Towards Noninvasive Accurate Detection of Intrapartum Fetal Hypoxic Distress

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Abstract— **Current intrapartum fetal well-being assessment is performed using electronic fetal monitoring (EFM), technically referred to as cardiotocography (CTG), which transabdominally monitors fetal heart rate (FHR) in relationship to maternal uterine contractions. Sometimes the deceleration in FHR following a uterine contraction can be sign of fetal hypoxic distress, but it may also be a normal physiological response. Multiple studies have shown that EFM has a high false positive rate for detecting fetal hypoxia. This has caused a rise in emergency Cesarean section (C-section) deliveries performed in the US over the years, while the rates of various conditions associated with anoxic brain injury at birth remain unchanged. The underlying problem is that many factors other than hypoxia can cause non-reassuring CTG traces and a more objective measure of oxygen supply to the fetal brain is not conveniently available. We are working to develop a transabdominal fetal pulse oximetry (TFO) system to non-invasively measure fetal arterial blood oxygen saturation (FSpO2) in order to enhance intrapartum fetal monitoring. This paper gives an overview of the past and ongoing work performed to develop TFO, highlights the main engineering and clinical challenges faced and presents preliminary results that demonstrate feasibility of TFO in both pregnant sheep models and human subjects.**

I. Introduction

In the 1970s, electronic fetal monitoring (EFM), technically referred to as cardiotocography (CTG), was introduced to hospitals for early identification of fetal asphyxia and anoxic brain injury [1]. Strikingly, the rate of Cesarean section (C-section) deliveries in the US have risen five folds since then, while the rates of various conditions associated with anoxic brain injury at birth, such as cerebral palsy, remain unchanged [2, 3].

The current paradigm for intrapartum EFM is to transabdominally monitor fetal heart rate (FHR) in relationship to maternal uterine contractions. Sometimes the deceleration in the FHR after a uterine contraction is suggestive of fetal distress, but it may be a normal physiological response [4]. Since the possibility of inadequate oxygen supply to the fetal brain may cause irreversible anoxic brain injury, medical interventions, such as emergency C-section, become compelling options [5]. EFM is highly sensitive for the detection of fetal hypoxia. The problem with CTG trace interpretation is that many factors other than hypoxia cause non-reassuring CTG traces [1]. That is, CTG is not specific enough (high rate of false positives) for detection of hypoxic babies [6]. The underlying problem is that a more objective measure of oxygen supply to the fetal brain is not conveniently available during labor. Transabdominal fetal pulse oximetry (TFO) is a promising technology to non-invasively measure fetal arterial blood oxygen saturation (FSpO2) and thus, it stands to enhance fetal monitoring intrapartum [7, 8].

This invited paper presents a brief overview of our past and ongoing activities in developing TFO, highlights important challenges and presents preliminary results that demonstrate feasibility of TFO in both animal models and human subjects.

II. Background

A. Pulse Oximetry

Pulse oximetry is a classic method to estimate arterial blood oxygen saturation (SaO2) levels of a patient [9]. SaO_2 is the percentage of oxyhemoglobin [HbO_2] to the total functional hemoglobin (oxy- [HbO_2] and deoxyhemoglobin [Hb]). SaO_2 values measured by a pulse oximeter are denoted SpO_2. Pulse oximetry utilizes light-based measurements to estimate arterial oxygen saturation by examining the variations in transcutaneous light-intensity caused by subtle geometrical changes in the vascular tissue from the cardiac cycle. At each cardiac cycle, a slight expansion of arterial vessels results in an increase to the blood-tissue volume ratio, and is captured as a photoplethysmogram (PPG), which enables SpO_2 calculation [10]. At least two PPG waveforms, obtained at two distinct wavelengths, are required for SpO_2 measurement. Typically, wavelengths at red and near-infrared (NIR) regions of light are chosen. Red light better captures changes in Hb, and the NIR is more sensitive to changes in HbO_2 [11].

The light intensity signal seen in pulse oximetry is commonly referred to as a combination of two signals, an AC signal that corresponds to the light that passes through the portions of tissue that pulsate (arteries) and a DC signal, corresponding to the light that passes through non-pulsating tissue. The AC to DC ratio calculated at two wavelengths (λ_1, λ_2) can be used to estimate the modulation ratio R and SpO_2, using the relationships described in (1) and (2) [12, 13]. Molar extinction coefficients ϵ are constant and the light path length factor B can be theoretically estimated from photon diffusion equation [12].

$$R = \frac{\Delta A^{\lambda_1}}{\Delta A^{\lambda_2}} = \frac{\log\left(I^{\lambda_1}_{systole}/I^{\lambda_1}_{diastole}\right)}{\log\left(I^{\lambda_2}_{systole}/I^{\lambda_2}_{diastole}\right)} \approx \frac{(AC/DC)^{\lambda_1}}{(AC/DC)^{\lambda_2}} \quad (1)$$

$$SpO_2 = \frac{\epsilon^{\lambda_1}_{Hb} - \epsilon^{\lambda_2}_{Hb} \cdot R \cdot (B^{\lambda_2}/B^{\lambda_1})}{\epsilon^{\lambda_1}_{Hb} - \epsilon^{\lambda_1}_{Hb} + (\epsilon^{\lambda_2}_{HbO} - \epsilon^{\lambda_2}_{Hb}) \cdot R \cdot (B^{\lambda_2}/B^{\lambda_1})} \quad (2)$$

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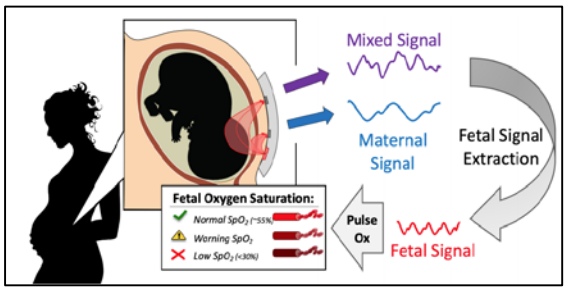

Figure 1. High-Level overview of Transabdominal Fetal Pulse Oximetry [14].

III. Transabdominal Fetal Pulse Oximetry

A. Approach

Fig. 1 illustrates a simplified view of TFO. An optical probe with red/NIR LEDs and at least two photodetectors (PDs) is placed on the maternal abdomen. LEDs emit photons into maternal skin at two distinct wavelengths. The detectors are placed at different judiciously selected distances from the LEDs. We aim to capture PPG waveforms from the fetus, which can then be processed to infer $FSpO_2$. Due to physics of light propagation, the near PD receives light that has traveled only through maternal layers, which enables us to infer information about maternal heart rate (MHR) and her oxygen saturation in the local area. The light received at the far PD, however, is a combination of photons that have traveled through only maternal layers, and photons that have made it deep enough to the fetal layers. Thus, the far detector generates a mixed signal with both maternal and fetal contributions. The fetal signal should be isolated from this mixed signal by leveraging the output of the near detector (maternal signal) and potentially other available sources of information (e.g., CTG or ultrasound). Once a clean PPG due to fetal pulsation is obtained, algorithms and calibration schemes akin to conventional pulse oximetry can be applied to derive $FSpO_2$.

B. Challenges

Direct extension of pulse oximetry concept to transabdominal fetal SpO_2 measurement faces several fundamental engineering and clinical challenges.

1) Light attenuation: For a transabdominal $FSpO_2$ measurement system to work, some photons need to travel deep enough to interrogate fetal layers, and then make it back to the outside of the mother's abdomen to be sensed by a photodetector. However, light quickly attenuates in tissue and amniotic fluid, which limits the depth that can be sensed transabdominally [12]. We conducted Monte Carlo simulations using a multi-layered tissue model in order to optimize the LED wavelengths and source-detector separation so that fetal signal can be sensed from 2-5 cm deep fetus [15]. An optical probe with optimal selection of peak wavelengths at 740nm and 850nm was validated on a tissue phantom mimicing the maternal abdomen.

2) Separation and Recovery of Fetal Signal: The weak fetal signal should be separated from the sensed mixed signal, which is contaminated with substantial noise, due to maternal pulsating arteries, as well as other sources of noise, e.g., instrumentation noise, motions, respiration and mayer waves [16].

Adaptive noise cancellation (ANC) techniques have been investigated in a pre-clinical setup and found to be successful at filtering the fetal signal from the noisy mixed signal [16]. But ANC guarantees excellent performance if the maternal and fetal signal are uncorrelated. In reality, however, the maternal signal has some correlation with the fetal signal [17]. Therefore, we also built a contextually-aware sensing approach to extract the fetal signal using additional information about the physical system (physiological, spatial, and temporal) [18]. The latter approach was evaluated on data captured from pregnant sheep.

3) Validation and Calibration: System characterization and calibration, a universal issue for pulse oximetry systems, is more challenging for fetal oximetry due to inherent difficulty in accessing reference values ($FSaO_2$). $FSaO_2$ ground truth cannot be collected during intrapartum patient validation studies. Animal models can be used for validation and collecting $FSaO_2$, but they are very slow, expensive and yield a low volume of ground truth $FSaO_2$. We have taken a few steps to address this calibration challenge by employing data augmentation on collected $FSaO_2$ from animal models and developing a real-time $FSpO_2$ estimation model that uses a machine learning algorithm to learn the relation between computed modulation ratio R and $FSpO_2$ ($FSpO_2 = f(R)$) as described in (3).

4) Patient variability: Fetal depths vary drastically between pregnant women due to anatomical differences. Combined with the light attenuation challenge, patient variability largely impacts the robustness of TFO in sensing weak fetal signal. We conducted a design space exploration to design a clinically-robust optical probe with optimal number of detectors and optimal source-detector separation [14]. The optimal design obtained as a result of the multi-objective optimization problem is evaluated both through simulation and in-vivo measurements on pregnant sheep [14].

IV. Feasibility Demonstration

A. Device Prototype

The prototyped TFO system is comprised of a multi-detector optical probe (optode), an embedded optode control system and a real-time software. A picture of the TFO system is shown in Fig. 2. A detailed overview of the device prototype can be found in [13].

The optode houses two high-power LEDs at 740nm and 850nm wavelengths and five photodetectors placed at 1.5, 3, 4.5, 7, and 10 cm away from the LEDs [13]. The wavelengths and source-detector distances are optimized to overcome light-attenuation and patient variability challenges described above and as a result the optode can sense information from fetus up to ~5cm deep [14, 15]. The LEDs and photodetectors are soldered on a flexible PCB and placed inside the flexible black silicone housing. Flexible components are chosen so that the optode can be easily placed on the curved maternal abdomen and provide good skin contact. The color black is especially chosen for the housing to block ambient light. The light sensed by the photodetectors is converted to an electrical current (photocurrent), and then to electrical voltage through a transimpedance amplifier.

The embedded optode control system is responsible for adjusting the drive current and amplitude modulation frequency of the LEDs, amplifying and sampling the electrical voltages

Figure 2. A picture of the prototyped Transabdominal Fetal Pulse Oximetry (TFO) system [13].

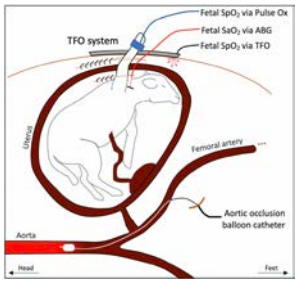

Figure 3. Illustration of the Hypoxic Lamb Model [19].

available from the photodetectors using a programmable gain amplifier and high-resolution analog-to-digital converter (ADC), respectively.

The real-time software includes a graphical interface that provides easy control over TFO settings, a visualization of collected electrical voltages and is capable of saving the measurement data for post-processing.

B. Hypoxic Lamp Model

For evaluation and calibration purposes, we need to evaluate the device over a range of different ground truth $FSaO_2$. Given that such an experiment cannot be designed in human subjects, we use the pregnant sheep model. Sheep offers a reasonable and widely used animal pregnancy model for humans, due to several factors including the favorable balance between anatomic/physiologic similarity and cost.

We demonstrated the feasibility and accuracy of non-invasive transabdominal $FSpO_2$ measurement in vivo using three gravid-term singleton pregnant ewes (136 to 140 days of gestation) [19]. We induced controllable fetal hypoxia, by inserting an inflatable balloon catheter into ewe's infrarenal aorta. The ewe's mean arterial pressures (dMAP) was decreased in 5mmHg increments and maintained for 10 minutes at each increment. Three arterial blood gas (ABG) samples from fetus were collected at each dMAP step, through a fetal carotid arterial line inserted into lamb's neck, to establish gold standard $FSaO_2$ values against which the accuracy of TFO $FSpO_2$ measurements is benchmarked. TFO was placed on the ewe's abdomen to continuously collect data during the experiment. The balloon catheter was fully deflated once fetal SaO_2 observations dropped below 15%, the fetus was recovered, and the protocol was repeated for a second round [19]. An illustration of the hypoxic lamb model is shown in Fig. 3.

The sampled $FSaO_2$ measurements from three hypoxic lamb models presented in Fig. 4 shows that hypoxia was induced in a controlled fashion.

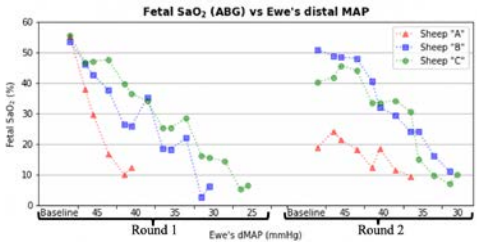

Figure 4. Plot of Fetal SaO_2 measurements from arterial blood gases (ABG) vs. Ewe's distal mean arterial pressure (dMAP).

The hypoxic fetal lamb protocol was approved by the UC Davis Institutional Animal Care and Use Committee (IACUC).

C. Pregnant Human Subjects

We developed a protocol to evaluate TFO in pregnant women. The protocol was reviewed and approved by UC Davis Institutional Review Board (IRB). The evaluation of TFO in antenatal testing is an important step towards its integration into intrapartum fetal monitoring in hospitals. The TFO is evaluated concurrently with non-stress test (NST) visits of the patients participating in the study. Only healthy pregnant women with no expected risk or complication to themselves or their babies, with a singleton pregnancy, and cephalic fetal presentation at >36 weeks of gestation are enrolled in the study. During the study, the skin tone of the patient is recorded based on a reference skin color catalog (Fig. 5), since skin tone plays an important role in light scattering and absorption [14]. Less light is scattered back to the surface with darker skin color, thereby weakening the fetal and maternal signal received. The distance from maternal abdomen's surface to closest fetal tissue is measured using ultrasound. The TFO optode is placed on the abdomen where the fetal depth is measured. Double-sided skin-safe tape is used under the optode to ensure good skin contact, and to prevent the optode from moving or falling. EFM used in NST visits is placed concurrently with the TFO and monitors maternal heart rate (MHR), maternal SpO_2 and fetal heart rate (FHR) (Fig. 6). This study aims to perform a preliminary demonstration of feasibility of TFO in human subjects via proxy metrics, e.g., detection of FHR and MHR.

V. Results and Discussion

We evaluated the performance of TFO's fetal SpO_2 estimation model using the three hypoxic lamb experiments described in section IV. We used 10-fold cross validation to generate the plot in Fig. 7 and computed the mean absolute error (MAE) as well as Pearson's correlation factor (r) between the estimated $FSpO_2$ and measured reference $FSaO_2$. The results show that TFO's estimated $FSpO_2$ values are correlated with reference SaO_2 with a Pearson's r of 0.56, and TFO $FSpO_2$ estimates have a MAE of 10.29%.

The second feasibility study of TFO was performed on human subjects. In this paper, we present preliminary results from three different pregnant women enrolled in the study. A 15 to 20-minutes-long dataset is collected during each study. The feasibility is demonstrated by examining TFO's ability to estimate maternal (MHR) and fetal (FHR) heart rates accurately.

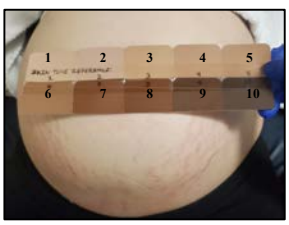

Figure 5. A picture of reference skin tone catalog on a pregnant woman enrolled in our study.

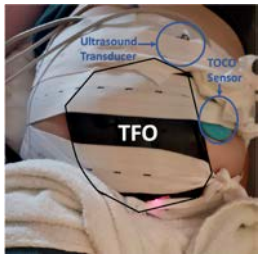

Figure 6. A picture of TFO placed on maternal abdomen together with EFM sensors.

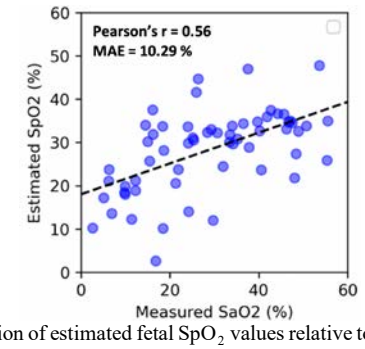

Figure 7. Validation of estimated fetal SpO_2 values relative to the measured fetal SaO_2s from arterial blood gases collected in three hypoxic lamb models (2 rounds each).

Reference heart rate values are collected using cardiotocography. The TFO MHR is extracted from the data collected by nearest detector (PD1) to the light source on the TFO optode. In order to extract the fetal signal from the mixed signal, following steps are applied to the data: (1) Mixed-signal is bandpass filtered between maternal heart rate and 360 beats per minute (BPM) to remove low and high frequency noise components, (2) Recursive Least Squares (RLS) Adaptive Noise Cancellation (ANC) is applied to the filtered mixed-signal using the maternal signal from nearest detector (PD1) as the reference signal [16], (3) The output of adaptive noise cancellation is analyzed in frequency domain to obtain its signal power spectral density (PSD), (4) The highest peak in the PSD between 110 BPM – 270 BPM (typical range for FHR [20]) is estimated as FHR.

Fig. 8 shows an example of maternal, mixed and noise cancelled fetal signal spectrograms computed on 1-minute long windows with 30 seconds of overlap. The reference and estimated FHR and MHR are also plotted on top of the spectrograms. We see that applying ANC to the mixed signal resulted in reducing the amplitude of MHR and its second harmonic, and therefore made FHR peak more distinguishable. Cancelling 2nd harmonic of MHR is particularly important since it could sometimes lie very close to FHR.

The results of estimating FHR and MHR in three different patients are summarized in Table I. The skin tone is based on the reference catalog shown in Fig. 5. The results show that MHR could be very accurately estimated, and FHR could be extracted with reasonable accuracy in human subjects with various skin colors and fetal depths.

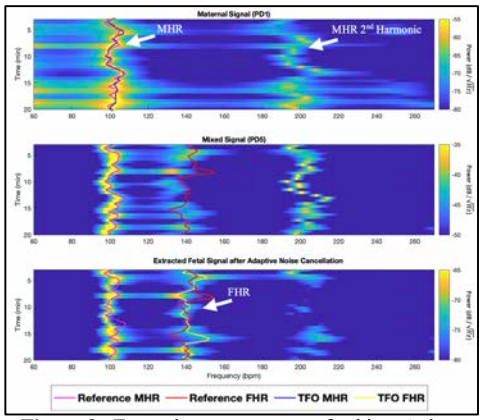

Figure 8. Example spectrograms of subject A data.

TABLE I. ESTIMATING FHR & MHR VIA TFO VS. CARDIOTACOGPRAHY

Subject	Gestational Age (week)	BMI	Skin Tone	Fetal depth	FHR		MHR	
					RMSE (BPM)	MAE (BPM)	RMSE (BPM)	MAE (BPM)
A	36	30.8	1	1.75 cm	7	4.76	1.62	1.30
B	38	28.4	1	1.82 cm	10	8.28	1.69	1.42
C	38	38.3	3	4.46 cm	7.67	6.06	1.56	1.10

REFERENCES

[1] Z. Alfirevic, G. Gyte, A. Cuthbert and D. Devane, "Continuous cardiotocography (CTG) as a form of electronic fetal monitoring (EFM) for fetal assessment during labour," *Cochrane Database of Systematic Reviews*, 2017.

[2] K. Nelson, T. Sartwelle and D. Rouse, "Electronic fetal monitoring, cerebral palsy, and caesarean section: assumptions versus evidence", *BMJ*, p. i6405, 2016.

[3] J.A. Martin, Hamilton BE, Oserman JK, Driscoll AK, Drake P, "Births: final data for 2018," *Natl Vital Stat Rep*, vol. 68, no.13, pp. 1–47, 2019.

[4] B.S. Schifrin, "Fetal Heart Rate Monitoring During Labor," JAMA: *The Journal of the American Medical Association*, vol. 222, no. 2, p. 196, 1972.

[5] Macones, G.A., *Management of labor and delivery.* 2nd ed., Chichester, West Sussex; Hoboken, NJ: John Wiley & Sons Inc. p., 2015.

[6] "ACOG Practice Bulletin No. 106: Intrapartum Fetal Heart Rate Monitoring: Nomenclature, Interpretation, and General Management Principles," *Obstetrics & Gynecology*, vol. 114, no. 1, pp. 192-202, 2009.

[7] S. Ghiasi and D. Fong, "Robust, clinical-grade transabdominal fetal pulse oximetry," US Patent, US20200245879A1, 2016.

[8] S. Ghiasi and D. Fong, "Contextually aware fetal sensing in transabdominal fetal pulse oximetry," US Patent, US20200214603A1, 2020.

[9] Sinex, J.E., "Pulse oximetry: Principles and limitations," *American Journal of Emergency Medicine*, vol. 17, no. 1, pp. 59-66, 1999.

[10] Chan, E.D., M.M. Chan, and M.M. Chan, "Pulse oximetry: Understanding its basic principles facilitates appreciation of its limitations," *Respiratory Medicine*, vol. 107, no. 6, pp. 789-799, 2013.

[11] P. D. Mannheimer *et al.*, "Wavelength selection for low-saturation pulse oximetry," *IEEE Trans. Biomed. Eng.*, vol. 44, no. 3, pp. 148–158, Mar. 1997.

[12] A. Zourabian, A.Siegel, B. Chance, N. Ramanujam, M. Rode and D. Boas, "Trans-abdominal monitoring of fetal arterial blood oxygenation using pulse oximetry," *Journal of Biomedical Optics*, vol. 5, no. 4, p. 391, 2000.

[13] D. Fong et al., "Design and In Vivo Evaluation of a Non-Invasive Transabdominal Fetal Pulse Oximeter," *IEEE Transactions on Biomedical Engineering*, vol. 68, no. 1, pp. 256-266, 2021.

[14] D. Fong, V. Srinivasan, K. Vali and S. Ghiasi, "Optode Design Space Exploration for Clinically-robust Non-invasive Fetal Oximetry," *ACM Transactions on Embedded Computing Systems*, vol. 18, no. 5, pp. 1-22, 2019.

[15] D. Fong, A. Knoesen and S. Ghiasi, "Transabdominalfetalpulseoximetry: The case of fetal signal optimization," *2017 IEEE 19th International Conference on e-Health Networking, Applications and Services (Healthcom)*, 2017.

[16] D. Fong, A. Knoesen, M. Motamedi, T. O'Neill and S. Ghiasi, "Recovering the fetal signal in transabdominal fetal pulse oximetry," *Smart Health*, vol. 9-10, pp. 23-36, 2018.

[17] P. Van Leeuwen, D. Geue, S. Lange, D. Cysarz, H. Bettermann and D. Grönemeyer, *BMC Physiology*, vol. 3, no. 1, p. 2, 2003.

[18] D. Fong, K. Vali and S. Ghiasi, "Contextually-aware Fetal Sensing in Transabdominal Fetal Pulse Oximetry," *2020 ACM/IEEE 11th International Conference on Cyber-Physical Systems (ICCPS)*, 2020.

[19] K. Vali et al., "Non-invasive transabdominal assessment of In-Utero fetal oxygen saturation in a hypoxic lamb model," *American Journal of Obstetrics and Gynecology*, vol. 224, no. 2, p. S604, 2021.

[20] S. Pildner von Steinburg, A.-L. Boulesteix, C. Lederer, S. Grunow, S. Schiermeier, W. Hatzmann, K.-T. M. Schneider, and M. Daumer, "What is the normal fetal heart rate," *PeerJ,* vol. 1, pp. e82–e82, 06 2013.