



**HAL**  
open science

## Simulation study of an X-ray diffraction system for breast tumor detection

Fanny Marticke, G Montémont, C Paulus, Olivier J.J. Michel, Jerome I. Mars,  
L I Verger

► **To cite this version:**

Fanny Marticke, G Montémont, C Paulus, Olivier J.J. Michel, Jerome I. Mars, et al.. Simulation study of an X-ray diffraction system for breast tumor detection. Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment, 2017, 867, pp.20 - 31. 10.1016/j.nima.2017.04.026 . hal-01552429

**HAL Id: hal-01552429**

**<https://hal.science/hal-01552429>**

Submitted on 24 Aug 2017

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1 Simulation study of an X-ray diffraction system for  
2 breast tumor detection

3 F. Marticke<sup>a,b</sup>, G. Montemont<sup>a</sup>, C. Paulus<sup>a</sup>, O. Michel<sup>b</sup>, J. I. Mars<sup>b</sup>,  
4 L. Verger<sup>a</sup>

5 <sup>a</sup>*Univ. Grenoble-Alpes, F-38000 Grenoble, France*

6 *CEA, LETI, Minatec Campus, F-38054 Grenoble, France*

7 <sup>b</sup>*Univ. Grenoble-Alpes, Gipsa-Lab, F-38000 Grenoble, France*

8 *CNRS, Gipsa-Lab, F-38000 Grenoble, France*

---

9 **Abstract**

10 X-ray diffraction (XRD) is a powerful technique used to determine the molec-  
11 ular structure of biological tissues. In breast tissues for example, the scattering  
12 signatures of dense fibroglandular tissue and carcinoma have been shown to be  
13 significantly different. In this study, XRD was used as a second control level  
14 when conventional mammography results were unclear, for instance because of  
15 overly high breast density. A system optimized for this issue, called multifocal  
16 XRD, was developed combining energy dispersive spectral information at dif-  
17 ferent scattering angles. This system allows depth-imaging in one go but needs  
18 an x,y-direction scan to image the region conventional mammography identified  
19 as suspect. **The scan-time for about 10 cm<sup>3</sup> with an incident flux of about**  
20 **4.8·10<sup>7</sup> photons per second would be around 2 seconds.** For this study, breast  
21 phantoms with and without cancerous nodule were simulated to assess the sep-  
22 aration power of the method and to determine the radiation dose required to  
23 obtain nearly ideal separation. For tumors situated in the center of the breast,  
24 the required dose was only about 0.3 mGy, even for breasts with high density.  
25 The tumor position was shown to have a low impact on detectability provided  
26 it remained in a zone where the system was sufficiently sensitive. The influence  
27 of incident spectrum maximum energy was also studied. The required dose re-  
28 mained very low with any of the incident spectra tested. Finally, an image slice  
29 was reconstructed in the x-direction and showed that the system can detect the

30 presence of a small tumor (4 mm). Hence, XRD is a very promising tool to  
31 reduce the number of unnecessary invasive breast biopsies.

32 *Keywords:* X-ray scattering, breast cancer, breast phantom simulation,  
33 radiation dose, system optimization, depth imaging, reconstruction.

---

## 34 1. Introduction

35 Conventional mammography is based on the premise that normal breast  
36 tissue and cancerous tissue differ in how they absorb X-rays. Mammography is  
37 currently believed to be the most effective breast screening tool. However, it is  
38 limited by the low contrast between the details to be detected (e.g. nodules) [1]  
39 and the background composed of adipose and fibroglandular tissues. The higher  
40 the proportion of fibroglandular tissue (i.e., the more dense the breast tissue),  
41 the more difficult it will be to detect a small lesion. This difficulty can lead to  
42 false negative or false positive diagnoses, resulting in missed cancer detection or  
43 unnecessary biopsies.

44 As breast biopsy is an invasive technique which causes patients considerable  
45 stress, the number of unnecessary ones should be reduced. This article proposes  
46 a non-invasive X-ray diffraction (XRD) method which could reduce the number  
47 of unnecessary breast biopsies. XRD can detect the molecular structure of  
48 biological tissues [2] which is not possible with X-ray absorption. Hence, it  
49 delivers additional information about the tissue to be classified. The potential  
50 of XRD to improve breast cancer diagnosis was recognized by numerous authors.  
51 Some of them suggested to enhance contrast of conventional mammography by  
52 combining transmission and coherent scattering images [3–5]. XRD as a stand-  
53 alone technique was also considered. Different XRD computed tomography  
54 systems were proposed [6–9]. The most important problem of XRD in breast  
55 cancer diagnosis is the system sensitivity, which implies long measurement time  
56 [10–12] and high dose delivery. Chaparian *et al.* [13, 14] proposed a method to  
57 optimize an energy dispersive X-ray diffraction system for clinical applications in  
58 terms of sensitivity notably. Though, this system only acquires at one scattering

59 angle and acquisition of thicker objects requires a depth scan. Moreover, their  
60 study did not include dose considerations. Ghammraoui *et al.* [15, 16] analyzed  
61 the impact of delivered dose on image quality in coherent scatter computed  
62 tomography (CSCT) of the breast. **The present study does not use tomography**  
63 **but a system requiring only a simple x,y-scan to perform volumic XRD imaging.**  
64 **Its purpose was to determine the dose necessary to detect a 4 mm breast tumor**  
65 **using this XRD technique.**

66 We propose an optimized XRD system for use as a second control after  
67 conventional mammography with suspicious outcome. Using a convergent col-  
68 limation system and a spectroscopic imaging detector, the system combines  
69 energy dispersive X-ray diffraction (EDXRD) spectral information at different  
70 scattering angles. A multi-angle EDXRD approach **was** suggested by other re-  
71 search teams [17, 18] and it was shown that this technique allows an increase  
72 of system sensitivity **as well as an increase in** the accessible momentum transfer  
73 range [19].

74 The aim of this study was to show that this system **can** detect a small  
75 tumor **of about 4 mm** in a fibroglandular tissue background while only requiring  
76 exposure to a reasonable (**not more than in conventional mammography**) dose of  
77 radiation. This feasibility was demonstrated using simulations of XRD spectra  
78 for breast phantoms with different tissue compositions (varying breast density,  
79 with or without carcinoma nodule). The ability of the system to distinguish  
80 between spectra with or without carcinoma was assessed, and the dose required  
81 to obtain faithful distinction between samples was determined. The impact of  
82 tumor position and the energy level of the incident spectrum on the required  
83 dose were also studied. Finally, one scan slice measurement in the x-direction  
84 was simulated and reconstructed to confirm assessed system performances.

85 **2. Theory**

86 *2.1. X-ray diffraction*

Coherent X-ray scattering or Rayleigh X-ray scattering, leading to X-ray diffraction when analyzing crystalline samples, is commonly used to determine the molecular structure of matter. Classically, coherent scattering is explained by the interaction between the electric field associated with the X-ray beam and the distribution of the electron charge in the analyzed sample. Under the action of the incident electric field, electrons oscillate and emit radiation with the same energy as the incident X-ray photon, but in a different direction. Radiation emitted by different electrons in the same or different atoms can constructively interfere to produce a typical X-ray scattering pattern. These patterns depend on the variable  $\chi$  defined as:

$$\chi = \frac{E}{hc} \cdot \sin\left(\frac{\theta}{2}\right) \quad (1)$$

87  $\chi$  is given in  $\text{nm}^{-1}$  and is proportional to the momentum transferred to the  
88 photon causing it to be scattered at an angle  $\theta$ .  $E$  corresponds to the photon en-  
89 ergy,  $h$  to Planck's constant and  $c$  to the speed of light ( $1/hc \approx 0.806 \text{ keV}^{-1} \cdot \text{nm}^{-1}$ ).  
90 Hereafter, we will refer to  $\chi$  as the momentum transfer.

91 The differential cross-section per electron for each solid angle is given by:

$$\frac{d\sigma_{coh}}{d\Omega} = \frac{d\sigma_{Th}}{d\Omega} \cdot f_{IAM}^2(\chi, Z) \cdot s(\chi) \quad (2)$$

92 where  $\frac{d\sigma_{Th}}{d\Omega} = r_e^2 \frac{1+\cos^2\theta}{2}$  is the classical Thomson cross-section for a free  
93 electron,  $f_{IAM}$  is the coherent scatter form factor for independent atoms, ac-  
94 counting for interference between X-rays scattered by different electrons from  
95 the same atom;  $s$  is the molecular interference function accounting for intra-  
96 and intermolecular interference. This function corresponds to discrete Bragg  
97 peaks for materials with well defined long range orders, such as crystals. In the  
98 case of amorphous materials presenting a short-range order, such as biological  
99 tissues,  $s$  will be a continuous function with an oscillatory behavior around unit  
100 value, and a decreasing amplitude as  $\chi$  tends toward higher values.

101 According to equation (1), XRD spectra can be measured in two ways. Usu-  
102 ally, XRD spectra are measured by acquiring the diffraction signal as a function  
103 of  $\theta$  at a fixed beam energy. This technique is called angular dispersive X-ray  
104 diffraction (ADXRD). For their acquisition a monochromatic X-ray beam is  
105 necessary, which strongly reduces the photon flux if a conventional X-ray tube  
106 is used. The second technique, energy dispersive X-ray diffraction (EDXRD),  
107 requires X-ray spectroscopic detectors capable of measuring the scattered inten-  
108 sity at a fixed scattering angle  $\theta$ , across a range of energies. As a conventional  
109 polychromatic X-ray tube can be used for this method, there is no photon flux  
110 problem. In general, EDXRD spectra present a lower resolution than ADXRD  
111 as in addition to resolution factors that are common to both methods (e.g. pixel  
112 size, object voxel size, angular resolution of the system...) spectral resolution  
113 of the detector also degrades the resolution. In ADXRD, the spectral width  
114 of the incident spectrum impacts the resolution but this spectral width only  
115 exists around the chosen energy whereas in EDXRD each energy bin of the de-  
116 tector presents a given spectral width. Nevertheless, EDXRD presents certain  
117 advantages compared to ADXRD. First of all, as has already been mentioned,  
118 the use of a polychromatic conventional X-ray tube is possible. Furthermore,  
119 one detector pixel can acquire the entire XRD pattern of a given object voxel.  
120 Therefore, it is possible to acquire the XRD signatures of different object in  
121 one pass which significantly increases the acquisition speed. It is also possible  
122 to combine the classical ADXRD and EDXRD techniques in order to increase  
123 system sensitivity, which will be proposed in the following study.

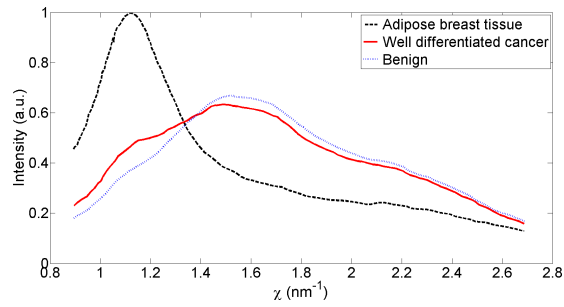
## 124 2.2. X-ray diffraction in breast imaging

125 The diffraction patterns of biological tissues, which correspond to a molecu-  
126 lar structure with short-range order, are characterized by one or more smooth  
127 peaks at well-defined momentum transfer values (Fig. 1). Several studies at-  
128 tempted to classify different breast tissues using EDXRD [9, 10, 12, 20, 21], or  
129 ADXRD [8, 22–25]. A common result of these studies is that healthy adipose tis-  
130 sue produces a sharp peak at low momentum transfer values around  $1.1 \text{ nm}^{-1}$ ,

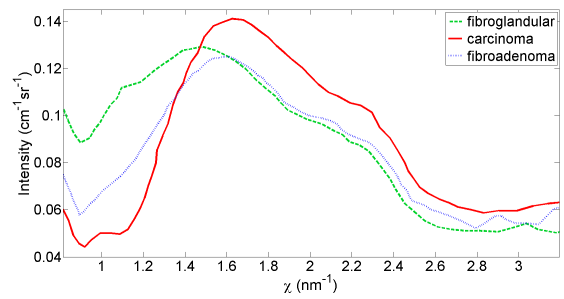
131 while carcinoma presents a broad peak at higher momentum transfer values  
132 around  $1.6 \text{ nm}^{-1}$  (Fig. 1). This higher value corresponds to the maximum of  
133 the water scattering signature. Though, the difference between the scattering  
134 signatures of cancerous tissue and benign tumor was found to be very small by  
135 Pani *et al.* [9] (Fig. 1.a), and it does not seem possible to distinguish these two  
136 tissue types by XRD. Kidane *et al.* [10] found fibroadenoma scattering signature  
137 to have a maximum around  $1.6 \text{ nm}^{-1}$  as carcinoma and with scattering inten-  
138 sity at lower momentum transfer values between fibroglandular and cancerous  
139 tissue (Fig. 1.b). This signature seems to be easier to separate from carcinoma  
140 than the pattern determined by Pani *et al.* but more difficult than fibroglan-  
141 dular tissue. The attenuation of carcinoma and benign tumors is very similar.  
142 However, their shape is different. A fibroadenoma is well defined and sharply  
143 demarcated, whereas a carcinoma is ill-defined and has a stellate form. Hence,  
144 using the anatomical information from classical mammography or breast CT, it  
145 might be possible to distinguish between benign and malignant neoplasm.

146 Therefore, in this study we concentrate on distinguishing between healthy  
147 fibroglandular tissue and carcinoma. Both tissue types are very dense and it  
148 is often difficult to distinguish between them using conventional mammography  
149 because of their very similar absorption coefficients. Their XRD signatures, in  
150 contrast, are quite different. Fig. 1.b shows scattering profiles for the two types  
151 of tissue, as determined by [10] on a statistically significant number of samples.  
152 We used these scattering profiles as reference signatures for this study.

153 The main difference between fibroglandular and cancerous tissues is situated  
154 at low momentum transfer values around the fat peak (around  $1.1 \text{ nm}^{-1}$ ), as  
155 shown in Fig. 1.b. The  $\chi$ -values of interest are between  $1 \text{ nm}^{-1}$  and  $2.5 \text{ nm}^{-1}$   
156 in the present work.



(a) Breast adipose tissue (black dashed line), cancerous tissue (red line) and benign tumor (blue broken line) [9].



(b) Fibroglandular tissue (light green dashed line), pure carcinoma (red line) and fibroadenoma (blue broken line) [10].

Figure 1: Scattering signatures for different breast tissues.



157 **3. Materials and methods**

158 *3.1. X-ray diffraction system*

159 As explained previously, XRD is proposed to be used as a second control  
160 when conventional X-ray mammography results do not give a clear diagnosis.  
161 Conventional mammography allows to determine the position of the suspect  
162 region in the (x,y) plane, but not its depth within the breast. Hence, the  
163 proposed XRD system must be able to target a specific region in the (x,y) plane  
164 and to image the whole breast thickness, i.e., to obtain a diffraction pattern as  
165 a function of momentum transfer for each depth position in the breast.

166 A classical EDXRD setup consists of a collimated polychromatic X-ray source,  
167 a secondary collimation system to select the nominal diffraction angle, and a  
168 spectroscopic detector. In our setup, we associate a collimated polychromatic  
169 incident pencil beam with convergent secondary collimation targeting (x,y) (Fig.  
170 2). This type of system corresponds to a multi-angle EDXRD system, since dif-  
171 ferent diffraction angles will be intercepted (convergent system). Furthermore,  
172 intercepting different scattering angles makes it possible to use a larger detector  
173 surface for the region to be imaged, hence increasing the systems sensitivity.  
174 The use of a thin pencil beam means that the diffraction signal is only emitted  
175 from a thin line in the sample, which will be referred to as the Z-axis hereafter.

176 Another possible solution to inspect the suspicious region would be CSCT  
177 [7, 15, 26]. Batchelar *et al.* [26] used an ADXRD CSCT system working without  
178 secondary collimation. This results in an increase of the system sensitivity.  
179 Though, the sample to be analyzed must be thin. Otherwise, there would be  
180 mixing between different scattering angles and tissues. As we want to analyze  
181 the whole breast thickness, this system is not suitable. Ghamraoui *et al.*  
182 [15] compared the performance of two CSCT system configurations: fan-beam  
183 and pencil-beam configuration. Fan-beam geometry allows to acquire a whole  
184 image slice at once but to avoid mixing of different scattering angles strong  
185 collimation is required, which significantly reduces system sensitivity. Pencil  
186 beam configuration requires less collimation. Though, measurement lines (or

187 translations) and sample rotation are required, which is not always easy in  
 188 clinical routine. They also investigated the use of multiplexed-beams geometry  
 189 which is faster than pencil beam configuration but still requires sample rotation  
 190 typical for CT imaging.

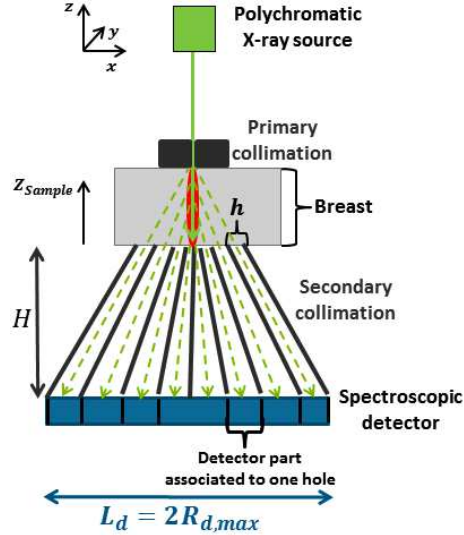
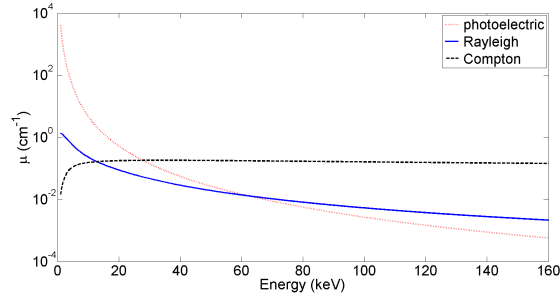


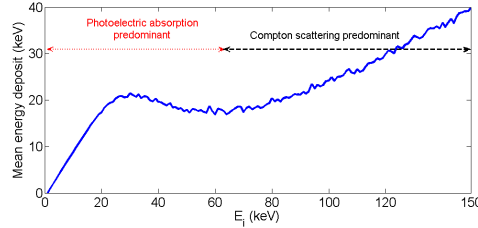
Figure 2: Schematic representation of a system combining EDXRD information at multiple scattering angles: a polychromatic incident pencil beam, a convergent (multifocal) secondary collimation system and a spectroscopic detector.

### 191 3.1.1. Incident X-ray beam

192 The incident X-ray source was simulated using SpekCalc [27]. The anode  
 193 material was chosen to be tungsten. The choice of a tungsten anode instead  
 194 of a molybdenum as normally used in mammography, can be justified by the  
 195 fact that molybdenum presents low bremsstrahlung intensity compared to its  
 196 characteristic peaks. In EDXRD, it is important to have a more continuous  
 197 distribution of photons over the different energies of the incident spectrum in  
 198 order to cover the required  $\chi$ -range at the chosen scattering angle. Hence, tung-  
 199 sten is a suitable choice. A 0.2 mm copper filter was used to suppress photons  
 200 below 20 keV as these photons would be almost entirely absorbed by photo-  
 201 electric interaction (Fig. 3) producing a dose deposit without generating any



(a) Linear attenuation coefficients.



(b) Mean energy deposit.

Figure 3: a) Linear attenuation coefficients of water for different types of interaction. b) Mean energy deposit (multiple interactions included) for one photon in 50 mm of a material with average chemical composition of breast tissue as a function of incident photon energy (generated with PENELOPE 2008 [28]).

202 diffraction signal. Similarly, energies above 100 keV appear superfluous as the  
 203 probability of Rayleigh scattering becomes very low compared to Compton scat-  
 204 tering. This is illustrated by Fig. 3 showing the linear attenuation coefficients  
 205 of water (a) and the mean energy deposit (generated with PENELOPE 2008  
 206 [28]) in 50 mm of a material whose chemical composition is close to average  
 207 breast tissue (H: 9.82%, C: 33.15%, N: 3.41%, O: 51.96%, P: 0.50%, S: 0.52%,  
 208 K: 0.63% [29], percentages correspond to mass fractions). Hence, the reference  
 209 incident X-ray spectrum in this work is between 20 and 100 keV. Though, to  
 210 study the impact of the maximum energy of the incident X-ray spectrum on  
 211 system performances, a range of tube voltages, between 40 kV and 150 kV, was  
 212 tested.

213 *3.1.2. Secondary collimation*

214 Two possible convergent collimation systems were considered here: a mono-  
215 focal system and a multifocal system. Monofocal collimation systems only target  
216 at one point in the object and require a depth scan, whereas multifocal systems  
217 focus on several sample points simultaneously, and can acquire the whole depth  
218 in one shot. Both systems require an (x,y)-scan to image the region identified as  
219 suspect by mammography. A convergent monofocal system has been considered  
220 by Malden and Speller [17] who used a multi-angle approach for baggage inspec-  
221 tion. Though, as it is focused on only one voxel this kind of system would also  
222 require a scan in the z-direction. This would significantly increase dose delivery  
223 and it appears too complex for routine use in practice. Hence, this article only  
224 presents results obtained with a multifocal collimation system able to image the  
225 whole sample thickness in one go. A schematic representation of a multifocal  
226 collimation system is illustrated in Fig. 2.

227 To obtain the best possible resolution and sensitivity in all directions, a con-  
228 ical secondary collimation setup was chosen, in line with the intrinsic symmetry  
229 of XRD. Circular symmetry for the secondary collimation was previously sug-  
230 gested by Harding and Schreiber [30] for instance. However, their system is a  
231 mono-angle EDXRD system with one slit focused on only one object voxel,  
232 whereas the collimation system proposed here corresponds to a multi-angle  
233 EDXRD system with several slits focused on a whole sample line. It is composed  
234 of seven hollow cones nested one inside the other. A beam-stop was placed in the  
235 center to stop transmission signal. The collimation system in Fig. 2 represents  
236 a cross-section of this type of collimation system.

237 The collimation system was designed without multiplexing, **which means**  
238 **that each detector pixel only receives the diffraction signal from a single object**  
239 **voxel. In the case of the presented system, this means that each detector pixel**  
240 **only receives the diffraction signal from a single collimation hole (a concentric**  
241 **annulus in our case) as the system was conceived to adress only one connected**  
242 **depth-region in the target.** Therefore, the detector was divided into as many

243 parts as the number of holes, and each part was associated with a single hole  
 244 (Fig. 2). It has to be noted that a detector part contains several pixels. The total  
 245 detection surface is the same for each part. Fig. 4 illustrates the subdivision of  
 246 the detector and the definition of a pixel annulus.

247 Each hole targets a different sample depth position (multifocal collimation)  
 248 and covers a well defined region in the sample. Collimation height  $H$  and hole  
 249 aperture  $h$  were adjusted in order to intercept the required momentum transfer  
 250 range (combination of incident photon energies and covered scattering angles)  
 251 between  $\chi = 1$  and  $2.5 \text{ nm}^{-1}$  (Fig. 1) and to obtain a momentum transfer  
 252 resolution of at least  $0.2 \text{ nm}^{-1}$  while maintaining system sensitivity as high  
 253 as possible. Table 1 summarizes the system parameters used for this study.  
 254 Resolution was mostly influenced by collimation height and hole size. "Pixel  
 255 size" (annular thickness) was not limiting if it remained small (around 1 mm  
 256 or smaller). The number of holes was fixed in order to have as much holes by  
 257 respecting a septa thickness of at least 0.3 mm and by targeting the desired  
 258 scattering angles. Covered scattering angles range from  $0.1^\circ$  to  $11^\circ$ , where each  
 259 hole intercept a different range of angles. The first hole corresponds to low  
 260 scattering angles (up to  $5^\circ$ ), whereas the last hole covers the highest scattering  
 261 angles. Collimator material was simulated as iron, which is less expensive than  
 262 tungsten and easier to manufacture. Septa thickness was about 1 mm at detector  
 263 side and between 0.3 and 0.5 mm at sample side.

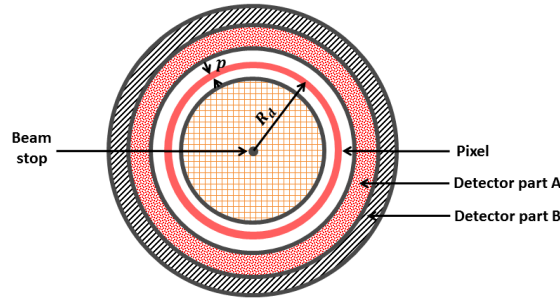


Figure 4: Schematic representation of detector partitioning (detection surface of detector part A = detection surface of detector part B). One detector part contains more than one pixel. The red pixel, which is represented here, is part of the white detector part.

Table 1: System parameters.  $H$ : collimation height;  $h$ : collimation hole size;  $p$ : annular thickness;  $L_d$ : detector dimension.

Number of holes	$H$ (mm)	$h$ (mm)	$p$ (mm)	$L_d$ (mm)
7	230	0.8	1.0	100

264 Obviously, eventhough this kind of collimation allows to collect the scattering  
 265 signal following the whole annulus associated to one scattering angle, it strongly  
 266 restricts the number of detected photons compared to the number of incident  
 267 photons. Coded aperture systems combining EDXRD and ADXRD [31, 32]  
 268 use less collimation and can also be used to obtain a 2D image. However, this  
 269 kind of systems seems more adequate for discrete scattering signatures than  
 270 for continuous tissue signatures. Eventhough the number of detected photons  
 271 is higher, the amount of information that can be retrieved is not necessarily  
 272 higher because of ambiguity between scattering angle and momentum transfer  
 273 (due to multiplexing) with coded apertures, **which seems to be more difficult**  
 274 **to resolve for amorphous spectra than for crystalline spectra.** The amount of  
 275 information carried by the photons is not the same for each detected photon.  
 276 We tested to add slight multiplexing to our system in order to increase system  
 277 sensitivity, but the required dose to detect **the** small tumor also increased.

### 278 3.1.3. Detector

279 For this study, we considered a 5 mm thick 2D  $10 \times 10$  mm<sup>2</sup> spectroscopic  
 280 CdZnTe detector with 2.5 mm anode pitch. CdZnTe is a room temperature  
 281 semiconductor detector with high resistivity ( $\rho = 5 \cdot 10^{10} \Omega \cdot cm$ ), good transport  
 282 properties ( $\mu\tau = 5 \cdot 10^{-3} cm \cdot V^{-1}$ ) and a crystallinity compatible with fabrication  
 283 of devices measuring several  $cm^3$ . The thickness of 5 mm is hence feasible and  
 284 is well appropriate for the considered range of energies. In a previous study [33],  
 285 we showed that a spatial resolution of 0.4 mm can be achieved at 60 keV with  
 286 this detector geometry using transient signal processing, a technique known as

287 subpixel positioning. The advantage of this technique is that it can improve  
 288 spatial resolution without degrading the spectral response by charge sharing  
 289 (due to smaller anode size). Here, 1 mm subpixel size was used for our system  
 290 simulations. The associated ASIC (Application-Specific Integrated Circuit) was  
 291 based on IDeFX-HD [34], which combines low noise and low power. In practice,  
 292 the average energy resolution was about 2.5% at 122 keV.

293 Using these characteristics, a detector response matrix (DRM), accounting  
 294 for limited energy resolution of the detector, was obtained using Tasmania, a  
 295 simulation environment developed in our laboratory. It gives the probability  
 296 of detecting a given amplitude  $A$  knowing the incident photon energy  $E_d$  on  
 297 the detector. This detector response model takes into account the following  
 298 elements: radiation (photons & photoelectrons) transport based on PENELOPE  
 299 [28], a 3D electric field model (for applied and weighting fields), 3D charge  
 300 carrier transport (diffusion, drift, trapping & Coulomb repulsion) [35], a detailed  
 301 noise model (detector & readout electronics) and a behavioral model of analog  
 302 electronics (shaping, trigger & peak detector).

#### 303 3.1.4. Sensitivity and resolution

304 System sensitivity only depends on the geometric parameters of the acquisi-  
 305 tion system and not on the interaction cross-section of the sample. The sensitiv-  
 306 ity achieved with detector position  $r$  for the position in the sample  $Z_{Sample}$  can  
 307 be defined as the ratio of the surface (Fig. 5.a), at detector level, of an isotrop-  
 308 ically radiating point located at  $Z_{Sample}$  to the intercepted detector surface at  
 309 detector position  $r$ :

$$dS(Z, r) = \int_0^{2\pi} \frac{Zrdr}{4\pi(r^2 + Z^2)^{\frac{3}{2}}} d\varphi \quad (3)$$

310 where  $Z = Z_{Sample} + H + g$  with  $g$  the gap between secondary collimation and  
 311 sample. Integration over the cylindrical coordinate,  $\varphi$ , is necessary to consider  
 312 the whole detector annulus of radius  $r$  and thickness  $dr$  (Fig. 5.b). To obtain a  
 313 system sensitivity in the pixel range with a radius,  $R_d$ , from the center to the

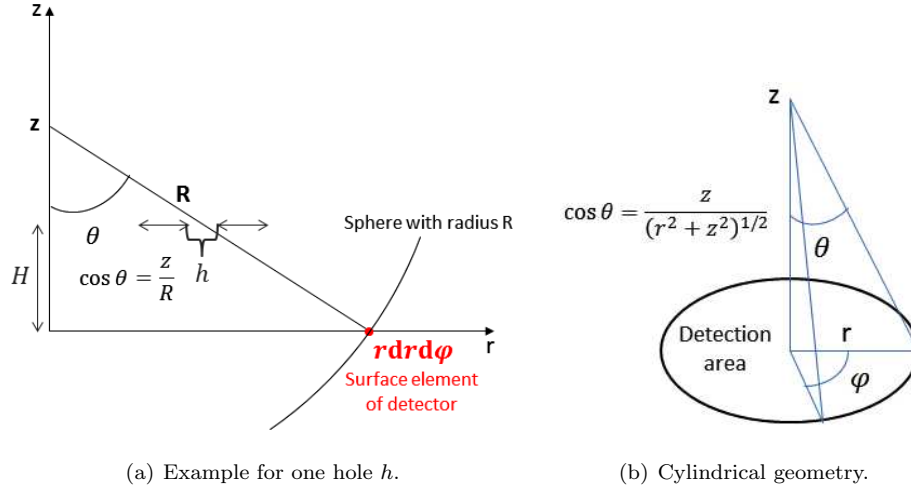


Figure 5: Schematic illustration of sensitivity calculations.

314 sampling point,  $Z_{Sample}$ , it is sufficient to integrate all  $r$  from which  $Z_{Sample}$   
 315 can be "seen" and which are part of the pixel.

316 Fig. 6.a shows the sensitivity distribution on the detector (detector position  
 317  $R_d$ ) and in the sample (depth position in the sample  $Z_{Sample}$ ) which was cal-  
 318 culated analytically. The higher the sensitivity value the more of the photons  
 319 (isotropically) emitted from  $Z_{Sample}$  can be detected at a given detector posi-  
 320 tion  $R_d$ . A gap of 10 mm between the secondary collimation and the breast  
 321 sample was considered to produce maximum sensitivity at the center of the  
 322 breast. The size of the gap was determined by considering the analytically cal-  
 323 culated sensitivity profile in the sample for the case, where the sample and the  
 324 secondary collimation are in contact. In this case, maximum sensitivity was at  
 325  $Z_{Sample} = 35$  mm ( $Z_{Sample} = 0$  mm corresponds to the sample edge at sec-  
 326 ondary collimation side). The different detector parts were obviously sensitive  
 327 to different sample zones. Hence, the system is a multifocal collimation system.  
 328 This multifocal nature was also confirmed by the sensitivity profile in the sam-  
 329 ple represented in Fig. 6.b, which corresponds to the sum over  $R_d$  of Fig. 6.a.  
 330 The systems sensitivity was good almost throughout the samples thickness with  
 331 its maximum, which is indeed at the center ( $Z_{Sample} = 25$  mm). Because it is



332 close to the pencil beam axis (Z-axis) where the diffraction signal originates, the  
 333 first hole is sensitive to the whole sample thickness (Fig. 6.a), meaning that its  
 334 spatial resolution is very poor. Global resolution of the system is significantly  
 335 deteriorated by the first hole, but it allows detection of features in the lower  
 336 sample regions and thus increases the systems overall sensitivity as a whole.

337 The overall system performance of the collimation was assessed based on  
 338 detective quantum efficiency (DQE) and modulation transfer frequency (MTF)  
 339 calculations [19, 36]. It has to be noted this is not the commonly used definition  
 340 of DQE for detectors. Here it indicates the performance of the collimation  
 341 system associated to a given detector area. This wider concept of DQE was also  
 342 considered by Starck *et al.* [37] to characterize gamma camera systems. We  
 343 adapted these calculations do XRD imaging systems [19]. In photon counting  
 344 systems (Poisson noise) such as XRD systems, the DQE is the product of the  
 345 sensitivity and squared modulus of the MTF [36]:  $DQE(\nu) = S \cdot MTF^2(\nu)$ .

346 We are able to determine the MTF of one pair hole-pixel ( $MTF_{hp}(\nu_z)$ ). Use  
 347 of the DQE allows to obtain a synthetical figure of merit combining sensitiv-  
 348 ity and resolution [19]. The DQE of a pair hole-pixel is given by the squared  
 349  $MTF_{hp}(\nu_z)$  weighted by its sensitivity  $S_{hp}$ . To get the DQE of the whole colli-  
 350 mation system, the contributions of the different pairs hole-pixel can simply be  
 351 summed if there is no multiplexing [36]:

$$DQE(\nu_z) = \sum_{pixels} S_{hp} \cdot MTF_{hp}^2(\nu_z) \quad (4)$$

352 The global spatial resolution,  $\mathcal{R}$ , can be determined from the modulation  
 353 transfer function curve:

$$\frac{1}{\mathcal{R}} = 2 \int_0^{+\infty} \frac{DQE(\nu_z)}{DQE(0)} d\nu_z = 2 \int_0^{+\infty} MTF^2(\nu_z) d\nu_z \quad (5)$$

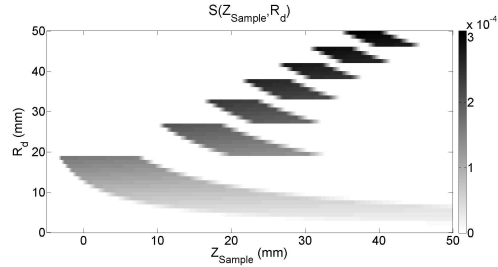
354 This definition is consistent with the full width at half maximum (FWHM)  
 355 for a rectangular gate-shaped point spread function. Angular  $MTF_{hp}(\nu_\theta)$  is de-  
 356 termined by geometrical considerations linking  $z$  and  $\theta$ , and momentum transfer  
 357  $MTF_{hp}(\nu_\chi)$  can be calculated using the relationship between  $\theta$  and  $\chi$  (Eq. 1).

358 The calculated overall system resolutions are summarized in table 2. With  
 359 9.6 mm in the direction of the samples thickness, the spatial resolution is low,  
 360 but it is nevertheless better than other XRD systems, which do not offer any  
 361 depth resolution. Some XRD imaging techniques such as CSCT [7, 16] and  
 362 coded aperture coherent spectral imaging [31, 38] allow to obtain better spatial  
 363 resolution in beam direction. Greenberg *et al.* [38], for instance, obtained a  
 364 spatial resolution of 5 mm in beam direction. However, contrast is lost due  
 365 to multiplexing inherent in coded aperture methods. In CSCT the resolution  
 366 is good but in clinical routine it is not always easy to rotate while imaging,  
 367 especially in breast imaging. We seek to propose an imaging system able to  
 368 acquire the whole sample thickness in one go with a satisfying spatial resolution  
 369 and having a good sensitivity while maintaining the best possible momentum  
 370 transfer resolution without the need of rotating movements.

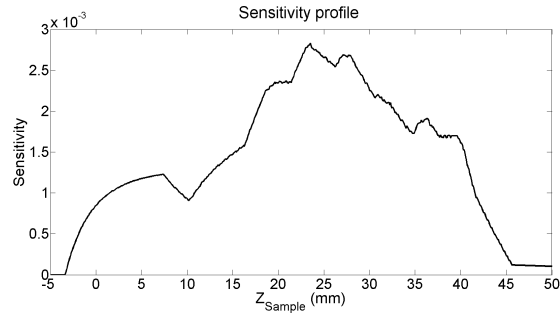
371 The momentum transfer resolution meets the constraint of  $0.2 \text{ nm}^{-1}$  for  
 372 almost every energy tested due to adequate angular resolution. Integration  
 373 over the whole incident X-ray spectrum (between 20 and 100 keV) leads to  
 374 an average momentum transfer resolution of about  $0.07 \text{ nm}^{-1}$ . However, the  
 375 calculations did not take the detectors energy resolution into account because  
 376 we were interested in proposing the best possible collimation system. Doing  
 377 so slightly deteriorates the momentum transfer resolution, as this resolution  
 378 depends on both angular and spectral resolution:

$$\Delta\chi = \frac{E}{2hc} \cdot \cos\left(\frac{\theta}{2}\right) \Delta\theta + \frac{1}{hc} \sin\left(\frac{\theta}{2}\right) \Delta E \quad (6)$$

379 If a mean energy resolution of 3 keV is considered, this corresponds to 5%  
 380 at 60 keV. This leads to a resolution of  $0.1 \text{ nm}^{-1}$  at  $2 \text{ nm}^{-1}$ . At 20 keV this  
 381 resolution will be lower and 100 keV it will be higher, but in average the global  
 382 momentum transfer resolution is not worse than the required  $0.2 \text{ nm}^{-1}$ . In  
 383 the following simulation study both contributions (angular resolution of the  
 384 collimation and energy resolution of the detector) are taken into account.



(a) Sensitivity distribution.



(b) Sensitivity profile.

Figure 6: Sensitivity distribution and sensitivity profile of the simulated X-ray diffraction system across the sample (sample starts at 0 and ends at 50 mm).

Table 2: Resolutions of the X-ray diffraction system considered (the spectral resolution of the detector not taken into account).

Spatial (mm)	Angular ( $^{\circ}$ )	$\chi$ at 20 keV ( $\text{nm}^{-1}$ )	$\chi$ at 60 keV ( $\text{nm}^{-1}$ )	$\chi$ at 100 keV ( $\text{nm}^{-1}$ )	$\chi$ at 150 keV ( $\text{nm}^{-1}$ )
9.6	0.21	0.029	0.09	0.15	0.22

385 *3.2. Simulations*

386 Our X-ray diffraction system’s capacity to distinguish between carcinoma  
387 and fibroglandular tissue was assessed using Monte-Carlo simulations of the  
388 whole system and a breast phantom. These simulations were performed with  
389 PENELOPE [28], by adapting cross-sections for coherent scattering to take  
390 intra- and intermolecular radiation interference, i.e., X-ray diffraction, into ac-  
391 count. Cross-sections used in PENELOPE for Rayleigh scattering only contain  
392 the Thomson cross-section and the coherent scatter form factor (Eq. 2). We  
393 replaced these cross-sections by the diffraction signatures determined by [10]  
394 (Fig. 1.b).

395 Simulations take into account all kinds of interaction (Rayleigh scattering,  
396 Compton scattering, Photoelectric absorption, multiple scattering, fluorescence)  
397 and all possible locations of interaction (collimation, phantom, detector).

398 *3.2.1. Breast phantom*

399 The simulated breast phantom was a 50 mm thick, and 150 mm diameter  
400 cylinder of adipose tissue containing an ellipsoid of fibroglandular tissue (**axis**  
401 **in x- and y-direction: 70 mm**) corresponding to a region with altered compo-  
402 sition. To assess the impact of the thickness (**i.e. the axis in z-direction**) of  
403 fibroglandular tissue, this ellipsoid was simulated in a range of thicknesses: 20,  
404 30 and 40 mm. This allowed us to verify whether high density breast tissue  
405 can be imaged with XRD. A small spherical carcinoma nodule was located in  
406 the center of the phantom, in the case of a phantom with tumor. The diameter  
407 of this nodule was about 4 mm, which corresponds to a very small tumor size.  
408 In scintimammography, for instance, tumors smaller than 6 mm are difficult to  
409 detect [39, 40]. Fig. 7 shows a schematic representation of the breast phantom.

410 As system sensitivity is not the same over the whole of the samples thickness,  
411 it is important to study the impact of tumor position on its detectability. The  
412 tumor was always located in the fibroglandular mass at this location will result  
413 in doubtful mammography results. Therefore, tumor position variation study  
414 was realized with 40 mm fibroglandular thickness. Four tumor offset positions

415 were tested: +20 mm, +10 mm, -10 mm and -20 mm. A positive tumor offset  
 416 corresponds to a greater distance between tumor and detector, while a negative  
 417 offset corresponds to a shorter distance.

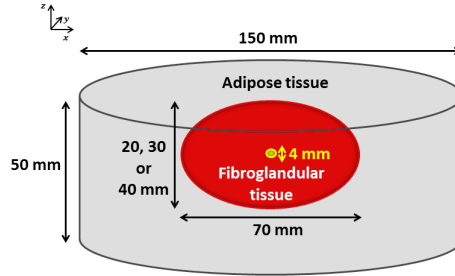


Figure 7: Simulated breast phantom presenting a nodule (yellow sphere) composed of pure carcinoma.

418 Scans in x-direction (N.B.: scans in y-direction were not simulated as they  
 419 are equivalent to scans in x-direction.) were simulated with and without tumor  
 420 for a fibroglandular thickness of 30 mm and incident spectra at 60 kVp and  
 421 100 kVp. The scan step was chosen to be 1 mm.

### 422 3.3. Data analysis

#### 423 3.3.1. Separation power and required incident photon number

424 The contrast to noise ratio (CNR) is a measure of the separation power of a  
 425 given imaging system and is defined as:

$$CNR = \frac{\Delta M}{\sigma} \quad (7)$$

426 where  $\Delta M = M_A - M_B$  corresponds to the difference between the expected  
 427 signal intensities  $M_A$  and  $M_B$  produced by materials A and B, and  $\sigma$  corre-  
 428 sponds to the standard deviation of the noise.

429 Diffraction measurements follow a Poisson law, but for CNR calculations a Gaus-  
 430 sian approximation ( $\mu = \sigma^2 = \lambda$ , where  $\lambda$  is the Poisson parameter) of photon  
 431 noise was used.

432 If A and B are the two tissue types to be distinguished (carcinoma and fibrog-

433 glandular tissue), using the Gaussian approximation, the squared CNR is given  
 434 by:

$$CNR^2 = \sum_i \frac{(M_{A,i} - M_{B,i})^2}{\sigma_i^2} \quad (8)$$

435 where  $M_A$  and  $M_B$  are the expected diffraction signatures of A and B nor-  
 436 malized by the number of incident photons, and  $\sigma_i^2 = M_{A,i} + M_{B,i}$  the standard  
 437 deviation of  $M_A - M_B$  on channel  $i$ .

438 In fact, the  $CNR^2$  defined above corresponds to the quadratic distance be-  
 439 tween the two distributions, A and B, per incident photon. Hence, the inverse  
 440 of the  $CNR^2$  corresponds to the number of photons,  $N_{ph,1\sigma}$ , requested to obtain  
 441 a distance of one standard deviation between the two distributions. This is a  
 442 very low-level separation. Hereafter, a separation of  $3\sigma$  will be considered:

$$N_{ph,3\sigma} = \frac{9}{CNR^2} \quad (9)$$

### 443 3.3.2. Dose estimation

444 The radiation dose was estimated using the incident X-ray spectrum,  $S_{inc}$ ,  
 445 the mean energy deposit for one photon in 50 mm of breast tissue similar ma-  
 446 terial,  $E_{mean}$ , as a function of incident photon energy,  $E_i$  (Fig. 3.b), and the  
 447 calculated incident photon number,  $N_{ph}$ , required to obtain the desired separa-  
 448 tion between XRD spectra with and without carcinoma.

449 The mean total energy deposit per photon,  $D_E$ , for a given incident spectrum  
 450 is calculated using:

$$D_E = \frac{\sum_{E_i} E_{mean}(E_i) \cdot S_{inc}(E_i)}{\sum_{E_i} S_{inc}(E_i)} \quad (10)$$

451 The result is expressed in keV. For an incident spectrum with a maximum  
 452 energy of 100 keV, the mean total energy deposit will be about 18.88 keV.  
 453 Knowing the required number of incident photons, the required mean dose is  
 454 given by:

$$D = \frac{D_E \cdot 1.6 \cdot 10^{-16} \cdot N_{ph}}{m_{irr}} \quad (11)$$

455 where  $1.6 \cdot 10^{-16}$  is the conversion factor to transform keV into joules (J),  
 456 and  $m_{irr}$  corresponds to the directly irradiated mass. In the present case, the  
 457 irradiated mass is about  $5 \cdot 10^{-8}$  kg (i.e. pencil beam surface  $\times$  sample thickness  
 458  $\times$  sample density =  $10^{-6} m^2 \times 50 \cdot 10^{-3} m \times 1 kg \cdot m^{-3}$ ).

459 Note that this dose corresponds indeed to the total dose deposited in the  
 460 whole breast thickness. The mean energy deposit for one photon  $E_{mean}$  was  
 461 obtained by Monte-Carlo simulations taking into account every possible inter-  
 462 action within the whole sample thickness.

### 463 3.3.3. Reconstruction method

464 The simulated scan measure  $m$  is modeled linearly by:

$$m(A, R_d, x) = \sum_{Z, i} Resp(A, R_d, Z, i) \cdot t(Z, i, x) \quad (12)$$

465 where  $x$  corresponds to the scan position and  $Resp(A, R_d, Z, i)$  to the sys-  
 466 tem response matrix depending on the detected amplitude  $A$ , the position on  
 467 the detector  $R_d$ ,  $Z$  and the tissue type  $i$  (adipose tissue, fibroglandular tissue,  
 468 carcinoma).  $t(Z, i, x)$  is a coefficient indicating whether tissue  $i$  is present at  
 469 the position  $Z$  and detected at scan position  $x$ . As there is no tissue mixing  
 470 in the breast phantoms considered here, it is either equal to zero (tissue  $i$  not  
 471 present) or to one (tissue  $i$  present).

472 The aim of reconstruction is to process measurements,  $m(A, R_d, x)$ , to es-  
 473 timate the material coefficients,  $t(Z, i, x)$ , which can be represented in a color  
 474 image, using material  $i$  as a single color channel.

475 Methods using material decomposition were also suggested by other authors,  
 476 Westmore *et al.* [7] who proposed a non-negative least squares fitting algorithm  
 477 to estimate the amount of a given material, or Ghammraoui *et al.* [16] who  
 478 suggested a version of maximum likelihood expectation maximization algorithm  
 479 with ordered subsets.

480 In this study, we used the maximum likelihood expectation maximization  
 481 algorithm for reconstruction[41]. This algorithm is based on the iterative max-  
 482 imization of the log-likelihood function, which is very common in the likelihood  
 483 maximization framework.

484 The estimated measurement,  $\tilde{m}$ , can be written assuming an ideal direct  
 485 system operator,  $\mathcal{F}$ :

$$\tilde{m}(A, R_d, x) = \sum_{Z,i} \mathcal{F}(A, R_d, Z, i) \cdot t(Z, i, x) \quad (13)$$

486 The most significant noise source in diffraction is photon noise, which by its  
 487 nature follows a Poisson law with parameter  $\sum_{Z,i} \mathcal{F}(A, R_d, Z, i) \cdot t(Z, i, x)$ . A  
 488 maximum likelihood approach consists in determining:

$$\hat{t} = \arg \max_{t \geq 0} P(m | t) \quad (14)$$

An iterative solution is thus given by the following algorithm [41]:

$$\hat{t}^{n+1}(Z, i, x) = \frac{\hat{t}^n(Z, i, x)}{\sum_{A, R_d} \mathcal{F}(A, R_d, Z, i)} \sum_{A, R_d} \frac{\mathcal{F}(A, R_d, Z, i) \cdot m(A, R_d, x)}{\sum_{Z, i} \mathcal{F}(A, R_d, Z, i) \cdot \hat{t}^n(Z, i, x)} \quad (15)$$

489 where  $\hat{t}^{n+1}$  is the estimate of  $t$  at the  $n$ th iteration. Choosing a positive  
 490 value for  $\hat{t}^0$  will ensure that the final results are non-negative. Here, a uniform  
 491 initialization was used.

#### 492 4. Results and discussion

493 Fig. 8 shows two sample XRD spectra (normalized by the number of incident  
 494 photons) to be distinguished; the fibroglandular region was 30 mm thick and  
 495 the incident spectrum had a maximum energy of 100 keV. These spectra were  
 496 simulated for  $x = 0$  and  $y = 0$  corresponding to the phantom center in x,y-  
 497 plane. All the following results are given for this position except the scan slice  
 498 reconstruction, where x-position varied. The gap between secondary collimation  
 499 and object was 10 mm for each simulation in this work.



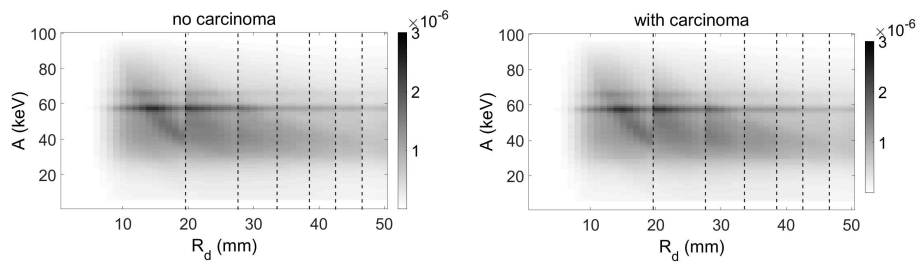
500 The segments visible in the spectra and even more clearly in their difference  
501 correspond to the limits of the different collimation holes. The dotted lines in  
502 Fig. 8.c indicate these limits. By summing the normalized spectra from Fig. 8  
503 in both directions, the object depending global sensitivity can be determined,  
504 which takes into account geometrical factors as well as the sample interaction  
505 cross-section. It corresponds to the ratio between the number of incident pho-  
506 tons on the sample and the number of detected photons. This is not exactly the  
507 same quantity as defined in section 3.1.4, which is purely geometrical (which  
508 proportion of photons emitted isotropically at a given  $Z$  can be detected by the  
509 system) and does not take into account interaction cross-section in the sample.

510 In this case, object depending global sensitivity is approximately  $2 \cdot 10^{-3}$ .  
511 Multiplication of this value by the number of incident photons gives the total  
512 number of photons detected. The  $CNR^2$  per incident photon is about  $2 \cdot 10^{-6}$ ,  
513 which is very low, explaining why the differences between the two XRD spectra  
514 (without tumor (Fig. 8.a); with tumor (Fig. 8.b)) are hardly visible. Fig. 8.c  
515 shows the difference spectrum in absolute value. The difference to be detected  
516 is only in the order of a few percent (difference values per pixel and per channel  
517 between  $10^{-8}$  and  $10^{-7}$  compared to XRD spectrum values per pixel and per  
518 channel of about  $10^{-6}$ ).

519 Hereafter, the photon number and associated dose are given for a separation  
520 of  $3\sigma$  between XRD spectra with and without tumor. This degree of separation  
521 corresponds to an almost perfect separation based on the associated analyti-  
522 cally calculated ROC curve [42]. The number of incident photons required is  
523 determined using equation 9 and will be around  $5 \cdot 10^6$ . The associated dose is  
524 calculated using equation 11. Thus, all given dose values correspond to the dose  
525 delivered to the irradiated sample volume over the whole sample thickness.

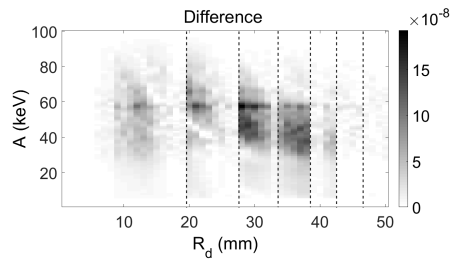
#### 526 4.1. Fibroglandular thickness

527 The results for the required photon number and the corresponding dose  
528 for an incident spectrum with a maximum energy of 100 keV and different  
529 fibroglandular thicknesses are summarized in table 3. Fibroglandular thickness



(a) XRD spectrum without tumor.

(b) XRD spectrum with tumor.



(c) Difference spectrum (absolute value).

Figure 8: Simulated XRD spectra ( $x = 0$ ,  $y = 0$ , 10 mm gap between sample and secondary collimation) normalized for the number of incident photons and the absolute value of their difference. Fibroglandular thickness: 30 mm; incident spectrum maximum energy: 100 keV. The difference to be detected is minute compared to XRD spectrum values. Dotted lines correspond to the limits of the detector parts addressed by the different holes.

530 has a negligible impact on the number of photons required, thus averaging at  
 531 about  $4 \cdot 10^6$  for a corresponding dose of about 0.24 mGy. This dose is low  
 532 compared to conventional mammography, where the dose delivered is between  
 533 1 and 3 mGy [43–45].

534 Hence, scattering signatures for cancerous tissues and fibroglandular tissues  
 535 are sufficiently decorrelated to be distinguished even when the number of de-  
 536 tected photons is small. Furthermore, as the required dose does not significantly  
 537 vary with fibroglandular tissue thickness, high density breast regions pose no  
 538 problems in XRD, unlike in conventional mammography. In fact, as used tube  
 539 voltage is significantly higher than in classical mammography photons have  
 540 higher energy and reduction of expected counts due to increased breast den-  
 541 sity is less significant. Moreover, the incident spectrum was filtered in order to  
 542 remove photons at energies below 20 keV in order to avoid unnecessary dose de-  
 543 posit by photons that are almost completely absorbed, whereas mammography  
 544 typically uses photons at these energies.

Table 3: Incident photon number and dose required to obtain a separation of  $3\sigma$  for an incident spectrum with maximum energy of 100 keV.

Fibroglandular thickness (mm)	Required photon number	Required dose (mGy)
20	$3.85 \cdot 10^6$	0.232
30	$4.20 \cdot 10^6$	0.253
40	$4.12 \cdot 10^6$	0.244

#### 545 4.2. Influence of different maximum energies

546 Fig. 9 shows the dose received by samples analyzed using our optimized sys-  
 547 tem, as a function of the maximum energy of the incident spectrum for a phan-  
 548 tom with 40 mm thick fibroglandular tissue section with a tumor at the center of  
 549 the field of view. A minimum was observed at 60 and 70 keV corresponding to a

550 dose of about 0.21 mGy. For incident spectra with lower maximum energy, the  
 551 combination of photon energy and intercepted angles is less appropriate and  
 552 absorption remains higher than coherent scattering. At higher energies, the  
 553 probability of absorption and coherent scattering continue to decrease, whereas  
 554 Compton scattering probability remains constant. Hence, the proportion of sig-  
 555 nal due to Compton scattering increases steadily with increasing photon energy,  
 556 causing blurring of the measured XRD spectrum and unnecessary radiation ex-  
 557 posure. However, even though the received dose increases with higher maximum  
 558 energy of the incident spectrum, the total dose still remains low and acceptable  
 559 compared to conventional mammography.

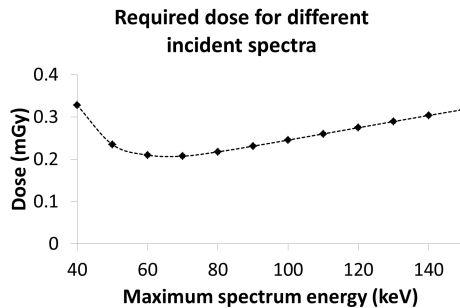


Figure 9: Dose required to separate ( $3\sigma$  separation) phantoms (40 mm fibroglandular thickness) with and without tumor as a function of the maximum energy of the incident X-ray spectrum.

560 *4.3. Impact of tumor position*

561 The dose required to distinguish between spectra with and without tumor for  
 562 different tumor offsets and maximum incident spectrum energies are presented  
 563 in Fig. 10. If the tumor is located in the center (no offset), the required dose is  
 564 the lowest. In fact, the maximum of sensitivity is in the center and the tumor  
 565 can be "seen" by five holes (Fig. 6.a). If a tumor offset is introduced, the  
 566 difference between spectra with and without tumor will not be detected by the  
 567 same holes, as the system has a variable sensitivity distribution. The first hole  
 568 always detects part of the difference, as it is sensitive throughout the sample

569 thickness. Required doses are slightly higher for other tumor positions but as  
 570 long as the tumor is in the field of view (sensitivity zone), these doses stay very  
 571 small. The detection of the tumor for the +20 mm offset, where the tumor  
 572 was positioned at  $Z_{Sample} = 45$  mm, requires an approximately 5-fold higher  
 573 dose. This position corresponds to a very low sensitivity region for the presented  
 574 system configuration. However, the total dose received still remains not higher  
 575 than with conventional mammography (1-3 mGy).

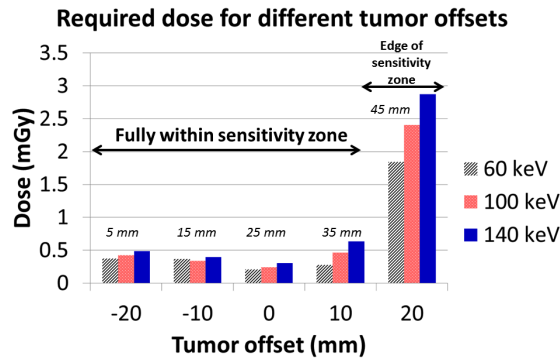


Figure 10: Dose required to distinguish ( $3\sigma$  separation) between spectra with and without carcinoma depending on the position of the tumor within the sample (depth).

#### 576 4.4. Reconstruction results

577 Fig. 11 shows an example of a simulated XRD spectrum for a phantom  
 578 (30 mm fibroglandular tissue thickness, 100 kVp incident spectrum) with a  
 579 tumor at its center, for scan position  $x=0$ , corresponding to the center of the  
 580 phantom in the  $x,y$ -plane. The number of incident photons was about  $5 \cdot 10^6$ ,  
 581 corresponding to approximately  $10^4$  detected photons and to a dose deposit of  
 582 about 0.3 mGy. This dose is consistent with the required dose determined in the  
 583 previous parts of the study and with the dose given by Ghammraoui *et al.* [15].  
 584 With an incident dose of about 0.5 mGy a small tumor of similar size could be  
 585 reconstructed in a CSCT image when pencil beam geometry was used.

586 The number of photons per channel is very low, producing a relatively noisy  
 587 spectrum. However, the number of incident photons is within the order of

588 magnitude determined previously to obtain a  $3\sigma$  separation between phantoms  
589 with and without tumor.

590 Each scan slice was simulated using the same incident photon parameters,  
591 and the image of the breast phantom was reconstructed (Fig. 12) using the  
592 previously presented reconstruction method. It should be noted that the field  
593 of view for the image was set smaller than the phantom height. Hence, only  
594 5 mm of adipose tissue is visible on the upper and lower parts of the image,  
595 rather than 10 mm.

596 This reconstruction clearly shows that the tumor will only be reconstructed  
597 if it is actually in the simulated phantom slice (Fig. 12.b and fig 12.d), and  
598 therefore no false positive results **should be produced for a tumor positioned**  
599 **in the center of the phantom**. The tumor is sharper and more intense in the  
600 reconstruction at 60 kVp. This is consistent with the fact that the optimal  
601 incident spectrum to detect the small tumor was found to be at 60 kVp. Hence,  
602 using this incident spectrum the best tumor reconstruction should be obtained.  
603 Though, compared to reconstructions at 60 kVp, reconstructions at 100 kVp  
604 present fewer edge artifacts at the limit between fibroglandular tissue and adi-  
605 pose tissue, especially at low depths within the sample. This difference is due  
606 to lack of information in the momentum transfer space at low depths. In fact,  
607 as can be seen in Fig. 6.a, the first hole in the collimation system is the only  
608 hole sensitive to low depth values. Though the corresponding scattering angles  
609 are also low because the corresponding detector part is close to the center in  
610 the x,y-plane (small  $R_d$ , Fig. 2 and Fig. 4). Thus, to cover the same momentum  
611 transfer range as for other holes intercepting higher scattering angles (higher  $R_d$   
612 values), higher energies are needed. It appears that the information obtained at  
613 60 keV maximum energy is not sufficient to distinguish between fibroglandular  
614 and adipose tissue. Reconstruction artifacts (i.e. detection of carcinoma) in the  
615 upper corners of the images at 60 kVp are also caused by the lack of informa-  
616 tion in momentum transfer space at this energy level. As for low depths, these  
617 high depth values are only covered by the first hole with very low diffraction  
618 angles. In addition to this, these edges correspond to very low system sensitivity

619 (Fig. 6.b), which further decreases the amount of available information in these  
 620 regions. Tumor detection in these regions would not be reliable for the given  
 621 position of the system especially at 60 keV.

622 To conclude, the detection of a small tumor situated in regions covered  
 623 also by another hole than the first one is optimum (in terms of dose received)  
 624 with a 60 kVp incident spectrum, for the considered system. This detection  
 625 corresponds to a binary task, presence or absence of a tumor, where it is not  
 626 necessary to identify the different tissue types present in each sample voxel.  
 627 Reconstruction of an image slice is more complex task. Here, we require spatial  
 628 information concerning each tissue type everywhere in the sample. In this case,  
 629 energies higher than 60 keV provide useful information for regions imaged with  
 630 low scattering angles. If the collimation system was conceived in a way that  
 631 edge regions were also covered by other holes, i.e. higher scattering angles, edge  
 632 artifacts might be avoided even with an incident spectrum at 60 kVp.

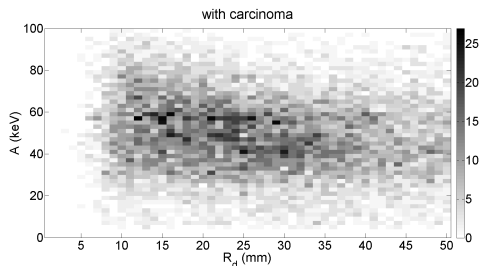


Figure 11: Example of a simulated XRD spectrum with a tumor at its center for scan position  $x = 0$  (center in  $x,y$ -plane): 30 mm thick fibroglandular region, 100 kVp incident spectrum,  $5 \cdot 10^6$  incident photons.

## 633 5. Conclusion

634 The present study indicates that coherent scattering of X-rays appears as a  
 635 very promising technique to classify breast tissues when classical mammography  
 636 gives an unclear result, and to reduce the number of unnecessary breast biopsies.

637 We dimensioned an XRD system, in particular the secondary collimation  
 638 (hole size, collimation height, number of holes, sensitivity distribution), com-

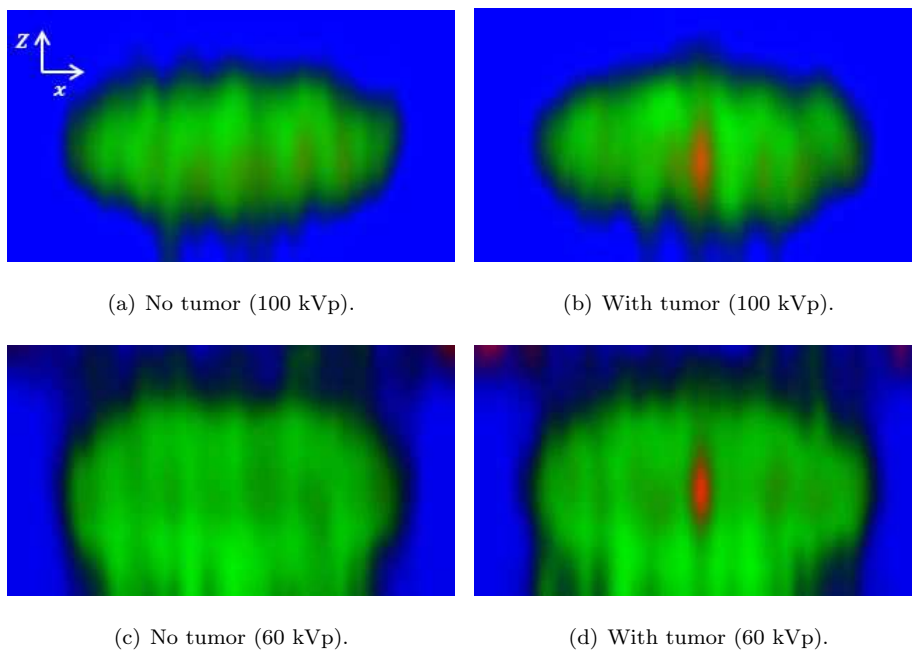


Figure 12: Reconstructed images for incident spectra with 100 keV or 60 keV maximum energy (blue = adipose tissue, green = fibroglandular tissue, red = carcinoma, black = blue+green).



639 binning EDXRD information at different scattering angles, for use as a second  
640 control after conventional mammography. In this article, we evaluated its per-  
641 formance in breast imaging in terms of separation power. Therefore, XRD  
642 spectra for phantoms with and without tumor were used and the required dose  
643 to distinguish between these two kinds of spectra was calculated.

644 It was found that the sensitivity and specificity of the method were good  
645 even when the dose delivered was moderate. To achieve a  $3\sigma$  separation, a  
646 dose around 0.3 mGy is needed if the tumor is situated in the center of the  
647 breast. This dose is very acceptable compared to conventional mammography  
648 (1-3 mGy). When the tumor was not in the center of the breast, the required  
649 dose increased slightly, but remained very low provided the tumor was located  
650 within the field of sensitivity.

651 Delivered dose is also impacted by the choice of the incident X-ray spectrum  
652 used for imaging. In fact, the number of photons, i.e. the incident dose, nec-  
653 essary to detect the tumor depends on the amount of information carried by  
654 each detected photon after coherent scattering. This information corresponds  
655 to its momentum transfer value, given by the combination of photon energy  
656 and its scattering angle. The detected scattering angles are determined by the  
657 secondary collimation. Testing of incident tungsten spectra at different tube  
658 voltages showed that for the present system the combination of scattering an-  
659 gles and photon energies was the best with an incident spectrum at 60 kVp. A  
660 system with a different distribution of intercepted scattering angles will have an  
661 optimal incident spectrum at a different tube voltage.

662 As the detection of tumors in dense breasts are often a problem in classical  
663 mammography, the impact of varying breast density on separation power of the  
664 system was tested. It turned out that different breast densities do not affect  
665 the detectability of the tumor or the order of magnitude of the required dose.  
666 Hence, XRD imaging with the presented system appears to be a well adapted  
667 solution at a second control level after conventional mammography. Though,  
668 mammography does only allow to identify a suspicious region in the plane and  
669 not the exact location of the possible tumor. Therefore, an x,y-scan of this

670 region is required, but scan-time appears to be acceptable. With an incident  
671 flux of about  $1.5 \cdot 10^8$  photons per  $\text{cm}^2$  per mAs at 1 m distance (tube current  
672 of about 10 mA), scan-time for  $10 \text{ cm}^3$  would be about 2 seconds. A scan slice  
673 in x-direction was simulated to assess the imaging qualities of the proposed  
674 XRD system. Reconstruction results confirmed that the small tumor can be  
675 detected using this system, although spatial resolution was poor compared to  
676 other imaging techniques.

677 In future work, it will be necessary to manufacture the XRD system pre-  
678 sented here so as to be able to make experimental measurements in order to  
679 confirm the simulation results. The impact of variability of breast thickness  
680 and tissue scattering signatures should also be studied.

## 681 References

- 682 [1] P. C. Johns, M. J. Yaffe, X-ray characterisation of normal and neoplastic  
683 breast tissues, *Physics in Medicine and Biology* 32 (1987) 675–695.
- 684 [2] S. H. Evans, D. A. Bradley, D. R. Dance, J. E. Bateman, C. H. Jones,  
685 Measurement of small-angle photon scattering for some breast tissues and  
686 tissue substitute materials, *Physics in Medicine and Biology* 36 (1991) 7–18.
- 687 [3] S. Pani, G. Royle, R. Speller, A. Castoldi, A. Galimberti, C. Guazzoni, Use  
688 of a novel controlled drift detector for diffraction enhanced breast imaging,  
689 *Nuclear Instruments and Methods in Physics Research Section A: Accel-*  
690 *erators, Spectrometers, Detectors and Associated Equipment* 573 (2007)  
691 133–136.
- 692 [4] G. J. R. A. Taibi, A Monte Carlo simulation study to investigate the poten-  
693 tial of diffraction enhanced breast imaging, *Nuclear Science, IEEE Trans-*  
694 *actions on* 3 (2000) 1581 – 1586.
- 695 [5] D. Cunha, A. Tomal, M. Poletti, Diffraction enhanced breast imaging  
696 through Monte Carlo simulations, *Nuclear Instruments and Methods in*

- 697 Physics Research Section A: Accelerators, Spectrometers, Detectors and  
698 Associated Equipment 652 (2011) 878–882.
- 699 [6] G. Harding, M. Newton, J. Kosanetzky, Energy-dispersive X-ray diffraction  
700 tomography, *Physics in Medicine and Biology* 35 (1990) 33–41.
- 701 [7] M. Westmore, A. Fenster, I. Cunningham, Tomographic imaging of  
702 the angular-dependent coherent-scatter cross section, *Medical Physics* 24  
703 (1997) 3–10.
- 704 [8] J. Griffiths, G. Royle, J. Horrocks, A. Hanby, S. Pani, R. Speller, Angular  
705 dispersive diffraction microCT of small breast tissue samples, *Radiation*  
706 *Physics and Chemistry* 77 (2008) 373–380.
- 707 [9] S. Pani, E. Cook, J. Horrocks, J. Jones, R. Speller, Characterization of  
708 breast tissue using energy-dispersive X-ray diffraction computed tomogra-  
709 phy, *Applied Radiation and Isotopes* 68 (2010) 1980–1987.
- 710 [10] G. Kidane, R. D. Speller, G. J. Royle, A. M. Hanby, X-ray scatter signatures  
711 for normal and neoplastic breast tissues, *Physics in Medicine and Biology*  
712 44 (1999) 1791–1802.
- 713 [11] M. J. Farquharson, K. Geraki, The use of combined trace element XRF  
714 and EDXRD data as a histopathology tool using a multivariate analysis  
715 approach in characterizing breast tissue, *X-Ray Spectrometry* 33 (2004)  
716 240–245.
- 717 [12] R. J. LeClair, M. M. Boileau, Y. Wang, A semianalytic model to extract  
718 differential linear scattering coefficients of breast tissue from energy disper-  
719 sive x-ray diffraction measurements, *Medical Physics* 33 (2006) 959–967.
- 720 [13] A. Chaparian, M. Oghabian, V. Changizi, M. Farquharson, The optimiza-  
721 tion of an energy-dispersive X-ray diffraction system for potential clinical  
722 application, *Applied Radiation and Isotopes* 68 (2010) 2237–2245.

- 723 [14] M. A. O. Ali Chaparian, Introducing an Optimized Method for Obtaining  
724 X-ray Diffraction Patterns of Biological Tissues, *Iranian Journal of Medical*  
725 *Sciences* 8 (2012) 9–17.
- 726 [15] B. Ghammraoui, L. M. Popescu, A. Badal, Monte carlo evaluation of the  
727 relationship between absorbed dose and contrast-to-noise ratio in coherent  
728 scatter breast CT, in: *Proc. SPIE 9412, Medical Imaging 2015*, 2015.
- 729 [16] B. Ghammraoui, A. Badal, L. M. Popescu, Maximum-likelihood estima-  
730 tion of scatter components algorithm for x-ray coherent scatter computed  
731 tomography of the breast, *Physics in Medicine and Biology* 61 (2016) 3164–  
732 3179.
- 733 [17] C. Malden, R. Speller, Cdznite array for the detection of explosives in bag-  
734 gage by energy-dispersive X-ray diffraction signatures at multiple scatter  
735 angles, *Nuclear Instruments and Methods in Physics Research, Section*  
736 *A: Accelerators, Spectrometers, Detectors and Associated Equipment* 449  
737 (2000) 408–415.
- 738 [18] D. O’Flynn, C. B. Reid, C. Christodoulou, M. D. Wilson, M. C. Veale,  
739 P. Seller, D. Hills, H. Desai, B. Wong, R. Speller, Explosive detection using  
740 pixellated X-ray diffraction (PixD), *Journal of Instrumentation* 8 (2013)  
741 P03007.
- 742 [19] F. Marticke, C. Paulus, G. Montémont, O. Michel, J. I. Mars, L. Verger,  
743 Multi-angle reconstruction of energy dispersive X-ray diffraction spectra.,  
744 in: *Workshop on Hyperspectral Image and Signal Processing: Evolution in*  
745 *Remote Sensing (IEEE)*, 2014.
- 746 [20] J. A. Griffiths, G. J. Royle, A. M. Hanby, J. A. Horrocks, S. E. Bohndiek,  
747 R. D. Speller, Correlation of energy dispersive diffraction signatures and  
748 microCT of small breast tissue samples with pathological analysis, *Physics*  
749 *in Medicine and Biology* 52 (2007) 6151–6164.

- 750 [21] E. Ryan, M. Farquharson, Breast tissue classification using x-ray scatter-  
751 ing measurements and multivariate data analysis, *Physics in Medicine and*  
752 *Biology* 52 (2007) 6679–6696.
- 753 [22] M. E. Poletti, O. D. Goncalves, I. Mazzaro, X-ray scattering from human  
754 breast tissues and breast-equivalent materials, *Physics in Medicine and*  
755 *Biology* 47 (2002) 47.
- 756 [23] C. R. F. Castro, R. C. Barroso, M. J. Anjos, R. T. Lopes, D. Braz, Coherent  
757 scattering characteristics of normal and pathological breast human tissues,  
758 *Radiation Physics and Chemistry* 71 (2004) 649–651.
- 759 [24] O. R. Oliveira, A. L. C. Conceição, D. M. Cunha, M. E. Poletti, C. A. Pelá,  
760 Identification of Neoplasias of Breast Tissues Using a Powder Diffractome-  
761 ter, *Journal of Radiation Research* 49 (2008) 527–532.
- 762 [25] A. Conceio, M. Antoniassi, M. Poletti, L. Caldas, Preliminary study of  
763 human breast tissue using synchrotron radiation combining WAXS and  
764 SAXS techniques, *Applied Radiation and Isotopes* 68 (2010) 799–803.
- 765 [26] D. L. Batchelar, Bone-composition imaging using coherent-scatter com-  
766 puted tomography: Assessing bone health beyond bone mineral density,  
767 *Medical Physics* 33 (2006) 904–915.
- 768 [27] G. Poludniowski, G. Landry, F. DeBlois, P. M. Evans, F. Verhaegen,  
769 SpekCalc: a program to calculate photon spectra from tungsten anode  
770 x-ray tubes, *Physics in Medicine and Biology* 54 (2009) N433.
- 771 [28] J. S. Francesc Salvat, Jos M. Fernndez-Varea, PENELOPE-2008: A Code  
772 System for Monte Carlo Simulation of Electron and Photon Transport,  
773 OECD, 2008.
- 774 [29] F. A. Duck, *Physical Properties of Tissue: A Comprehensive Reference*  
775 *Book*, Academic Press, 1990.

- 776 [30] G. Harding, B. Schreiber, Coherent X-ray scatter imaging and its applica-  
777 tion in biomedical science and industry, *Radiation Physics and Chemistry*  
778 56 (1999) 229–245.
- 779 [31] J. Greenberg, K. Krishnamurthy, D. Brady, Snapshot molecular imaging  
780 using coded energy-sensitive detection, *Optics Express* 21 (2013) 25480–  
781 25491.
- 782 [32] M. N. Lakshmanan, R. E. Morris, J. A. Greenberg, E. Samei, A. J. Kapa-  
783 dia, Coded aperture coherent scatter imaging for breast cancer detection:  
784 a Monte Carlo evaluation, in: *Proc. SPIE 9783, Medical Imaging 2016:*  
785 *Physics of Medical Imaging*, 2016.
- 786 [33] G. Montemont, S. Lux, O. Monnet, S. Stanchina, L. Verger, Studying Spa-  
787 tial Resolution of CZT Detectors Using Sub-Pixel Positioning for SPECT,  
788 *IEEE Transactions on Nuclear Science* 61 (2014) 2559–2566.
- 789 [34] A. Michalowska, O. Gevin, O. Lemaire, F. Lugiez, P. Baron, H. Grabas,  
790 F. Pinsard, O. Limousin, E. Delagnes, IDeF-X HD: A low power multi-gain  
791 CMOS ASIC for the readout of Cd(Zn)Te detectors, in: *2010 IEEE Nuclear*  
792 *Science Symposium Conference Record (NSS/MIC)*, 2010.
- 793 [35] G. Montemont, M.-C. Gentet, O. Monnet, J. Rustique, L. Verger, Simu-  
794 lation and Design of Orthogonal Capacitive Strip CdZnTe Detectors, in:  
795 *IEEE Nuclear Science Symposium Conference Record*, 2006, 2006.
- 796 [36] I. A. Cunningham, R. Shaw, Signal-to-noise optimization of medical imag-  
797 ing systems, *Journal of the Optical Society of America A, Optics and Image*  
798 *Science* 16 (1999) 621–632.
- 799 [37] S. ke Starck, M. Bth, S. Carlsson, The use of detective quantum efficiency  
800 (DQE) in evaluating the performance of gamma camera systems, *Physics*  
801 *in Medicine and Biology* 50 (2005) 1601–1609.

- 802 [38] J. A. Greenberg, M. N. Lakshmanan, D. J. Brady, A. J. Kapadia, Opti-  
803 mization of a coded aperture coherent scatter spectral imaging system for  
804 medical imaging, in: Proc. SPIE, 2015.
- 805 [39] D. J. Rhodes, M. K. O'Connor, S. W. Phillips, R. L. Smith, D. A. Collins,  
806 Molecular Breast Imaging: A New Technique Using Technetium Tc 99m  
807 Scintimammography to Detect Small Tumors of the Breast, Mayo Clinic  
808 Proceedings 80 (2005) 24–30.
- 809 [40] M. K. O'Connor, S. W. Phillips, C. B. Hruska, D. J. Rhodes, D. A. Collins,  
810 Molecular breast imaging: Advantages and limitations of a scintimammo-  
811 graphic technique in patients with small breast tumors, The Breast Journal  
812 13 (2007) 3–11.
- 813 [41] L. Shepp, Y. Vardi, Maximum likelihood reconstruction for emission to-  
814 mography, IEEE Transactions on Medical Imaging 1 (1982) 113–122.
- 815 [42] F. Marticke, G. Montémont, C. Paulus, O. Michel, J. I. Mars, L. Verger,  
816 Calcul analytique de courbes COR en imagerie de diffraction X, in: Gretsi,  
817 2015.
- 818 [43] R. A. Parry, S. A. Glaze, B. R. Archer, The aapm/rsna physics tutorial for  
819 residents: Typical patient radiation doses in diagnostic radiology, Radio-  
820 Graphics 19 (1999) 1289–302.
- 821 [44] D. Hintenlang, Dose measurement in mammography; what are we measur-  
822 ing?, in: ACMP Annual Meeting, 2008.
- 823 [45] T. Olgar, T. Kahn, D. Gosch, Average glandular dose in digital mammog-  
824 raphy and breast tomosynthesis, RöFo - Fortschritte auf dem Gebiet der  
825 Röntgenstrahlen und der bildgebenden Verfahren 184 (2012) 911–918.