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Detection of the smallest microcalcifications for early diagnostic of breast cancer

Detecção das menores microcalcificações para o diagnóstico precoce do câncer das mamas

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Abstract

Even though breast cancer is a cancer with relatively easy early diagnostic and has an appropriate treatment, it has high mortality rates in Brazil. This is in part because the disease is diagnosed only in advanced stages, but also because the whole information contained in the mammograms is not used by physicians and radiologists. There are many parameters to be considered in assessing the quality of a mammogram image. Among these parameters are contrast, spatial resolution, the signal-to-noise ratio, and the efficiency of the applied dose. Even with the improvement of the quality of radiographs, many structures, such as small microcalcifications, are not always identified by radiologists in the images. To determine the lowest detectable structures in digital mammograms, we made a numerical analysis of a few digital mammography using simulators, determining the spatial and intensity resolutions, and studying the noise and its distribution. With this, we could determine the detection levels, quantifying the probability that any point is due to statistical noise or a real change in breast density. This is the first step towards early detection of microcalcifications. In our work, it was possible to detect even the smallest microcalcifications of the simulator, 0.18 mm in diameter, with false alarm probability smaller than 1/1000.

Keywords: breast cancer, computer-aided diagnosis, mammography, radiology.

Resumo

Apesar do câncer de mama ser um câncer com diagnóstico precoce relativamente fácil e possuir tratamento adequado, o câncer de mama possui taxas de mortalidade muito elevadas no Brasil. Isso deve-se provavelmente ao fato da doença ser diagnosticada somente em estágios avançados, mas também pela não utilização de todas as informações fornecidas pelo exame mamográfico por parte dos radiologistas e médicos. Existem muitos parâmetros a serem considerados para avaliar a qualidade de uma imagem mamográfica. Mesmo com a melhoria da qualidade dos exames radiográficos, muitas estruturas, como as pequenas microcalcificações, nem sempre são identificadas pelos radiologistas nas imagens. Para determinar as menores estruturas detectáveis nas mamografias digitais, fizemos uma análise numérica de algumas mamografias digitais, utilizando simuladores mamográficos, determinando as resoluções espaciais e em intensidade, estudando o ruído e sua distribuição. Com isso, foi possível determinar os níveis de detecção, quantificando a probabilidade de uma estrutura ser devido ao ruído estatístico ou uma alteração real na densidade da mama, sendo esse o primeiro passo para a detecção precoce de microcalcificações. Estudamos as menores microcalcificações do simulador, de 0,18 mm de diâmetro, e determinando que possuem probabilidades de serem devido a ruído menores que 1/1000.

Palavras-chave: câncer de mama, diagnóstico com auxílio do computador, mamografia, radiologia.

Introduction

The significant increase in the incidence of breast cancer, and consequently the mortality associated, has occurred throughout the world in recent decades. The estimation of new cases of breast cancer in Brazil was 49,240 for the year 2010, with a rate of 49 new cases for each 100 thousand women, and, in the Southern Region, the risk is estimated as 64 cases for each 100 thousand women, according to data of the Brazilian National Institute for Cancer (INCA)[1].

Breast cancer is the most common type of cancer among women and the second most frequent in the world, only behind lung cancer. It is much feared due to its high frequency, the uncertainty of the success of treatment, the possibility of recurrence, death, and, above all, by their psychological effects[2], which affect both the perception of sexuality, as the very self image. It is relatively rare before the age of 35 years, but above this age group its incidence grows rapidly and progressively. In Brazil, it is responsible for most deaths among women, with an estimate of 22% new cases per year of cancer in women[1]. It also occurs in men, but much less frequently.

Mammography

The objective of mammography is the early detection of breast cancer screening in asymptomatic women[3].

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Mammography is the most usual technical detection method for non-palpable masses, intended for diagnostic imaging of the breasts, using low doses of X-ray. However, it is very important that it presents a good quality image and diagnostic, having high contrast and resolution, a high signal/noise, since the contrast of various tissues that compose the breast is low.

The early discovery of this type of cancer through mammography can provide the increase of the chances of a successful treatment. For this, it is necessary to use all the information contained in mammographic images. However, retrospective analyzes of the mammographic examinations revealed that a large number of breast cancer cases were already visible previously[4], which demonstrates that not all the data contained in the mammography was used, making necessary to increase the efficiency of the diagnostic, never to replace the radiologist, but in order to help radiologists render better clinical decisions.

Microcalcifications

One of early signs of malignancy in breast cancer may be through non-palpable lesions, linked to certain forms and patterns of distribution[5]. The detection of microcalcifications represents the earliest sign of possible breast cancer, but the visual interpretation make the mammogram a fatiguing and time-consuming work because of the small size of the microcalcifications[6].

Mammography is still the most widely used technique, widespread and promoted because its low cost for the detection of microcalcifications, which are composed basically by calcium, with great attenuation in relation to other tissues. Their detection is relatively easy when on a uniform region, but hampered by the low contrast and signal/noise of complex images[7].

For the assessment of mammography, one must observe: the sizes, number, shape, density and distribution of microcalcifications, which are important factors to be taken into account for the analysis criteria[5] (Figure 1).

Materials and methods

Mammographic simulator

Mammogram simulators are used to evaluate the image quality[8], with different objects, of different sizes, representing small structures of the breast, as fibers, microcalcifications and tumor masses. Placed in the X-ray apparatus where the breast should be placed and simulating the size of an average breast, it generates an image basis to be examined.

The simulator used in our analysis was the Phantom *Mama*, formed by a body of acrylic with a plate of wax containing the objects, which were used in the simulations of microcalcifications with dimensions of 0.45, 0.35, 0.30, 0.25 and 0.18 mm (Figure 2).

Another object for tests is a PMMA acrylic plate, entirely homogeneous, of 2x25x30 cm. The plate must be larger than the size of the detector, so that all pixels are equally illuminated.

Noise

Noise is any external signal or statistical fluctuation superimposed on the signal of source. Even when exposing a detector to a uniform X-ray beam, the actual number of photons counted by the detector varies for each pixel of the image. This occurs because of the statistical nature of the emitting source, of the attenuation processes, so that the number of photons absorbed varies from pixel to pixel, and these are the source of the information[9]. The noise can conceal the information in the image, for example, low contrast structures. It also affects the spatial resolution, reducing the system capability of separate small and nearby structures, as microcalcifications.

The signal-to-noise ratio is a fundamental limitation on the perception of effects; it must be high to maximize the information, but the attempt to increase the signal-to-noise ratio increases the dose damaging to the patient. It

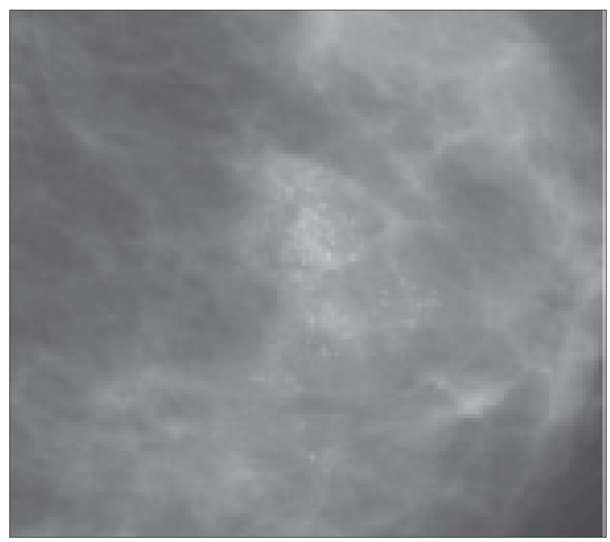

Figure 1. Microcalcifications example.

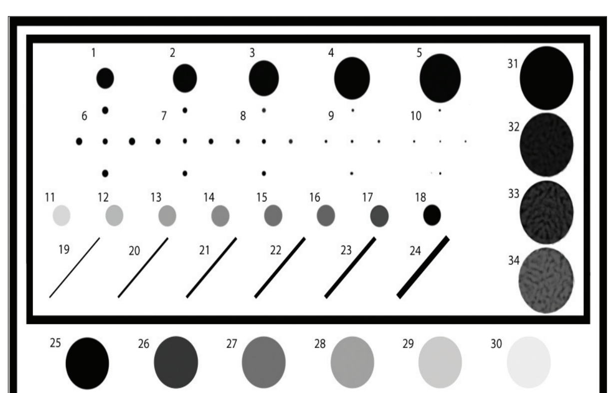

Figure 2. Objects of the mammographic simulator Phantom *Mama*.

is necessary to balance an acceptable image for the diagnostic and the lowest exposure possible to the patient.

Noise sources include random noise, due to fluctuations in counts, and the noise of reading, caused by thermal noise, due to the movement of atoms, dark, since even in the absence of the signal there may be formation of pairs of electron-gap in the detector, generally temperature dependent[9].

Dense regions are generally noisy and present low contrast, while microcalcifications have properties of high attenuation, but their small size tends to present low local contrast.

The number of photons counted in images presents statistical fluctuations, causing low contrast structures to present difficulties in differentiating from noise. To assess the probability that a point is a real detection, as a lesion of the breast, or is due to noise, we study the noise and its distribution in order to determine detection levels both spatial and in intensity. The noise distribution is Poissonic, as shown in Figure 3, which shows the values of background Regions of Interest (ROIs), i.e., without any object, and in the direction not affected by the anodic effect.

The detector of the digital mammogram apparatus used is 19x23 cm, forming images of 1917x2294 pixels, with pixel size of approximately 0.1 mm on the side[10].

The equipment used in this work was the DR model Senographe 2000D GE Medical Digital Systems Mamography[11], used in a radiographic clinic in Porto Alegre.

Simulator analysis

To study the effect of changes in energy and current in the images, we exposed the mammographic simulator to various current values and energy of the X-ray beam. To analyze the spatial resolution and the sensitivity of images, we examine how many standard deviations each one of the simulator objects presented. For this, first, we must study the background, that is, the regions which contain no objects, and determine what their fluctuations are, calculating the standard deviation of the background.

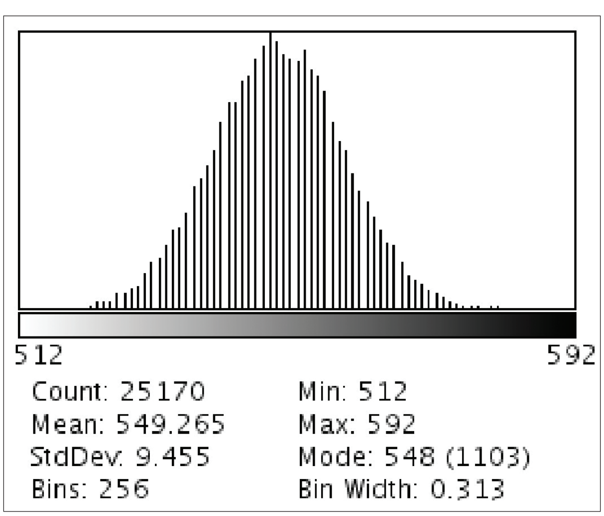

Figure 3. Distribution of background counts obtained in a mammogram.

Once estimated the background, we measure the value of greatest absolute frequency, defined as *mode* of the distribution, using a ring around the object of study.

Using ImageJ, a free software in the public domain written in Java[12], developed from NIH Image and available to every office computer, it is possible to study the areas of interest. These ROIs must be chosen parallel to the length of the detector to avoid the reduction of intensity caused by the anodic effect, which is an irregular distribution of the X-ray intensity caused by the inclination of the anode. With the histogram of the image, the software also shows the values: maximum, minimum, *mode*, counts, mean and standard deviation, determined for each region of interest. Subsequently, we calculated the standard deviation of the background, σ (background).

For each structure (object) of the simulator, we determined:

$$\frac{|\text{mode}(\textit{structure}) - \text{mode}(\textit{background})|}{\sigma(\textit{background})} \qquad (1)$$

Results

Data were collected using the simulator Phantom *Mama* images, irradiated in the Senegraphe 2000D mammographic equipment, with different values of voltage and current. The values of 28 kV with 138 mA correspond to the automatic value chosen by the equipment for the simulator, and 26 kV and 60 mA parameters are recommended by the manufacturer in the manual for the quality control image. All images correspond to the effects simulating an examination of the breasts in position craniocaudal (CC), with molybdenum target and filter (Mo/Mo).

In the analysis of the values of background *mode*, in regions where there are no objects, the distribution of the values of pixels may be represented by a Gaussian function. The histogram may be described by Gaussians, following the Central Limit Theorem, which states that the distribution of many averages is a Gaussin distribution.

After we obtained the values of the mean and standard deviation, we can plot the signal-to-noise ratio for each image versus the power of the X-ray beam, given by the product of voltage and energy in each image.

The points for the automatic exposure present the best signal-to-noise ratio, proving that it was well selected by the manufacturer and the equipment is operating within the specifications.

Microcalcification simulators

Table 1 shows the values of the signal-to-noise ratio measured for smallest simulators of microcalcifications, with 0.18 mm (Figure 4).

The detection of a signal smaller than 3 σ occurs for energy values of 28 kV and current of 80 mA. Table 1 lists the voltages, current, average and standard deviation (σ) of the background, with their respective values of signal-to-noise ratio of the smallest sets of microcalcifications (0.18 mm) in the Phantom *Mama*, in relation to the probability that the points are real or only noise of the image.

The second group of phantoms of microcalcifications, with 0,25 mm, has the signal-to-noise ratio of 3.9 even for the image with energy of 26 kV and current of 50 mA, already presenting likelihood of been real greater than 99.9%.

Table 1. Signal-to-noise ratio with their respective likelihood for assemblies of the smallest microcalcifications (0,18 mm) to be real or only noise of images, with relation to the values of tension and current, average background and standard deviation σ.

kV	mA	Average	Sigma	S/R	Real (%)	Noise (%)
26	50	361	7.3	1.9	94.3	5.7
28	50	559.6	9.6	2.3	97.8	2.3
30	50	818.8	11.9	3.0	99.7	0.3
26	80	585.5	9.8	2.2	97.3	2.7
28	80	903.5	12.7	3.2	99.9	0.1
30	80	1325.4	16.1	3.4	99.9	0.1
26	125	920.4	12.6	2.5	99.9	0.1
28	125	1423.1	17.5	3.4	99.9	0.1
30	125	2087.1	22.2	4	99.99	0.01
28	138	1572.3	15.5	2.3	99.9	0.1

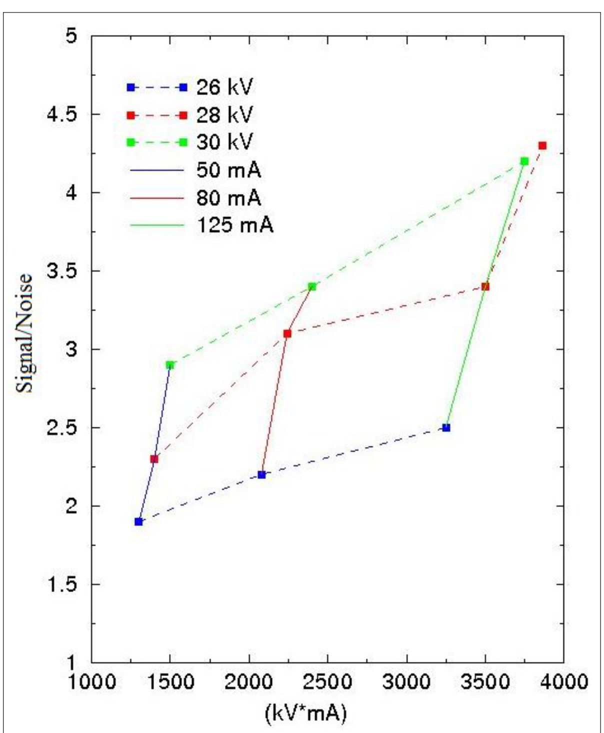

Figure 4. Signal-to-noise ratio for microcalcification simulators of 0.18 mm for different powers of the X-ray beam.

All other images, as well as the other sets of larger microcalcifications, have even greater probability of being real.

Conclusion

The smallest dimension microcalcification tested is 0.18 mm and is above the limit of detection, with signal-to-noise ratio of the order of 3.2 and likely to be real, and not only noise of the image of 99.9% for exposures of 28 kV and 80 mA. Statistically, this means that part of the information of real image is not being considered in the evaluation or diagnosis, as they are detecting in general only masses of 0.5 mm or larger[4], i.e., information is not been used. The smallest microcalcifications that the authors can see by eye have 0.25 mm, already with signal-to-noise ratio of 3.9. If the probability distribution is Poissonic, for signal=3σ, the probability of being due to noise is already smaller than 0.1%.

The analysis of images is a process of finding, identifying and understanding the patterns that are relevant for the function for which the image is designed. An important goal of the analysis of images using computation is to provide the machine capacity to simulate the human senses, and, in addition, use their tools and speed to make analysis less subjective, independent of human abilities, having the capacity to recognize patterns at previously established levels, as well as to considerate probabilities.

Our next steps will be to analyze real breast mammograms, which have signal distribution much more complex because of the density variations of breast tissues, and to develop a software showing the regions that are above a certain level of detection, which may be altered progressively. The objective is to use all the information contained in mammograms and not only those of high signal/noise that are easily identified by the naked eye.

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