Feasibility of uterine speckle tracking for improved embryo implantation

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Abstract—Infertility problems are involving an increasing number of women, also due to the trend of postponing conception. In-vitro fertilization represents nowadays the most advanced technology to approach infertility problems, but it still shows a low success rate of about 30%. A possible cause may reside in the uterine movement during embryo transfer, possibly hampering successful implantation. Unfortunately, no objective tools are nowadays available for the assessment of uterine movement. With the aim of filling this gap, here we present the first method for quantitative analysis of uterine movement. Being widespread accessible, ultrasound imaging is employed for the analysis. In particular, a speckle-tracking algorithm has been implemented that is based on block matching by normalized cross correlation. Wiener deconvolution is used to regularize the image resolution prior to speckle tracking and correlation filtering is adopted to improve the method reliability. The method feasibility was tested in vitro as well as for its ability to distinguish between active and non-active phase of a natural menstrual cycle in six women. Two pairs of sites were manually defined on the uterine muscle and automatically tracked over time. The extracted movement features permitted successful separation between the two classes (p < 0.05 by paired, double-tailed Student t-test). Additional validation is however required to prove the clinical value of this method for in-vitro fertilization.

I. INTRODUCTION
Up to 20% of couples have difficulties conceiving [1], and this rate is expected to increase because of the trend in postponing childbirth in developed societies [2], [3]. As a result, assisted reproductive technology is experiencing a tremendous development [4]. In this context, in-vitro fertilization (IVF) is the most advanced technology; an embryo is generated by external in-vitro egg fertilization and transferred into the uterus with a catheter. Unfortunately, the effectiveness per treatment cycle remains below 30% [5]. This rate shows a progressive decline as age increases and drops to just 8% at 40 years [6]. Most IVF failures remain unexplained; yet, there is evidence of a major involvement of uterine contractions in IVF failure, especially during and shortly after embryo transfer [7], [8], [9]. However, the role of uterine contractions in IVF failure is not yet understood. This is also because of the lack of methods for a quantitative characterization of the uterine activity outside pregnancy.

Uterine contractions can be quantitatively assessed by intrauterine pressure catheters [9], but the use of invasive catheterization may interfere with the natural contraction due to irritation and other reactions [10]. Hysterosalpingoscopy can be used for indirect assessment of contraction direction by measuring displacements of uterine content [11]. The main disadvantages relate to the time and cost of the procedure, and its inability to assess contraction amplitude and frequency. Furthermore, due to the employment of ionizing radiations, it is not suitable for use after embryo transfer.

Ultrasound imaging represents a valid, safe alternative for quantitative analysis of the uterus. Up until now, only qualitative evaluation of uterine movement has been performed, evidencing variations during the menstrual cycle [12] and the important role of peristaltic movements in IVF outcome [9]. However, the resulting image sequences are hard to interpret even for experienced sonographers [11]. Moreover, the operator-dependency of qualitative ultrasound analysis complicates its adoption for clinical studies aimed at understanding and characterizing uterine contractions outside pregnancy [13]. As a result, uterine ultrasound imaging is not considered as a standard procedure for IVF.

In this paper, the use of quantitative ultrasound imaging of the uterus is proposed for the first time. To this end, ultrasound motion tracking, already established for other clinical applications [14], [15], is employed. A general approach, not requiring access to the scanner hardware and radio-frequency signals, consists of tracking the characteristic speckle pattern of ultrasound images [16], [17]. This is pursued by block matching, where the matching of corresponding areas (blocks) in subsequent frames is determined by the peak of the Normalized Cross Correlation (NCC) function [18], [19]. The method performance is enhanced by the use of a correlation filter [20]. The size of the block and the search region are optimized according to speckle size and tissue velocity (relative to the frame rate). Compensation for the effect of strain within the blocks is also considered and implemented in an iterative fashion.

Especially with the adopted transvaginal probe, the convexity of the ultrasound imaging array enhances the anisotropy and depth dependency of the image resolution, complicating the block-matching implementation. To overcome this problem, the image resolution is regularized prior to the speckle tracking analysis by means of a Wiener deconvolution filter as proposed in [21]. The feasibility of the proposed uterine speckle tracking was tested with promising results by comparing the ability to distinguish between uterine active and non-active periods in six women. Dedicated in-vitro experiments were also carried out to optimise the proposed method.
II. Methodology

A. Ultrasound acquisition

Ultrasound acquisitions were performed at the Catharina Hospital Eindhoven (the Netherlands) both in vitro and in vivo. In vitro, a dedicated phantom was used to optimize the off-line analysis. In vivo, twelve 4-min ultrasound scans were recorded in six women. For each woman, two scans were performed at different phases of the menstrual cycle, suggested to show the most active and non-active behavior, respectively [22]. This study was approved by the relevant ethical committee and each participant signed an informed consent. An ultrasound scanner Accuvix 20 (Samsung-Medison) equipped with a transvaginal EC4-9IS probe was used for the acquisition. The acquisition frame rate was 25 frames/s, which is amply sufficient to meet Nyquist condition given the limited bandwidth of the uterine movement [12]. The gray-level data were then exported in AVI (Audio Video Interleave) format for off-line analysis, implemented in Matlab® (MathWorks).

B. Image preprocessing

Each image in the acquired loops was first preprocessed to regularize the spatial resolution, here represented by the speckle size. Image regularization was obtained by Wiener deconvolution filtering as proposed in [21]. Wiener filtering is optimal in the case of additive white Gaussian noise [23]. Although ultrasound images are mainly affected by multiplicative Rayleigh noise [24], this becomes additive Fisher-Tippet noise after log-transformation [25]. The latter is often approximated by additive white Gaussian noise [26]. As for most ultrasound gray-level images, log-transformation was also applied to our data. After regularization, the resulting images presented an isotropic resolution with speckle size of 1 mm (calculated as the full-width half-maximum of the autocorrelation function).

C. Speckle tracking

After preprocessing, speckle tracking was performed by a block-matching algorithm based on the NCC function. In essence, a predefined search area is used to find the image block corresponding to (matching) the block determined in the previous frame. The best matching is determined by the peak of the NCC function. Normalization is made by dividing the signals by their standard deviations after subtracting their mean value within the block. Eventually, the tissue displacement is estimated between each subsequent couple of frames.

Due to the high frame rate (25 Hz) compared to the slow myometrial movement \( \leq 1.2 \) cm/s, the movement between two frames is limited. Therefore, upsampling was adopted to increase the tracking resolution. For a block matching design, two critical parameters must be determined: block size and search area. The block size should be the smallest representing a unique speckle pattern, to be matched in the following frame. Larger blocks limit the spatial resolution of the displacement estimates. The search area should be as small as possible, yet covering the maximum expected displacement of the block in the case of maximum tissue velocity. In our case, this corresponds to 0.48 mm. Upsampling and block size were optimized based on a dedicated in vitro setup and our preliminary scans in vivo.

D. Correlation filter

In order to improve the robustness of the method, a correlation filter is implemented that estimates the strain as the average for a number of shifted blocks. Assuming the strain of neighboring pixels to be comparable, this averaging approach reduces the risk of NCC “peak hopping” and, therefore, it improves the overall robustness of the tracking [20]. Referring to Fig. 1, the estimated NCC, including correlation filtering, can be written as

\[
NCC_{xy}(q,p) = \frac{1}{(2I+1)(2J+1)} \sum_{i=-I}^{I} \sum_{j=-J}^{J} NCC_{x+i,y+j}(q,p),
\]

with \( 2I+1 \) and \( 2J+1 \) being the filter size in both directions, \((x, y)\) the coordinates of the original block of size \( M \times N \), and \((q, p)\) the NCC displacement domain, representing the displacement between two blocks at two subsequent frames.

![Figure 1: Schematics of the implemented NCC with correlation filter.](image-url)

An optimal compromise must however be found between the number of shifts included, improving the averaging statistics, and the maximum distance of the shifted blocks; for increasing distance, the assumption of comparable strain does no longer hold.

E. Strain compensation

The correlation filter relies on the fact that the same correlation function can be found for shifted blocks. However, strain is also reflected in displacement within the block. Larger strain introduces larger deformations, shifting the NCC peaks for neighboring blocks and, therefore, affecting the effectiveness of the correlation filter. In order to overcome this problem, the strain can be taken into account when averaging by correlation filtering. To this end, the strain is first estimated by a regular correlation filter, providing the initialization for a recursive approach where the strain is used for improving the NCC.
estimation by correlation filtering, resulting in a better strain estimate that can again be used for improving the NCC estimation. The method shows fast convergence with usually less than three iterations. Bilinear interpolation is used for estimating and representing the fractional displacements due to strain.

\( F. \) In-vitro validation

The algorithm was first validated by a simple in-vitro setup where a wheat-gluten (seitan) phantom was marked with two needles and imaged in water while being slowly compressed, reproducing uterine movement. An image is shown in Fig. 2. The distance between the two markers could accurately be tracked because of the strong signal produced in the image. Close to the markers, in a way that shadowing was avoided, two blocks were defined and tracked with the proposed algorithm. The estimated distances between the two blocks and the two markers were compared and the mean squared error (MSE) used as quality measure for the proposed block matching algorithm.

\( G. \) In-vivo validation

Validation in patients aimed at testing the proposed method for its ability to discriminate between active and non-active phases of the uterus. Four-minute ultrasound loops were acquired in six women during active and non-active phase, respectively. For each loop, four sites were manually defined along the uterine muscle (myometrium) near the fundus (Fig. 3) and tracked over time; the fundus is known to show more activity than the cervix [27]. These sites were coupled in pairs: one pair (P1) in the anterior wall and one pair (P2) in the posterior wall of the myometrium. The distance and strain between each pair was then recorded over time by the proposed speckle tracking algorithm. The strain was defined per frame as the relative variation of the distance between the tracked sites.

Based on the recorded signals, four features were extracted and evaluated for their ability to discriminate between active and non-active phase. In particular, standard deviation (SD) and mean frequency \( (f_m) \) of distance and strain were considered. Prior to the strain estimation, the distance estimate was low-pass filtered with cut-off frequency equal to 0.2 Hz. The mean frequency was estimated as the first statistical moment of the amplitude spectrum of the signals after band-pass filtering between 0.02 and 0.2 Hz. The same band-pass filter was applied prior to the SD estimation. The choice for the filters’ cut-off frequencies was based on the bandwidth of the signals of interest. For each feature, paired, double-tailed Student t-test was performed to assess the significance (p-value) of the mean difference between the feature mean values for the two phases.

\section{III. Results}

The in-vitro validation indicated optimal correlation filtering for \( I = J = 3 \), with MSE = 0.44 ± 0.31 pixels when a block size of 125 × 125 pixels (corresponding in our setup to 0.152 mm) is adopted. The upsampling was fixed to a factor five, as it produced the best results. Fig. 4 shows an example of in-vitro tracking.

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\( I. \) Discussion

Based on the recorded signals, four features were extracted and evaluated for their ability to discriminate between active and non-active phase. In particular, standard deviation (SD) and mean frequency \( (f_m) \) of distance and strain were considered. Prior to the strain estimation, the distance estimate was low-pass filtered with cut-off frequency equal to 0.2 Hz. The mean frequency was estimated as the first statistical moment of the amplitude spectrum of the signals after band-pass filtering between 0.02 and 0.2 Hz. The same band-pass filter was applied prior to the SD estimation. The choice for the filters’ cut-off frequencies was based on the bandwidth of the signals of interest. For each feature, paired, double-tailed Student t-test was performed to assess the significance (p-value) of the mean difference between the feature mean values for the two phases.
in vivo settings the design choices and providing indications for the optimal of the proposed method in the context of IVF.

Moreover, 3D imaging will be employed to avoid block decorrelation due to out-of-plane motion. More frequency features could not show significant differences. The measured distance between pairs of tracked sites showed a significant difference between the two classes. Instead, frequency features could not show significant differences. In future work, additional features can be considered for the analysis. Moreover, 3D imaging will be employed to avoid block decorrelation due to out-of-plane motion. More in general, extensive validation is necessary to show the value of the proposed method in the context of IVF.

IV. DISCUSSION AND CONCLUSION

An algorithm for quantitative ultrasound imaging of uterine movement is presented. Movement is assessed by speckle tracking on the gray-level images performed by block matching based on the NCC function. Correlation filtering with strain compensation are employed to boost the method robustness and reliability. Despite a higher computational complexity, correlation filtering by interpolation was preferred over phase rotation methods due to the use of demodulated signals [28]. The in-vitro results were promising, confirming the design choices and providing indications for the optimal settings in vivo.

The results in six women confirmed the ability of the method to distinguish between active and non-active phases of the uterus during a natural menstrual cycle. In particular, among the tested features, the standard deviation of the measured distance between pairs of tracked sites showed a significant difference between the two classes. Instead, frequency features could not show significant differences. In future work, additional features can be considered for the analysis. Moreover, 3D imaging will be employed to avoid block decorrelation due to out-of-plane motion. More in general, extensive validation is necessary to show the value of the proposed method in the context of IVF.

ACKNOWLEDGMENT

This work was supported by the STW HTSM grant 13901.

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