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AdvFPCG-Delineator:
Advanced Delineator for Fetal Phonocardiography

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Abstract

Fetal phonocardiogram (FPCG) consists in the recording of fetal heart sounds by means of a sensor placed on the mother's abdominal surface. Usually, FPCG includes two major sounds for each fetal cardiac cycle: S1, produced by the sudden closure of mitral and tricuspid valves, and S2 produced by the closure of aortic and pulmonary valves. The aim of the present study was to propose AdvFPCG-Delineator for automatic fetal S1 and S2 identification and to demonstrate its reliability in different clinical conditions. The method consists of a wavelet-based filtering procedure followed by the computation of the scalogram, from which S1 and S2 were identified using a threshold-based algorithm. AdvFPCG-Delineator was tested on the "Simulated Fetal PCGs database" (37 FPCG signals) and on the experimental "Shiraz University fetal heart sounds database" (119 FPCG signals), both available at PhysioNet (https://physionet.org). Manual S1 and S2 annotations and simultaneously acquired cardiotocographic recordings were used to compute reference fetal heart rate (FHR) for the simulated and experimental databases, respectively. No statistically significant difference was observed between estimated vs reference FHR (median: 140 bpm vs 140 bpm, respectively) for the simulated database, for which AdvFPCG-Delineator was also be able to track beat-to-beat variability (correlation over 92%). Additionally, no statistically significant difference was observed between estimated vs reference FHR (141 bpm vs 140 bpm, respectively) for the experimental database, even when stratifying by clinical conditions (maternal age, gestational age, etc.). In conclusion, AdvFPCG-Delineator proved to be a reliable method to automatically identify S1 and S2 from fetal phonocardiograms.

Keywords: Fetal heart-rate extraction; Fetal heart-sound identification; Fetal phonocardiography; Phonocardiographic features; Scalogram; Wavelet denoising

1. Introduction

Fetal phonocardiography (FPCG) consists in the recording of fetal heart sounds (FHSs) occurring during each fetal cardiac cycle by means of a sensor placed on the mother's abdominal surface [1-4]. FHSs are produced by the mechanical action of the cardiac muscles and valves and by the blood motion through the heart chambers [2,4]. Under normal conditions, a FPCG signal includes two major FHSs during each cardiac cycle [2-8]: the first sound (S1), produced by the sudden closure of mitral and tricuspid valves, *i.e.* atrio-ventricular valves, and the second sound (S2), produced by the closure of aortic and pulmonary valves, *i.e.* semilunar valves. S1 represents the longest and the loudest sound since the mitral valve closes with greater force.

Since representing specific phenomena of the cardiac cycle, FPCG is considered a potentially useful technique for fetal monitoring [9]. Indeed, it provides important diagnostic information for the assessment of fetal well-being during pregnancy [2] in a non-invasive, harmless (or passive, since no energy is emitted to the mother's abdomen and thus to the fetus), affordable (low-cost instrumentation), reliable and simple fashion, even as a user-independent home monitoring tool [2,4]. FPCG analysis allows measurement of the cardiac cycle, defined by the time interval between two consecutive S1 (S1S1 interval), from which fetal heart rate (FHR) can be assessed. In turn, from the 24th gestational week on, continuous and long-term FHR monitoring represents the most frequently used diagnostic tool for fetal health assessment [10]. Additionally, FPCG analysis provides information about the systolic time interval, defined as the time interval between an S1 and the subsequent S2 (S1S2 interval) [7-8], and the diastolic time interval, defined as the time interval between an S2 and the subsequent S1 (S2S1 interval) [7], with S1S2 interval being rather constant and normally shorter than S2S1 interval (S1S2>0.1 s; S2S1>0.2 s) [11]. FPCG analysis is however not trivial. FPCG signals are highly non-stationary and weak because of the high attenuation along the sound transmission pathway due to the physical distance between the acoustic source and the transducer [4,12-13]. In addition, there could be impedance mismatch between the transducer and the maternal abdominal surface during the acquisition [5]. Consequently, FPCG signals are typically heavily corrupted by several sources of noise, *i.e.* internal noise from the mother (such as mother respiratory sound) and external noise from the environment (such as electrode motion artifact) [2-3,10,14-16], thus requiring filtering procedures to be applied before S1 and S2 identification [2-4,6,15-17]. Moreover, quality of FPCG signals highly depends on fetal position, also with respect to FPCG sensor location [18], which is highly uncertain and variable, even though usually, starting from the 30th-35th weeks of gestation, the fetus presents the vertex position [18].

Development of accurate techniques to automatically analyze FPCG is currently very desirable [9]. Several algorithms proposed in the literature are mainly focused on S1 identification in order to evaluate FHR [1-2,9,11]; others also challenged to detect S2 [4,6,9,19] in order to have additional information on the systolic and diastolic intervals and on cardiac valves functioning. Still, a reliable automatic software able to denoise FPCG signals and to characterize FHSs when applied to different clinical conditions is yet nonexistent [9]. In a recent study, we proposed PCG-Delineator as an efficient algorithm for automatic identification of both S1 and S2 in FPCG [11], which included a procedure based on the wavelet transform (4th-order Coiflet mother wavelet with thresholding settings consisting of soft universal thresholding rule and 7 decomposition levels) for noise suppression. When tested on the "Simulated Fetal PCGs database" [20] of PhysioNet [21], PCG-Delineator provided promising results, being able to significantly reduce noise (median signal-to-noise ratio increased from 0.15 dB to 15.86 dB) and to accurately detect S1 (sensitivity: 88%; positive predictive value: 91%). Sensitivity of S2 detection, however, was under 80% (sensitivity: 77%; positive predictive value: 99%). Additionally, PCG-Delineator was tested only on simulated and not on experimental data. In a successive study reporting a comparative analysis of wavelet-transform filtering procedures [22], we concluded that the filter based on wavelet transform, obtained by combining the 4th-order Coiflet mother wavelet with the thresholding settings constituted of the soft universal rule and 7 decomposition levels, is optimal for FPCG filtering according to evaluation criteria based on both noise and clinical features. The aim of the present study was to propose AdvFPCG-Delineator (Advanced FPCG-Delineator) as an improved version of PCG-Delineator integrating all our most recent findings on FPCG filtering and fetal S1 and S2 identification, and to demonstrate its reliability in different clinical conditions. The scope is to make available a clinically useful tool able to reliably provide information on FHR as well as fetal cardiac valves functioning based on FPCG. To this aim, both PCG-Delineator and AdvFPCG-Delineator were tested on two FPCG databases (the "Simulated Fetal PCGs database" [20] and the "Shiraz University fetal heart sounds database" [13,15]) and results were compared. Eventually, AdvFPCG-Delineator will be freely available to researches for additional testing and evaluations.

2. Methods

In this work, FPCG signals from two databases (the "Simulated Fetal PCGs database" [20] and the "Shiraz University (SU) fetal heart sounds database" [13,15]) were submitted to PCG-Delineator [11] and AdvFPCG-Delineator for FPCG denoising and S1 and S2 identification. Performances of both methods were evaluated in terms of correctness of FHR computed from both S1S1 and S2S2 intervals.

2.1. Data

2.1.1. Simulated data

The "Simulated Fetal PCGs database" [20], freely available at PhysioNet/PhysioBank [21], contains 37 simulated FPCG signals (8-min long) related to different fetal states and recording conditions. Specifically, simulated FPCG signals were obtained by summation of a sequence of simulated S1 and S2 waveforms with different levels of noise. Noise was obtained as superimposition of several contributions simulating internal noise (maternal heart sounds, maternal body organs sounds and fetal movements) and external noise (surrounding environments and white Gaussian noise). Signal-to-noise ratio values ranged from -26.7 to -4.4 dB and sampling frequency was 1 kHz. S1 and S2 were manually annotated.

2.1.2. Experimental data

The "Shiraz University (SU) fetal heart sounds database" [13,15], freely available at PhysioNet/PhysioBank (and thus usable without any further institutional review board approval) [21], contains 119 raw experimental FPCG signals acquired from 109 pregnant women. Out of the 109 pregnancies, 102 were single pregnancies (double recording available in 3 cases) and 7 were twin pregnancies (one recording for each fetus), corresponding to 116 fetuses. Of these, 60 were males, 54 females and 2 with unknown gender. Additionally, 102 fetuses were healthy and 14 were not healthy (4 with decrease of amniotic fluid, 3 with abnormality in fetus non-stress test, 1 with severe change in FHR, 2 with high FHR, 3 with slow fetal growth and 1 with both decrease of amniotic fluid and slow fetal growth). Maternal age (MA) was 29±6 years; specifically, 59 pregnant women were young ($MA<30$ years), 43 middle-aged ($30\leq MA\leq 39$ years) and 7 were old ($MA>39$ years) [23]. Maternal body mass index (BMI) was 29±4 kg/m^2; specifically, 12 pregnant women were normal ($BMI<25$ kg/m^2), 55 overweight ($25\leq BMI\leq 30$ kg/m^2) and 42 were obese ($BMI>30$ kg/m^2) [24]. Gestational age (GA) was 36±3 weeks; specifically, 75 pregnancies were early-term ($GA<39$ weeks), 32 full-term ($39\leq GA<41$ weeks) and 2 late-term ($GA\geq 41$ weeks) [25]. All pregnant women were volunteers and data were fully deidentified before being placed in the public domain.

FPCG signals were recorded with the JABES^{TM} electronic stethoscope, placed on the lower maternal abdominal parts, according to the locations advised by an expert gynecologist [15]. The FPCG length ranged from 29 s to 133 s (mean duration 90 s). Sampling frequency was 16 kHz except for few cases (termed f9-1, f63, f64, f65, f88 in the database) for which it was 8 kHz. FPCG signals originally sampled at 8 kHz were oversampled at 16 kHz in order to have all experimental FPCG signals equally sampled. No S1 and S2 annotations were available.

2.2. Automatic fetal phonocardiogram delineation

Both simulated and experimental data were submitted to AdvFPCG-Delineator and PCG-Delineator in order to automatically identify S1 and S2. Both procedures were implemented in Matlab®.

2.2.1. AdvFPCG-Delineator

AdvFPCG-Delineator integrates a wavelet-based filtering procedure, finalized to reduce the level of noise affecting FPCG signals, followed by the scalogram computation and by the S1 and S2 identification procedures. The block diagram of the algorithm is reported in Figure 1.

According to the wavelet-based filtering procedure, each FPCG signal was normalized by its maximum amplitude and rescaled so that its amplitude could vary between ±100. Normalized FPCG signals were pre-filtered by application of a 6th-order bandpass bidirectional Butterworth filter with lower and upper cut-off frequencies of 20 Hz and 120 Hz, respectively [11,16,22,26], before being passed through a filter based on the wavelet transform [22], for further noise removal. Such filter consisted in a combination of the 4th-order Coiflet mother wavelet [4,11-12,15-16,22,26-28] with soft universal thresholding rule [2-4,11,22,27-29], using 7 decomposition levels [11,16,22]. According to the standard dyadic structure of the wavelet transform, at first level, the pre-filtered FPCG signal was decomposed into approximation coefficients (*i.e.* low-frequencies FPCG components) and detail coefficients (*i.e.* high-frequency FPCG components); then, at every level, the approximation coefficients were further decomposed into approximation and detail coefficients through a cascade of low-pass and high-pass filters followed by down-sampling, while the detail coefficients were not decomposed any further [12,30]. To denoise FPCG signal, the detail coefficients were thresholded at each level. Finally, the detail coefficients of all the levels and the approximation coefficient of the last level were summed up to reconstruct the wavelet-transform filtered FPCG signal [12,30].

The scalogram [4,31-32] of filtered FPCG signal (Figure 1) was obtained using the 4th-order Coiflet mother wavelet; the continuous wavelet coefficients were computed using the conventional scale interval 1 to 100 [33].

Eventually, S1 and S2 identification was performed on the scalogram using widely accepted FPCG physiological properties. At first, S1 were identified, one after another, with a procedure based on a temporal threshold. An S1, to be physiologically acceptable, had to occur at least 300 ms from the previous S1. Successively, S2 were identified. S2 identification was also based on a temporal threshold. An S2 had to satisfy the following conditions: there is only one S2 between two consecutive S1; and S2 had to fall at least 100 ms after the preceding S1 and at most 200 ms before the successive S1, in order to have the S2S1 interval longer than the S1S2 interval [5,7-8,11].

2.2.2. PCG-Delineator

Details of the PCG-Delineator algorithm can be found elsewhere [11]. Briefly, PCG-Delineator integrates the same wavelet-based filtering procedure in AdvFPCG-Delineator directly followed by the S1 and S2 identification procedures (no scalogram computation is performed).

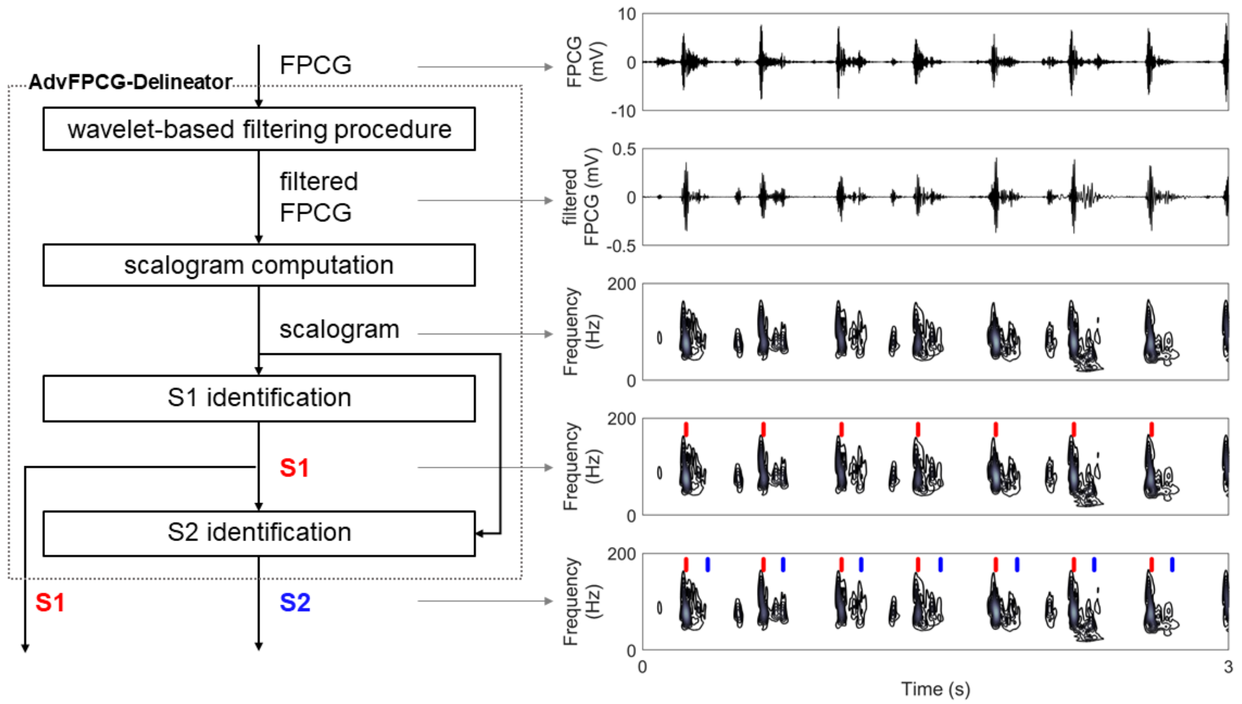

Figure 1: The block diagram of AdvFPCG-Delineator.

2.3. Performances evaluation

S1 and S2 annotations were available for the simulated data but not for the experimental data. Thus, while for simulated FPCG signals reference FHR (FHR_{ref}) could be computed by means of S1S1 intervals obtained using the annotations, for the experimental FPCG signals FHR_{ref} had to be indirectly obtained from the simultaneously acquired cardiotocographic (CTG) recordings [15] available at Shiraz University. However, cardiotocography provides mean FHR values obtained by averaging over 10-second windows. Thus, for consistency, in all cases we referred to FHR_{ref} as the mean FHR over 10-second windows, obtained using S1 annotations for the simulated data, and CTG data for the experimental data.

Performances of PCG-Delineator and AdvFPCG-Delineator were evaluated in terms of number of S1 and S2 identifications (which should be equal), S1S1, S2S2, S1S2 and S2S1 intervals (which should be physiologic), and of mean FHR over 10-second windows (FHR_{10s}, which should be equal to FHR_{ref}). In particular, performances evaluation in terms of FHR was performed by estimating FHR_{10s} through S1S1 interval (FHR_{S1S1} in bpm) and S2S2 interval (FHR_{S2S2} in bpm):

$$FHR_{S1S1} = 60/mean(S1S1), \qquad (1)$$

$$FHR_{S2S2} = 60/mean(S2S2). \qquad (2)$$

In Equations (1) and (2), 60 is the number of seconds in a minute, and mean(S1S1) and mean(S2S2) are mean intervals (in s) over 10-second windows.

Next, FHR-estimation errors with respect to reference were computed as in Equations (3) and (4) (by definition, reference errors were equal to zero):

$$\varepsilon_{S1S1} = FHR_{ref} - FHR_{S1S1}, \qquad (3)$$

$$\varepsilon_{S2S2} = FHR_{ref} - FHR_{S2S2}. \qquad (4)$$

For simulated data only, performances of AdvFPCG-Delineator and PCG-Delineator in evaluating beat-to-beat variations was performed by comparing estimated S1S1 and S2S2 intervals against corresponding intervals computed using reference annotations, and by computation of the correlation coefficient (ρ) as well as slope (m) and intercept (q) of regression line between estimated vs reference S1S1 and S2S2 intervals (in case of perfect automatic S1 and S2 identification ρ=1, m=1 and q=0).

For the experimental data only, robustness of AdvFPCG-Delineator was also evaluated in relation to MA, BMI, GA, single vs twin pregnancies, gender of the fetus and fetus clinical conditions.

In all cases, to compare FPCG features (either intervals, FHR values and errors), normality of distributions were first assessed by means of the Lilliefors test [34]; then, non-normal distributions were described in terms of 50th [25th; 75th] percentiles and compared by means of the Wilcoxon Rank-Sum test [35]. Statistical level of significance (*P)* was set at 0.05.

3. Results

3.1. Simulated data

FPCG features obtained using reference S1 and S2 annotations and S1 and S2 identifications by PCG-Delineator and AdvFPCG-Delineator over the simulated FPCG database are reported and compared in Table 1. Overall, AdvFPCG-Delineator identified more S1 and S2 than PCG-Delineator so that the number of missed S1 and especially S2 identifications was lower for AdvFPCG-Delineator (343 for S1 and 380 for S2) than for PCG-Delineator (627 for S1 and 3583 for S2). Additionally, no statistically significant difference was observed between FPCG intervals obtained using AdvFPCG-Delineator and the reference ones; instead, FPCG intervals obtained using PCG-Delineator were all significantly longer than the reference ones, and thus than those obtained using AdvFPCG-Delineator.

	Reference	**PCG-Delineator**	**AdvFPCG-Delineator**
Number of S1	41440	40813	41097
Number of S2	41440	37857	41060
S1S1 interval (ms)	410[410;410]	420[419;436]*	413[406;417]
S2S2 interval (ms)	411[411;411]	424[423;443]*	418[417;426]
S1S2 interval (ms)	138[138;138]	140[129;160]*	138[120;145]§
S2S1 interval (ms)	272[272;272]	294[245;305]*	274[240;286]§

Table 1. Phonocardiographic features of FPCG signals in the "Simulated Fetal PCGs database" according to reference annotations, PCG-Delineator and AdvFPCG-Delineator.
n.a. not applicable.
*: *P*<0.05, when comparing PCG-Delineator and AdvFPCG-Delineator FPCG features vs reference;
§: *P*<0.05, when comparing PCG-Delineator vs AdvFPCG-Delineator FPCG features.

Figure 2 displays beat-to-beat associations between S1S1 and S2S2 intervals obtained using PCG-Delineator and AdvFPCG-Delineator vs reference S1S1 and S2S2 intervals. Compared to PCG-Delineator, AdvFPCG-Delineator provided much higher ρ (ρ=0.94 vs 0.40 for S1S1; ρ=0.92 vs 0.38 for S2S2), a value of m closer to 1 (m=0.93 vs 0.64 for S1S1; m=0.91 vs 0.73 for S2S2) and a value of q closer to 0 (q=28 vs 156 for S1S1; q=36 vs 117 for S2S2).

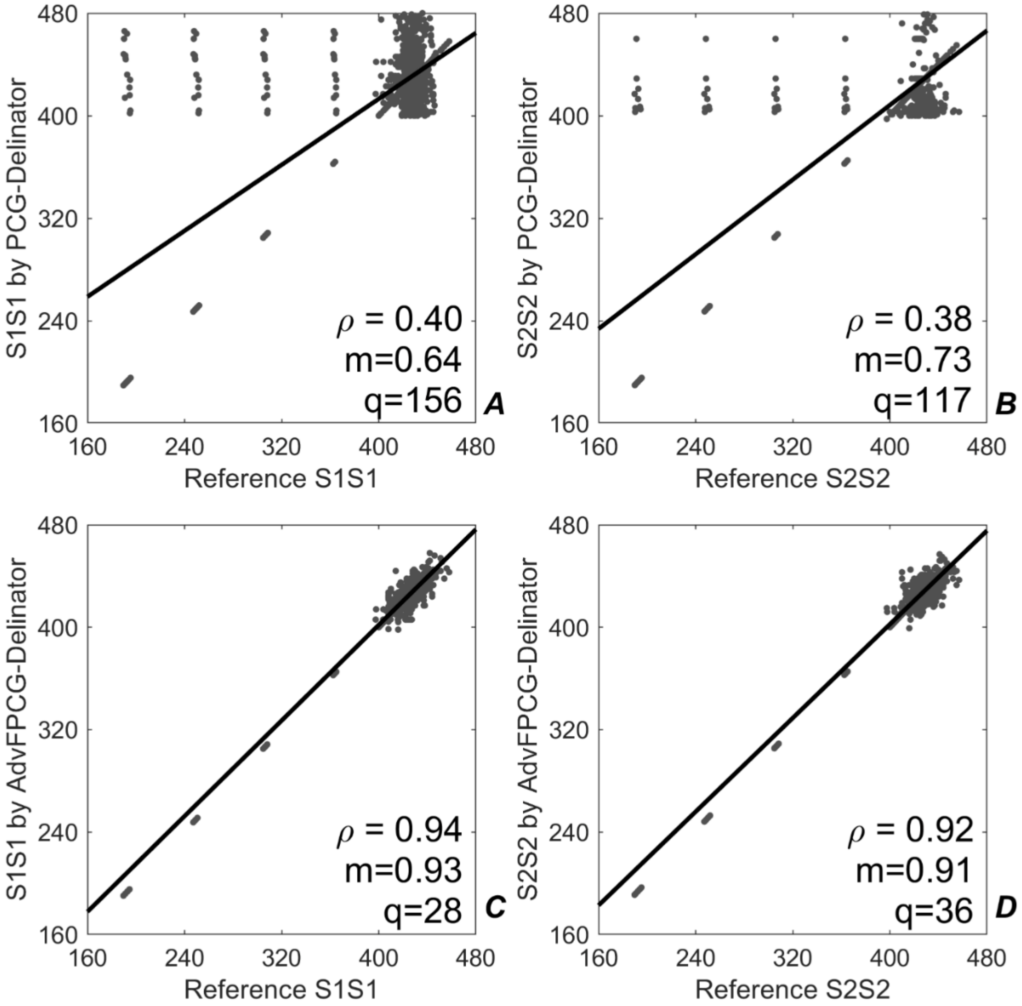

Figure 2. Beat-to-beat associations between S1S1 and S2S2 intervals obtained using PCG-Delineator (panel A and panel B) and AdvFPCG-Delineator (panel C and panel D) vs reference S1S1 and S2S2 intervals; ρ, m and q indicate correlation coefficients and slopes and intercepts of the regression lines, respectively.

Table 2 reports the comparison of FHR_{10s} and related errors obtained using reference annotations, PCG-Delineator and AdvFPCG-Delineator. AdvFPCG-Delineator correctly estimated FHR_{10s} using both S1S1 and S2S2 intervals, so that errors were zero in all cases. Instead, PCG-Delineator provided correct estimate of FHR_{10s} when using S1S1 interval but not when using S2S2 interval; errors were different from zero in both cases.

FPCG feature	Reference	PCG-Delineator		AdvFPCG-Delineator	
		S1S1	**S2S2**	**S1S1**	**S2S2**
FHR_{10s}(bpm)	140[140;140]	140[140;141]	134[127;139]*	140[139;140]	140[139;140]
Ɛ (bpm)	0[0;0]	-1[-1;-1]	6[1;13]*	0[0;0]	0[0;0]

Table 2. Comparison between FHR_{10s} estimated using PCG-Delineator and AdvFPCG-Delineator vs reference for the "Simulated Fetal PCGs database".

n.a.: not applicable;

*: *P*<0.05, when comparing PCG-Delineator and Advanced PCG-Delineator vs reference.

3.2. Experimental data

FPCG features obtained using S1 and S2 identifications by PCG-Delineator and AdvFPCG-Delineator over the experimental database are reported and compared in Table 3. AdvFPCG-Delineator identified more S1 and S2 than PCG-Delineator; moreover, the difference between the number of S1 and the number of S2 (ideally equal to zero) is much smaller for AdvFPCG-Delineator (124) than for PCG-Delineator (3357). No statistically significant difference was observed only between S1S1 intervals, while S2S2, S1S2 and S2S1 intervals obtained using AdvFPCG-Delineator were all significantly shorter than the ones obtained using PCG-Delineator.

	PCG-Delineator	**AdvFPCG-Delineator**
Number of S1	20383	20829
Number of S2	17026	20705
S1S1 interval (ms)	429[421;435]	421[413;428]
S2S2 interval (ms)	473[461;494]	422[413;429]*
S1S2 interval (ms)	147[137;170]	140[129;152]*
S2S1 interval (ms)	284[255;343]	283[268;292]*

Table 3. Phonocardiographic features of the "Shiraz University (SU) fetal heart sounds database" according to PCG-Delineator and AdvFPCG-Delineator.

n.a. not applicable.

*: $P<0.05$, when comparing AdvFPCG-Delineator vs PCG-Delineator.

Overall, CTG recordings provided FHR_{ref} values relative to 653 (61%) out of 1071 10-second windows available from experimental FPCG signals (the other windows were too noisy). The number of windows for which it was possible to evaluate FHR_{S1S1} and FHR_{S2S2} was 825 (77%) for AdvFPCG-Delineator and 931 (87%) for PCG-Delineator, both including the above-mentioned 653 windows for which CTG FHR_{ref} were available.

Table 4 reports the comparison of FHR_{10s} and related errors according to PCG-Delineator and AdvFPCG-Delineator vs CTG reference over the 653 10-second windows. AdvFPCG-Delineator provided FHR_{10s} estimates (*i.e.* FHR_{S1S1} and FHR_{S2S2}) not significantly different from reference and thus corresponding errors not significantly different from 0. Instead, PCG-Delineator provided FHR_{10s} estimate by S2S2 interval (*i.e.* FHR_{S2S2}) significantly different from reference and corresponding error significantly greater than zero.

FPCG feature	**CTG**	**PCG-Delineator**		**AdvFPCG-Delineator**	
	Reference	**S1S1**	**S2S2**	**S1S1**	**S2S2**
FHR_{10s}(bpm)	141[135;149]	139[135;145]	122[116;135]*	141[138;145]	141[137;145]
Ɛ (bpm)	0 [0;0]	1[-4;10]	19[11;27]*	-1[-6;6]	-1[-6;6]

Table 4. Comparison between FHR_{10s} estimated using PCG-Delineator and AdvFPCG-Delineator vs cardiotocographic (CTG) reference for the "Shiraz University (SU) fetal heart sounds database" (specifically, for the 653 10-second windows for which CTG HR_{10s} were available).

n.a.: not applicable;

*: $P<0.05$, when comparing PCG-Delineator and AdvFPCG-Delineator vs CTG reference.

The results of the robustness of AdvFPCG-Delineator in relation to MA, BMI, GA, single vs twin pregnancies, gender of the fetus and fetus clinical conditions are reported in Table 5. In all cases, no statistically significant differences were obtained when comparing FHR_{10s} and related errors according to AdvFPCG-Delineator vs CTG reference.

		N	FPCG Feature	CTG	AdvFPCG-Delineator	
				Reference	S1S1	S2S2
MA (years)	<30	59 (54%)	FHR_{10s} (bpm)	141[135;147]	142[136;148]	142[137;147]
			Ɛ (bpm)	0[0;0]	0[-2;0]	0[-2;0]
	30-39	43 (40%)	FHR_{10s} (bpm)	143[143;150]	143[136;151]	143[136;151]
			Ɛ (bpm)	0[0;0]	0[-2;1]	0[-2;0]
	>39	7 (6%)	FHR_{10s} (bpm)	140[138;144]	140[137;144]	140[137;144]
			Ɛ (bpm)	0[0;0]	0[-1;0]	0[-1;0]
BMI (kg/m^2)	<25	12 (11%)	FHR_{10s} (bpm)	138[132;144]	139[133;145]	139[133;146]
			Ɛ (bpm)	0[0;0]	0[-3;1]	0[-3;0]
	25-30	55 (50%)	FHR_{10s} (bpm)	140[133;147]	141[135;148]	141[136;148]
			Ɛ (bpm)	0[0;0]	0[-2;0]	0[-2;0]
	>30	42 (39%)	FHR_{10s} (bpm)	143[137;150]	144[138;150]	144[138;150]
			Ɛ (bpm)	0[0;0]	0[-3;1]	0[-3;2]
GA (weeks)	<39	75 (69%)	FHR_{10s} (bpm)	141[135;147]	141[136;148]	142[136;148]
			Ɛ (bpm)	0[0;0]	0[-2;0]	0[-2;0]
	39-41	32 (29%)	FHR_{10s} (bpm)	143[137;149]	143[137;148]	144[137;149]
			Ɛ (bpm)	0[0;0]	0[-1;1]	0[-2;0]
	≥41	2 (2%)	FHR_{10s} (bpm)	156[139;163]	155[143;162]	155[143;159]
			Ɛ (bpm)	0[0;0]	0[-2;1]	0[-2;3]
Pregnancy type	Single	102 (94%)	FHR_{10s} (bpm)	141[135;149]	142[136;149]	142[136;148]
			Ɛ (bpm)	0[0;0]	0[-3;1]	0[-3;1]
	Twin	7 (6%)	FHR_{10s} (bpm)	143[138;149]	143[138;148]	144[139;149]
			Ɛ (bpm)	0[0;0]	0[-1;0]	0[-1;0]
Fetus gender	Male	60 (52%)	FHR_{10s} (bpm)	143[136;150]	144[137;150]	144[137;150]
			Ɛ (bpm)	0[0;0]	0[-3;1]	0[-3;1]
	Female	54 (46%)	FHR_{10s}(bpm)	140[133;145]	141[135;147]	141[135;147]
			Ɛ (bpm)	0[0;0]	0[-2;0]	0[-2;0]
	Unknown	2 (2%)	FHR_{10s} (bpm)	132[131;138]	137[135;140]	137[133;139]
			Ɛ (bpm)	0[0;0]	-2[-7;1]	0[-6;2]
Fetus health condition	Healthy	102 (88%)	FHR_{10s} (bpm)	140[134;148]	141[135;148]	141[135;148]
			Ɛ (bpm)	0[0;0]	0[-2;1]	0[-2;1]
	Not healthy	14 (12%)	FHR_{10s} (bpm)	144[138;150]	145[140;150]	145[139;150]
			Ɛ (bpm)	0[0;0]	0[-3;0]	0[-3;0]

Table 5. Robustness of AdvFPCG-Delineator in relation to MA, BMI, GA, single vs twin pregnancies, gender of the fetus and fetus health condition.

*: $P<0.05$, when comparing AdvFPCG-Delineator vs CTG reference.

4. Discussion

This study proposed AdvFPCG-Delineator for FPCG filtering and fetal S1 and S2 identification from fetal phonocardiograms, and demonstrated its reliability in different clinical conditions.

AdvFPCG-Delineator is an improved version of the previously proposed PCG-Delineator. Improvement of AdvFPCG-Delineator was obtained by adding the scalogram computation in its algorithm (Figure 1). Filtering is always required because FPCG signal is typically very noisy [2-3,10,14-16] and here it was performed using a filter based on the wavelet transform obtained by combining the 4th-order Coiflet mother wavelet with soft rule, universal thresholding algorithm and 7 decomposition levels, since this combination was recently found to be optimal for FPCG filtering

[22]. Then, the scalogram [4,31-32] was computed to enhance FPCG signals by performing a time-frequency characterization before S1 and S2 identification. As a result, S1 and especially S2 identification by AdvFPCG-Delineator resulted much more accurate. Indeed, when tested on the "Simulated Fetal PCGs database" [20] and the "Shiraz University (SU) fetal heart sounds database" [13,15], the number of identified S1 and S2 increased (+0.7% and +8.5%, respectively, for the simulated data, and +2.2% and +21.6%, respectively, for the experimental data) and the number of cardiac beats in which S1 and S2 were both detected increased (from 92.8% to 99.9% for the simulated data; and from 83.5% to 99.4% for the experimental data).

To further assure that the new identifications were not actually false positive identifications, FHR values were computed from S1S1 and S2S2 intervals and compared against FHR reference values. S1 and S2 annotations were available for the simulated data but not for the experimental data. Thus, while for simulated FPCG signals reference FHR could be computed by means of S1S1 intervals obtained using the annotations, for experimental FPCG signals it had to be indirectly obtained from the simultaneously acquired cardiotocographic recordings [14] available at Shiraz University. However, cardiotocography provides mean FHR values obtained by averaging over 10-second windows. Thus, for consistency, in all cases we referred to reference FHR as the mean FHR over 10-second windows, obtained using S1 annotations for the simulated data, and cardiotocographic data for the experimental data. For both simulated and experimental data, results indicate that, only for AdvFPCG-Delineator, FHR estimated using both S1S1 interval and S2S2 interval were not significantly different from reference (Tables 2 and 4), confirming the outperformance of this method with respect to PCG-Delineator.

Beside on FHR, the two methods were also evaluated on beat-to-beat variations, since these latter have an important prognostic value [36-37]. Such evaluation was not possible for the experimental data, since no S1 and S2 annotations were available; thus, it was performed only on the simulated data. Results indicated that AdvFPCG-Delineator is able to track S1S1 and S2S2 beat-to-beat variability accurately (high ρ, m close to 1 and q close to 0). In particular, AdvFPCG-Delineator overcame the major limit of PCG-Delineator, which consists in the tendency to miss S1 and S2 identifications (especially those belonging to short cardiac beats) and thus to provide estimated S1S1 and S2S2 intervals too long with respect to reference (Figure 2, panel A and B).

AdvFPCG-Delineator also demonstrated to be reliable when evaluated in different clinical conditions. Indeed, its performance was independent on maternal age, maternal body mass index, gestational age, type of pregnancy (single vs twin), gender of the fetus and fetus health condition. AdvFPCG-Delineator robustness to fetal position and sensors location was not evaluated because such information was not annotated during recordings, and thus was not available to our knowledge. However, it should be observed that it is not possible to identify the optimal sensor position since it depends on fetal position, which is highly uncertain and variable. Consequently, sensor is usually located based on clinician experience. This solution allows to have good quality signals but implies having different sensors locations for different women.

Eventually, it is worth to observe that AdvFPCG-Delineator was designed exclusively for fetal monitoring and not for maternal monitoring. Nevertheless, real-time simultaneous monitoring of both fetus and mother is fundamental during pregnancy, since fetal wellbeing implies maternal wellbeing and vice versa. Future studies will evaluate possibility of using AdvFPCG-Delineator in real-time applications. Instead, maternal monitoring requires different tools specifically designed for adult subjects, since they have a completely different structural and physiological hearth morphology from fetuses [18].

4.1. Conclusions

In this study, it was demonstrated that the hereby proposed AdvFPCG-Delineator represents a reliable method to identify S1 and S2 from fetal phonocardiograms, which is a very practical means of fetal cardiac status assessment.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

1. H.E. Bessil and J.H. Dripps, Real-time processing and analysis of fetal phonocardiographic sensor, *Clinical Physics and Physiological Measurement*, 1989, 10 Suppl B (4B): 67-74. DOI: 10.1088/0143-0815/10/4B/011.
2. V.S. Chourasia, A.K. Tiwari et al., A novel approach for phonocardiographic signals processing to make possible fetal heart rate evaluations, *Digital Signal Processing*, 2014, 30: 165-183. DOI:10.1016/j.dsp.2014.03.009.
3. V.S. Chourasia and A.K. Tiwari, Design methodology of a new wavelet basis function for fetal phonocardiographic signals, *The Scientific World Journal*, 2013, 505840. DOI: 10.1155/2013/505840.
4. V.S. Chourasia and A. Tiwari, Time-frequency characterization of fetal phonocardiographic signals using wavelet scalogram, *Journal of Mechanics in Medicine and Biology*, 2011, 11 (02). DOI: 10.1142/S0219519410003782.
5. F. Kovács, C. Horváth et al., Fetal phonocardiography-past and future possibilities, *Computer Methods and Programs in Biomedicine*, 2011, 104 (1): 19-25. DOI:10.1016/j.cmpb.2010.10.006.
6. S.D. Min and H. Shin, A localization method for first and second heart sounds based on energy detection and interval regulation, *Journal of Electrical Engineering and Technology*, 2015, 10 (5): 2126-2134. DOI: 10.5370/JEET.2015.10.5.2126.
7. A.N. Pelech, The physiology of cardiac auscultation, *Pediatric clinics of North America*, 2004, 51: 1515-1535. DOI: 10.1016/j.pcl.2004.08.004.
8. H. Boudoulas, Systolic time intervals, *European Heart Journal*, 1990, 11: 93-104. DOI: 10.1093/eurheartj/11.suppl_I.93.
9. P.C. Adithya, R. Sankar et al., Trends in fetal monitoring through phonocardiography: Challenges and future directions, *Biomedical Signal Processing and Control*, 2017, 33: 289-305. DOI:10.1016/j.bspc.2016.11.007.
10. P. Várady, L. Wildt et al., An advanced method in fetal phonocardiography, *Computer Methods and Programs in Biomedicine*, 2003, 71 (3): 283-296. DOI: 10.1016/S0169-2607(02)00111-6.
11. A. Strazza, A. Sbrollini et al., PCG-Delineator: an efficient algorithm for automatic heart sounds detection in fetal phonocardiography, *Computing in Cardiology*, 2018, 45: 1-4. DOI:10.22489/CinC.2018.045.

12. P.C. Adithya, R. Sankar et al., Trends in fetal monitoring through phonocardiography: challenges and future directions, *Biomedical Signal Processing and Control*, 2017, 33: 289-305. DOI:10.1016/j.bspc.2016.11.007.
13. C. Liu, D. Springer et al., An open access database for the evaluation of heart sound algorithms, *Physiological Measurement*, 2016, 37 (12): 2181-2213. DOI: 10.1088/0967-3334/37/12/2181.
14. V.S. Chourasia and A. Mittra, Wavelet-based denoising of fetal phonocardiographic signals, *International Journal of Medical Engineering and Informatics*, 2010, 2 (2). DOI: 10.1504/IJMEI.2010.031516.
15. M. Samieinasab and R. Sameni, Fetal phonocardiogram extraction using single channel blind source separation, *23rd Iranian Conference on Electrical Engineering*, 2015, 78-83. DOI: 10.1109/IranianCEE.2015.7146186.
16. A. Sbrollini, A. Strazza et al., Fetal phonocardiogram denoising by wavelet transformation: robustness to noise, *Computing in Cardiology*, 2017, 44: 1-4. DOI: 10.22489/CinC.2017.331-075.
17. A. Misal and G.R. Sinha, Denoising of PCG signal by using wavelet transforms, *Advances in Computational Research*, 2012, 4 (1): 46-49. http://www.bioinfo.in/contents.php?id=33.
18. R. Sameni and G.D. Clifford, A review of fetal ECG signal processing; issues and promising directions, *The Open Pacing Electrophysiology & Therapy Journal*, 2010, 3: 4-20. DOI:10.2174/1876536X01003010004.
19. S. Sun, Z. Jiang et al., Automatic moment segmentation and peak detection analysis of heart sound pattern via short-time modified Hilbert transform, *Computer Methods and Programs in Biomedicine*, 2014, 114 (3): 219-230. DOI:10.1016/j.cmpb.2014.02.004.
20. M. Cesarelli, M. Ruffo et al., Simulation of foetal phonocardiographic recordings for testing of FHR extraction algorithms, *Computer Methods and Programs in Biomedicine*, 2012, 107 (3): 513-523. DOI: 10.1016/j.cmpb.2011.11.008.
21. A.L. Goldberger, L.A. Amaral et al., PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals, *Circulation*, 2000, 101 (23): 215-220. DOI: 10.1161/01.cir.101.23.e215.
22. S. Tomassini, A. Strazza et al., Wavelet filtering of fetal phonocardiography: a comparative analysis, *Mathematical Biosciences and Engineering*, 2019, 16 (5): 6034-6046. DOI: 10.3934/mbe.2019302.
23. A.P. Londero, E. Rossetti et al., Maternal age and the risk of adverse pregnancy outcomes: A retrospective cohort study, *BMC Pregnancy and Childbirth*, 2019, 19(1):261. DOI:10.1186/s12884-019-2400-x.
24. N. Heslehurst, L.J. Ells et al., Trends in maternal obesity incidence rates, demographic predictors, and health inequalities in 36821 women over a 15-year period, *BJOG: an International Journal of Obstetrics & Gynaecology*, 2007, 114(2):187-94. DOI:10.1111/j.1471-0528.2006.01180.x.
25. ACOG Committee Opinion No 579: Definition of term pregnancy, *Obstetrics and Gynecology*, 2013, 122(5):1139-40. DOI: 10.1097/01.AOG.0000437385.88715.4a.
26. A. Strazza, A. Sbrollini et al., PCG-Decompositor: a new method for fetal phonocardiogram filtering based on wavelet transform multi-level decomposition, *IFMBE Proceedings - MEDICON 2019*, 2020, 76: 47-53. DOI: 10.1007/978-3-030-31635-8_6.
27. V.S. Chourasia and A.K. Mittra, Selection of mother wavelet and denoising algorithm for analysis of foetal phonocardiographic signals, *Journal of Medical Engineering & Technology*, 2009, 33 (6): 442-448. DOI: 10.1080/03091900902952618.

28. B. Ergen, Comparison of wavelet types and thresholding methods on wavelet based denoising of heart sounds, *Journal of Signal and Information Processing*, 2013, 4 (3): 164-167. DOI: 10.4236/jsip.2013.43B029.
29. D. Messer, S. Agzarian et al., Optimal wavelet denoising for phonocardiograms, *Microelectronics Journal*, 2001, 32 (12): 931-941. DOI: 10.1016/S0026-2692(01)00095-7.
30. E. Koutsiana, L.J. Hadjileontiadis et al., Detecting fetal heart sounds by means of fractal dimension analysis in the wavelet domain, *Frontiers in Bioengineering and Biotechnology*, 2017, 5: 49. DOI: 10.1109/EMBC.2017.8037291.
31. J.T. Bialasiewicz, Application of wavelet scalogram and coscalogram for analysis of biomedical signals, *Proceedings of the World Congress on EECSS*, 2015, 333.
32. O. Rioul and P. Flandrin, Time-scale energy distributions: a general class extending wavelet transforms, *IEEE Transactions on Signal Processing*, 1992, 40 (7): 1746–1757. DOI: 10.1109/78.143446.
33. S.G. Mallat, A theory for multiresolution signal decomposition: the wavelet representation, *IEEE Transaction on Pattern Analysis and Machine Intelligence*, 1989, 11 (7): 674-693. DOI: 10.1109/34.192463.
34. H.W. Lilliefors and W. Hubert, On the Kolmogorov-Smirnov test for normality with mean and variance unknown, *Journal of the American Statistical Association*, 1967, 62 (318): 399-402. DOI:10.1080/01621459.1967.10482916.
35. H.B. Mann, D.R. Whitney et al., On a test of whether one of two random variables is stochastically larger than the other, *Annals of Mathematical Statistics*, 1947, 18 (1): 50-60. DOI:10.1214/aoms/1177730491.MR 0022058.Zbl0041.26103.
36. D. Ayres-De-Campos, C.Y. Spong et al., FIGO consensus guidelines on intrapartum fetal monitoring: Cardiotocography, *International Journal of Gynecology and Obstetrics*, 2015, 131(1), 13-24. DOI:10.1016/j.ijgo.2015.06.020.
37. M.G. Signorini, G. Magenes et al., Linear and nonlinear parameters for the analysis of fetal heart rate signal from cardiotocographic recordings, *IEEE Transactions on Biomedical Engineering*, 2003, 50(3), 365-374. DOI:10.1109/TBME.2003.808824.