,4)
Peak	16	1.875	1.360	(0,4)
Rad	16	0.500	0.632	(0,2)
Reader	#obs	Mean	Std dev	Range
Reader1	32	1.156	1.139	(0,3)
Reader2	32	1.719	1.250	(0,4)

Table 5. Marginal statistics for the number of stars seen in Misty

Beam energy	# obs	Mean	Std dev	Range
18	16	2.000	3.347	(0,10)
25	16	5.187	6.295	(0,19)
30	16	3.000	3.483	(0,14)
40	16	0.375	0.885	(0,3)
Crystal reflection	#obs	Mean	Std dev	Range
111	32	2.031	3.605	(0,15)
333	32	3.250	4.833	(0,19)
Curve position	#obs	Mean	Std dev	Range
N	16	2.812	4.037	(0,15)
P	16	3.187	5.128	(0,15)
Peak	16	4.187	5.009	(0,19)
Rad	16	0.375	0.806	(0,3)
Reader	#obs	Mean	Std dev	Range
Reader1	32	4.156	5.430	(0,19)
Reader2	32	1.125	1.699	(0,6)

Table 6. Marginal statistics for the cluster number with all 29 points seen in Misty

Beam energy	# obs	Mean	Std dev	Range
18	16	0.125	0.341	(0,1)
25	16	0.375	0.719	(0,2)
30	16	2.687	10.486	(0,42)
40	16	0	0	(0,0)
Crystal reflection	#obs	Mean	Std dev	Range
111	32	1.437	7.414	(0,42)
333	32	0.156	0.448	(0,2)
Curve position	#obs	Mean	Std dev	Range
N	16	2.750	10.478	(0,42)
P	16	0.250	0.577	(0,2)
Peak	16	0.187	0.403	(0,1)
Rad	16	0	0	(0,0)
Reader	#obs	Mean	Std dev	Range
Reader1	32	1.594	7.396	(0,42)
Reader2	32	0	0	(0,0)

Table 7. Marginal statistics for the number of specks seen in Misty

Beam energy	# obs	Mean	Std dev	Range
18	16	38.562	5.215	(27,42)
25	16	41.875	0.341	(41,42)
30	16	39.400	4.702	(28,42)
40	16	14.937	12.615	(0,37)
Crystal reflection	#obs	Mean	Std dev	Range
111	32	33.935	13.394	(0,42)
333	32	33.281	13.056	(0,42)
Curve position	#obs	Mean	Std dev	Range
N	16	35.667	9.155	(17,42)
P	16	31.187	18.605	(0,42)
Peak	16	38.312	7.208	(24,42)
Rad	16	29.375	13.490	(6,42)
Reader	#obs	Mean	Std dev	Range
Reader1	32	33.226	13.576	(0,42)
Reader2	32	33.969	12.870	(0,42)

Table 8. Marginal statistics for the number of distinct regions in Grayscale series seen in Misty

Beam energy	# obs	Mean	Std dev	Range
18	16	4.562	0.964	(2,6)
25	16	4.312	1.014	(3,6)
30	16	4.687	1.250	(2,6)
40	16	0.562	1.093	(0,4)
Crystal reflection	#obs	Mean	Std dev	Range
111	32	3.687	2.086	(0,6)
333	32	3.375	1.996	(0,6)
Curve position	#obs	Mean	Std dev	Range
N	16	3.937	1.948	(0,6)
P	16	3.375	2.094	(0,5)
Peak	16	3.937	2.351	(0,6)
Rad	16	2.875	1.668	(0,5)
Reader	#obs	Mean	Std dev	Range
Reader1	32	3.687	2.039	(0,6)
Reader2	32	3.375	2.044	(0,6)

3-way factorial ANOVA with a block factor is used to fit all eight outcomes. In the models, we include all the interactions among beam energy, crystal reflection and curve position as well as reader ID in the model. Some responses in the models may require transformation in order to ensure the validity of the normal assumption. Especially, for fitting the first three outcomes on the volume of the circles in the CD phantom, we use the following transformed responses in the ANOVA:
Y=the cubic root of (Total volume of the circles in the CD phantom-the volume visible).

Since multiple tests are conducted in comparing all the factors for each of eight outcomes, we use the Bernoulli test to adjust the Type I error by setting 0.05/8 as the significance level in the tests for each outcome. Using such a significance level, we adopt the Tukey test to compare the difference of the performances among different levels of each factor. The test results and the conclusions are given in the following (the order "A>B" means that level A produces significantly better visibility than level B and the equation "A=B" means that there is not significant difference between level A and level B).

1. When the variable is the volume of the circles with entire circumference visible, only the factors of *Reader*, *Beam energy* and *Curve position* are significant with p-values being less than 0.001, equal to 0.0027, and less than 0.001, respectively.

Reader 1 tends to observe more volume than Reader 2. The Tukey test does not find the difference among all the levels in beam energy but it appears that 25keV performs better than 30keV and the latter performs better than both 40keV and 18keV. The curve position=rad gives the least visible volume and there seems to be little difference among the other three positions. However, it appears that peak position gives the most visible volume.

2. When the outcome is the volume of the circles with at least half circumference visible, all the factors are significant with p-values less than 0.001. There also appears to be significant interaction between crystal reflection *Angle* and *Curve position* (p-value<0.001). Reader 1 tends to observe more volume than Reader 2. The test shows that *Beam energy* level 25keV performs best and both 25keV and 30keV produce more visible volume than energy level 18keV and energy level 40keV. It also appears that the combination of the levels crystal reflection *Angle*=333 and *Curve position*=peak produces the most visible volume, although there is not enough evidence to support that it performs better than the combinations *Angle*=333 *Curve position*=p and *Angle*=333 *Curve position*=n.
3. When the variable is the volume of the circles with any part of circumference visible, both crystal reflection *Angle* and *Curve position* as well as their interactions are significant (all three p-values<0.001). The Tukey test results indicate that more volume can be seen with crystal reflection *Angle*=333 and *Curve position*=p. But there does not appear to be any significant difference between this combination and the combinations of *Angle*=333, *Curve position*=peak and *Angle*=333, *Curve position*=n.
4. When the variable is the number of line pair groups observed in MISTY, all the factors of *Reader, Beam energy, crystal reflection Angle and Curve position* are significant with all the p-values less than 0.001. Moreover, there appears to be significant interactions between crystal reflection *Angle and Curve position* (p-value<0.001) and there is significant interaction among *Beam energy, crystal reflection Angle and Curve position* (p-value<0.001). The test results indicate the following: for Reader, Reader2>Reader 1; the combinations of keV=18, Angle=333, Curve position=peak or keV=25, Angle=333, Curve position=peak/p or keV=30, Angle=333, Curve position=p give the best performance.
5. When the variable is the number of stars observed in MISTY, only the factors of *Reader and Beam energy* are significant (p-values are 0.009 and 0.0026 respectively). The test results indicate the following relationship (the order "A>B" means the left level produces more line pair groups visible than level B and the equation "A=B" means that there is not significant difference between level A and level B): Reader 1> Reader 2; for beam energy, 25keV is the best choice but it is not significantly different from 30keV.
6. When the variable is the number of cluster with all points seen in MISTY, none of all the factors or their interactions is significant.
7. When the variable is the number of specks observed in MISTY, there appears to be significant difference among the different levels in *Beam energy* and among the different *Curve positions*. Moreover, the three-way interaction among *Beam energy, Curve position and Angle* is significant. The test results indicate the following relationship: the best combinations include (KeV=18, Angle=111,

Curve position=n/p/peak), (KeV=18, Angle=333, Curve position=peark), (KeV=30, Angle=111/222, Curve position=n/p/peak).

8. When the variable is the number of line clusters in grayscale series observed in MISTY, there appears to be significant difference among the difference levels in *Beam energy* and among the different *Curve positions*. The test results indicate the following relationship: for beam energy, 18keV=30keV=25keV>40keV (it appears 30keV performs slightly better than 18keV while 18keV works slightly better than 25keV); for curve position, n=p=peak>rad (peak/n positions perform slightly better than p position).

SUMMARY OF ACCOMPLISHMENTS BASED ON STATEMENT OF WORK

First six months

-The image raw data was transferred from files at the National Synchrotron Light source to UNC.
-The images were converted to the proper format to be displayed on the UNC mammography workstations and for compatibility to the Kodak laser printer.
-They were first be presented on high brightness, high resolution monitors for intensity windowing by Dr. Pisano.
-The tissue samples were provided to the Pathology Laboratory for histologic whole-mounts. Dr. Pisano and Dr. Geradst reviewed path slides and indicated regions of interest on the tissue specimens. Detailed path reports generated.

Second six months:

-Display parameters applied to images and printed on Kodak 50 um/pixel 12 bits gray scale laser printer.
-Observer scoring data sheets developed.
-Details of observer study finalized.
-Images packaged into six sets of 15 images each .
-Pilot observer study carried out to test methods and data flow.
-Discovered that tissue specimens were not consistent enough to extract the necessary information needed to determine the imaging parameters. Challenging mammography phantoms were substituted for tissue specimens.

Third six months:

A second trip was made to Brookhaven National Laboratory to image the phantoms using the same configurations as defined in the initial proposal.

Fourth six months:

-Images processed and prepared for reader study.
-The statistical design of the study was changed to better extract the data from the phantoms.

-Raw data of experiment made available to physics group at NSLS and APS via Dr. Chapman for preliminary design of compact source.
-New data from Dr. Chapman's group reveals that DEI imaging, especially for refraction images, may be optimal at 40 keV. This new data indicates that detailed DEI images can be obtained at a fraction of the dose received from an 18 keV image. In order to characterize the full set of parameters, a fourth energy was added to the data set.
-A third trip was made to Brookhaven National Laboratory to obtain the final set of images.

No-Cost Extension Period

-Images processed as before and added to the data set.
-Final design of reader study completed
-Reader study completed
-Statistical analysis of data completed

KEY RESEARCH ACCOMPLISHMENTS:

-Imaged four breast tissue samples with DEI at each of the selected acquisition parameters

-Transferred images from Brookhaven National Laboratory to the University of North Carolina

-Applied image enhancements, cropping, and registration to each image

-Determined that tissue samples did not provide the quantitative data needed to evaluate the acquisition parameters

-Selected two mammographic phantoms to simulate breast tissue

-Acquired images of both phantoms at the selected parameters

-Discovered that DEI images can be acquired at 40 keV, providing high resolution images with a dramatic decrease in dose.

-Acquired additional set of phantom images from Brookhaven National Laboratory at 40 keV

-Processed all images and randomized for reader studies

-Completed final statistical design for DEI reader study

-Completed reader study

-Completed statistical analysis of data

-All study data disseminated to the DEI Research and Development Group for integration into the DEI Clinical Prototype system design

REPORTABLE OUTCOMES:

Manuscripts:

The statistical analysis of the study has only recently been completed, but the manuscript is in preparation and will be submitted for publication in the near future.

This research involved in this project has to date led to four presentation:

Parham, CA. Medical Applications and Physical Characterization of Diffraction Enhanced Imaging. Presented at the UNC Radiology Research Symposium. March 2002.

Parham, CA. Medical Applications and Physical Characterization of Diffraction Enhanced Imaging. Illinois Institute of Technology. April 2002.

Parham, CA. Medical Applications and Physical Characterization of Diffraction Enhanced Imaging. Brookhaven National Laboratory Seminar Series. July 2002.

Parham, CA. Radiologist Evaluation of DEI Breast Specimen Imaging. UNC Biomedical Engineering Research Review. March 2003

Degrees Supported:

The DEI project at UNC is the core doctoral research work of Christopher Parham, a 5^{th} year MD/PhD student in the UNC Department of Biomedical Engineering. He is the lead graduate student on this project and the information obtained in this project has helped to make significant advancements in his doctoral research.

Key Personnel with Research Components Funded by This Research Effort:

Dr. Etta D. Pisano, M.D.
Dr. Eugene Johnston, Ph.D.
Dr. Dean Chapman, Ph.D.
Dr. Keith Muller, Ph.D.

CONCLUSIONS:

The data obtained from this study has provided key insight into the optimal imaging parameters for Diffraction Enhanced Imaging. The results of the study conclude that for the best visibility, the best setting would be a beam energy level equal to 25 keV OR 30 keV. Earlier studies had indicated that the optimal beam energy would be between 30 keV and 40 keV based on a signal to noise analysis, but this is most likely only for the refractive components of the image. The statistical analysis indicates that 30 keV has the optimal balance between absorption and refraction. This is a key determination for the group, because it will have a considerable effect on all DEI imaging studies currently underway.

The crystal reflection that provided the best visualization is the Bragg [333] configuration. This configuration has a high degree of photonic scatter rejection based on its physical profile, and this is confirmed by the analysis of the reader study. In regards to the analyzer crystal position, the optimal positions were found to be the negative ½ Darwin With and the Peak positions. In addition to these overall peak system parameters, the study also provided valuable insights into how the modality performs across different configurations and with different types of phantoms. As system development progresses, the statistical analysis will undoubtedly be referenced as a way to interpret the corresponding changes in image quality.

The completion of this study marks the first major step towards the development of a DEI clinical prototype imaging system. Now that the optimal system parameters have been determined, the necessary hardware and physics and engineering modifications can be implemented. The results from this study will help to shape the source of the x-ray system as well as the internal crystal configurations. On a more clinical note, the study will be invaluable in subsequent tissue studies for validation of the system. The data will be immediately applied to another USAMRMC funded experiment, DAMD17-02-1-0523, entitled "Comparison of Image Quality Among Variations in Specimen Tissue Compression for Diffraction Enhanced Imaging." This study evaluates the need for tissue compression in the acquisition phase of DEI. The combination of these studies will provide the foundation necessary for the clinical prototype. If the overall goal of the DEI Research and Development Group is reached, than a new imaging system will be created capable of detecting the early signs of breast cancer in a way that has heretofore not been possible. A system with increased visualization will have a corresponding increase in sensitivity and specificity, and this could potentially be a tremendous advancement in breast cancer diagnosis and detection.

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2. Hendrick RE, Smith RA, Rutledge JH. Benefit of screening mammography in women ages 40-49: a new meta-analysis of randomized controlled trials. Journal of the National Cancer Institute Monograph 22:87-92, 1997.

3. Nystrom L, Rutqvist LE, Wall S. Breast cancer screening with mammography: overview of Swedish randomized trials. Lancet 342(8851): 973-8, 1993.

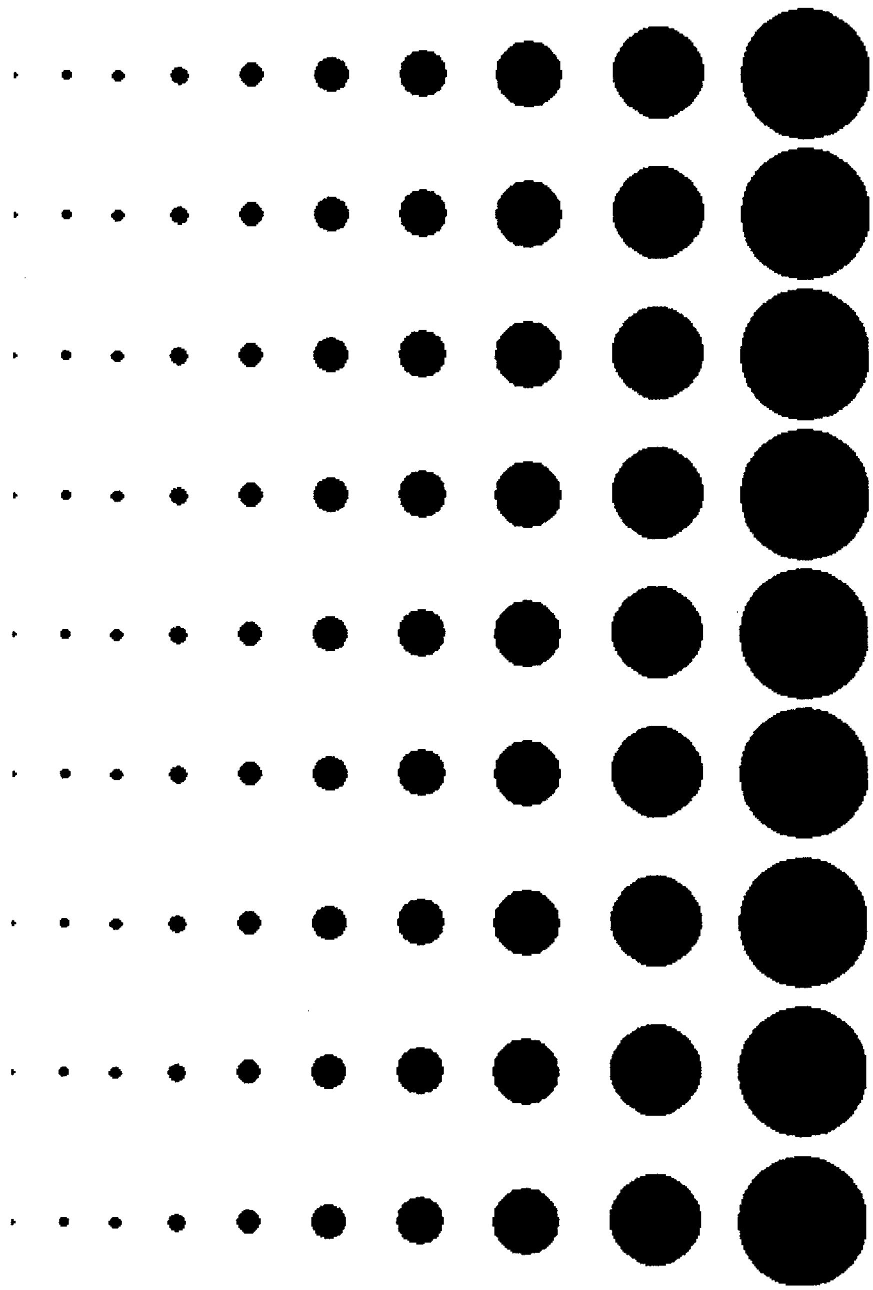
4. Pisano ED, Parham, CA. Digital Mammography, Sestamibi Breast Scintigraphy, and Positron Emission Tomography Breast Imaging. Radiologic Clinics of NA. 38(4): 861-870, 2000.

5. Pisano ED, Johnston, RE, Chapman D, Geradts J, Sayers D, Tomlinson W. Diffraction Enhanced Imaging of Human Breast Cancer Specimens: Improved Conspicuity of Lesion Detail with Histologic Correlation. Radiology 241(3); 895-901, 2000.

APPENDIX A

DEI PARAMETER STUDY READER SHEETS

DEI PARAMETER STUDY IMAGE#______



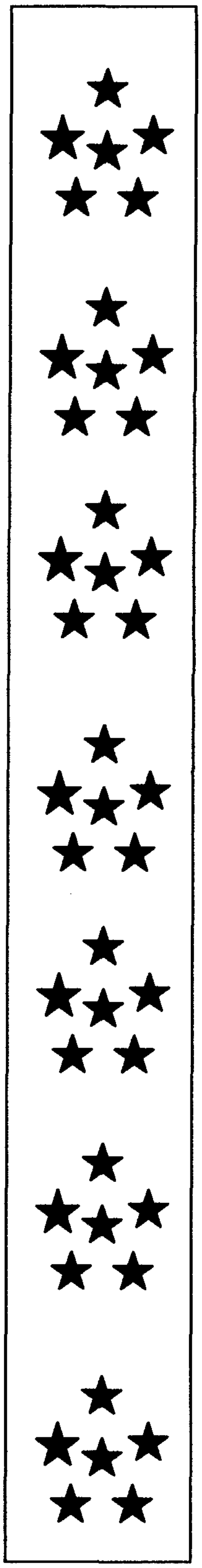
<u>TASK 1:</u> USE THE BLUE MARKER TO DEFINE THE REGION IN WHICH THE ENTIRE AREA OF THE CIRCLES CAN BE VISUALIZED.

<u>TASK 2:</u> USE THE RED MARKER TO DEFINE THE REGION IN WHICH MORE THAN ½ OF THE AREA OF THE CIRCLES CAN BE VISUALIZED.

<u>TASK 3:</u> USE THE BLACK MARKER TO DEFINE THE REGION IN WHICH ANY OF THE CIRCLES CAN BE VISUALIZED, REGARDLESS OF THE AREA.

DEI PARAMETER STUDY IMAGE #________

1

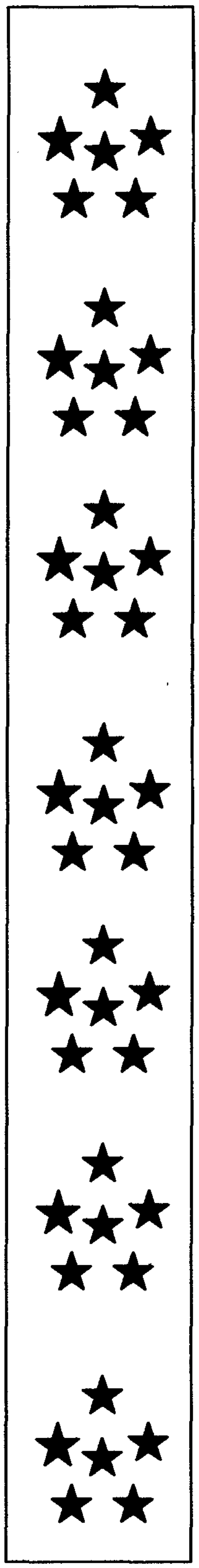


TASK 1

COUNT AND RECORD THE NUMBER OF STARS THAT CAN BE SEEN IN EACH GROUP IN THE SPACE PROVIDED

START AT THE BOTTOM CLUSTER AND MOVE UP

DEI PARAMETER STUDY IMAGE #__________



2

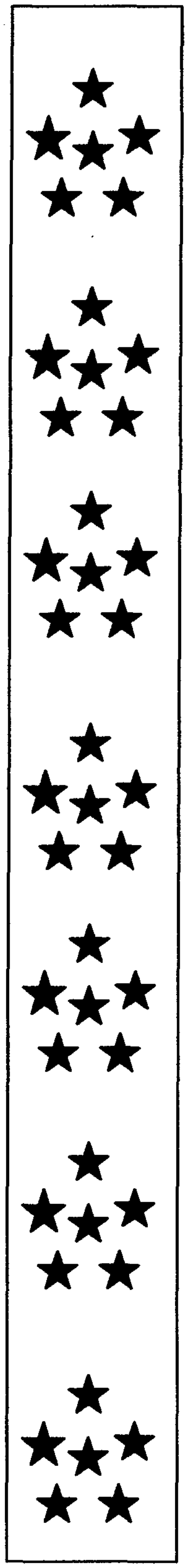
TASK 2

CIRCLE THE HIGHEST CLUSTER IN WHICH YOU CAN SEE THAT ONLY **ONE** STAR IN EACH CLUSTER IS MISSING A POINT

START AT THE BOTTOM CLUSTER AND MOVE UP

DEI PARAMETER STUDY IMAGE # ________

3

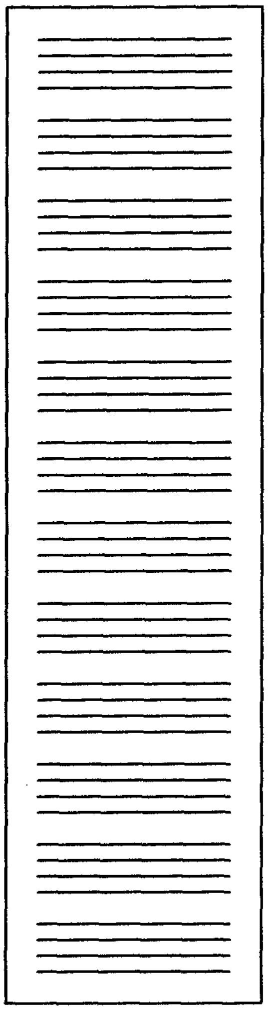


TASK 3

COUNT AND RECORD THE NUMBER OF **SPECKS** THAT CAN BE VISUALIZED IN EACH GROUP IN THE SPACE PROVIDED.

START AT THE BOTTOM CLUSTER AND MOVE UP

DEI PARAMETER STUDY IMAGE #____



CIRCLE THE HIGHEST GROUP IN THE SERIES IN WHICH THE THREE SPACES BETWEEN THE LINES MAY BE CLEARLY DISTINGUISHED.

PLEASE MOVE FROM BOTTOM TO TOP

DEI PARAMTER STUDY **IMAGE #_______**

PLEASE PLACE A CHECK ON EACH LINE IN THE SERIES THAT CAN BE VISUALIZED