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Lucas Rodrigues Borges

**Método de simulação da redução da
dose de radiação na mamografia digital
a partir da análise das características do
ruído dos equipamentos mamográficos**

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Dedico este trabalho aos meus pais Nivan e Dulcinéia.

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*“We cannot solve our problems
with the same thinking we used
when we created them.”
(Albert Einstein)*

Resumo

Borges, Lucas Rodrigues **Método de simulação da redução da dose de radiação na mamografia digital a partir da análise das características do ruído dos equipamentos mamográficos.** 78 p. Tese de mestrado – Escola de Engenharia de São Carlos, Universidade de São Paulo, 2015.

Este trabalho tem como objetivo o desenvolvimento de um novo método para a simulação de redução da dose de radiação em imagens mamográficas clínicas. Assim, estudos sobre a influência da redução da dose de radiação no diagnóstico do câncer de mama podem ser realizados sem que o paciente se exponha à doses extras de radiação. Uma análise preliminar foi realizada para a caracterização do ruído produzido pelo equipamento mamográfico no processo de aquisição da imagem. Essa análise evidenciou a importância de um método local de simulação, uma vez que o ruído depende da posição ao longo do campo. O novo método proposto consiste em ajustar os níveis de cinza e adicionar uma máscara de ruído Poisson, dependente do sinal, nas imagens clínicas adquiridas com a dose de radiação padrão, simulando sua aquisição com doses de radiação reduzidas. A dependência entre ruído e sinal foi criada com o uso da transformada de Anscombe. O desempenho do método proposto foi avaliado utilizando-se imagens mamográficas de um phantom antropomórfico obtidas com diferentes doses de radiação. As imagens simuladas pelo método proposto foram comparadas com as imagens reais. A similaridade entre os espectros de ruído permitiu a comparação de métricas locais da imagem. O erro percentual entre os níveis de cinza das imagens reais e simuladas se manteve inferior a 1%. O ruído adicionado manteve um erro percentual inferior a 1%. Testes de t-Student mostraram que não existe diferença estatística significativa ($p < 0,05$) entre as imagens reais e simuladas pelo método proposto.

Palavras-chave: Redução de dose de radiação, mamografia digital, transformada de Anscombe, ruído quântico.

Abstract

Borges, Lucas Rodrigues **Method for simulating dose reduction in digital mammography through the analysis of the noise characteristics of the mammographic equipment.** 78 p. Master Thesis – São Carlos School of Engineering, University of São Paulo, 2015.

This work aims to develop a new method for simulating reduction of the radiation dose in clinical digital mammography. Using such method, studies regarding the influence of dose reduction in cancer diagnosis can be performed without unnecessary exposure of patients to X-ray radiation. A preliminary study characterized the noise produced by the digital mammography equipment during the acquisition process. This analysis emphasized the importance of simulating noise locally, since noise is dependent on the spatial position of the pixel. Therefore, the proposed method consists of adjusting the gray levels and adding signal-dependent Poisson noise to images acquired at the standard radiation dose. Dependency between noise and signal was created using the Anscombe transformation. The performance of the proposed method was evaluated using mammographic images of an anthropomorphic phantom acquired at different radiation doses. Images simulated using the proposed method were compared to real images acquired using the clinical equipment. Similarity between noise power spectra and local metrics validated the similarity between images. The gray level of the simulated and real images were compared using local mean and reported averaged errors smaller than 1%. The added noise was also compared and the averaged error was smaller than 1%. Statistical Student's t-test tests showed no statistical difference ($p < 0.05$) between real images and the ones simulated using the proposed method.

Keywords: Reduction of the radiation dose, digital mammography, Anscombe transformation, quantum noise.

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Abbreviations

A	Anscombe Transformation
ALARA	As Low As Reasonably Achievable
DQE	Detective Quantum Efficiency
FFDM	Full Field Digital Mammography
MTF	Modulation Transfer Function
NNPS	Normalized Noise Power Spectrum
NPS	Noise Power Spectrum
SNR	Signal-to-Noise Ratio
var	Variance

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Introduction

Breast cancer is the second most frequent cancer and the most lethal among women all over the world. According to recent statistics, approximately 57,100 women were diagnosed with breast cancer in Brazil in 2014 (INCA, 2014).

Modern medicine is still working on the causes of breast cancer, and the most effective method for improving cancer outcome and survival rates is the early detection of the disease, which can increase patient's chances of cure in up to 30% (VERONESI et al., 2005). For this reason, many countries have adopted breast cancer screening policies, in which all women older than a specified age are recommended to periodically undergo an X-ray mammography (ICSN, 2014).

Along the benefits achieved by screening programs, the exposure to low doses of X-ray radiation during the exam includes a risk of radiation induced cancers to the patient. Recent studies have shown that the repetition of the exam along the screening program can induce new cancer cases (GONZALEZ et al., 2009; MATTSSON; LEITZ; RUTQVIST, 2000; YAFFE; MAINPRIZE, 2011). Statistics indicate that out of 100,000 women attending to a screening program (with 1 yearly mammogram from age 40 to 55 years, and biannially from age 56 to 75), 497 lives will be saved by the early detection of the disease. However, 86 new cases will be induced, and 11 of these patients will die because of the disease (YAFFE; MAINPRIZE, 2011).

Decreasing patient exposure to X-ray radiation during mammography exams would help reduce risks associated with screening programs. However, the radiation dose is also directly related to the image quality. Decreasing the radiation dose may result in lower image quality, due to the increase in the quantum noise which may reduce the visibility of breast lesions, which can harm the performance of radiologists (SAUNDERS et al., 2007; RUSCHIN et al., 2007).

Due to this trade-off between the radiation-related risks and image quality, the general principle for selecting radiation dose is ALARA ("as low as reasonably achievable") (ICRP, 1973). However, practical optimization between radiation dose and image quality remains challenging for digital mammography systems (SAMEI et al., 2007; HAUS; YAFFE, 2000;

YOUNG et al., 2006; HUDA et al., 2003).

To validate studies regarding reduction of the radiation dose it is necessary to have a set of clinical images, acquired from the same patient, at different radiation levels. Availability of such images is limited, since they require repeatedly exposing same patients, thus increasing their risk.

A way to overcome this limitation is the use of realistic breast phantoms. These phantoms should be capable of mimicking the anthropomorphic behavior of breast tissues, either as physically built models of the breast anatomy (CARTON et al., 2011; NOLTE et al., 2014) or through digital simulation (POKRAJAC; MAIDMENT; BAKIC, 2012; BLIZNAKOVA et al., 2010; KIARASHI et al., 2014).

Another approach to validate the methods for dose reduction is to simulate the effect of reduced exposure in mammograms by post processing clinical images (SAUNDERS; SAMEI, 2003; BATH et al., 2005; KROFT et al., 2006; VELDKAMP et al., 2009; SVALKVIST; BATH, 2010; MACKENZIE et al., 2012; MACKENZIE et al., 2014). In fact, such simulation methods have been used as tools in most studies regarding the influence of dose reduction on the detection of breast lesions (TIMBERG et al., 2006; SAUNDERS et al., 2007; RUSCHIN et al., 2007).

To simulate dose reduction in a clinical mammography, two steps are very important: to match the gray level of a lower dose image, and to simulate the noise behavior from a lower dose acquisition. The most problematic step is adding noise to clinical images, since these images are already degraded with noise from the original acquisition. Therefore, simply adding Poisson noise is not a good approximation of the real behavior of the noise. Thus, many methods from the literature investigate methods for inserting noise in clinical mammograms to simulate dose reduction.

Saunders and Samei (SAUNDERS; SAMEI, 2003) proposed a method for changing characteristics of an image in order to simulate different exposure parameters. Such method assumes a noiseless image as input, which cannot be provided in clinical applications. Furthermore, the method is based on a radially symmetric noise power spectrum (NPS) (CUNNINGHAM, 2000), which does not account for the anisotropic behavior of the noise found in digital mammograms.

(BATH et al., 2005) presented a method capable of simulating dose reduction in radiographic images using information extracted from the two-dimensional NPS, therefore accounting for the anisotropic behavior of the noise. However, the method is based on the assumption that the detective quantum efficiency (DQE) (CUNNINGHAM, 2000) is approximately constant over the dose variations. In digital mammography, noise has a relevant influence on the DQE when operating with low-radiation doses (YAFFE, 2000).

Other authors (KROFT et al., 2006) argued that in order to be clinically useful, the noise simulation algorithm has to be simple. With this argument, the authors proposed an alternative approach for measuring the amount of noise to be added to the image,

discarding the NPS. This method was based on the local standard deviation of the image. However, as shown by the authors themselves (VELDKAMP et al., 2009), although the simulated images have the same local standard deviation as real images, they have different NPS. Since the standard deviation is not a good metric of the image noise when comparing images with different NPS (BURGESS, 1999), the clinical application of such method can be questioned.

Recent work (SVALKVIST; BATH, 2010) presented a modification of the method proposed previously (BATH et al., 2005), now accounting for the DQE variations over different doses. However, as pointed by the authors themselves (SVALKVIST; BATH, 2010), the method does not account for local fluctuations of the pixel gain, caused by the non-uniformities along the radiation field. Furthermore, the method is based on the NPS, which can be argued to be too complicated to be applied clinically. (KROFT et al., 2006)

Other methods have been proposed recently (MACKENZIE et al., 2012; MACKENZIE et al., 2014). However, all of them are based on the noise information provided by the NPS, therefore not accounting for the variation on the noise behavior along the radiation field. In digital mammography, such variations are relevant due to the influence that the heel effect, the oblique incidence and the inverse square law may exert on the local pixel gain. In order to be clinically useful the simulation method has to be loyal to the real acquisition system and maintain the simplicity of the algorithm.

This work proposes a new method for simulating dose reduction in digital mammograms. The method is based on the local simulation of noise calculated using the local variance of uniform images. In order to overcome difficulties presented by the previous methods, and to accurately simulate the noise found in digital mammograms, a novel application of the Anscombe transformation is used. With this transformation it is possible to create dependency between noise and signal, to account for the spatial dependency of the noise and to separate signal from noise, making it possible to calculate how much noise has to be added to the original image.

1.1 Objectives

In this section we summarize the objectives of this work as items, to allow better comprehension:

- ❑ Analyze and characterize the noise found in digital mammograms;
- ❑ Search for methods capable of simulating dose reduction in mammograms, study their advantages and limitations and analyze if they are the best approach for the problem;
- ❑ Propose a new method for simulating dose reduction, based on the characteristics found previously and possible improvements from methods found on the literature.

1.2 Study Framework

- ❑ Chapter 2 – Theoretical introduction to the breast anatomy, definition of what is characterized as cancer, characteristics of digital mammography systems, and methods for correcting non-uniformities in mammograms (flat-fielding);
- ❑ Chapter 3 – Brief explanation of the methods found on the literature for the simulation of dose reduction, discuss these methods and possible improvements;
- ❑ Chapter 4 – Theoretical background on the Anscombe transformation, which is used in this work;
- ❑ Chapter 5 – Identifies how we proceed with the preliminary noise analysis, proposal of new application for the Anscombe transformation to create dependency between signal and noise, explanation of each step of the new method proposed in this work, explanation of the materials and metrics used to validate the new algorithm;
- ❑ Chapter 6 – Results of the noise analysis and the performance of the new simulation method;
- ❑ Chapter 7 – Discussion of the results found in chapter 6. States possible implications about the data found. Enumerates positive findings of this work, presents possible improvements and future work.

Digital Mammography

2.1 Breast Cancer

The female human breast can be described as a cone with the base at the chest wall and the apex at the nipple. It is composed of different types of tissue and produces milk to feed infant child. Figure 1 shows how the female human breast is structurally organized.

Figure 1: Female human breast anatomy. Image created by medical illustrator Patrick J. Lynch and cardiologist C. Carl Jaffe (September, 3 2007). Downloaded from Wikimedia Commons.

The breast is a mass of glandular, fatty and fibrous tissues, positioned over the pectoral muscles of the chest wall. The glandular tissue of the breast houses the lobules, which are glands capable of producing milk. The ducts are responsible for transporting milk towards the nipple during the lactation period. Fibrous and fatty tissues surround the lobules and ducts forming the breast (PANDYA; MOORE, 2011).

Breast cancer is a disease in which mutated glandular cells start to reproduce out of control, forming cancer tumors. It occurs usually within the lobules or milk ducts, shown

in Figure 1 as numbers 3 and 6, respectively. If the cancer cells remain within the region where it was first originated, the cancer is considered non-invasive. Lobular Carcinoma in Situ and Ductal Carcinoma in Situ are the non-invasive forms of cancer located within the lobules and ducts, respectively.

If the cancer cells start to emigrate outside the area where it was originated, it is considered an invasive cancer. Commonly, these cells enter the lymphatic system and may lodge into the axillary lymph nodes or even in further organs into the body, such as liver and brain. This stage is called metastasize, and in most cases it is the stage which causes death from breast cancer (BERMAN et al., 2013).

Although in the last few years some genes were discovered to be indicators of high cancer risk (VEER et al., 2002), the causes of breast cancer are still unknown. Consequently, there are no objective ways of preventing cancer and the most effective method for increasing chances of cure is the early detection of the tumor, while the cancer is in situ, and the most effective means to detect such structure is the X ray mammography (VERONESI et al., 2005).

2.2 Mammographic Equipment

The X-ray mammography was developed to enhance the detection of structures within the human breast. The system was created specially to work with the low contrast between tissues within the breast. In digital mammography systems, the screen-film is replaced by a series of detectors capable of providing an electronic signal proportional to the X-rays transmitted through the tissue.

A mammographic imaging system can be divided into two important parts: the X-ray tube, responsible for generating X-rays that will penetrate the breast, and the acquisition system, which measures the amount of X-ray transmitted through each region of the breast and reports these values as a matrix of pixels. In this section we explain each part in details.

2.2.1 X-ray tube

The source of X-rays in a mammographic system is the X-ray tube. It consists of a vacuum housing containing a metallic target, called anode, and an electron emitter arrangement called cathode.

Although there are different designs for X-ray tubes, the basic principle for generating this type of energy is the same in every system. Figure 2 shows a general schematic of an X-ray tube.

Inside the tube, a high voltage source (kV) is applied between the cathode and the anode. A low voltage supply heats the cathode, and due to a phenomenon called thermionic emission, electrons are emitted from the cathode and accelerated towards the anode.

Figure 2: General schematic of the X-ray tube. Image extracted from the Handbook of Medical Imaging. (BOONE, 2000)

Once the electrons hit the anode, 99% of its energy is converted into heat and a motor is responsible for rotating the anode to allow each region to refrigerate before it is hit again by the electron beam. The anode is also denoted target, and is a disk-shaped piece of metal, usually built of tungsten or molybdenum (WILKS, 1981).

The remaining energy is converted into X-rays. There are two possible interactions between the electron and the anode atoms that can result in X-rays. In the first one, the electron is diverted from its path by the anode's nucleus, losing some energy in the process. This energy is released as X-rays and originates the bremsstrahlung radiation, which can be literally translated to breaking radiation. Figure 3 shows a schematic of the process and the plot of the quantity of photons at each energy level (YESTER, 2009).

Figure 3: (a) Schematic of the production of Bremsstrahlung radiation. (b) Spectrum of the energy generated. Image extracted from the Handbook of Medical Imaging. (BOONE, 2000)

The second interaction that generates X-rays happens between the electron traveling from the cathode towards the anode and the electrons from the target atoms. When the electron coming from the cathode collides with an electron positioned at the inner

shells of an atom within the anode, this electron can be ejected from the material. If this phenomenon happens, an electron positioned at the outer shells of the atom will fill in the inner shell, and in order to be stable in a lower energy state, the exceeding energy is liberated as X-rays with characteristic energy (HENDEE; RITENOUR, 2003).

This process causes the bremsstrahlung spectrum to spike at some specific energies, called characteristic radiation. Figure 4 shows an illustration of the process along with a plot showing the spikes of characteristic radiation superposed to the bremsstrahlung radiation.

Figure 4: (a) Schematic of the production of characteristic radiation. (b) Spectrum of the energy generated. Image extracted from the Handbook of Medical Imaging, 2000. (BOONE, 2000)

The amount of X-ray radiation (radiation dose), emitted by the X-ray tube is proportional to the area underneath the bremsstrahlung curve, shown in Figure 4 (b). There are a few parameters that can be changed in order to reach different radiation doses. Some of them, as the tube peak voltage kVp, and the target material, will change the shape of the spectrum, therefore changing the area underneath it. The relation between radiation dose and these parameters is not linear, since changing them will change the energy that each photon has (HENDEE, 1999).

The second parameter that can be changed is the exposure. This value is the multiplication between the exposure time in seconds and the current that flows through the system, in Amperes. Differently from the previous parameters, the mAs maintains the shape of the spectrum, therefore it changes linearly with the radiation dose. In practical terms, if we double the mAs value and maintain all the other parameters, the radiation dose will double as well (HENDEE; RITENOUR, 2003).

In clinical practice, the mammographic unit is equipped with a system named Automatic Exposure Control (AEC), which automatically selects optimal acquisition parameters (kVp, target, filter and mAs) for each patient. In AEC, the imaging system controls the exposure by maintaining the pixel value close to an optimal value. Therefore, the best filter, target and kVp are chosen taking into account parameters such as thickness and

density of the breast and the mAs is set by a closed loop control that stops the X-rays emission tube when the desired pixel value is reached (WILLIAMS et al., 2008).

The design of an X-ray tube aims to optimize the quality of the generated X-rays. One example of such optimization is the angled surface of the anode, as noticeable in Figure 2. This small angle (from 7° to 15°) makes the area bombarded by electrons larger, allowing heat dissipation over a larger area. At the same time, the effective focal spot is small on the normal direction towards the object being imaged. This geometric trick is called line-focus principle (BOONE, 2000).

The line-focus principle generates minor problems such as the heel effect. The angled surface of the anode, inside the X-ray tube, causes the x-ray beam intensity to decrease towards the anode side of the field of view, as illustrated by Figure 5.

Figure 5: Illustration of the heel effect. X-rays that cross the entire path through T_a will have higher attenuation if compared to T_c , therefore intensity will decrease towards the anode side of the field. Image extracted from the Handbook of Medical Imaging. (BOONE, 2000)

After colliding against the anode's surface, the electron (e^-) will penetrate the material at an average depth (D_{ave}). The path through the anode's material is larger on the anode side (T_a) if compared to the cathode side (T_c) of the x-ray field. This difference in length results in different filtration of the beam, which causes reduction in x-ray intensity on the anode side of the field. Figure 5 shows the heel effect on a conventional X-ray system, which uses the full range of the X-rays. In digital mammography, half of the beam is used for the imaging process, as shown in Figure 6.

Another phenomenon that happens to the X-rays after they leave the tube is the in-

verse square law. After light is emitted from a source, such as the sun or a light bulb, its intensity decreases proportionally to the square of the distance traveled before being transmitted or reflected by an object. X-ray sources exhibit the same characteristic. Figure 6 illustrates the effect of the inverse square law during the acquisition of mammography (BOONE, 2000).

Figure 6: Illustration of the inverse square law. X-ray beam on the anode side will travel a longer path (D_A) before reaching the detectors, therefore these photons will have lower intensity.

The reason for the intensity to decrease is that the total number of photons emitted by the x-ray source spreads out over a larger area. Therefore, the X-rays that reach the detectors close to the chest wall will have higher intensity since it only went through a path of length D_c , which is shorter than the path of the beam that reaches the opposite side of the field (D_A) (BOONE, 2000).

2.2.2 Flat Panel Detectors

After photons leave the X-ray tube, they can go through various interactions with the breast tissues. Characteristics such as density and thickness will represent different attenuation of the X-rays; therefore photons with different energies will be transmitted by the breast.

In order to be interpreted by radiologists, the remaining energy on each of these photons has to be measured and converted to a visible media. The flat panel detector is responsible for measuring the energy from each photon transmitted through the breast.

Flat panel detectors can be divided into two groups: based on the indirect and direct detection. In the indirect detection, a phosphor layer containing a scintillator screen converts the intensity of X-rays into a different form of energy, such as visible light. The detector panel, made of photosensitive elements, will then be charged electrically on a value proportional to the light intensity. Thus, it is called indirect detection once the

X-rays are transformed into visible light before being detected by the panel. Figure 7 shows a schematic of the indirect detection (YORKSTON; ROWLANDS, 2000).

Figure 7: Indirect detection of X-rays. The incident X-rays excite a phosphor layer which emits light photons. These photons are detected by photosensitive elements. Image extracted from the Handbook of Medical Imaging. (YORKSTON; ROWLANDS, 2000)

The most common technology for the indirect detection is the computed radiography (CR) which uses a CR reader to extract electronic information from a charged phosphor panel.

In the direct detection, a thick layer of photoconductive material, usually amorphous-selenium (a-Se), is in direct contact with an underlying flat-panel. After the X-rays reach the panel, the photoconductive material will be charged electrically; a conductive electrode will collect the charge and store it in a capacitor. Figure 8 shows a schematic of the direct process.(YORKSTON; ROWLANDS, 2000)

Figure 8: Direct detection of X-rays. The incident X-rays electrically charge a photo-conductor layer. A conductive electrode collects the charges and stores them in a capacitor. Image extracted from the Handbook of Medical Imaging. (YORKSTON; ROWLANDS, 2000)

For the direct detection, the most used technologies are the charge-coupled devices (CCD), complementary metal oxide semiconductor (CMOS) and thin-film-transistor (TFT) arrays.

It is important to notice that, in the detection process the signal goes through amplifiers which contain a multiplicative gain, therefore the image reported by the imaging system is proportional to the x-ray intensity transmitted by the breast.

Before any processing is done to the matrix, the image is stored as a raw image, also denoted “for processing”. This image is then processed to enhance the contrast and other parameters, in order to be easily interpreted by the radiologist. The processed image is also denoted “for presentation”.

One important characteristic that all flat panel detectors must provide is uniformity, i.e., detector sensitivity must be the same in each pixel of the image. In practical terms, when a uniform image is acquired by the panel, the pixels reported by the detectors as a matrix must be constant over the entire area of the image. Otherwise, patterns that are not part of the image may affect the correct interpretation of the radiologist. As pointed previously, a few effects such as the inverse square law and the heel effect causes the x-ray incidence to be non-uniform through the field, and such issue must be corrected by the detection panel. The following subsection will explain the method commonly used for correction, called flat-fielding. (YAFFE, 2000)

2.2.3 Flat Fielding

As mentioned previously, it is important that mammography systems provide uniformity in its detection plate. The two subsections presented indicate that some characteristics of the acquisition systems create non-uniformities. The flat fielding process is responsible for changing parameters of the detectors in order to guarantee uniformity.

Uniformity is achieved by exposing a homogeneous block, where each X-ray beam is transmitted with the same attenuation by the material. After acquiring at least two homogeneous masks (for detectors with linear response), the original detector signal is altered to maintain a homogeneous response throughout the field.

During the process, it is important to guarantee that the random realizations of the noise will not alter the results; therefore several flat-fielding images are acquired at each dose and averaged to filter noise components.

2.3 Noise

During the acquisition of a digital mammography, detectors provide an electronic signal which is proportional to the intensity of X-rays transmitted by the breast. This signal is reported as a matrix of values, where each element is a pixel of the image.

Like any other real physical system, a real digital mammography system is not ideal; therefore it has degradation functions that change the final result. Besides, noise is generated from different sources. Figure 9 shows a schematic of a generic image acquisition process, where $f(x, y)$ is the real image, $h(x, y)$ is the degradation function, $\eta(x, y)$ is additive noise and $g(x, y)$ is the resulting image.

Figure 9: Classical model of a generic image acquisition process.

Mathematically, image $g(x, y)$ is given by (GONZALEZ; WOODS; EDDINS, 2003):

$$g(x, y) = h(x, y) * f(x, y) + \eta(x, y) \quad (1)$$

where “*” indicates convolution.

Usually, $\eta(x, y)$ is an additive, signal-independent noise, i.e., it is incorporated to the image as an additive portion of the signal, and its variance and mean do not depend on any aspect of the signal. This noise can follow different statistic distributions, such as Gaussian, Rayleigh, Erlang, etc.

Another type of noise is the non-additive, signal-dependent noise, which cannot be described as an additive portion of the signal, and has one of its parameters, such as the variance, dependent on the signal. This noise can be described as different statistical distributions, such as Poisson and Binomial.

There are a few sources of noise that can be found in digital mammography systems, but the most expressive are the electronic and quantum noise (YOUNG; ODUKO, 2008).

Electronic noise can originate from different sources such as: readout noise and amplifier noise. It is assumed to be additive, signal-independent and follows the statistical Gaussian distribution. The quantum noise originates from the counting nature of the imaging system and respects the Poisson statistical distribution.

In this work we give special attention to the quantum noise, which is the most relevant for this application considering that it is more eminent in low dose mammograms. The next section will give a detailed explanation about this source of noise.

2.3.1 Quantum Noise

Quantum noise, also known as Shot noise, is related to the counting process and follows the Poisson distribution, described by equation 2 (HAIGHT, 1967).

$$Pr_{(N=k)} = \frac{e^{-\lambda t} (\lambda t)^k}{k!} \quad (2)$$

where e is the base of the natural logarithm, λ is the signal mean and t is either a temporal or spatial interval. This type of noise is commonly found in applications where it is important to count a discrete quantity, such as photons in a digital mammography.

The main characteristic that makes the quantum noise difficult to treat is that it is non-additive and signal-dependent. Let X be a discrete random variable, $var(X)$ its

variance and $E(X)$ its expected value. Equation 3 shows the definition of variance for any random discrete variable:

$$\text{var}(X) = E(X^2) - E(X)^2 \quad (3)$$

For a Poisson distribution, the expected value $E(X)$ is equals to the counting number (λ). Also, it is known that:

$$E(X^2) = \sum_{x \in \Omega_x} x^2 \text{Pr}(X = x) \quad (4)$$

Combining equations 2 and 4:

$$E(X^2) = \lambda^2 + \lambda \quad (5)$$

And finally, equations 3 and 5 can be combined resulting in:

$$\text{var}(X) = (\lambda^2 + \lambda) - (\lambda^2) = \lambda \quad (6)$$

Thus, differently from other conventional noise models, quantum noise is signal-dependent, since its variance is dependent on the counting number. Because of this characteristic, the amount of quantum noise found in a mammography depends on the mean pixel value of that image. Also, image quality will depend on the mean pixel value, as shown in equation 7:

$$\text{SNR} = \frac{\lambda}{\sqrt{\lambda}} = \sqrt{\lambda} \quad (7)$$

where SNR is the Signal-to-Noise Ratio and λ is the number of photons counted. As explained previously in this chapter, the image obtained after the acquisition of a mammography has each pixel value proportional to the amount of energy that reach the flat panel detectors. Therefore, if higher radiation dose is used during the exam, the pixel values reported by the detectors are higher. Equation 7 shows that the signal-to-noise ratio of the image is directly proportional to the counting values. Thus, it is correct to affirm that lower radiation dose implies lower image quality. Recent work have shown that mammograms acquired with reduced radiation dose impaired the performance of radiologists on the detection of breast lesions in digital mammography (SAUNDERS et al., 2007; RUSCHIN et al., 2007; TIMBERG et al., 2006).

Taking into account image quality, the ideal image would be the one acquired with the highest radiation dose. However, higher radiation dose also implies higher chances of inducing new cancer cases for the patients (GONZALEZ et al., 2009; MATTSSON; LEITZ; RUTQVIST, 2000; YAFFE; MAINPRIZE, 2011).

Therefore, there is a trade-off between image quality and radiation dose and the commonly applied principle for selecting radiation dose is “as low as reasonably achievably”

(ALARA) (ICRP, 1973). The best operating point is still under discussion, and to validate studies about dose reduction in mammograms, it is necessary to have clinical images acquired with different radiation doses. Such images are difficult to be arranged because it would imply exposing patients to several levels of radiation. To solve this issue, some works propose algorithms capable of simulating dose reduction in clinical mammograms (SAUNDERS; SAMEI, 2003; BATH et al., 2005; KROFT et al., 2006; VELDKAMP et al., 2009; SVALKVIST; BATH, 2010; MACKENZIE et al., 2012; MACKENZIE et al., 2014). The next chapter will present methods of performing this simulation and it will discuss limitations associated with these methods.

State of the art

As mentioned previously, some methods from the literature are focused on simulating different quality parameters for X-ray images. This section presents methods capable of simulating dose reduction in X-ray systems.

3.1 Saunders et al., 2003

This section presents the method proposed by (SAUNDERS; SAMEI, 2003). It is capable of simulating images with quality parameters that respect a desired behavior, measured by the modulation transfer function (MTF) and by the noise power spectrum (NPS).

To do so, two routines are created. One of them is responsible for modifying the spatial resolution of an ideal super-sampled input image, and the second is responsible for inserting noise.

Modification of the spatial resolution is responsible for blurring the super-sampled image using information contained in the system MTF. Then, the blurred image is reduced to a smaller size that account for the sampling process of the digital acquisition system.

Noise is created by filtering the frequency components of a white Gaussian unitary noise mask. The filter is created using information from the one-dimensional NPS given as input. Noise is then incorporated to the image by a running ROI that creates dependency between noise and signal.

This method was created to be applied to synthetic images, therefore it assumes a noiseless image as input, which cannot be provided in clinical applications. Furthermore, the one-dimensional radially symmetric NPS does not account for the anisotropic behavior of the noise found in digital mammograms. Thus, the method is not appropriate to be applied to clinical mammographic images.

3.2 Båth et al., 2005

This section will present the main characteristics and comments on the method proposed by (BATH et al., 2005). It is based on the noise power spectrum and extracts all noise information from it.

The algorithm takes into account a few assumptions hereby described. The first one is that the NPS is enough to describe the noise of an image. Therefore, two images containing the same NPS will present the same noise characteristics. Such assumption is truthful as long as we consider the ergodicity of the system, i.e., the spatial average of the signal is equivalent to its temporal average.(BATH et al., 2005)

The second assumption is that the modulation transfer function (MTF) and the detective quantum efficiency (DQE) are both invariant to radiation dose. The last assumption is that the system is linear, with the mean pixel value varying linearly with the radiation dose.

Using the flat fielding images the method calculate the NPS that must be added to the original image in order to reach the simulated radiation dose.

The noise mask is created by filtering a mask of Gaussian noise with unity variance at the frequency domain. The NPS calculated previously is the filter used for such operation. The last step is to create dependency between the signal and the noise mask created previously, since the noise present in digital mammograms is mostly signal-dependent and non-additive. The dependency is created by multiplying the image by a factor which is function of the mean pixel value.

The validation presented by the authors is the comparison between the NPS of the simulated image and of the real image acquired at the simulated dose. Although the NPS presented by the authors matches the NPS of a real image, it does not represent the spatial dependency of the noise, i.e., even though both NPS are very similar, we cannot guarantee that there will be no local differences if both images were analyzed in the spatial domain.

Furthermore, the method is based on the assumption that the DQE is constant over dose variations. In digital mammography, such assumption can be questioned, since noise has a relevant influence on the DQE when operating with low radiation doses.

3.3 Kroft et al., 2006

A few years later, (KROFT et al., 2006) argued that in order to be clinically useful, the noise simulation algorithm has to be simple, therefore questioning the use of NPS for simulating dose reduction.

With this argument, the authors proposed a method which simulates dose reduction by inserting noise on a pixel-to-pixel basis. Reduced dose images are simulated by digitally

adding zero-mean Gaussian white noise with standard deviation depending on the original pixel value.

However, as shown by the authors themselves (VELDKAMP et al., 2009), although the simulated images have the same local standard deviation as real images, they have different NPS. Since the standard deviation is not a good metric of the image noise when comparing images with different NPS (BURGESS, 1999), the clinical application of such method can be questioned.

3.4 Svalkvist et al., 2010

In (SVALKVIST; BATH, 2010), the authors presented a modification of the method proposed (BATH et al., 2005) which accounts for DQE variations over different doses.

The authors argued that due to the low radiation doses used in digital tomosynthesis, variations on the DQE cannot be discarded and may exert great influence on the noise behavior.

Although the new algorithm accounts for DQE variations over dose reductions, the authors themselves identified that the method is not capable of simulating local fluctuations on the noise variance, caused by the different pixel gain adjusted during the flat fielding process. In digital mammography such fluctuations are important and may exert influence on the resulting image.

Anscombe Transformation

The Anscombe transformation is a variance-stabilizing transformation that converts a random variable with Poisson distribution into an approximately Gaussian distribution, with unity variance (ANSCOMBE, 1948). Let the degraded image, $g(x,y)$, at coordinates x and y , be the random variable. Thus, the Anscombe transformation applied on $g(x,y)$ is given by the following:

$$A\{g(x,y)\} = 2\sqrt{g(x,y) + \frac{3}{8}} \quad (8)$$

Such transformation is commonly explored in the field of image denoising, where a noisy image $g(x,y)$ is filtered in the Anscombe domain using filters designed to treat Gaussian signal-independent noise (MASCARENHAS; SANTOS; CRUVINEL, 1999; ROMUALDO et al., 2013). Equation 8 can be represented by the following additive model (MASCARENHAS; SANTOS; CRUVINEL, 1999):

$$A\{g(x,y)\} = 2\sqrt{g(x,y) + \frac{1}{8}} + v(x,y) \quad (9)$$

where $v(x,y)$ is the additive term, which is signal-independent. If the direct inverse transformation is applied to the image, it will return a biased result due to the non-linearity of the transformation. Therefore, an algebraic inverse transformation was proposed by Anscombe (ANSCOMBE, 1948):

$$g(x,y) = \frac{G(x,y)^2}{4} - \frac{1}{8} \quad (10)$$

where $G(x,y)$ is a variable in the Anscombe domain and $g(x,y)$ is the same variable in the spatial domain. The algebraic inverse transformation still presents a biased result for small counting values ($\lambda < 10$), as shown by the author (ANSCOMBE, 1948). The transformation is considered asymptotically unbiased.

Since several applications of the Anscombe transformation have limited counting values and require the inverse transformation to be exact, recent work proposed a new version

of the Anscombe transformation (MAKITALO; FOI, 2011). The new version is unbiased even for small counting values. Although counting values are considerably high in mammography images ($\lambda \gg 10$), in this work we used the unbiased exact inverse, available at the author's webpage (MAKITALO; FOI, 2011).

Figure 10 shows an example where a synthetic image containing three distinct regions with different gray levels is contaminated by Poisson noise. After applying the Anscombe transformation to the noisy image and the noiseless image, we perform the subtraction in the Anscombe domain. The remaining noise mask follows the Gaussian distribution, is uniform, signal independent and has unity variance.

Figure 10: Application of the Anscombe transformation: converts a signal-dependent non-additive Poisson noise into a signal-independent additive Gaussian noise. Top: Residual noise before application of the Anscombe transformation. Center-left: Noiseless synthetic image. Center-right: Image contaminated with Quantum noise. Bottom: Residual Gaussian noise obtained after the Anscombe transformation.

Table 1 reports the local variance measured before and after the Anscombe transformation was applied to the synthetic image with three distinct regions presented in Figure 10 (Center-right).

Table 1: Comparison between the pixel variance in images from Fig. 10, calculated before and after the application of the Anscombe transformation.

Region	Number of photons (λ)	Spatial domain (Variance)	Anscombe Domain (Variance)
I	60,000	60,000	1.03
II	30,000	30,000	1.02
III	1,000	1,000	1.03

Methods and Materials

The first subsection of this chapter consists of a preliminary analysis that provides information about the spatial dependency of the noise to allow a more accurate simulation of the radiation dose reduction. Next section will present the new method proposed by the authors. Each step of the method is explained in details and illustrative schematics are presented at the end of each subsection, to allow better comprehension of the method.

5.1 Noise characteristics in digital mammography

As evidenced in chapter 2, the intensity of the X-ray beam that reaches the detectors throughout the detector field is non-uniform, caused mainly by the heel effect and the inverse square law. The flat fielding process is capable of correcting such non-uniformities by changing some of the detector parameters. Therefore, the average mean pixel of a homogeneous image acquired after the flat-fielding is approximately uniform.

However, at the same time that the flat fielding corrects the mean pixel value of the homogeneous image, it also scales the noise in the image, which is mostly signal-dependent as explained in chapter 2.

Thus, in this work we made a preliminary investigation of the effect of the flat fielding process on the image noise and how it creates spatial dependency. To do so, homogeneous images were acquired and analyzed by a square ROI that runs through the image. Local variance, mean and the relation between mean and variance were calculated to allow better interpretation of the noise behavior, also supporting the development of the proposed method.

5.2 Novel simulation method

Let Y_o be a clinical mammogram at coordinates x and y , acquired using the automatic exposure mode. In order to simulate a low-dose mammogram (Y_{sim}) acquired at the simulated dose D_{sim} it is necessary to acquire two homogeneous images (H_o and H_{sim}) at

the original and simulated doses respectively. The homogeneous images allow to calculate how much noise must be added to each pixel of the original dose image before it reaches the noise from a lower-dose acquisition.

The proposed method consists of three steps. In the first step, all images are linearized and the ones acquired at the original dose are scaled by the dose reduction factor. Second step is used to simulate the noise distribution for each pixel of the image, using local information extracted from both homogeneous images acquired in the mammography machine. Lastly, dependency is created between the simulated noise and the clinical image acquired using the standard radiation dose to generate an image as if it were acquired using lower radiation dose.

Each processing step from this method was developed assuming that the input images are in the raw format. Figure 11 shows an overview of the proposed method:

Figure 11: Overview of the method proposed in this work.

This section will be divided into three sub-sections where each step of the algorithm will be explained with more details. Indexes L, S and A indicate linearized, scaled and variable in the Anscombe domain, respectively.

5.3 Linearization and scaling

Changes in the radiation dose used for imaging cause changes in the overall brightness of the image; therefore initially we need to adjust the gray level of the clinical mammogram.

If we consider an X-ray system where the radiation dose is the input variable and the mean pixel value is the output, it is possible to scale the gray level of an image acquired by this equipment as long as the relation between these quantities is linear.

Although the relation between radiation dose and mean pixel value usually have a non-linear behavior in digital mammography, it is possible to linearize this relation (BATH et al., 2005). One simple way to correct this problem is subtracting the offset value

from the image. To find the offset it is necessary to acquire at least two homogeneous images at different radiation doses using the equipment to be simulated. Then, we must calculate a linear regression to find the relation between dose and mean pixel value of the homogeneous images. The constant term of the regression is the photo-detector offset.

Equation 11 shows the generic form of a linear regression, where $\bar{Y}$ is the mean pixel value of the image, m is the angular coefficient of the relation, D is the radiation dose at which the image was acquired and θ is the constant term.

$$\bar{Y} = mD + \theta \quad (11)$$

Equation 12 describes how to linearize an image $Y(x, y)$.

$$Y^L(x, y) = Y(x, y) - \theta \quad (12)$$

Where $Y^L(x, y)$ is the linearized image, $Y(x, y)$ is the original image and θ is the detector offset.

After linearizing the image, it is possible to scale the gray level to simulate the distribution of an image acquired at lower radiation dose. Thus, to scale a linearized image every pixel must be multiplied by a constant term hereby denoted reduction rate (α). This constant can be calculated by the expression presented on equation 13.

$$\alpha = \frac{\sum_{i=1}^M \sum_{j=1}^N H_{sim}^L(i, j)}{\sum_{i=1}^M \sum_{j=1}^N H_o^L(i, j)} \quad (13)$$

Where M and N are the dimensions of the homogeneous images, $H_{sim}^L(x, y)$ and $H_o^L(x, y)$ are the linearized homogeneous images acquired at the simulated and original doses, respectively. Therefore, the linearized scaled image, $Y^{L,S}(x, y)$, is given by:

$$Y^{L,S}(x, y) = \alpha.Y^L(x, y) \quad (14)$$

Since this work is based on the assumption that the Modulation Transfer Function (MTF) (CUNNINGHAM, 2000) does not change with dose, there is no need for further processing of the signal itself, only the addition of noise has to be done. Such assumption is discussed on the discussion section. Figure 12 summarizes all the processing done in this step.

5.3.1 Noise calculation

The next step is to calculate the noise to be added to the scaled image. The most intuitive way of simulating noise would be adding signal-dependent Poisson noise using local statistics of the signal. However, as shown by (VELDKAMP et al., 2009), such method

Figure 12: Overview of the linearization and scaling process where $Y_o(x, y)$ is the full dose mammogram, $H_o(x, y)$ and $H_{sim}(x, y)$ are the homogeneous images acquired at full dose and simulated dose, respectively, and the indexes L and S indicate linearized and scaled images, respectively. θ is the detector offset as calculated from equation 11 and α is the reduction rate as calculated in equation 13.

is not accurate when analyzed in the frequency domain. This error is associated with the bias added by the noise to the local statistics, since the image acquired with the AEC is not a good approximation of the noiseless signal.

Since clinical mammograms are not noiseless, it is vital to have information about the amount of noise present in an image acquired by that particular system which will be simulated. Using a homogeneous image exposed with the same parameters as the clinical image it is possible to have a good approximation of the amount of noise present in the clinical exam.

Another challenge is to measure the amount of noise present in the low dose configuration. Again, this information can be extracted from a homogeneous image acquired at the simulated radiation dose.

Due to the flat fielding process, noise in a mammogram is also a function of the spatial position. Thus, noise must be simulated locally.

Expected local standard deviation of the noise to be added to the original image is calculated by the following expression:

$$\sigma_{sim}(x, y) = \sqrt{\sigma_a^2(x, y) - \sigma_b^2(x, y)} \quad (15)$$

where $\sigma_{sim}(x, y)$ is the expected local standard deviation of the noise, $\sigma_a^2(x, y)$ and $\sigma_b^2(x, y)$ are the variance masks calculated locally using a square window that runs through H_{sim}^L and $H_o^{L,S}$ respectively.

To create the noise mask, randomly generated Gaussian noise with zero mean, unity variance and the same size as the clinical image is multiplied by the standard deviation calculated using equation 15. Next step is to add the noise mask to the scaled clinical mammogram $Y_o^{L,S}$ in order to reach the intended results.

Although adding the calculated noise to the clinical scaled mammogram would be the simplest way to incorporate the noise to the signal, two problems are associated with this

practice. First, the quantum noise present in digital mammograms is signal dependent, i.e., its local variance depends on the local mean of the signal. The noise calculated in this step only depends on the local signal of a homogenous image, thus dependency must be created between the noise mask and the clinical mammography before adding them together. Also, quantum noise is a non-additive noise; therefore it cannot be added to the signal in the spatial domain.

The following section will present the new approach proposed by this work for creating signal-dependency of the noise and to create additivity between noise and signal. Figure 13 shows an overview of the noise creation process.

Figure 13: Overview of the noise creation process where $H_o^{L,S}(x,y)$ is the homogeneous image acquired with full dose after linearization and scaling; $H_{sim}^L(x,y)$ is the homogeneous image acquired with the simulated dose after linearization and $\sigma_{sim}(x,y)$ is the standard deviation mask as calculated from equation 15. $N(x,y)$ is the noise mask modulated by $\sigma_{sim}(x,y)$.

5.3.2 Signal-dependency and additivity

As pointed previously, the noise calculated so far is signal independent and non-additive; therefore it cannot be simply added to the image in the spatial domain.

As shown in Figure 10, the Anscombe transformation is capable of converting a signal-dependent non-additive noise into a signal-independent additive noise. In this work the authors propose the use of the Anscombe transformation in a different approach, using its properties to create dependency between a signal-independent noise and an image. The new approach consists on adding signal-independent noise to the image in the Anscombe domain and applying the inverse transformation afterwards. Figure 14 shows a schematic of the new application.

Let $Im(x,y)$ be the noiseless original image and $\eta(x,y)$ be a mask of signal-independent noise. The image contaminated by signal-dependent noise, $Im_{Noisy}(x,y)$, is given by equation 16. In the particular case when $\eta(x,y)$ is a Gaussian signal-independent mask with unity variance and zero mean, the inserted noise will follow the Poisson distribution.

$$Im_{Noisy}(x,y) = A^{-1} \{A \{Im(x,y)\} + \eta(x,y)\} \quad (16)$$

Figure 14: Novel application for the Anscombe transformation.

When the Anscombe transformation is applied to a signal, Poisson noise is converted into additive signal-independent noise (ANScombe, 1948). Therefore, once in the Anscombe domain, the noise mask can be added to the signal. After applying the inverse transformation, the dependency between noise mask and signal is also created and the resulting image has a similar behavior as a low-dose mammogram.

The first step to add the noise mask and create dependency between it and the scaled clinical mammogram is applying the Anscombe transformation to both images, using equation 8.

However, the Anscombe transformation must be applied to a signal contaminated with noise, and the noise mask calculated previously does not contain a signal incorporated (ANScombe, 1948). Therefore, to allow the correct use of the Anscombe transformation, a positive DC signal has to be added to the noise mask prior to the application of the transformation. The added signal is the mean pixel value of the homogeneous image acquired at the simulated dose ($H_{sim}^L(x, y)$). Once in the Anscombe domain, it is necessary to subtract the homogeneous DC signal added previously to get only the noise mask. Equation 17 presents the mathematical expression for the process.

$$N^A(x, y) = A \left\{ N(x, y) + A(\bar{H}_{sim}^L) - A \left\{ \bar{H}_{sim}^L \right\} \right\} \quad (17)$$

Where $\bar{H}_{sim}^L$ is the mean pixel value of the linearized homogeneous image acquired at the simulated dose, $N(x, y)$ is the noise mask calculated as shown in Figure 13, A indicates the Anscombe transformation and $N^A(x, y)$ is the noise mask in the Anscombe domain.

After that, the noise mask and the linearized scaled clinical image can be added together to generate an image with additive Gaussian noise in the Anscombe domain. This image is approximately the image obtained if the Anscombe transformation were applied to a mammographic image acquired with lower radiation dose. Thus, the next step for our method is to apply the inverse Anscombe transformation to that image in order to obtain the simulated image in the spatial domain. Figure 15 shows an overview of the process.

Finally, the last step of the method is adding the offset back to the image, to guarantee

Figure 15: Novel method for creating dependency between noise and signal, where $Y_o^{L,S}(x,y)$ is the clinical mammogram acquired with full dose after linearization and scaling process, $N(x,y)$ is the noise mask calculated previously, $(\bar{H}_{sim}^L)$ is the mean pixel value of the homogeneous image acquired with the simulated dose.

the same behavior as a clinical image, as shown in equation 18.

$$Y_{sim}(x,y) = Y_{sim}^L(x,y) + \theta \quad (18)$$

5.4 Materials

To assess the performance of the simulation method proposed in this work a set of FFDM images was acquired using an anthropomorphic breast phantom, prototyped by CIRS, Inc. (Reston, VA) with a license from the University of Pennsylvania (COCK-MARTIN et al., 2014). Four different exposure configurations (6.05 mGy, 5.29 mGy, 4.53 mGy and 3.02 mGy) were used to validate the simulation method.

A few reasons justify why a physical phantom was chosen to validate this work. First, the physical phantom allows repeated exposures at different radiation levels without putting the patient's health at risk due to excessive exposure to radiation. Also, using the incompressible physical phantom properly fixed would guarantee that the breast will stay still throughout the experiment, avoiding the need for image registration. Lastly, physical phantoms are subjected to the clinical image acquisition process, therefore every noise characteristic found in the image of the physical phantom is found in a clinical situation. In digital phantoms, the exposure process is simulated using a mathematical model; therefore the noise behavior is simulated and might have slight differences when compared to a clinical exposure.

The breast phantom consists of six slabs, each containing simulated anatomical structures manufactured using tissue mimicking materials, based upon a realization of the companion breast software phantom (POKRAJAC; MAIDMENT; BAKIC, 2012). The phantom simulates a 450 ml breast, compressed to 5 cm, with 17% volumetric breast density (excluding the skin). In addition to the normal breast anatomy, individual pieces of calcium oxalate (99%, Alfa Aesar, Ward Hill, MA), with different sizes were placed between slabs of the phantom to mimic a cluster of microcalcifications. Figure 16 shows a photograph of all slabs of the anthropomorphic breast phantom used in this study.

Figure 16: Slabs of the physical phantom used in this work.

A set of phantom images was acquired using a clinical machine (Selenia Dimensions, Hologic, Bedford, MA) from the hospital of the University of Pennsylvania. First, we acquired one FFDM image of the phantom using the automatic exposure control mode (AEC) of the clinical machine. This acquisition provides us with all the optimized parameters automatically set for this phantom. Then, we switched to manual mode and acquired 4 sets of images, containing 5 images each, using the same kVp and target/filter combination as provided by the AEC mode but changing the exposure time in steps ranging from the original value (standard dose) to half of the standard dose. Each of these sets had a different exposure resulting in different radiation doses: 6.05 mGy, 5.29 mGy, 4.53 mGy and 3.02 mGy. These doses correspond to 100%, 87.5%, 75% and 50% of the standard dose provided by the AEC mode for this particular breast phantom. Figure 17 shows one exposure example for each radiation dose.

Each exposure configuration was set once again in manual mode, but this time the physical phantom was replaced by a Hologic flat fielding block, i.e., a 4 cm thick acrylic block commonly used for the flat-fielding process. Two homogeneous images were acquired for each combination of exposure parameters.

All images acquired by the AEC mode were used as input for the method and generated reduced dose simulated mammograms. Thus, we created two image datasets; one of them containing 20 clinical images acquired at 4 different radiation doses, and the other one containing 15 simulated images, at 3 different radiation levels. All images are in the raw (“for processing”) format and are stored using 16 bits per pixel, but only 14 bits are used. The images dimensions are 4096 pixels for the height and 3328 pixels for the width.

The validation was performed by comparing simulated images to clinical images acquired at the simulated radiation dose.

Figure 17: Examples of phantom images. The rectangle evidences the area used for calculating metrics, avoiding biased results from the background.

5.5 Metrics

Evaluation metrics used to compare real and simulated images were chosen taking into account two characteristics of the image: gray level distribution and noise. Since both gray level and noise depends on the position of the pixel in the field, metrics were calculated locally inside a 14.3×3.5 cm ROI containing the breast, to avoid false statistics from the background, as shown in Figure 17.

Normalized Noise Power Spectrum (NNPS) was used to analyze noise at the frequency domain. Each dose reduction was plotted to allow visual evaluation of the similarity between simulated and clinical images. A t-student test was performed and the p-value showed the statistical difference between spectra. Relative error is reported in Table 3.

A 0.45×0.45 cm non-overlapping square mask was used to calculate the mean pixel value and the variance from both simulated and clinical images. Each point was plotted in a graph to allow visual comparison of the results and a t-student test was performed to detect statistical difference between real and simulated images. Relative error reported in Tables 4 and 5 was calculated to quantify similarity between images.

Comparisons between simulated and real image sets were performed using the method shown in Figure 18 in which each simulated image is compared to each clinical image, generating more statistically relevant data.

Figure 18: Method used for crossed comparison between simulated and real images.

Results

This section will be divided into three subsections. In the first one, we present the results of the noise analysis performed prior to the development of the method. The second subsection reports the results obtained after empirical test of the novel application of the Anscombe transformation, proposed by the authors of this work. The last subsection will present all the results obtained using the simulation method proposed in this work.

6.1 Noise analysis

Preliminary investigation of the noise was performed using homogenous images. This subsection reports the results obtained after analyzing the noise that contaminated different homogeneous images acquired at different radiation doses. It also supports the development of a novel simulation method.

6.1.1 Local mean

In this section we present the local mean pixel value calculated on a squared full-overlapping 64×64 pixels (0.45×0.45) cm ROI that runs through each the image. Figure 19 reports the results as 3D plots containing each spatial coordinate at which the central pixel of the ROI is positioned, and the mean pixel value calculated in that region.

Notice that the response of the system is uniform, as explained in chapter 2. If the flat-fielding process were not applied to the system, results would have shown a great difference in value between pixels located close and far from the chest wall.

6.1.2 Local variance

In this section we present the local variance calculated using the same ROI as previously. Figure 20 reports the results as 3D plots containing each spatial coordinate at which the central pixel of the ROI is positioned, and the variance calculated in that region.

Figure 19: Local mean at different doses.

Figure 20 evidence that the variance increases considerably when the analyzed pixel is distant from the chest wall in the X direction. In the discussion section we present an explanation for this behavior and its consequences while simulating dose reduction.

6.1.3 Local variance/mean ratio

The graphs shown in Figure 21 report the ratio between local noise variance and local mean pixel value at different radiation doses.

Equation 6 indicates that a homogeneous image contaminated by Poisson noise would have a constant ratio equals to one. However, it is noticeable from observation of Figure 21 that the ratio between noise variance and mean pixel value ranges from 0.1 to 0.3. Moreover, this ratio depends on the position along the field. This effect happens due to the flat fielding adjustment discussed in chapter 2. In the discussion section we present a discussion about this behavior. At any rate, this behavior supports the importance of using a method for simulating dose reduction that is locally adaptive, as the one we are proposing in this work.

Figure 20: Local variance at different doses.

6.2 Preliminary test of the Anscombe transformation

As a preliminary empirical test of the method presented in Figure 14 we created a 512×512 pixels synthetic image containing three distinct regions with different gray levels. Each region simulated a counting process with different mean (λ).

The Anscombe transformation was applied to the synthetic image and a Gaussian signal-independent mask with zero mean and unity variance was added to the image in the Anscombe domain.

After applying the inverse transformation, dependency was created between the noise mask and the signal. Figure 22 shows a schematic containing the results of the process described previously.

Table 2 shows the variance from each region of Figure 22 (bottom), along with the number of photons detected in that region (λ) and the expected theoretical standard deviation for a Poisson distribution, calculated using equation 6. (HAIGHT, 1967)

Data from Table 2 indicates that the new application of the Anscombe transformation as proposed in this work is capable of contaminating a noiseless image with signal-dependent noise.

Figure 21: Local ratio between mean and variance at different doses.

Table 2: Comparison between theoretical variance and measured variance obtained using the inverse Anscombe transformation to convert Gaussian signal-independent noise into Poisson signal-dependent noise.

Region	Number of photons (λ)	Measured Variance	Expected Variance (Equation 6)
I	60,000	60,240	60,000
II	30,000	29,915	30,000
III	1,000	1,001	1,000

6.3 Photo-detector offset

The first step for the evaluation of the new method was calculating the photo-detector offset. To calculate the value, 4 different doses were used and the relation between mean pixel value and entrance dose was represented by a linear regression. To calculate the linear regression, the mean pixel value was calculated at 207 different regions of the homogeneous images using a 64×64 pixels window, totalizing 1656 measured points. Figure 23 shows the results.

It is important to notice from Figure 23 that the offset for the machine used in this study is approximately 44. Although the manufacturer of the mammographic unit we used in our experiments estimates the offset to be around 50 (STRUDLEY; YOUNG, 2013),

Figure 22: Top-left: Synthetic noiseless image. Top-center: Gaussian signal-independent noise (zero mean and unity variance). Top-right: Noisy image. Bottom: Poisson signal-dependent noise mask. Contrast and brightness were improved for better visualization.

Figure 23: Linear regression of the relation between mean pixel value and entrance dose. The linear coefficient is important for the linearization process.

it is important to experimentally calculate this value to guarantee the correct linearization of the images.

6.4 Method evaluation

Examples of simulated and real images are shown in Figure 24. It shows a magnified view of a region of interest extracted from real and simulated images at two radiation doses: 5.29 mGy and 3.02 mGy. The magnified view allows better visualization of the noise in each image. Along with the ROIs are the residual noise masks calculated by subtracting the noiseless signal from each image. The noiseless signal was approximated by averaging 5 realizations for each dose.

Figure 24: Top-line: magnified view of a region of interest extracted from real and simulated images. Bottom-line: residual noise calculated for real and simulated images.

Visual analysis of Figure 24 evidence that simulated and real images are very similar. However, it is important to use appropriate metrics to evaluate the proposed method objectively.

6.4.1 Normalized noise power spectrum

Local metrics such as mean and variance are not good measurements of similarity when comparing X-ray images with distinct noise power spectra. (BURGESS, 1999) Thus, the first metric used for evaluating the performance of the proposed method is the normalized power spectrum (NNPS).

The NNPS allowed better comprehension of the noise behavior in the frequency domain. Figure 25 allows visual comparison between NNPS at different doses for clinical and simulated images.

As expected, lower radiation doses resulted in images with higher NNPS, meaning that the signal-to-noise ratio is decreasing. We performed cross comparison between real and simulated images resulting in Table 3. For the NNPS a regular non-overlapping 128×128 (0.90×0.90) cm window was used, resulting in 1,600 comparisons per dose, 4,800 in total.

Table 3: Comparison between normalized power spectrum for the simulated and clinical images acquired at 3 different doses and the p -value from a t -student test to check if the samples are statistically different.

Image		5.29 mGy		4.53 mGy		3.02 mGy	
Simulated	Real	Error (%)	p -values	Error (%)	p -values	Error (%)	p -values
1	1	2.79 ± 1.88	0.9894	2.39 ± 1.92	0.9895	2.46 ± 2.05	0.9754
1	2	2.89 ± 1.97	0.9845	2.65 ± 1.78	0.9873	2.56 ± 2.14	0.9770
1	3	2.88 ± 2.03	0.9859	2.39 ± 1.93	0.9867	2.33 ± 1.89	0.9769
1	4	2.78 ± 2.01	0.9841	2.99 ± 1.55	0.9861	2.27 ± 1.41	0.9780
1	5	2.76 ± 1.37	0.9820	2.92 ± 1.54	0.9855	2.45 ± 2.16	0.9761
2	1	2.74 ± 1.88	0.9929	2.36 ± 1.99	0.9931	2.52 ± 1.98	0.9793
2	2	2.76 ± 1.78	0.9879	2.37 ± 1.93	0.9909	2.31 ± 2.29	0.9808
2	3	2.51 ± 2.07	0.9893	2.26 ± 1.67	0.9903	1.81 ± 2.06	0.9808
2	4	2.55 ± 1.75	0.9876	2.89 ± 1.77	0.9897	2.01 ± 1.51	0.9818
2	5	2.53 ± 1.84	0.9854	2.71 ± 2.06	0.9890	1.93 ± 2.31	0.9799
3	1	2.60 ± 1.95	0.9946	2.31 ± 1.83	0.9949	2.07 ± 1.70	0.9811
3	2	2.68 ± 1.70	0.9897	2.17 ± 1.53	0.9927	2.15 ± 1.35	0.9820
3	3	2.37 ± 1.63	0.9911	2.05 ± 1.65	0.9921	2.03 ± 1.12	0.9826
3	4	2.22 ± 1.53	0.9893	2.64 ± 1.81	0.9915	2.16 ± 1.25	0.9836
3	5	2.60 ± 1.61	0.9872	2.25 ± 1.74	0.9908	2.13 ± 1.54	0.9818
4	1	2.57 ± 1.75	0.9944	2.09 ± 2.18	0.9947	2.10 ± 1.74	0.9809
4	2	2.32 ± 1.80	0.9895	2.01 ± 2.38	0.9925	1.86 ± 1.53	0.9825
4	3	2.00 ± 1.89	0.9909	1.62 ± 1.96	0.9919	1.91 ± 1.61	0.9824
4	4	1.96 ± 1.36	0.9891	2.21 ± 1.93	0.9913	1.77 ± 1.33	0.9834
4	5	2.27 ± 1.60	0.9870	2.14 ± 2.07	0.9906	2.45 ± 1.72	0.9816
5	1	2.27 ± 1.91	0.9931	2.39 ± 2.06	0.9933	1.84 ± 1.63	0.9796
5	2	2.19 ± 1.65	0.9881	2.38 ± 1.90	0.9911	2.51 ± 1.41	0.9812
5	3	2.20 ± 2.15	0.9895	2.34 ± 1.65	0.9905	2.06 ± 1.56	0.9811
5	4	2.20 ± 1.80	0.9877	2.86 ± 1.61	0.9899	1.91 ± 1.47	0.9821
5	5	2.07 ± 1.52	0.9856	2.59 ± 2.18	0.9893	2.20 ± 1.57	0.9803
Averaged error		2.47 ± 1.78	-	2.41 ± 1.88	-	2.15 ± 1.69	-

The averaged error for the NNPS is lower than 2.5% in every comparison and the reported p -values are much higher than 0.05, showing that there is no statistical difference between simulated and real images. Since we found no statistical difference between NNPS for simulated and real images, the following sections will report metrics calculated in the spatial domain in order to evaluate locally the simulated noise along the image.

6.4.2 Local mean

To assess the performance of the linearization and scaling process it is important to compare the similarity of the gray level distribution between real and simulated images.

A regular non-overlapping 64×64 (0.45×0.45) cm window was used to calculate the local mean pixel value (as explained in section 5.5). Figure 26 shows lines as representative of the clinical images at different doses, averaged with 5 different realizations. Markers represent the average between 5 simulated images.

Table 4 reports the relative errors between clinical and simulated images. In each realization the error was calculated at 256 squared regions, totalizing 6,400 comparisons per dose, 19,200 in total. Table 4 also contains the p -values from a t -test comparing local mean pixel values from real and simulated mammograms of each dose.

Table 4: Comparison between local mean pixel value for the simulated and clinical images acquired at 3 different doses and the p -value from a t -student test to check if the samples are statistically different.

Image		5.29 mGy		4.53 mGy		3.02 mGy	
Simulated	Real	Error (%)	p -values	Error (%)	p -values	Error (%)	p -values
1	1	0.80 ± 0.19	0.5567	0.78 ± 0.19	0.5609	0.64 ± 0.26	0.6199
1	2	0.34 ± 0.21	0.8164	0.38 ± 0.19	0.7861	0.69 ± 0.27	0.5943
1	3	0.40 ± 0.22	0.7780	0.43 ± 0.19	0.7555	0.62 ± 0.27	0.6330
1	4	0.35 ± 0.23	0.8093	0.41 ± 0.20	0.7656	0.51 ± 0.27	0.7020
1	5	0.31 ± 0.22	0.8373	0.37 ± 0.21	0.7904	0.55 ± 0.27	0.6761
2	1	1.21 ± 0.16	0.3683	1.18 ± 0.16	0.3715	1.02 ± 0.22	0.4185
2	2	0.74 ± 0.18	0.5862	0.77 ± 0.16	0.5597	1.07 ± 0.24	0.3976
2	3	0.81 ± 0.19	0.5524	0.83 ± 0.16	0.53307	1.00 ± 0.24	0.4290
2	4	0.75 ± 0.20	0.5798	0.81 ± 0.17	0.5416	0.88 ± 0.24	0.4866
2	5	0.71 ± 0.20	0.6047	0.77 ± 0.18	0.5633	0.93 ± 0.24	0.4648
3	1	1.25 ± 0.15	0.3501	1.22 ± 0.14	0.3532	1.06 ± 0.14	0.3988
3	2	0.78 ± 0.16	0.5626	0.82 ± 0.14	0.5366	1.11 ± 0.14	0.3784
3	3	0.85 ± 0.17	0.5294	0.87 ± 0.14	0.5105	1.04 ± 0.14	0.4090
3	4	0.80 ± 0.18	0.5563	0.85 ± 0.16	0.5190	0.92 ± 0.16	0.4651
3	5	0.75 ± 0.18	0.5808	0.81 ± 0.16	0.5402	0.97 ± 0.16	0.4438
4	1	1.30 ± 0.14	0.3322	1.27 ± 0.14	0.3352	1.11 ± 0.14	0.3792
4	2	0.83 ± 0.16	0.5390	0.86 ± 0.14	0.5136	1.15 ± 0.14	0.3595
4	3	0.90 ± 0.17	0.5065	0.92 ± 0.14	0.4881	1.09 ± 0.14	0.3892
4	4	0.84 ± 0.18	0.5328	0.90 ± 0.15	0.4963	0.97 ± 0.15	0.4436
4	5	0.80 ± 0.18	0.5567	0.86 ± 0.16	0.5170	1.01 ± 0.16	0.4229
5	1	1.36 ± 0.12	0.3074	1.33 ± 0.12	0.3103	1.17 ± 0.12	0.3522
5	2	0.89 ± 0.14	0.5059	0.93 ± 0.12	0.4813	1.21 ± 0.12	0.3333
5	3	0.96 ± 0.15	0.4745	0.98 ± 0.12	0.4567	1.15 ± 0.12	0.3616
5	4	0.91 ± 0.16	0.4999	0.96 ± 0.13	0.4646	1.03 ± 0.13	0.4138
5	5	0.86 ± 0.16	0.5231	0.92 ± 0.14	0.4847	1.07 ± 0.14	0.3939
Averaged error		0.82 ± 0.18	-	0.85 ± 0.16	-	0.96 ± 0.23	-

It is important to observe that the averaged relative error is lower than 1% and the p -value yielded high values, indicating no statistical difference between simulated and real images at level $p < 0.05$, as p exceeded 0.05 in every comparison.

6.4.3 Local variance

Using the same 64×64 (0.45×0.45) cm window we calculated the local variance of the image noise and plotted the different regions in the graph shown in Figure 27 (as explained in section 5.5).

Similarly to the previous image, in Figure 27 lines represent clinical images acquired at different doses while markers identify the variance obtained after simulating dose reduction. Each point is the average of five different realizations.

Again we performed cross comparison between clinical and simulated images. A total of 19,400 comparisons were averaged and reported at Table 5, along with the resulting p -values from a t -test comparing local variance from real and simulated mammograms for each dose.

Table 5: Comparison between local variance for the simulated and clinical images acquired at 3 different doses and the p -value from a t -student test to check if the samples are statistically different.

Image		5.29 mGy		4.53 mGy		3.02 mGy	
Simulated	Real	Error (%)	p -values	Error (%)	p -values	Error (%)	p -values
1	1	0.78 ± 0.69	0.9817	0.74 ± 0.67	0.9977	1.09 ± 0.89	0.8975
1	2	0.95 ± 0.71	0.8935	0.83 ± 0.66	0.9286	1.17 ± 0.95	0.8824
1	3	0.93 ± 0.75	0.8995	0.93 ± 0.73	0.9203	1.12 ± 0.84	0.8842
1	4	1.04 ± 0.79	0.8804	0.96 ± 0.72	0.9144	1.19 ± 0.96	0.8634
1	5	1.01 ± 0.75	0.8866	0.87 ± 0.67	0.9133	1.16 ± 0.89	0.8726
2	1	0.90 ± 0.71	0.9203	0.95 ± 0.74	0.9000	0.95 ± 0.80	0.9939
2	2	0.69 ± 0.57	0.9914	0.76 ± 0.68	0.9733	1.07 ± 0.86	0.9788
2	3	0.72 ± 0.62	0.9975	0.82 ± 0.74	0.9816	0.95 ± 0.76	0.9807
2	4	0.81 ± 0.73	0.9782	0.82 ± 0.68	0.9875	1.01 ± 0.89	0.9594
2	5	0.76 ± 0.65	0.9845	0.78 ± 0.69	0.9886	0.91 ± 0.82	0.9688
3	1	0.93 ± 0.68	0.9025	1.00 ± 0.74	0.8833	0.93 ± 0.78	0.9885
3	2	0.72 ± 0.59	0.9906	0.79 ± 0.66	0.9565	0.92 ± 0.84	0.9964
3	3	0.70 ± 0.62	0.9845	0.86 ± 0.74	0.9649	0.91 ± 0.79	0.9982
3	4	0.75 ± 0.69	0.9960	0.82 ± 0.66	0.9707	0.91 ± 0.78	0.9769
3	5	0.72 ± 0.60	0.9975	0.78 ± 0.66	0.9718	0.90 ± 0.83	0.9863
4	1	0.92 ± 0.69	0.8954	1.06 ± 0.80	0.8748	0.95 ± 0.83	0.9785
4	2	0.72 ± 0.58	0.9835	0.76 ± 0.62	0.9478	1.00 ± 0.85	0.9935
4	3	0.71 ± 0.62	0.9774	0.86 ± 0.73	0.9562	0.97 ± 0.76	0.9917
4	4	0.79 ± 0.68	0.9967	0.79 ± 0.68	0.9620	0.89 ± 0.79	0.9869
4	5	0.75 ± 0.65	0.9904	0.76 ± 0.65	0.9631	0.97 ± 0.81	0.9963
5	1	0.97 ± 0.64	0.8889	1.07 ± 0.78	0.8696	0.97 ± 0.84	0.9741
5	2	0.73 ± 0.59	0.9768	0.83 ± 0.65	0.9425	1.06 ± 0.91	0.9892
5	3	0.71 ± 0.57	0.9707	0.84 ± 0.68	0.9508	1.01 ± 0.80	0.9873
5	4	0.79 ± 0.67	0.9901	0.84 ± 0.66	0.9567	0.94 ± 0.78	0.9913
5	5	0.75 ± 0.63	0.9838	0.82 ± 0.69	0.9578	0.93 ± 0.89	0.9992
Averaged error		0.81 ± 0.66	-	0.85 ± 0.70	-	1.00 ± 0.84	-

It is important to note that averaged errors are lower than 1% for the local variance. Again p -values exceeded 0.05 in every comparison.

Figure 25: Normalized noise power spectrum for images acquired with different radiation dose.

Figure 26: Local mean pixel value for images acquired with different doses.

Figure 27: Local variance for images acquired with different doses.

Discussion and Conclusions

This chapter presents the discussion of the results reported in the previous chapter. It also presents the conclusions of this work, limitations and future work.

7.1 Discussion

A new method for simulating dose reduction in digital mammograms is proposed in this work. It is based on the local variation of the noise calculated in uniform images and applies a novel interpretation of the Anscombe transformation to insert noise in a clinical mammogram acquired at the standard radiation dose.

The method accounts for the anisotropic behavior of the noise found in digital mammograms, since it uses 2D uniform images for measuring quantum noise. Also, it accounts for the noise present in the clinical mammography used as input by measuring the local variance of a uniform image acquired at the same exposure configurations. With the Anscombe transformation it is possible to have a good approximation of the noise and the signal separately, therefore it is easier to calculate how much noise is contaminating the original image and how much noise has to be added to this image before it reaches the noise level of a reduced dose mammography.

The method assumes no changes in the MTF when radiation dose is altered. This assumption is true if we consider that the main factors that modify the MTF in a clinical mammography are the detector size and the focal spot size. When radiation dose is altered, there are no modifications to the detector size and focal spot size.

No assumptions regarding the dependency between radiation dose and DQE are necessary, since noise is measured at the exact simulated dose. Furthermore, the method is capable of simulating noise locally, accounting for the spatial dependency between pixel value and variance along the field, caused by the digital mammography acquisition system. Such information is lost when NPS is used as descriptive of the noise. In the following subsections we discuss the results reported for each metric.

7.1.1 Noise

Preliminary analysis of the noise extracted from homogeneous images supported the development of the local simulation method proposed in this work.

Analysis of Figure 19 evidence that the flat fielding process is capable of correcting the non-uniformities of the mean pixel value on different points of the field. However, small fluctuations ($<3.00\%$) are still detectable when analyzing pixels located far away from the chest wall.

We can argue, from observation of Figure 20 that, although the mean pixel value is corrected, the flat fielding scales the noise variance with different gains throughout the field. Graphs show that the variation can be as high as 3 times the variance, supporting the importance of a method capable of simulating noise locally.

By observation of Figure 21 we can argue that the relation between variance and mean pixel value of the homogeneous image is as low as one tenth of the expected rate (HAIGHT, 1967). This happens because the raw image provided by the X-ray system is not the exact result of the counting process but is proportional to this number.

It is also noticeable that the quotient between variance and mean pixel value assume different values throughout the field, therefore it is also a function of the spatial position.

The discussion introduced above evidence that simple insertion of Poisson noise to clinical images is not an accurate simulation of dose reduction and shows the importance of applying appropriate methods for this purpose.

7.1.2 Method

7.1.2.1 Normalized noise power spectrum

Similarity between NNPS evidenced in Figure 25 shows that both simulated and clinical images have similar noise behavior when analyzed in the frequency domain. Table 3 shows that the averaged relative error between simulated and clinical images keeps values lower than 2.5%. Also, the p -value calculated for each crossed comparison shows that there is no statistical difference between NNPS (at level $p<0.05$), since high values were reported.

It is important to notice that, although the NPS is not used as descriptive of the noise during the noise simulation process, this metric showed no statistically relevant difference if compared to a real image.

7.1.2.2 Local Mean

Visual examination of Figure 26 indicates strong similarity between clinical and simulated images. As expected, decreasing radiation dose lead to lower mean pixel value, since the number of photons that reach the photo-detector is lower.

Values reported in Table 4 show that the method generated images with averaged errors below 1% for the local mean pixel value. Furthermore we found no statistically significant difference between local mean pixel value for the clinical and simulated images (at level $p < 0.05$). Many of the comparisons provided high p -values, suggesting good similarity between clinical and simulated images.

7.1.2.3 Local Variance

Similarly to the local mean pixel value, Figure 27 supports visual verification of the correspondence between clinical and simulated images in terms of local variance. Also, it is noticeable that lower levels of radiation produced lower local variance, which is consistent with the expected behavior from an image contaminated by quantum noise.

Averaged relative error for the local variance was stated on Table 5. Values found for the crossed comparison between clinical and simulated images are lower than 1.5%. Again, we found no statistically significant difference between the local variance for the real and simulated images (at level $p < 0.05$), also many of the comparisons provided high p -values, suggesting good similarity between clinical and simulated images.

7.2 Future work

Future work may include the study of the dependency between noise added to the original image and exposure parameters such as tube peak voltage (kVp) and the target/filter combination. This study could allow the dose reduction simulation without the homogeneous images.

Another potential application for this method is simulating various radiation dose levels in virtual clinical trials (VCTs).

Further studies are needed to separate and characterize the different components of the noise, this way it is possible to simulate the various sources of noise separately.

7.3 Conclusion

In this work we proposed a new application for the Anscombe transformation and investigated its usability for simulating dose reduction in clinical digital mammograms.

Obtained results show that the method has a good performance when simulating dose reduction using a clinical exam, acquired at the standard radiation dose, and two homogeneous images.

The method is capable of inserting the Poisson noise in the original image to simulate dose reduction, and the addition is made possible by the use of the Anscombe transformation, since in the spatial domain the noise is non-additive.

Also, the inverse transformation was capable of creating dependency between noise and signal, guaranteeing the same behavior as a clinical image acquired at the simulated dose, as shown in the results.

It was the first time, to the best of our knowledge, that the Anscombe transformation was used as a tool to create dependency between noise and signal, considering that the usual application of this transformation is to cease the dependency to allow easier treatment of the noise.

It is important to emphasize the influence of the use of local simulation proposed in this work, since the noise also depends on the spatial position of the pixel.

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