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# Optimization of Contrast to Tissue Ratio by Frequency Adaptation in Pulse Inversion Imaging

Sébastien Ménigot, Jean-Marc Girault, *Member, IEEE*, Iulian Voicu,  
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## Abstract

Contrast imaging has significantly improved clinical diagnosis by increasing the contrast-to-tissue ratio after microbubble injection. Pulse inversion imaging is the most commonly used contrast imaging technique, as it greatly increases the contrast-to-tissue ratio by extracting microbubble nonlinearities. The main purpose of our study was to propose an automatic technique providing the best contrast-to-tissue ratio throughout the experiment. For reasons of simplicity, we proposed to maximize the contrast-to-tissue ratio with an appropriate choice of the transmit frequency. The contrast-to-tissue ratio was maximized by a closed loop system including the pulse inversion technique. An algorithm based on the gradient provided iterative determination of the optimal transmit frequency. The optimization method converged quickly after six iterations. This optimal control method is easy to implement and it optimizes the contrast-to-tissue ratio by selecting the transmit frequency adaptively.

## Index Terms

Adaptive system, closed loop system, contrast enhancement, microbubbles, optimal control, optimization, pulse inversion technique, signal processing, transmitted pulse, ultrasound imaging.

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## I. INTRODUCTION

14

15 **O**VER the past twenty years, improvements in the sensitivity of medical ultrasound imaging systems  
16 have provided more accurate medical diagnoses through intravenous injection of ultrasound  
17 contrast agents containing microbubbles. The perfusion imaging thus obtained, as in the myocardium  
18 or in tumors for example, has provided physiological and pathological information [1]. Initially, the  
19 linear interactions between the microbubbles and the ultrasound waves were only operated in B-mode, to  
20 increase the sensitivity between the tissue and the microbubbles. However, the use of ultrasound contrast  
21 imaging was revolutionized in clinical practice when the nonlinear interaction was taken into account.  
22 The nonlinearity of contrast agent responses has become a major focus of research to obtain the best  
23 contrast-to-tissue ratio (*CTR*). However, obtaining an ideal method has been limited by two factors. First,  
24 good separation of the harmonic components requires a limited pulse bandwidth [2], which reduces the  
25 axial resolution as in second harmonic imaging [3], and secondly the effects of the ultrasound wave  
26 propagation limit the *CTR* because of the presence of nonlinear components generated in tissue [1].

27 Several imaging methods have been proposed to improve *CTR* and/or resolution. Some of the best known  
28 techniques such as second harmonic imaging [3], subharmonic imaging [4], super harmonic imaging [5],  
29 imaging using second order Volterra filter [6] and attenuation correction [7] have been mainly based  
30 on post-processing. Some techniques have been based on post-processing with discrete or continuous  
31 encoding of the amplitude, the phase or the frequency of the transmitted ultrasound wave. They use  
32 differences in nonlinear acoustic signatures of microbubbles and tissue, such as pulse inversion [8], power  
33 modulation [9], contrast pulse sequencing [10], pulse subtraction [11] and harmonic chirp imaging [12].

34 The setting parameters must be correctly adjusted for optimal use of these methods. However, there  
35 is usually no optimization process, the pulse settings to date being manual and pre-selected. The aim of  
36 the study presented here was to find the setting parameters of the technique to be used to provide the  
37 best *CTR*, the best resolution or the best compromise between *CTR* and resolution. This step is crucial.  
38 Unfortunately, solution of the problem often requires *a priori* knowledge of the medium and transducer  
39 that is inaccessible. Moreover, the existing methods cannot adjust to different variations throughout a  
40 qualitative medical examination, as may be the case for a variation in microbubble concentration [13] or  
41 microbubble size [14]. No method has been able to solve this problem to date.

42 In this study, we aimed to solve this problem through the concept of the optimal command: the system

43 parameters  $\theta$  were set by optimizing a cost function  $J$  (e.g. the  $CTR$ ):

$$\theta^* = \arg \max_{\theta} (J(\theta)), \quad (1)$$

44 where  $\theta^*$  are the optimal system parameters. We therefore replaced the current system with a closed loop  
 45 system whose transmitted pulse was modified by feedback. Implementation of optimization required two  
 46 steps: specification of the cost function  $J$  and specification of the setting parameters  $\theta$ .

47 In the first step, the cost function  $J$  was chosen to take into account the user's needs and the medical  
 48 application. Here, in contrast harmonic imaging, the cost function was the  $CTR$ . This choice was also  
 49 justified by the microbubble sensitivity of the  $CTR$ . Moreover, to complement our approach, microbubble  
 50 detection was performed by pulse inversion imaging [8], since it is one of the most common methods  
 51 used to increase  $CTR$  while ensuring good axial resolution.

52 In the second step, the  $CTR$  optimization must be achieved without *a priori* knowledge of the imaging  
 53 system [15] (*i.e.* explored medium, the transducer and pulse parameters), since such information is  
 54 inaccessible in practice. As we wanted to optimize the  $CTR$  by modifying the signal transmitted, we  
 55 could propose adjusting parameters characterizing the transmitted signal such as frequency, amplitude,  
 56 phase or pulse duration. It should be noted that both the amplitude and the frequency are relevant pulse  
 57 parameters which contribute to a significant increase in microbubble response, as in the case of power  
 58 modulation or chirp imaging, respectively. To simplify our approach, we therefore chose to optimize only  
 59 the transmit frequency  $f$ , for a pulse inversion imaging system, thereby producing a new device that can  
 60 adapt to changing conditions.

61 Consequently, the optimization problem can be written as follows:

$$f^* = \arg \max_f (CTR(f)), \quad (2)$$

62 where  $f^*$  is the optimal transmit frequency which provides the best  $CTR$ . We proposed an iterative approach  
 63 to find the optimal transmit frequency  $f^*$  and we applied it in simulations and in experiment.

## 64 II. CLOSED-LOOP IMAGING SYSTEM

65 The principle of pulse inversion imaging including feedback is described in Fig. 1. At the iteration  $k$ ,  
 66 two pulses  $x_{k,1}(t)$  and  $x_{k,2}(t)$  with opposite phases and with a frequency  $f_k$  were transmitted. The sum

67  $z_k(t)$  of the two respective echoes  $y_{k,1}(t)$  and  $y_{k,2}(t)$  formed a radiofrequency line of the image  $I_k$ . From  
 68 the  $CTR_k$  measured on this image  $I_k$ , a new transmit frequency  $f_{k+1}$  was computed by the algorithm to  
 69 optimize the  $CTR_{k+1}$  on the next image  $I_{k+1}$ .

70 [Fig. 1 about here.]

### 71 A. Transmitted Signal

72 The pulse signal  $x_{k,p}(t)$  at transmit frequency  $f_k$  was computed digitally with Matlab (Mathworks,  
 73 Natick, MA, USA):

$$x_{k,p}(t) = A \cdot w_{k,p}(t). \quad (3)$$

74 The sinus modulated by a Gaussian function [12]  $w_{k,p}(t)$  was constructed as follows:

$$w_{k,p}(t) = \exp\left[-\frac{(t-t_0)^2}{\frac{N_c}{2f_k}}\right] \sin(2\pi f_k t + \phi_p), \quad (4)$$

75 where  $t$  is the time,  $t_0$  the time for which the Gaussian function is maximum,  $N_c$  the cycle number and  
 76  $\phi_p$  the phase equal to  $0^\circ$  if  $p = 1$  and  $\pi$  if  $p = 2$ .

77 The amplitude of the driving pressure  $A$  was then adjusted so that the power of the pulse  $x_{k,p}(t)$  was  
 78 constant for all iterations:

$$A = \sqrt{\frac{A_0^2 \cdot P_{x_{ref}}}{P_w}}, \quad (5)$$

79 where  $A_0$  is the driving pressure amplitude of the reference signal  $x_{ref}$ . This signal  $x_{ref}$  was calculated  
 80 at the central frequency of the transducer. Its power  $P_{x_{ref}}$  constituted the reference power, while  $P_w$  was  
 81 the power of the signal  $w_{k,p}$ . The power of the transmitted wave thus remained constant by adjusting the  
 82 amplitude signal  $A$ .

### 83 B. Cost Function

84 In the receiver,  $CTR_k$  was computed from a line  $z_k(t)$  of pulse inversion image:

$$z_k(t) = y_{k,1}(t) + y_{k,2}(t), \quad (6)$$

85 where  $y_{k,p}(t)$  is the echo of the transmitted pulse  $x_{k,p}(t)$ . It is defined as the ratio of the power  $P_{b,k}$   
 86 backscattered by the area of the perfused medium to the power  $P_{t,k}$  backscattered by the area of the  
 87 non-perfused medium [6] as follows:

$$CTR_k = 10 \cdot \log_{10} \left( \frac{P_{b,k}}{P_{t,k}} \right), \quad (7)$$

88 These powers were measured from the lines  $z_k(t)$  of the pulse inversion image at iteration  $k$ . The areas  
 89 were determined manually before the optimization process, but a segmentation step could be implemented.

90 The contrast gain  $G_{dB}$  was also defined between the optimized system and the non-optimized system.  
 91 The  $CTR$  obtained with the non-optimized system was determined at the central frequency of the  
 92 transducer [16]. The contrast gain  $G_{dB}$  is obtained by the next equation:

$$G_{dB} = \frac{CTR(f^*)}{CTR(f_0)}, \quad (8)$$

93 where  $CTR(f_0)$  is the  $CTR$  obtained at the central frequency of the transducer.

### 94 C. Iterative Optimization Algorithm

95 The algorithm was based on the principle of the gradient descent [17]. It determined a new transmit  
 96 frequency  $f_{k+1}$  for the next pulse sequence to optimize the  $CTR_{k+1}$  by the following recurrence relation:

$$f_{k+1} = f_k + \mu_k \cdot d_k, \quad (9)$$

97 The first coefficient  $\mu_k$  set the speed of convergence as follows:

$$\mu_k = \begin{cases} 0 & \text{if } k \leq 3; \\ \Delta f & \text{if } k = 4; \\ \mu_{k-1} & \text{if } \text{sgn}(\nabla CTR(f_k)) = \text{sgn}(\nabla CTR(f_{k-1})); \\ \frac{\mu_{k-1}}{2} & \text{if } \text{sgn}(\nabla CTR(f_k)) \neq \text{sgn}(\nabla CTR(f_{k-1})). \end{cases} \quad (10)$$

98 where  $\Delta f$  fixed at 100 kHz provided the best compromise between speed of convergence and robustness,  
 99 the sign function  $\text{sgn}(t)$  is equal to 1 if  $t > 0$ , 0 if  $t = 0$  and  $-1$  if  $t < 0$ , and the  $CTR$  gradient defined

100 by:

$$\nabla CTR(f_k) = \frac{CTR_k - CTR_{k-1}}{f_k - f_{k-1}}. \quad (11)$$

101 The second coefficient  $d_k$  set the direction as follows:

$$d_k = \begin{cases} 1 & \text{if } k \leq 3; \\ 1 & \text{if } \text{sgn}(\nabla CTR(f_k)) = \text{sgn}(\nabla CTR(f_{k-1})); \\ -1 & \text{if } \text{sgn}(\nabla CTR(f_k)) \neq \text{sgn}(\nabla CTR(f_{k-1})). \end{cases} \quad (12)$$

102 In order to compute  $\mu_k$  and  $d_k$ , the system operated in open loop for the first three iterations ( $k =$   
 103  $\{1, 2, 3\}$ ). The first three frequencies  $f_1$ ,  $f_2$  and  $f_3$  were chosen initially. The appropriate choice could  
 104 increase the speed of convergence, but it was not essential to reach the optimal  $CTR$ , when the cost  
 105 function was concave.

### 106 III. SIMULATION EVALUATION

107 The optimization principle was initially applied in simulation. Several simulations were performed to  
 108 demonstrate the feasibility of our novel method.

#### 109 A. Simulation Model

110 The simulation model followed the same process as described in the experimental setup (Fig. 1). It was  
 111 composed of different phases: transmission, 2D nonlinear forward propagation, nonlinear oscillations  
 112 of microbubbles, 2D nonlinear backward propagation and reception. A pulse wave was nonlinearly  
 113 propagated into an attenuating intermediate medium without microbubbles. This wave, composed of  
 114 harmonic components, excited a microbubble in the vascular system. The nonlinear oscillations of this  
 115 microbubble were backscattered and measured by the receiver.

116 1) *Nonlinear Propagation in Tissue:* The core of the model was based on the free simulation program  
 117 developed by Anderson [18], and *e.g.*, used in [19]. It consisted of digitally solving the 2D nonlinear  
 118 wave propagation into an attenuating medium by using a pseudo-spectral derivative and a time-domain  
 119 integration algorithm.

120 A pulse signal was generated digitally at iteration  $k$  and filtered by the transfer function of the ultrasound  
 121 probe used in the experiment, centred at 4 MHz with a fractional bandwidth of 53% at  $-3$  dB. Here, to

122 reduce the computation time, only 8 elements of the ultrasound probe composed of 128 elements were  
 123 used. Note that linear beamforming was used in transmission and in reception [20] so that the beam was  
 124 focused at 15 mm from the transducer. The nonlinear wave propagation into the intermediate medium  
 125 was obtained by solving Anderson's model where the physical parameters were the following [20]:

- 126 • density of  $928 \text{ kg}\cdot\text{m}^{-3}$ ;
- 127 • speed of sound of  $1578 \text{ m}\cdot\text{s}^{-1}$ ;
- 128 •  $B/A$  nonlinearity parameter of 6.7;
- 129 • attenuation of  $0.45 \text{ dB}\cdot\text{MHz}^{-1.05}\cdot\text{cm}^{-1}$ .

130 This driving pressure at the focus point was included into the microbubble model described below. Finally,  
 131 the wave backscattered by the microbubble was nonlinearly backpropagated up to the receiver. This signal  
 132 was filtered by the transfer function of the same ultrasound probe used in experiment. To take into account  
 133 imperfections in our simulation, a white noise  $\varepsilon(t)$  was added to  $x_{k,p}(t)$ , and a signal-to-noise ratio (SNR)  
 134 of 50 dB was chosen.

135 2) *Microbubble*: The simulated ultrasound contrast agent had the properties of encapsulated micro-  
 136 bubbles of SonoVue (Bracco Research SpA, Geneva, Switzerland), with a phospholipid monolayer  
 137 imprisoning sulfur hexafluoride gas ( $\text{SF}_6$ ) [21] where the polytropic gas exponent  $\kappa$  was 1.095. The  
 138 microbubbles had the following properties:

- 139 • mean diameter:  $2.5 \mu\text{m}$  [21];
- 140 • resonance frequency: 2.6 MHz [22].

141 The acoustic response was computed for one microbubble from the model of Marmottant [23] based on  
 142 the Rayleigh-Plesset equation [24] and the polytropic transformation. The solver used was the fourth-order  
 143 Runge-Kutta method. Finally the surface pressure of the microbubble was transmitted to the nonlinear  
 144 propagation model in order to deduce the backscattered signal. In order to simulate the mean behavior of  
 145 a microbubble cloud, we hypothesized that the response of a cloud of  $N$  microbubbles was  $N$  times the  
 146 response of a single microbubble with the mean properties. To be more realistic, the attenuation effects  
 147 due to the high concentration of microbubbles were taken into account [25] for a dilution of 1/2000.

## 148 B. Simulation Results

149 1) *Empirical Optimization*: Fig. 2 represents the results of the first simulation, *i.e.* the *CTR* as a  
 150 function of the transmit frequency for different pressure levels  $A_0$  (from 240 to 400 kPa). The number of

151 cycles  $N_c$  was set at 2.3 cycles so that the relative bandwidth<sup>1</sup> was 100% at the central frequency of the  
 152 transducer.

153 The first results indicated that the  $CTR$  had a global maximum whatever the pressure level  $A_0$ , and  
 154 showed that the  $CTR$  can be improved by choosing the appropriate transmit frequency, thus confirming  
 155 the validity of our study. This property could be also interesting, because an automatic search could more  
 156 easily be achieved by a gradient algorithm. The second result demonstrated that the higher the pressure,  
 157 the higher the global maximum of the  $CTR$ , because the power backscattered by the microbubble increased  
 158 more quickly than the power backscattered by the tissue particle when the pressure level increased. The  
 159 maximum values of the  $CTR$  ranged between 21.2 dB and 22.2 dB for pressure levels  $A_0$  ranging from  
 160 240 to 400 kPa, and the contrast gain  $G_{dB}$  was from 14.3 to 9.1 dB, respectively. These results revealed  
 161 that the best transmit frequency was not the central frequency of the transducer, again confirming the need  
 162 to optimize the imaging process.

163 To summarize, the results shown in Fig. 2 confirmed the need to optimize the imaging system by  
 164 seeking the best transmit frequency which maximized the  $CTR$  function. Indeed, Fig. 2 shows that the  
 165  $CTR$  depended on transmit frequency  $f$  and could reach a single global maximum of approximately 22  
 166 dB. The single maximum of the  $CTR$  could be detected automatically by a simple technique such as the  
 167 gradient. Note that the optimal transmit frequency was lower than the transmit frequency which produced  
 168 the best axial resolution.

169 [Fig. 2 about here.]

170 2) *Automatic Optimization*: The maximum  $CTR$  was reached automatically using the gradient algo-  
 171 rithm. Fig. 3b shows the  $CTR$  measured at each iteration  $k$ , and Fig. 3a shows variations in the transmit  
 172 frequency during iterations.

173 The transmit frequency converged to a stable value after six iterations, whatever the pressure level  
 174  $A_0$ . As an illustration, the black solid line in Fig. 2 shows the first twenty iterations which confirmed  
 175 the convergence after the first six iterations. Moreover, the  $CTR$  reached its maximum when the transmit  
 176 frequency converged. Note that the  $CTR$  and the contrast gain  $G_{dB}$  obtained automatically were equal to  
 177 those obtained empirically in the first simulation.

178 As depicted in Fig. 2, the optimal transmit frequency was lower than the central frequency of the  
 179 transducer. Moreover, this optimal transmit frequency was equal to neither the central frequency of the

<sup>1</sup>The relative bandwidth was defined as the percentage of the bandwidth of the signal in the fractional bandwidth of the transducer.

180 transducer nor to the microbubble resonance frequency. However, this optimal transmit frequency obtained  
181 after convergence of the algorithm made it possible to receive the harmonic components necessary to  
182 optimize the *CTR*.

183 In summary, the results in Fig. 3 show that it was possible to find the transmit frequency which  
184 maximized the *CTR* automatically. No *a priori* knowledge was required, except for the choice of the first  
185 three transmit frequencies which impacted on the speed of convergence.

186 [Fig. 3 about here.]

187 3) *Adaptive Optimization*: Fig. 4 depicts the *CTR* and the transmit frequency as a function of iterations  
188 when:

- 189 1) the microbubble radius was fixed at  $2.5 \mu\text{m}$  throughout the simulation;
- 190 2) the microbubble radius was fixed at  $1.25 \mu\text{m}$  throughout the simulation;
- 191 3) the microbubble radius decreased with time, increasing its linear resonance frequency. In the  
192 simulation, the radius changed from  $2.5$  to  $1.25$  at iteration 10.

193 The results showed that the first optimization (*i.e.* with a microbubble of  $2.5 \mu\text{m}$ ) converged at a  
194 transmit frequency of  $1.9 \text{ MHz}$  for a *CTR* of  $22.1 \text{ dB}$ . The second optimization converged at a transmit  
195 frequency of  $2.1 \text{ MHz}$  for a *CTR* of  $16.6 \text{ dB}$ . For the third optimization, the values of the *CTR* converged  
196 to the previously obtained values. Our system provided a quasi-instantaneous adaptation of the *CTR* during  
197 simulation. In all three simulations, convergence was reached after ten iterations. Note that the optimal  
198 transmit frequency was different for different sizes of microbubbles. Furthermore, when the oscillations  
199 increased as the size of the microbubble increased and thus the backscattered power increased. Hence,  
200 the *CTR* was dependent on the microbubble size.

201 To summarize, our optimization method adjusted the transmit frequency throughout the simulation by  
202 taking into account the changes in the microbubble properties. When the contrast agent did not change, the  
203 *CTR* did not change. This adaptability was also demonstrated when the tissue or the transducer changed  
204 with time. Note that when the optimization was not quick or robust enough, another algorithm could  
205 be used. However, for the gradient algorithm, the speed of convergence could enable us to reset the  
206 optimization parameter  $\mu_k$  if the environment changed a great deal.

207 [Fig. 4 about here.]

208 4) *Note on Resolution:* In the previous results, the axial resolution varied with the transmit frequency  
 209 since the number of cycles  $N_c$  was constant. An alternative solution can ensure a constant axial resolution  
 210 if the variations in transmit frequency are compensated for by changing the number of cycles  $N_c(k)$  for  
 211 each iteration  $k$ . The length of the pulse  $x_{k,p}(t)$  thus remained constant whatever the transmit frequency  
 212 as follows:

$$2\sigma_t(k)^2 = \frac{N_c(k)}{2f_k} = \text{constant}, \quad (13)$$

213 where  $2\sigma_t(k)^2$  is the pulse duration at iteration  $k$ . In this case, when  $f_k$  decreased,  $N_c(k)$  decreased.  
 214 When the axial resolution was 100% of the relative bandwidth (*i.e.* 0.45 mm), the maximum values of  
 215  $CTR$  ranged between 17.9 dB and 19.8 dB for pressure levels  $A_0$  increasing from 240 to 400 kPa, and  
 216 the contrast gains  $G_{dB}$  ranged between 10.9 and 6.6 dB. Note that the  $CTR$  and the gain were smaller  
 217 with this setting compared to the previous results when was  $N_c$  constant. Indeed, the small number of  
 218 cycles reduced the good separation of harmonic components. Consequently, increasing the axial resolution  
 219 reduced the  $CTR$ . Finally, the system converged at the maximum  $CTR$  with the same speed of convergence  
 220 as indicated by Fig. 3.

#### 221 IV. EXPERIMENTAL VALIDATION

222 The aim of this section was to confirm experimentally the results obtained in the simulation.

##### 223 A. Experimental Setup

224 The experimental setup is presented in Fig. 1. The signals transmitted ( $x_{k,1}(t)$  and  $x_{k,2}(t)$ ) were first  
 225 generated digitally by a personal computer using equation 3. They were sent from an ultrasound scanner  
 226 to the medium via an ultrasound probe. The waves insonified the medium which was composed of tissues  
 227 and microbubbles. The reception system collected the echoes  $y_{k,1}(t)$  and  $y_{k,2}(t)$  and computed a pulse  
 228 inversion image line.

229 1) *Ultrasound Scanner and Transducers:* The transmitted signal  $x_{k,p}(t)$  was sent to an “open”  
 230 ultrasound scanner (MultiX WM, M2M, Les Ulis, France). This ultrasound scanner automatically  
 231 duplicated the signal  $x_{k,p}(t)$  for each element of the ultrasound probe. It applied the delays necessary  
 232 to obtain phased-array beamforming [20]. Then the signals were transmitted to a linear array of 128

233 elements (Vermon SA, Tours, France), centred at 4 MHz with a fractional bandwidth of 53% at  $-3$  dB.  
234 The beam was focused at 28 mm from the surface.

235 The pulse transfer time for a single focusing was high, because it took approximately two seconds per  
236 radio frequency line. Consequently, we proposed optimization carried out only on an ultrasound image of  
237 five lines sweeping an angle of  $0^{\circ}25'$ . The duration of the experiment was reduced to limit microbubble  
238 destruction.

239 2) *Medium Explored*: The wave propagated through a tissue-mimicking phantom (model 524, peripheral  
240 vascular Doppler flow phantom, ATS Laboratories Inc, Bridgeport, CT, USA), crossed by a 4 mm-diameter  
241 tube in which a 1/2000 diluted solution of SonoVue circulated.

242 The pulse was chosen with a cycle number corresponding to 55% of the relative bandwidth at the  
243 central frequency of the transducer (*i.e.*  $N_c = 4$ ) and with a pressure level  $A_0$  of 400 kPa at the focal  
244 point.

## 245 B. Experimental Results

246 The experimental results presented in Fig. 5 show the transmit frequency and the *CTR* during the  
247 iterations. Fig. 5b shows that the *CTR* converged to its optimal value after six iterations. The mean *CTR*  
248 achieved after convergence was around 12.22 dB  $\pm 2.4$  dB, *i.e.* a mean contrast gain of 7.77 dB. Fig.  
249 5a shows that the transmit frequency converged to 2.9 MHz  $\pm 0.1$  MHz. The temporal fluctuation of the  
250 transmit frequency showed that the system adjusted itself to changes. These variations may have been  
251 caused by two effects: (i) statistical fluctuation due to microbubble movements and (ii) fluctuation related  
252 to changes in the size distribution of microbubbles and number of microbubbles. However, these results  
253 did not permit definitive conclusion regarding the nature of the fluctuation and we could only conclude  
254 that our system automatically adjusted itself.

255 [Fig. 5 about here.]

256 Furthermore, the experimental results were in accordance with our simulation results: we observed  
257 that the optimal transmit frequency was lower than the central frequency of the transducer. This optimal  
258 transmit frequency obtained after the algorithm convergence also made it possible to receive the harmonic  
259 components required in the *CTR* optimization. Note that the difference between the gain value in our  
260 simulation and that obtained in our experiment might be due to the more simplistic hypothesis of the  
261 model used.

262 Finally, these experimental results confirmed the feasibility of our method.

## 263 V. DISCUSSION AND CONCLUSIONS

264 *CTR* optimization in pulse inversion imaging was performed automatically, without taking into account  
265 *a priori* knowledge of the medium or the transducer, except for the first three values of the transmit  
266 frequency chosen only for their impact on the speed of convergence. The optimal transmit frequency  
267 was reached automatically by feedback within only a few iterations. The algorithm itself adjusted the  
268 transmit frequency throughout the experiment by each time taking into account the changes in microbubble  
269 properties. This closed loop system gave the best compromise between the transducer bandwidth and the  
270 frequency responses of microbubbles and tissue. This trade-off has usually been calculated empirically  
271 to date. To make such automatic trade-off possible, the proposed algorithm itself adjusted the transmit  
272 frequency to maximize the power backscattered by microbubbles while minimizing the power backscattered  
273 by the tissue within the transducer bandwidth.

274 Our method was feasible for two reasons. Optimization was iteratively fulfilled by using (i) an easily  
275 implemented algorithm and (ii) a single setting parameter (here the transmit frequency). One major  
276 advantage of our approach was that it adjusted itself to any medium explored by taking into account  
277 the effects of attenuation and nonlinear propagation. This advantage was due to the fact that the cost  
278 function, on which the optimization was based, was exclusively the result of the input and the output  
279 measurements of our system. One interesting consequence is that our method can be applied to any  
280 imaging system and to any medium to be explored, since our algorithm should converge to the maximum  
281 of the cost-function. Note that for a robust optimization, this maximum must be exclusive.

282 We identified three major points for discussion, for future integration in an imaging system:

- 283 • the first concerned the gradient algorithm for which six basic operations were necessary to compute  
284 the transmit frequency for the next iteration. This low number of operations should not significantly  
285 change the frame rate;
- 286 • the second concerned the *CTR* computation from regions of interest ( $L \times L$  size) in the image of size  
287  $M \times M$ . For efficient optimization, it is important to determine the correct positions of the perfused and  
288 non-perfused areas. Indeed, poor assessment of the *CTR* could lead to poor optimization. Moreover,  
289 the *CTR* computation required  $2(2L+1)^2+1$  operations. It should not considerably change the frame  
290 rate;

291 • the third concerned the transfer time between the computer and the programmable analogue  
292 transmitter. Note that for our “open” ultrasound scanner, this transfer time was not negligible compared  
293 to the frame rate. Indeed, this had led us to limit the image size. However we do not think that is is  
294 a problem for future integration of our method in an imaging system, since the current development  
295 of new imaging methods based on chirp or time reversal also requires such instrumentation.

296 Finally, our method only focused on qualitative imaging. Although our technique could offer an optimal  
297 frequency for each image line, it was preferable to perform optimization on the whole image, because the  
298 image had a single resolution. For instance, our optimization without resolution constraints could offer  
299 the best tradeoff between the *CTR* and axial resolution. We therefore believe that the method would  
300 be particularly appropriate for contrast echocardiography where the tradeoff must favor contrast [3].  
301 Nevertheless, our method was suitable for quantitative contrast ultrasound imaging, since it adjusted  
302 itself to microbubble variations, although a possible solution may be to cease optimization during the  
303 quantification step.

304 To conclude, the method ensured optimal *CTR* throughout the experiments by adaptively selecting the  
305 transmit frequency. With our new approach, manufacturers and clinicians would not themselves need to  
306 tune the transmit frequency. The method should automatically adapt the transmit frequency to the medical  
307 examination conditions and maintain optimal *CTR*. Finally, our closed-loop method should be adapted  
308 using a larger number of contrast imaging techniques.

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## FIGURE CAPTIONS

378

379 **Fig. 1:** Block diagram of adaptive imaging by pulse inversion technique.

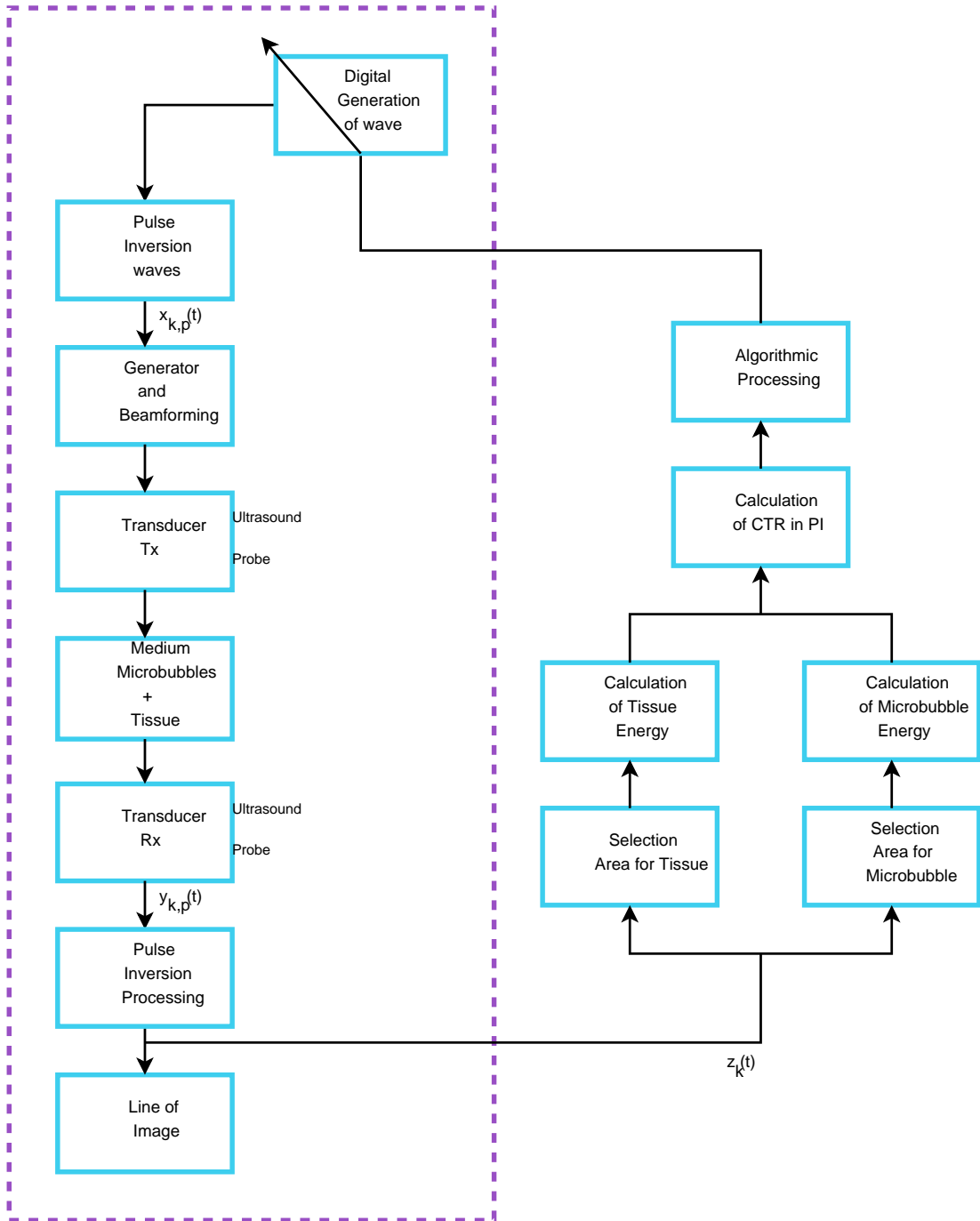
380 **Fig. 2:** Simulation of *CTR* for a transmit frequency of 1 to 4 MHz, a pressure level  $A_0$  of 240 to 400  
381 kPa and a constant number of cycles  $N_c$  of 2.3. The simulation included the transducer. Note  
382 that for transmit frequencies above the central frequency of the transducer, the axial resolution  
383 could not be reduced because of the transducer impulse response.

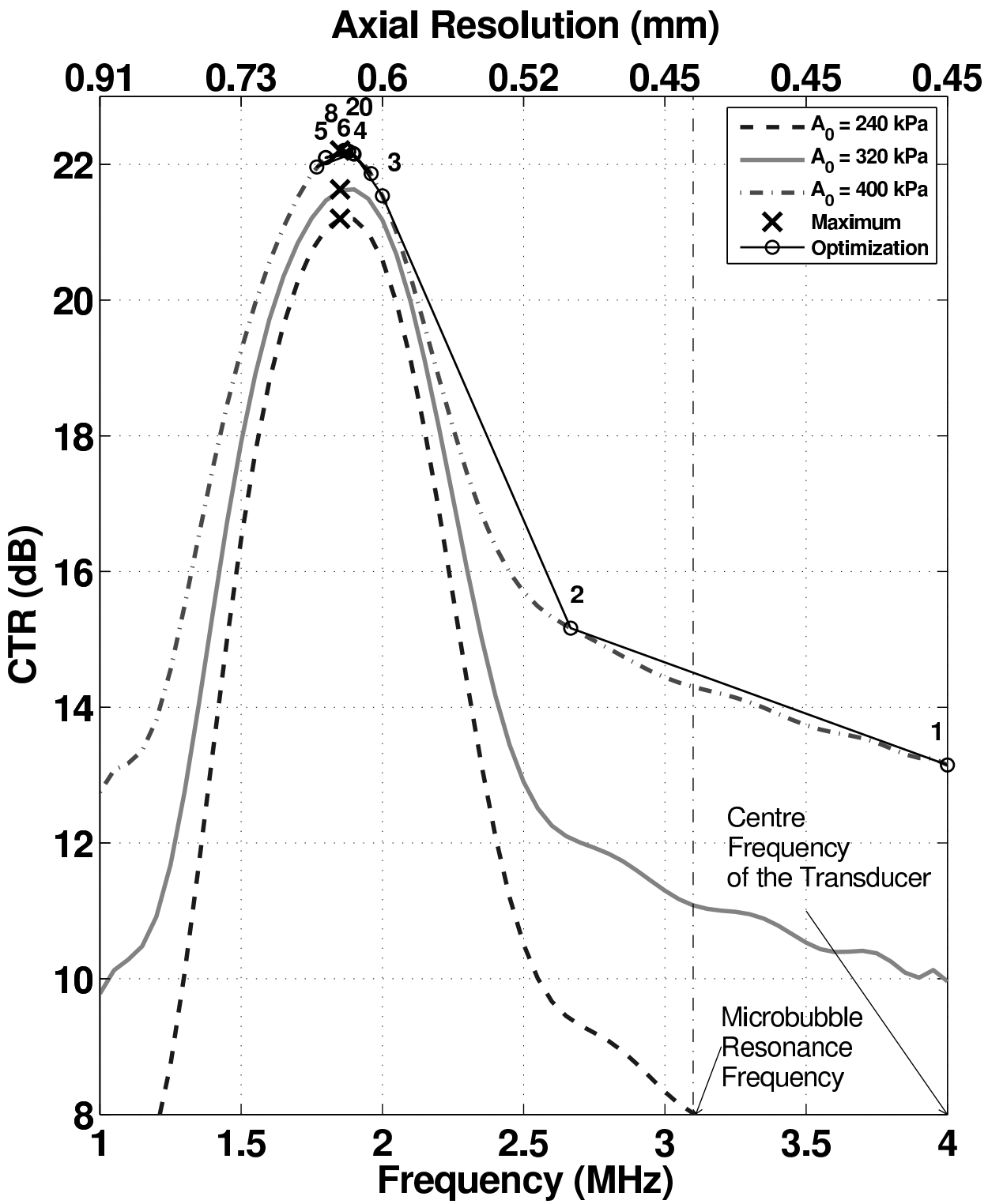
384 **Fig. 3:** Simulation of automatic optimization of the *CTR* by iterative searching for the optimal transmit  
385 frequency for different pressure levels  $A_0$  from 240 to 400 kPa and a constant cycle number  $N_c$   
386 of 2.3. The simulation included the transducer.

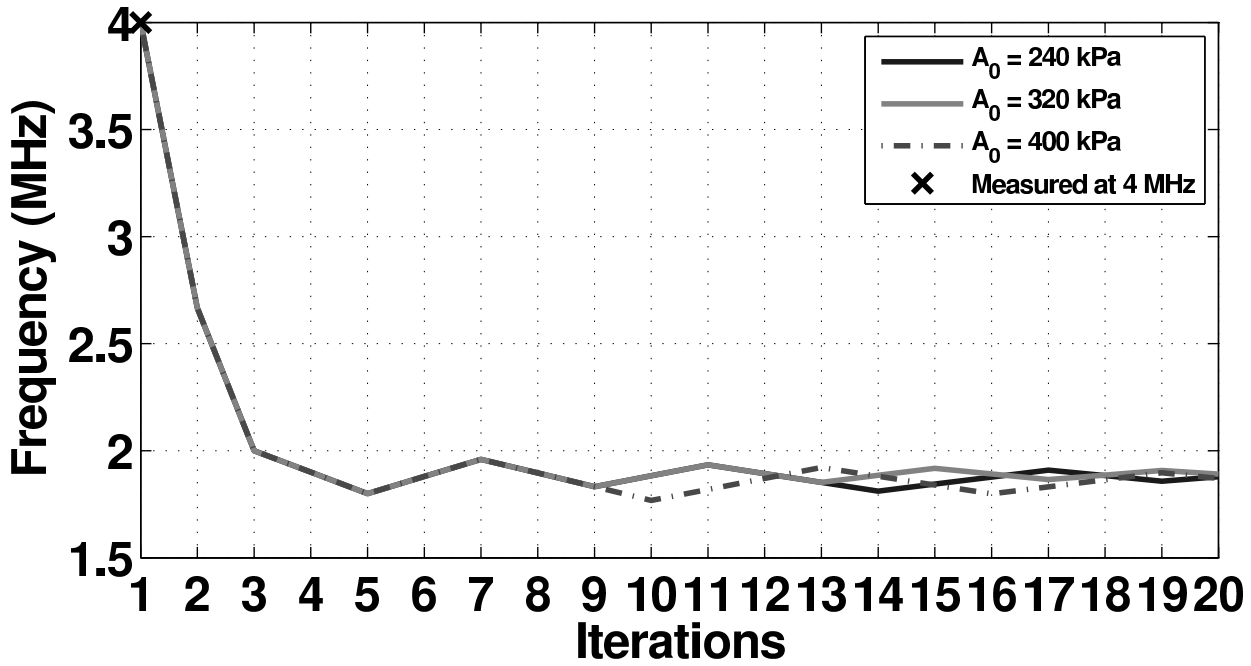
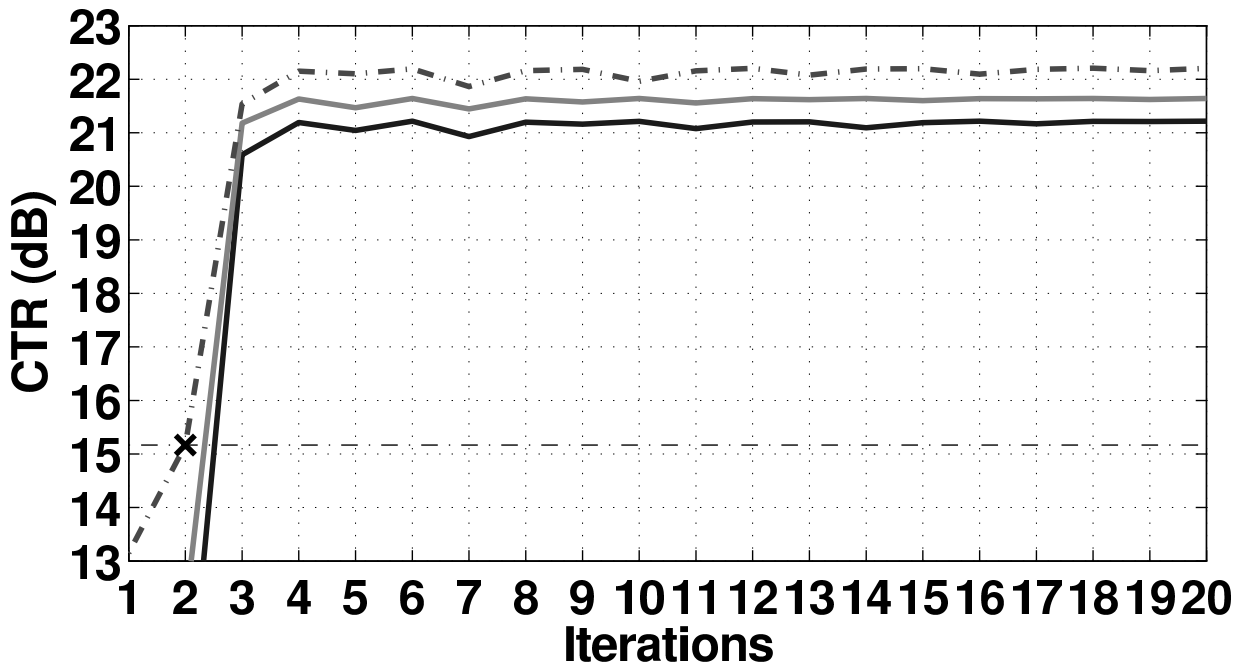
387 **Fig. 4:** Simulation of *CTR* optimization for a pressure level  $A_0$  of 400 kPa and a constant cycle number  $N_c$   
388 of 2.3 in the presence of changing microbubble properties. The first optimization was performed  
389 for a microbubble with a constant radius of  $2.5 \mu\text{m}$ ; the second for a microbubble with a constant  
390 radius of  $1.25 \mu\text{m}$ . The third optimization began with a microbubble of  $2.5 \mu\text{m}$  radius until  
391 iteration 10, the microbubble then changed to  $1.25 \mu\text{m}$  radius.

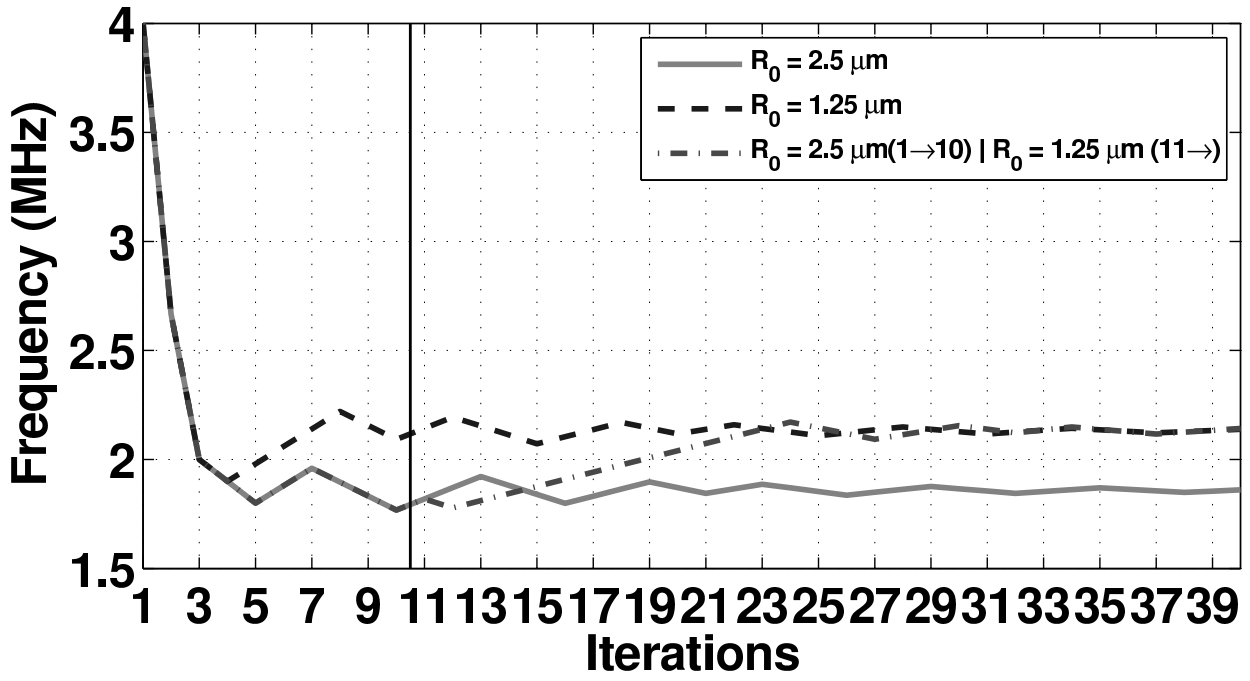
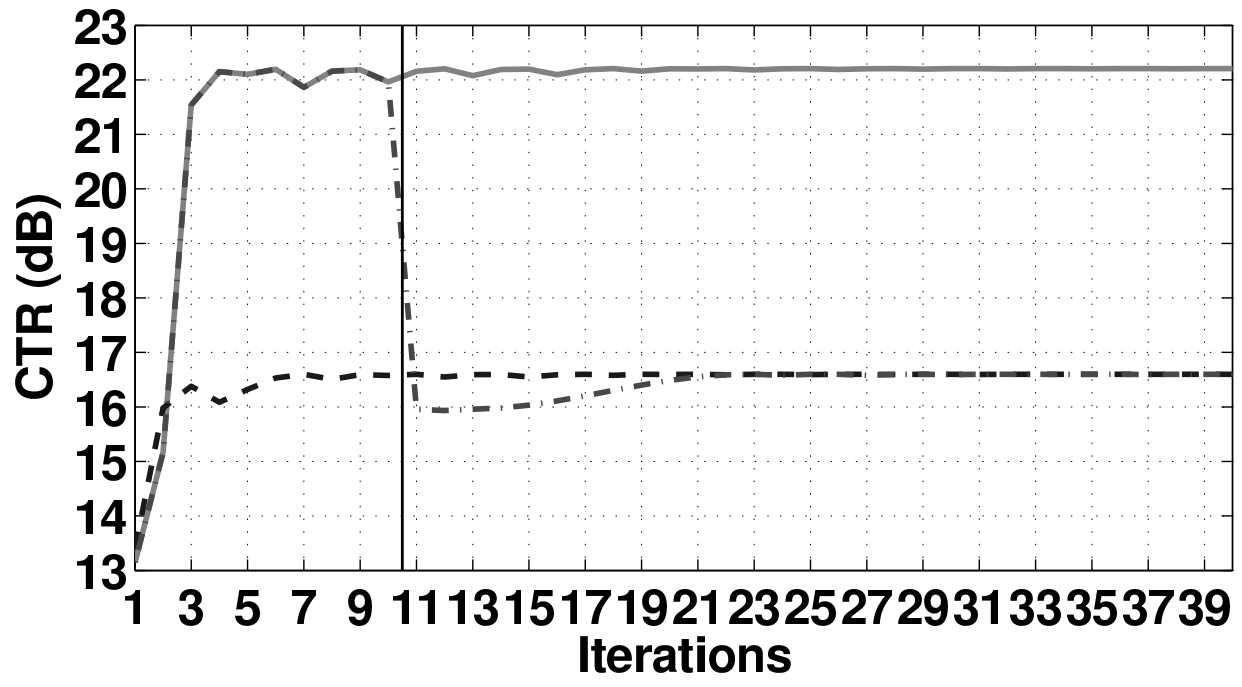
392 **Fig. 5:** Experiment of *CTR* optimization for a pressure level  $A_0$  of 400 kPa at the focal length and a  
393 constant cycle number  $N_c$  of 4.

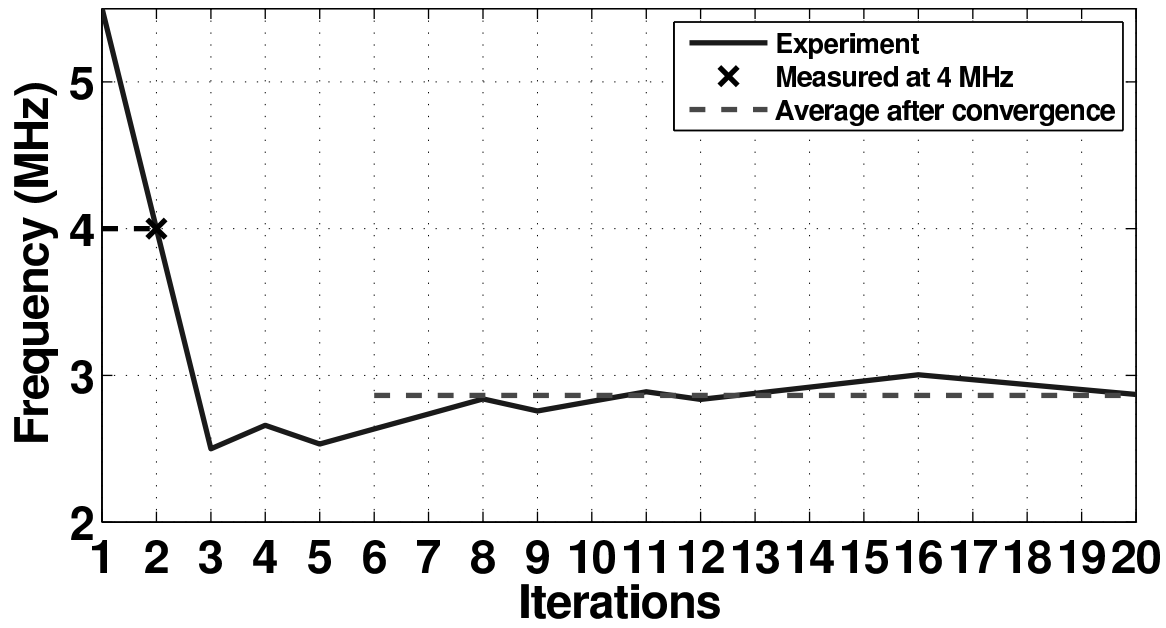
Opened Loop





**a****b**

**a****b**

**a****b**