

1 Dual energy subtraction method for breast calcification imaging

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18

19 Abstract

20 The aim of this work was to present an experimental dual energy (DE) method for the
21 visualization of microcalcifications (μCs). A modified radiographic X-ray tube
22 combined with a high resolution complementary metal-oxide-semiconductor (CMOS)
23 active pixel sensor (APS) X-ray detector was used. A 40/70 kV spectral combination
24 was filtered with 100 μm cadmium (Cd) and 1000 μm copper (Cu) for the low/high-
25 energy combination. Homogenous and inhomogeneous breast phantoms and two
26 calcification phantoms were constructed with various calcification thicknesses,
27 ranging from 16 to 152 μm . Contrast-to-noise ratio (CNR) was calculated from the
28 DE subtracted images for various entrance surface doses. A calcification thickness of
29 152 μm was visible, with mean glandular doses (MGD) in the acceptable levels
30 (below 3 mGy). Additional post-processing on the DE images of the inhomogeneous
31 breast phantom resulted in a minimum visible calcification thickness of 93 μm
32 (MGD=1.62 mGy). The proposed DE method could potentially improve calcification
33 visibility in DE breast calcification imaging.

34

35 **Key words:** breast imaging, dual energy, calcifications, X-rays, post-processing

36

37 **1. Introduction**

38 Breast cancer is a significant public health problem in the world up to date and is one
39 of the most common, accounting for approximately 12% of globally diagnosed
40 cancers in 2012 [1]. Among women, 16% of cancer deaths are attributed to breast
41 cancer [2]. Early detection through screening and adequate follow-up of women with
42 positive findings could significantly reduce breast cancer mortality (by 15-25%) [2].

43 Mammography is the standard method for early detection of breast carcinomas [3].

44 Microcalcifications (μ Cs) act as an early indicator of the presence of breast cancer [4]

45 and are found in around 86% of mammograms in women aged 76-79 years [5]. A

46 percentage of 30 to 50% of non-palpable breast cancers are detected solely through

47 the appearance of μ Cs during a mammogram scan [6]. Furthermore, 93% of the

48 ductal carcinoma in situ (DCIS), that is the most common type of non-invasive breast

49 cancer, is detected due to presence of calcifications in the mammograms [7].

50 Calcifications are characterized as μ Cs when their size is in the range of 0.1-1.0 mm.

51 The great majority of clustered calcifications have been proven to be within benign

52 lesions (approximately 80% of biopsies) and about 20% of these are cancerous

53 usually with no signs of tissue invasion [8]. However, since they are the smallest

54 objects that can be detected, any further improvement in the detection and

55 visualization of calcifications is an important step forward. Microcalcifications exhibit

56 higher X-ray attenuation than the surrounding breast tissue making them visible,

57 while masses are difficult to be detected because the X-ray attenuation is similar to

58 that of the healthy breast tissue [9]. However, visualization of μ Cs could be obscured

59 in mammograms by overlapping tissue structures. Therefore, small μ Cs could be

60 extremely difficult to be detected even if the signal-to-noise ratio (SNR) is high [10]

61 and [11]. Thus, their detection suffers from a high false negative rate [12].

62 Dual energy digital mammography (DEDM) can suppress the contrast between

63 adipose and glandular tissues improving the detectability of μ Cs and masses [13],[14]

64 and [15]. This technique requires two digital images, obtained with low- and high-

65 energy X-ray spectra. Weighted subtraction of the logarithmic transform of these

66 images is then performed to obtain a subtracted image that enhances μ Cs [10],[16].

67 Although dual energy (DE) imaging could suppress the tissue-structure background, it
68 also increases the intrinsic noise in the DE images [10],[17],[18] and [19].

69 Over the last decades, several researchers studied the capability of DE mammography
70 to detect microcalcifications and/or masses. Johns and Yaffe worked on a theoretical
71 optimization considering an ideal imaging system [13]. Considering monoenergetic
72 X-rays, the optimum pair of energies was 19 and 68 keV, for the low- and high-
73 energy images, respectively. The experimental evaluation was accomplished with a
74 prototype digital scanned projection radiography system using X-ray beams at 50 and
75 115 kV [20]. Brettle and Cowen [11] extended the theoretical model of Boone and
76 Shaber [21] who studied novel detector combinations for energies close to those
77 proposed in a previous study [13]. Asaga et al applied DEDM method to clinical
78 examinations using a molybdenum anode tube at 28 and 40 kV and a computed
79 radiography system [22]. The GE Senographe 2000D unit featuring dual-track anodes
80 (Mo and Rh) was used in DE studies for μ C detection, with tube voltages ranging
81 from 25 to 49 kV and a hydrogenated amorphous silicon (aSi:H) flat panel detector
82 coupled with a thallium-doped cesium iodide (CsI:Tl) converter layer [17],[18] and
83 [19]. The same configuration was used in another study aiming to the detection of
84 masses [15]. Furthermore, the use of dual energy iodine-based contrast enhanced
85 digital mammography (CEDM) has been evaluated for the improvement in the
86 detection of lesions [23] and [24]. Digital X-ray detectors, based on complementary
87 metal oxide semiconductor (CMOS) active pixel sensors (APS), have been recently
88 introduced in medical imaging applications [25], [26] and [27]. A pixel pitch smaller
89 than 70-100 μ m, that is currently available in flat panels, can improve the detection
90 and characterization of μ Cs [28].

91 In a previous simulation study [29], we investigated a dual energy method
92 incorporating a modified radiographic X-ray unit combined with a high resolution
93 CMOS sensor. Initially, monoenergetic X-ray beams were studied in the range
94 between 15 and 90 keV, at 1 keV increments. The optimum monoenergetic pair was
95 23 keV and 58 keV for the low- and high-energy, respectively. An approximation to
96 monoenergetic beams was followed using polyenergetic X-ray spectra under K-edge
97 filtration [29], [30], [31] and [32]. Various peak voltages, filter materials and
98 thicknesses were examined in order to obtain spectra with mean energies similar to
99 the optimal monoenergetic pair. This was achieved by 40/70 kV spectra combination

100 filtered with 100 μm cadmium (Cd) and 1000 μm copper (Cu) for the low/high
101 energy, respectively.

102 In the current study, an experimental DE method is presented based on the simulation
103 exposure conditions. The integrated prototype system used, consisted of a modified
104 tungsten (W) anode X-ray tube combined with a high resolution CMOS APS sensor
105 (pixel pitch of 22.5 μm), coupled with a 33.91 mg/cm^2 terbium-doped gadolinium
106 oxysulfide ($\text{Gd}_2\text{O}_2\text{S:Tb}$) scintillator screen. Custom-made homogenous and
107 inhomogeneous breast phantoms and two different calcification phantoms, as well as,
108 the ACR mammography accreditation phantom were used. Furthermore, post-process
109 noise reduction was applied on the dual energy images.

110

111 **2. Materials and Methods**

112 *2.1. Experimental image acquisition process*

113 The Del Medical Eureka radiographic system [33] with the following characteristics
114 was used: W anode, 3 mm aluminum (Al) nominal inherent filtration, maximum load
115 50 kW, tube voltage range 40-150 kV and focal spot size 0.6 mm. The added filtration
116 was 100 μm Cd (Alfa Aesar 11371, 99.9975%) at 40 kV and 1000 μm Cu (PTW
117 99.99%) at 70 kV for the low- and high-energy spectra, respectively. The detection
118 system that was used, consisted of a $\text{Gd}_2\text{O}_2\text{S:Tb}$ phosphor screen (Min-R 2190 with
119 mass thickness of 33.91 mg/cm^2) coupled to an optical readout device including a
120 CMOS Remote RadEye HR photodiode pixel array. The CMOS photodiode array has
121 a format of 1200 \times 1600 pixels, corresponding to an active area of 27 mm \times 36 mm,
122 with a pixel pitch of 22.5 μm . The $\text{Gd}_2\text{O}_2\text{S:Tb}$ screen was directly overlaid onto the
123 active area of the CMOS (no fiber optic plate or coupling gel were used) [34] and
124 [35]. This scintillator was selected due to its higher detective quantum efficiency
125 (DQE) compared to other scintillators [34], [35] and [36]. The source-to-detector
126 distance (SDD) was set at 66 cm and no antiscatter grid was used during image
127 acquisitions. A Radcal 2026C dosimeter was positioned at the surface of the breast
128 phantom and the entrance surface dose (ESD) was measured for various tube current-
129 time products (400, 200 mA s for the LE and 250, 200 mAs for the HE). Mean
130 glandular dose (MGD) was calculated using Eq. (1) [37]:

131

$$132 \quad MGD = DgN \text{ ESD} \quad (1)$$

133

134 Normalized glandular dose (DgN) data for a 4 cm breast thickness of 0% and 100%
135 glandularity were obtained from published data [38]. Then, DgN values of 0% and
136 100% glandularity were fitted with a modified Fermi-Dirac distribution function [29].
137 For 50% glandular tissue the averaged MGD value was used. MGD was calculated for
138 the low- and the high-energy exposures and then summed to obtain the total MGD.
139 The ESD and MGD values for the LE and HE image acquisitions are shown in Table
140 1.

141

142 **Table 1**

143 ESD and MGD values for 50% glandularity.

ESD (mGy)			MGD (mGy)		
LE	HE	Total	LE	HE	Total
2.28	0.97	3.25	1.27	1.12	2.39
2.28	0.78	3.06	1.27	1.00	2.27
1.14	0.97	2.11	0.62	1.12	1.74
1.14	0.78	1.92	0.62	1.00	1.62

144

145 Weighted log-subtraction was used to generate the DE subtraction images, according
146 to Eq. (2):

147

$$148 \quad \ln(DE) = \ln(HE) - w \ln(LE) \quad (2)$$

149

150 where HE and LE are the high- and low-energy images, and w is the weighting
151 factor.

152 For each pair of low- and high-energy images, a number of DE images were
153 generated for various weighting factors in the range of 0 to 1, at 0.1 intervals. The
154 standard deviation (σ) of various background regions in the inhomogeneous breast
155 phantom was calculated using a custom-developed algorithm. For the minimum σ , the
156 corresponding w was selected. A w factor of 0.6 was adopted in the whole study, as
157 indicated by the inhomogeneity.

158 The CNR was defined as the ratio of the absolute mean signal difference between
159 calcification and background regions divided by the standard deviation of the
160 background:

$$162 \quad CNR_{DE} = \frac{|\overline{S_C} - \overline{S_B}|}{\sigma_B} \quad (3)$$

163
164 where C and B denote the calcification and background regions [39].
165 The target signal ($\overline{S_C}$) was obtained as the mean pixel value over a 21×21 pixels
166 region of interest (ROI) in the middle of the circular region, while the mean
167 surrounding background ($\overline{S_B}$) was estimated by averaging six regions of the same size
168 located at positions around the target (for better statistics). The corresponding
169 standard deviation (σ_B) was also obtained from the mean surrounding background
170 regions. The CNR_{DE} threshold value for calcification visibility was 3 [10].

171

172 2.2. Phantoms

173 2.2.1. Custom-made breast phantoms

174 2.2.1.1. Homogenous phantom

175 Initially, a homogeneous breast phantom was used in order to validate the simulation
176 study. Polyethylene (PE) and polymethyl methacrylate (PMMA) slabs were used as
177 adipose and glandular tissue equivalent materials, respectively [40]. These materials
178 were selected due to their similarity to breast tissue X-ray transmission properties.
179 The total breast thickness was 4 cm, consisting of 50/50 (w/w) PE/PMMA slabs. Each
180 slab had uniform thickness, with dimensions of 10 cm×10 cm.

181

182 2.2.1.2. Inhomogeneous phantom

183 An inhomogeneous phantom, composed of lard and fresh egg whites, was used to
184 simulate adipose and glandular tissue, respectively, since they have similar
185 composition to the corresponding human tissues [41] and [42]. Lard and fresh egg
186 whites were placed in a tank, constructed by 0.5 cm thick PMMA slabs with
187 dimensions of 10 cm×10 cm×4 cm, in a proportion of 50% w/w. The mixture was
188 produced in our laboratory according to the method described by Freed et al [41] and
189 [42].

190

191 *2.2.1.3. Custom-made calcification phantoms*

192 Two different calcification phantoms were constructed. The two PMMA slabs used,
193 had dimensions of 10 cm×10 cm and thicknesses of 0.2 and 0.4 cm. In each slab, five
194 holes of 3 mm diameter were drilled and filled with a mixture of epoxy resin and
195 hydroxyapatite (HAp), described chemically as $\text{Ca}_5\text{HO}_{13}\text{P}_3$ (FLUKA 21223, $\geq 90\%$
196 purity). The various HAp thicknesses were obtained using different proportions of
197 epoxy resin and HAp. The proportions were calculated according to Eq. (4):

198

199
$$\frac{m_{\text{HAp}}}{m_{\text{epoxy}}} = \frac{t_{\text{HAp}} d_{\text{HAp}}}{(T - t_{\text{HAp}}) d_{\text{epoxy}}} \quad (4)$$

200

201 where m_{HAp} , m_{epoxy} are the masses of the HAp and epoxy resin (g), T is the thickness
202 of the PMMA slab (cm), t_{HAp} and d_{HAp} are the thickness (cm) and density (3.18
203 g/cm^3) [43] of HAp, respectively and d_{epoxy} is the density of epoxy resin ($1 \text{ g}/\text{cm}^3$).

204 The calcification phantoms are referred to as C_1 and C_2 phantoms corresponding to the
205 0.2 and 0.4 cm PMMA thicknesses, respectively. The HAp thicknesses, as well as, the
206 corresponding masses of HAp and epoxy resin in the C_1 and C_2 phantoms, are shown
207 in Table 2. The calcification thicknesses will be referred as 16, 31, 46, 61, 76 μm for
208 C_1 , and 31, 61, 93, 122, 152 μm for C_2 . The calcification phantoms were placed
209 below the breast phantoms.

210

211 **Table 2**

212 Calcification thicknesses and corresponding masses used in C_1 and C_2 phantoms.

Masses (g)		Calcification thicknesses (μm)	
HAp	Epoxy resin	C_1 phantom	C_2 phantom
0.02	0.62	15.85	31.70
0.03	0.68	30.77	61.54
0.06	0.78	46.32	92.63
0.10	1.01	60.76	121.52

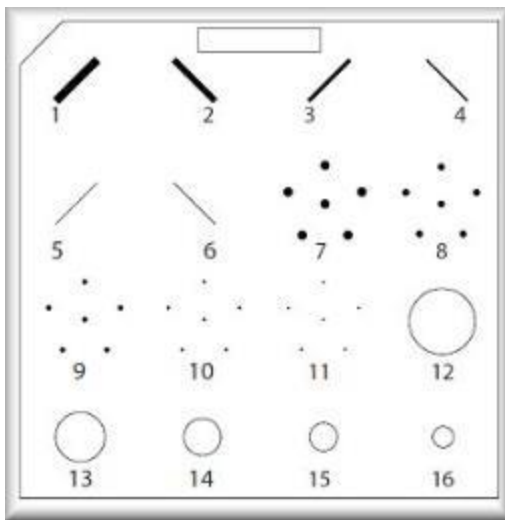
0.14 1.12 75.70 151.40

213

214 2.2.2. Accreditation phantom

215 The mammographic accreditation phantom RMI model 156 (Fig. 1) was also used for
 216 a perception of the calcification size and further verification of the present method
 217 [44]. Since the aim of this study is the calcification visibility, the calcification specks
 218 groups were selected for irradiation. The phantom specks with diameters 540 μm (7),
 219 400 μm (8), 320 μm (9), 240 μm (10), and 160 μm (11) correspond to an equivalent
 220 hydroxyapatite attenuation of 234.68, 173.71, 138.90, 104.14 and 69.40 μm ,
 221 respectively.

222



223

224 **Fig. 1.** ACR accreditation phantom.

225

226 Table 3 summarizes the details of the used phantoms.

227

228 **Table 3**

229 Summary of phantoms used.

Phantom number	Type	Features	Comments
1	<i>Homogenous breast phantom</i>	PE / PMMA slabs (50/50 w/w)	T = 4 cm
2	<i>Inhomogeneous breast phantom</i>	Lard / Egg whites (50/50 w/w)	T = 4 cm
3	Calcification phantom – C_1	Thicknesses:	Mixture of epoxy resin

		16, 31, 46, 61, 76 μm	and hydroxyapatite -
4	Calcification phantom – C_2	Thicknesses: 31, 61, 93, 122, 152 μm	holes of 3 mm diameter
5	ACR accreditation phantom	Speck groups of various sizes	Equivalent HAp thicknesses were computed

230

231 *2.3. Post-processing of the DE images*

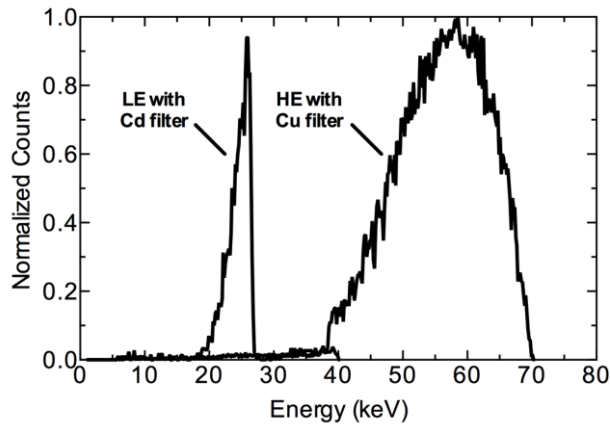
232 As aforementioned, the used CMOS APS X-ray detector has a pixel size of 22.5 μm ,
 233 which is much smaller compared to those used in previous dual energy studies
 234 [15],[17],[18] and [19]. This pixel pitch corresponds to the highest resolution that can
 235 be achieved, with lower SNR values. Such a small pixel pitch allows pixel binning in
 236 order to increase the SNR. Pixel binning is a simple method in which the signal in
 237 squares of neighboring pixels is averaged off-chip (after the signal is read-out).
 238 Hereto, the binning method was applied on the DE images generated by the lowest
 239 examined dose (MGD=1.62 mGy). Kernel sizes of 2 \times 2, 3 \times 3 and 4 \times 4 were tested,
 240 resulting in effective pixel sizes of 45, ~68 and 90 μm , respectively. For the DE
 241 images of the inhomogeneous breast phantom, we studied how pixel binning affects
 242 the measured CNR_{DE} values. Post-processing of the DE images of the ACR phantom
 243 was also included.

244

245 **3. Results**

246 Figure 2 shows the experimental Cd and Cu filtered spectra at 40 and 70 kV
 247 respectively, measured with a portable Amptek XR-100T spectrometer, based on a
 248 Cadmium Telluride (CdTe) crystal-solid-state detector [31]. The corresponding mean
 249 energies for the low- and high-energy spectra were 26 keV and 55 keV, resulting in
 250 29 keV difference between the two spectra.

251



252

253 **Fig. 2.** LE spectrum at 40 kV filtered with 100 μm Cd and HE spectrum at 70 kV
 254 filtered with 1000 μm Cu.

255

256 3.1. Custom-made breast phantoms

257 Two different *C* phantoms were constructed and irradiated with various beam
 258 conditions. Dual energy images were obtained after applying the logarithmic
 259 weighted subtraction technique.

260 Table 4 shows the measured CNR_{DE} values of the C_1 and C_2 phantoms and all
 261 examined ESD/MGD values, for the homogenous and inhomogeneous breast
 262 phantoms. For calcification thicknesses existing in more than one *C* phantom the
 263 CNR_{DE} values correspond to the averaged CNR_{DE} values (i.e. 31 μm and 61 μm
 264 thick calcifications). The calcification thicknesses of 16 μm and 31 μm of C_1 and C_2
 265 phantoms, respectively, could not be depicted either in the LE or DE image.

266 Calcification thickness of 152 μm was visible in both homogenous and
 267 inhomogeneous phantoms, as yielded CNR_{DE} values above the threshold of 3. For the
 268 former, this applies to MGD ranging from 1.74 to 2.39 mGy, while in the latter, only
 269 to the higher MGD value (2.39 mGy).

270

271 **Table 4**

272 CNR_{DE} values of C_1 and C_2 phantoms for the homogenous and the inhomogeneous
 273 breast phantom.

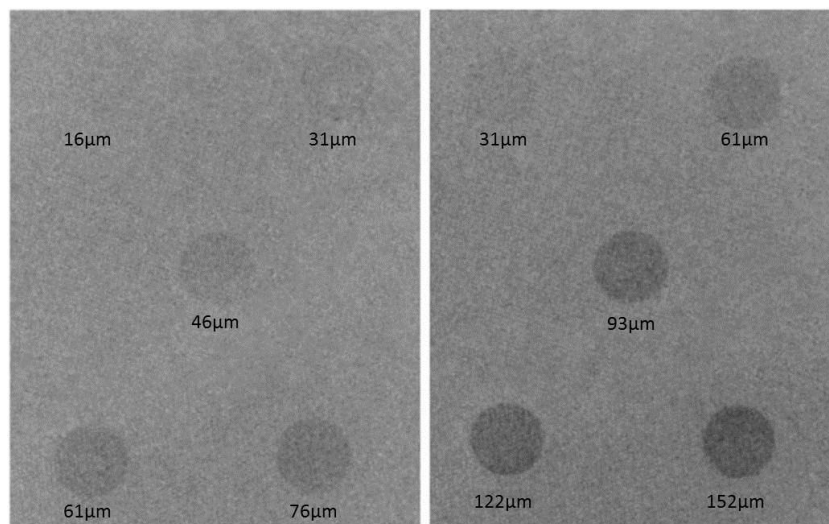
Breast Phantom	ESD/MGD (mGy)	CNR_{DE} 31 μm	CNR_{DE} 46 μm	CNR_{DE} 61 μm	CNR_{DE} 76 μm	CNR_{DE} 93 μm	CNR_{DE} 122 μm	CNR_{DE} 152 μm
Homogenous	3.25/2.39	0.71	1.03	1.85	2.10	2.32	2.85	3.47

	3.06/2.27	0.56	0.85	1.78	1.92	2.14	2.23	3.02
	2.11/1.74	0.62	0.92	1.81	1.98	2.25	2.61	3.05
	1.92/1.62	0.49	0.71	1.69	1.82	2.01	2.14	2.78
Inhomogeneous	3.25/2.39	0.45	0.84	1.40	1.56	1.76	2.28	3.05
	3.06/2.27	0.34	0.66	1.11	1.22	1.40	1.88	2.09
	2.11/1.74	0.38	0.72	1.17	1.29	1.60	2.07	2.37
	1.92/1.62	0.21	0.60	1.07	1.14	1.31	1.76	1.86

274

275 Figure 3 shows indicative DE images of the 4 cm thick homogenous phantom
 276 combined with C_1 , C_2 phantoms for MGD of 1.62 mGy.

277



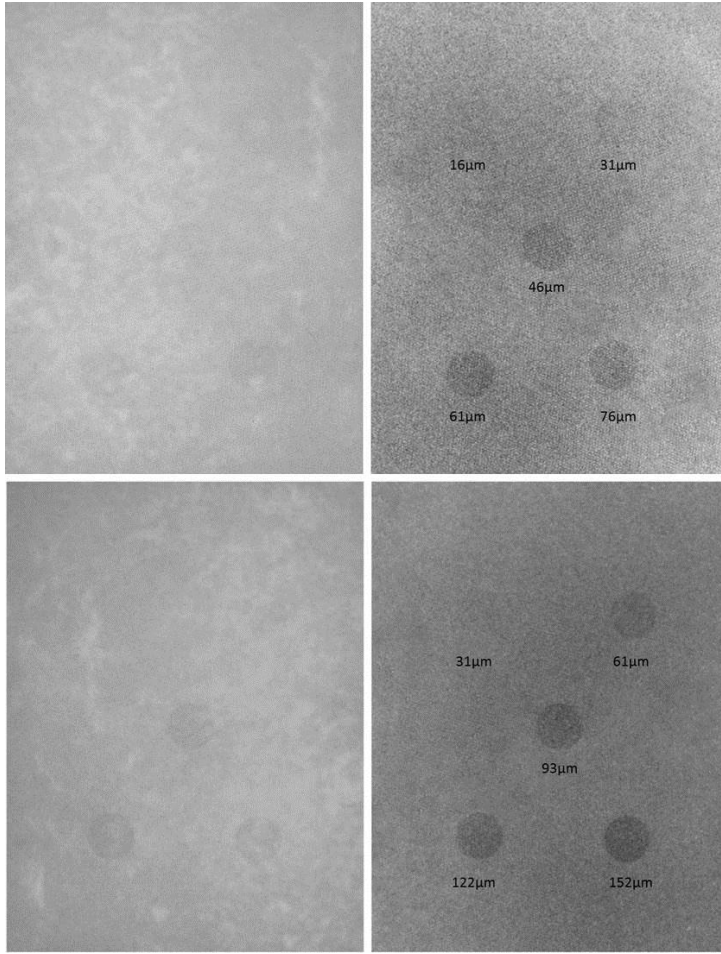
278

279 **Fig. 3.** DE images of the homogenous phantom with C_1 (left) and C_2 (right) phantoms.

280

281 Figure 4 shows indicative LE and DE images of the 4 cm thick inhomogeneous
 282 phantom combined with C_1 , C_2 phantoms for the lowest MGD. The calcification
 283 thicknesses ranged from 16 μm to 76 μm and 31 μm to 152 μm in the C_1 and C_2
 284 phantoms, respectively. The calcification thicknesses of 31 μm and 46 μm in C_1
 285 phantom and 61 μm in C_2 phantom that are obscured in LE images are revealed in
 286 DE images, due to the suppression of the background structures. Furthermore, for the
 287 calcifications depicted in both LE and DE images (i.e. 61 μm in C_1 phantom, 122 μm
 288 in C_2 phantom) their margins appear to be more distinct in DE images.

289



290

291 **Fig. 4.** LE (left) and DE (right) images of the inhomogeneous phantom for MGD of
 292 1.62 mGy. C_1 phantom images (top row) and C_2 phantom images (bottom row).

293

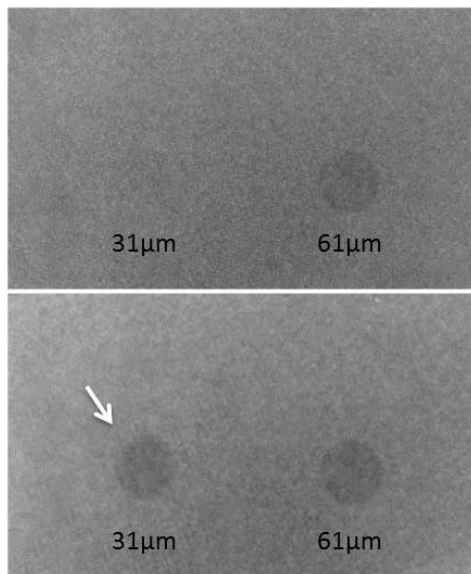
294 The CNR_{DE} values of the post-processed DE images of C_1 and C_2 phantoms
 295 combined with the inhomogeneous breast phantom are presented in Table 5.
 296 Similarly, for calcification thicknesses existing in both calcification phantoms, the
 297 averaged CNR_{DE} is used. In the original DE image (bin 1×1) the CNR_{DE} values of all
 298 calcifications were below the threshold. The visible calcification thickness was
 299 reduced to 93 μm with improved CNR_{DE} values (greater than 3) for kernel sizes of 3
 300 and 4 pixels. However, calcification thicknesses ranging from 31 to 76 μm were not
 301 visible in any of the processed DE calcification images.

302

303 **Table 5**
 304 CNR_{DE} values of C_1 and C_2 phantoms for the post-processed inhomogeneous breast
 305 phantom DE images.

Calcification thickness (μm)	CNR_{DE}			
	Bin 1 \times 1	Bin 2 \times 2	Bin 3 \times 3	Bin 4 \times 4
31	0.21	0.44	0.70	0.83
46	0.60	0.80	0.98	1.38
61	1.07	1.74	2.03	2.46
76	1.14	2.05	2.51	2.95
93	1.31	2.62	3.16	3.50
122	1.76	2.95	3.52	3.90
152	1.86	3.16	3.89	4.11

306
 307 Figure 5 shows a section of the original DE image (lowest MGD, 1.62 mGy) of the
 308 inhomogeneous breast phantom combined with the C_2 phantom and the same section
 309 of the binning image with a 4 \times 4 kernel size. The margins of the left calcification (31
 310 μm) appear more clearly in the post-processed image due to noise reduction.
 311



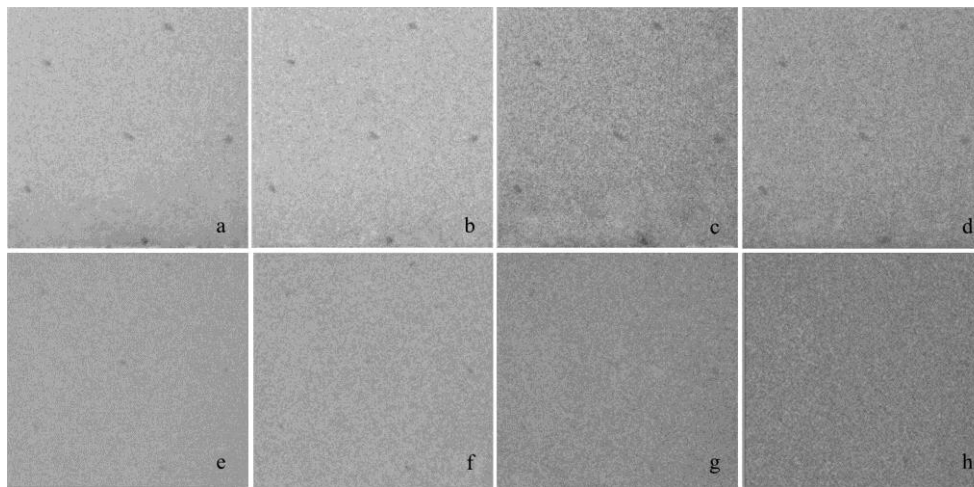
312
 313 **Fig. 5.** Same section of the inhomogeneous phantom image combined with the C_2
 314 phantom, without (top) and with (bottom) pixel binning using a 4 \times 4 kernel. The
 315 calcification thickness of 31 μm (arrow) is enhanced in the binning image.

316

317 *3.2. Accreditation phantom*

318 Figure 6 shows two sections of the accreditation phantom containing the speck groups
319 (7) and (8) (diameters 540 μm and 400 μm , corresponding to 234.68 μm and 173.71
320 μm hydroxyapatite, respectively) for all MGD values. The μCs of the specks group
321 (7) were visible in all DE images, Figs. 6(a-d). All the details of the specks group (8)
322 were visible in Figs. 6(e-f), while the specks were barely visible in Figs. 6(g-h).

323



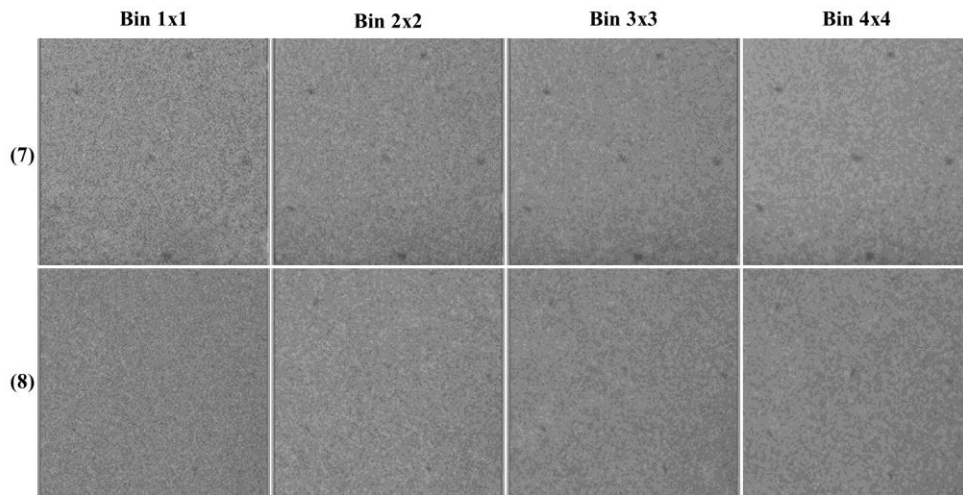
324

325 **Fig. 6.** Sections of the DE images of the accreditation phantom showing the specks
326 groups (7) and (8) at the top and bottom row respectively, for all MGD values.

327

328 The effect of post-process pixel binning on the DE images of ACR phantom is shown
329 in Fig. 7. All specks of speck group (8) are more clearly visible on the binning image
330 with a 4 \times 4 kernel, due to the decreased noise level.

331



332

333 **Fig. 7.** Sections of the post-processed DE images of the accreditation phantom
 334 showing the specks groups (7) and (8) for MGD value of 1.62 mGy.

335

336 **4. Discussion and Conclusions**

337 The main advantage of DE imaging is the ability to depict calcifications in a largely
 338 uniform background, where tissue structures (anatomical noise) have been suppressed
 339 [10] and [18]. In single energy techniques, the visible calcification thickness varies
 340 across the image [18] and [45]. When complex tissue structures are present, the
 341 visible calcification thickness increases [46]. On the other hand, when dual energy
 342 techniques are applied the visible calcification thickness is not changing across the
 343 image due to the suppression of tissue structures. Under the current implementations
 344 of DEDM, the minimum detectable μC size ranges from 300 to 355 μm [10],[19]
 345 and [45]. After noise reduction techniques, the minimum μC size was decreased to
 346 250 μm [19].

347 The CNR values depend on various factors such as irradiation conditions, dose to the
 348 subject and most importantly the size of the object [47]. For specific contrast and
 349 noise, when the shape of the object is the same but the size decreases, larger objects
 350 are more effectively visible compared to the smaller ones [47]. In the present DE
 351 study, the CNR in the subtracted images was calculated for various ESDs and breast
 352 phantoms, in order to determine the minimum detectable calcification.

353 In the case of the custom-made calcification phantoms, the thicknesses of the circular
 354 objects reproduce the absorption of μCs and not their sizes. The calcification CNR
 355 calculated for this phantom is expected to be higher than that of a spherical small size
 356 object. In the latter case, the mean pixel value (MPV) ranges from a peak,

357 corresponding to the attenuation from the maximum thickness of the sphere, to a pixel
358 value close to that of the background. Thus, the MPV will be lower than that of a
359 circular cylindrical object (custom-made calcification phantom) where the radiation
360 attenuates along its longitudinal axis. Each pixel value of this circular cylindrical
361 object will be almost equal to the peak pixel value of the spherical object.
362 Additionally, the pixel pitch will have a significant impact in degrading the CNR
363 value when it is comparable to that of a small size object. In our study, this effect is
364 reduced by the use of a CMOS detector with small pixel pitch (22.5 μm). For
365 example, if a spherical μC is irradiated with a diameter from 150 to 500 μm , the μC
366 diameter length will span across approximately from 7 to 22 pixels. Under these
367 conditions, the pixel values of the central area will be close to maximum.

368 In both breast phantoms, an inversion can be observed between the CNR_{DE} values of
369 DE images acquired with 3.06 and 2.11 mGy (Table 4). In addition to the total
370 entrance dose, the dose allocation between the low- and high-energy exposures affects
371 the calculation of CNR in the DE subtracted images. Based on a previous simulation
372 study, it was found that the optimal low-energy dose ratio, LDR (defined as low-
373 energy dose over total dose) ranged from 0.2 to 0.65 [29]. In the case of 3.06 mGy,
374 the LDR was 0.75 which was above the optimal range. On the contrary, for 2.11 mGy,
375 the LDR was 0.54 that falls within this range [29].

376 In the case of the lowest examined MGD (1.62 mGy), the DE images of the
377 inhomogeneous breast phantom were further processed and the CNR_{DE} was
378 recalculated. Hardware pixel binning (on-chip) is designed to increase the sensitivity
379 of an image sensor by combining multiple pixels into one larger pixel in the expense
380 of spatial resolution loss [48]. On the other hand, software pixel binning (off-chip)
381 combines multiple pixel values after the signal read out. The result of the off-chip
382 pixel binning can be considered as a filtered version of the input image where the
383 details are smoothed [48]. Between the two methods, there is a slight difference in the
384 image quality, however the spatial resolution of the off-chip method is better [49].
385 Comparing the different examined kernels, post-process pixel binning with a 4×4
386 kernel resulted in higher CNR_{DE} values, approximately 3 times that of the original DE
387 image (Table 5). Furthermore, calcification of 31 μm was clearly shown due to the
388 decrease of image noise (Fig. 5). Similar to the findings for the inhomogeneous

389 calcification phantom, image noise was decreased in the 4×4 binned image of the
390 ACR phantom and as a result all the specks of group (8) were clearly visible (Fig. 7).
391 The speck groups of the ACR phantom, corresponding to hydroxyapatite attenuation
392 of 138.90, 104.14 and 69.40 μm were not visible due to the fact that the phantom
393 specks are composed of aluminum oxide (Al_2O_3 , density 3.97 g/cm^3) instead of
394 calcium compound, such as hydroxyapatite. The low-/high-energy linear attenuation
395 coefficient ratio of Al_2O_3 is 4.287, while in a Ca compound (i.e. hydroxyapatite) this
396 ratio equals to 6.484. This value for Ca differs more than 50% from the value
397 corresponding to aluminum oxide. Thus, when an Al compound is used instead of Ca,
398 the unknown variables' coefficients of the linear equations system obtain from the
399 Beer-Lambert law [10] and [50] derived from Al compound, adipose and glandular
400 tissue are less different than those derived from Ca compound, adipose and glandular
401 tissue, resulting in limited speck visibility. Phantoms with Ca compound specks
402 would be more appropriate for DE studies; however they were not available in our
403 laboratory.

404 The improvement in visualization of calcifications, in the current method, is attributed
405 to the use of higher kV X-rays from a modified radiographic unit with heavy filtering
406 leading to larger spectral separation, while preserving MGD within acceptable levels
407 [51]. MGD can be reduced when the filter thickness increases and/or low- and high-
408 energy tube voltages decrease. This cannot be applied using commercially available
409 mammographic or radiographic units, since an increase in filter thickness demands
410 higher X-ray fluence. Furthermore, as indicated by initial simulation studies [29], the
411 optimum kV combination for low- and high-energy (35/70 kV) cannot be applied in
412 commercial units, since they operate either in the range of 20-49 kV (mammography)
413 or in the 40-150 kV range (radiography). On the other hand, the use of two different
414 units cannot be easily accomplished not only due to the misregistration of the focal
415 spots between the two acquired images, but the complete imaging geometry. A
416 modified unit with tungsten anode and X-ray tube voltage ranging from 20 to 70 kV
417 would be a preferable solution to these issues. Additionally, a focal spot size of 0.6
418 mm, used in this work, reduces the spatial resolution compared to the typical
419 mammographic focal spot sizes (0.1 mm, small and 0.3 mm, large). However, the use
420 of smaller focal spot sizes will require extended exposure times leading to excessive
421 heat load. Thus, an X-ray tube with focal spot size smaller than 0.3 mm and advanced

422 loading capability is preferable. Another solution to improve resolution, while
423 keeping the 0.6 mm focal spot size, would be increasing the SDD, which subsequently
424 decreases the penumbra. In this case, photon flux will be reduced. A compromise
425 between kV range, exposure time, focal spot size and SDD, is an open issue for the
426 manufacturing of a dedicated X-ray system. Furthermore, calcification visibility could
427 be improved with the use of antiscatter grid, in the expense of increased dose to the
428 patient [9]. A radiographic system considering all the above (kV range, exposure
429 time, focal spot size and SDD) would improve calcification visibility in DE images.
430 Additionally, using such a radiographic system, the masses will also be depicted in
431 the LE images, since mean energies similar to that of the conventional mammography
432 can be used.

433 In the future, the proposed DE method will be further assessed by phantoms of
434 different glandularities. Also, a special custom-made phantom with various μC sizes
435 will be constructed and it is expected that the CNR values will be degraded compared
436 to that of the current custom-made phantom. Moreover, commercially available
437 medical detector and CMOS APS X-ray detector with larger dimensions and
438 advanced characteristics [25],[26],[27],[52] and [53] will be used.

439

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443

444 **References**

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