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Authors

Etemadi, Mozziyar
Chung, Philip
Heller, J
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Publication Date

2013

DOI

10.1109/EMBC.2013.6609466

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Conf Proc IEEE Eng Med Biol Soc. Author manuscript; available in PMC 2015 October 15.

Published in final edited form as:

Conf Proc IEEE Eng Med Biol Soc. 2013 ; 2013: 176–179. doi:10.1109/EMBC.2013.6609466.

Novel Device to Trend Impedance and Fluorescence of the Cervix for Preterm Birth Detection

Mozziyar Etemadi [Student Member, IEEE],
Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, CA 94158 USA

Philip Chung,
Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, CA 94158 USA

J. Alex Heller [Student Member, IEEE],
Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, CA 94158 USA

Jonathan Liu,
Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, CA 94158 USA

Rebecca Grossman-Kahn, **Larry Rand**, and
Department of Obstetrics and Gynecology, University of California, San Francisco, CA.

Shuvo Roy [Member, IEEE]
Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, CA 94158 USA

Abstract

Preterm birth is the leading cause of worldwide neonatal mortality. It follows a pathologically accelerated form of the normal processes that govern cervical softening and dilation. Softening and dilation occur due to changes in cervical collagen crosslinking, which can be measured non-invasively by changes in tissue fluorescence and impedance. We present a novel device designed specifically to take fluorescence and impedance measurements throughout pregnancy, with the end goal of fusing and trending these measurements to form an early diagnosis of preterm labor.

I. Introduction

Preterm birth results in 1 million neonatal deaths each year—35% of all neonatal mortality worldwide [1]. Those infants that survive preterm birth are commonly met with lifelong morbidity and disabling illness [2]. In the United States, the total costs of preterm birth is over $26 billion dollars [3]. Preterm birth by itself is not a disease, but a syndrome: many

415-514-9784; Mozziyar.Etemadi@ucsf.edu.

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pathological mechanisms accelerating what would otherwise be the process of normal birth [4–6].

This process, whether or not it is accelerated, begins with firm cervical tissue, that is firm because the collagen within it is densely crosslinked [7–11]. The fetus develops behind this firm cervix, which prevents foreign bodies from entering the uterus, as well as preventing uterine contents from emerging. Days to weeks before (preterm) birth is to occur (see Figure 1), these tightly bound collagen fibers begin to unlink and become more disorganized [12–15].

After a period of microstructural changes in cervical collagen, the overall shape of the cervix begins to change. Socalled “cervical shortening” is precisely the gold-standard diagnostic predictor of preterm birth measured today via transvaginal ultrasound. With this technique, a short cervix observed too early in gestational age is an indication of accelerated cervical changes that will ultimately result in preterm birth. Unfortunately, cervical shortening often occurs very close in time to the actual preterm delivery, and diagnostic results from ultrasound can be complicated by normal anatomic variability [16].

In an attempt to improve on the diagnostic ability of the macroscopic changes seen on ultrasound, researchers have attempted to measure the microscopic changes in collagen structure. Collagen crosslinks present in the cervix are autofluorescent, and its emission spectra has been shown to change throughout human pregnancy [17]. Collagenous tissue also exhibits a unique impedance spectrum, and has also been studied in the pregnant cervix [18–21].

Fluorescence and impedance are promising methods of preterm birth detection: they can be obtained very quickly and non-invasively. Also, due to recent advances in LED technology, both impedance and fluorescence detection can now be performed at low cost. Unfortunately, both cervical fluorescence [17], [22–26] and impedance [20], [21] have primarily been used only as “spot checks” to predict if labor will occur within 24 hours. We hypothesize that by fusion of multiple impedance and fluorescence measurements over time for a particular patient, an earlier detection of preterm labor can be achieved. Because many of the causes of preterm birth are reversible, an earlier detection would afford the time needed for treatment (i.e. antibiotics) to take effect. To test this hypothesis, we have created a novel cervical collagen interrogation device, specially designed for trending (monitoring changes in) impedance and fluorescence measurements across multiple time points, non-invasively in a clinical feasibility study.

II. Benchtop Collagen Measurement

Bovine calf skin collagen (C3511, Sigma-Aldrich, St. Louis, MO) was prepared at various concentrations mimicking physiologic levels throughout the cervix during gestation. Impedance and fluorescence were measured using an impedance analyzer (Agilent 4294A, Agilent, Santa Clara, CA) and spectrophotometer (Tecan Infinite 200, Männedorf, Switzerland). Data from these instruments is shown in Figure 2 and was used to inform our design parameters.

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III. Device Design

The device consists of a silicone vaginal probe embedded with six electrodes and an optical window to accept a fiber optic bundle. The fiber optic both transmits and receives light to determine fluorescence, and the electrodes are paired in sequence to perform two electrode impedance measurements, as detailed below. A block diagram is given in Figure 3, and a photo of the device used in the clinic is in Figure 4. The device was made using a 3D-printed silicone mold, which was injected with silicone in-house using standard laboratory air pressure. Design iterations were informed from direct physician and human subject feedback, increasing device usability and comfort.

A. Impedance Measurement System

Device electrodes are connected internally within the silicone to modified microUSB 3.0 cable. Electrode pairs are selected via a multiplexer and connected to an Op-Amp based voltage controlled current source. One electrode is fed the current (10 μA AC at various frequencies) with the other connected to virtual ground. The resultant voltage, together with the drive signal, are fed into a gain/phase detector IC (AD 8302, Analog Devices), which outputs two voltages: one proportional to the gain ratio of drive voltage to output voltage, and the other proportional to the phase angle. These are converted to digital and fed over Bluetooth to a computer.

B. Fluorescence Measurement System

A specially arranged, commercially available fluorescence detection fiber bundle (QP600-025-UV, Ocean Optics) is passed down the length of a metal tube which is already molded in the silicone of the device, locking in place with a custom metal connector. The fiber bundle is designed such that excitation fibers minimally reflect their output upon emission fibers, as excitation and emission wavelengths are often close in wavelength and difficult to differentiate if excitation is too bright.

The excitation fibers are illuminated via a dual-LED light source (365nm & 385nm) that is first passed through a USB-operated wavelength selector (Optometrics). Emission fibers are fed into a low-cost, USB spectrometer (USB2000, Ocean Optics). Custom software controls the impedance and fluorescence measurement in synchrony, enabling rapid clinical setup and acquisition time.

IV. Clinical Procedure

Under IRB approval, high-risk pregnant women are actively being recruited from the OB/GYN clinic at our institution. Following the regular prenatal visit, a sterile speculum is inserted into the vagina per the procedures of a standard sterile speculum exam. Excess cervical mucus is cleaned with a few milliliters of deionized water and a cotton swab. The device itself is brought to the clinic having been sterilized using hydrogen peroxide plasma (STERRAD). It is inserted through the speculum and a few, brief test measurements are taken to inform the physician as to how closely the device is contacting the cervix.

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In practice, using these test measurements the physician is able to manually adjust the device to achieve contact on most if not all electrodes. A full measurement spanning all impedance frequencies and fluorescence wavelengths is then performed, which takes approximately 90 seconds. The device and speculum are removed, concluding the patient visit.

V. Pilot Data

Preliminary raw impedance and fluorescence data are seen in Figure 5 without post processing. There is general agreement with the raw collagen fluorescence data collected with gold-standard instruments seen in Figure 2. Of note, the impedance values shown in Figure 5 were computed from voltages proportional to impedance and phase (the outputs of the AD8302). Only a first-order conversion was applied, and thus could account for some discrepancies between gold-standard and patient-obtained impedance. Future work will more accurately calibrate and compare impedance to the gold standard across a wider frequency range, but the values here are still widely different from those obtained when there is no cervical contact (all electrodes > 10kΩ), indicating that we are indeed measuring cervical tissue impedance.

A peak in fluorescence emission is seen at approximately 450nm for around 390nm of incident light. This peak is the result of a superposition of collagen crosslink fluorescence and NADH fluorescence signals in the cervix [27], [28]. However, given that collagen is approximately 70% of cervical tissue, potential changes to this signal during pregnancy will be mostly attributed to collagen changes as the tissue microstructure rearranges [23], [29]. The use of LEDs centered at 365nm and 385nm as our light source limits the excitation range of our system to approximately 350–410nm, yet we have found results comparable to prior research which have used high-powered xenon arc lamps [17], [22–26]. An advantage to our approach is the ability to achieve substantially lower cost and portability. Use of 400nm and 420nm long-wave pass filters to remove excitation light from the measurement may slightly truncate the leading edge of the 450nm emission peak. Because the majority of the peak remains unfiltered, changes in fluorescence magnitude will still be visible as we continue data collection across gestation.

Impedance across the electrode pairs is similar except the face pair (electrodes C & D in Figure 5), which is relatively lower in magnitude. All impedance is within the range reported in the literature. Both magnitude and phase at high frequencies were relatively smaller and more tightly grouped. This has also been observed by other researchers and can be explained by greater ease of penetrating cell walls with high frequency signals [19–21]. Lower frequency signals have greater difficulty penetrating cell walls and injected current tends to follow extracellular paths. While data collection is ongoing, preliminary analysis shows good agreement of data from measurement to measurement for a particular patient. Future work will extract meaningful features from impedance and fluorescence data and correlate to birth outcome.

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VI. Conclusion

In this work we have presented a novel cervical device to capture changes in tissue impedance and fluorescence concordant with preterm labor. We presented preliminary data from the device which is in agreement with published single measurements of fluorescence and impedance. Future work will capture trends in these measurements over the course of pregnancy, comparing features extracted from these trends to pregnancy outcome. Finally, knowing which features trend best with outcome will allow significant miniaturization of the device using embedded LEDs & photodiodes for the optics and miniaturized electronics for impedance, allowing the entire device to be contained within the cervical cup portion of the current prototype.

Acknowledgement

The authors would like to acknowledge the women who have volunteered so generously as subjects in our pilot study. We also thank Dr. Michael Harrison, Dr. Doug Miniati, Dr. Eveline Shue, and Dr. Samuel Schecter for their useful discussions and clinical advice. We also acknowledge Dr. Omer T. Inan for his technical advice in analog circuit design.

Research is supported by the Bill and Melinda Gates Foundation, the Vodafone Americas Foundation, and the FDA (2P50FD003793).

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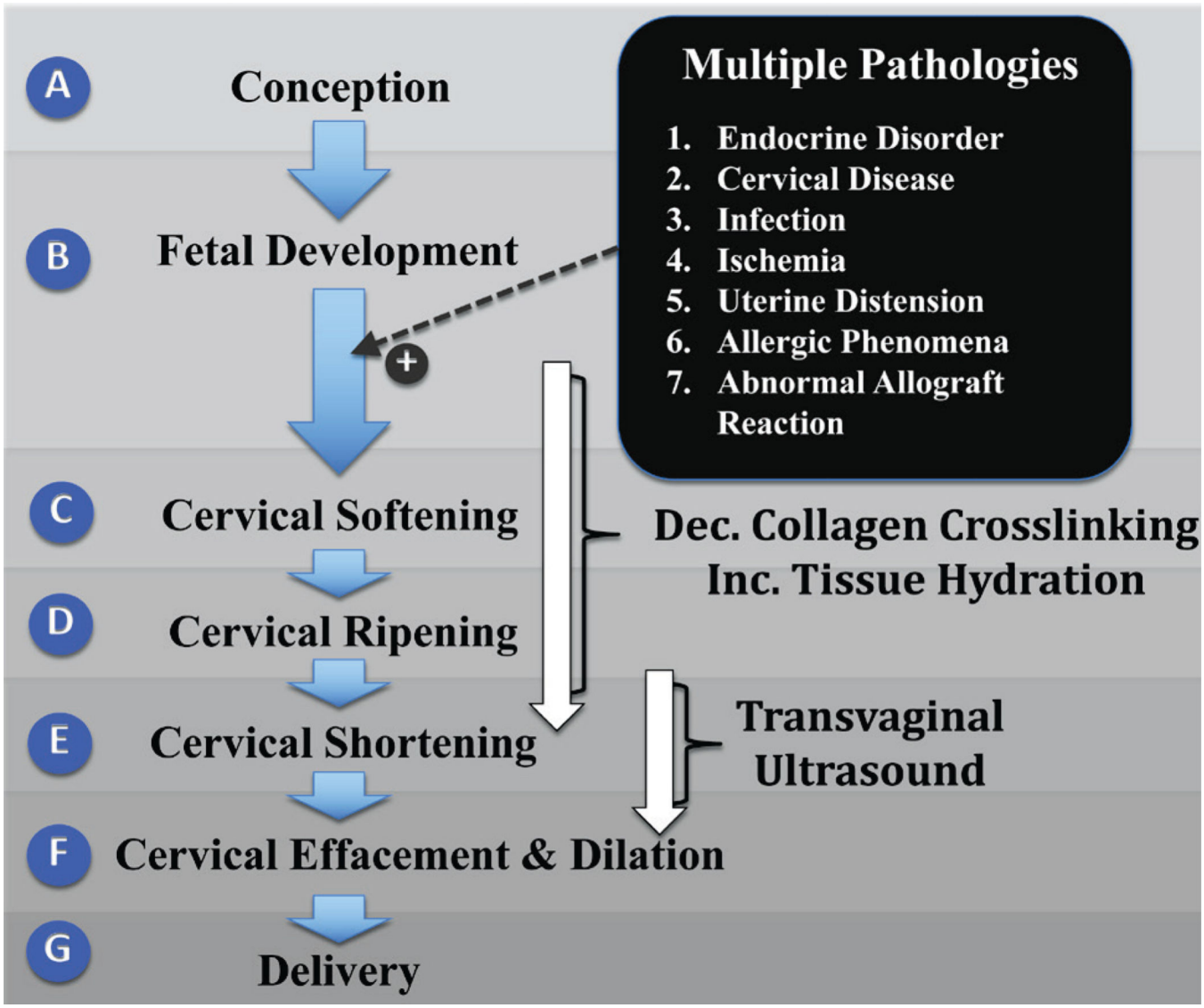

Figure 1.
The physiologic process that prepares the cervix for delivery can be brought about sooner by multiple pathologies, leading to preterm birth.

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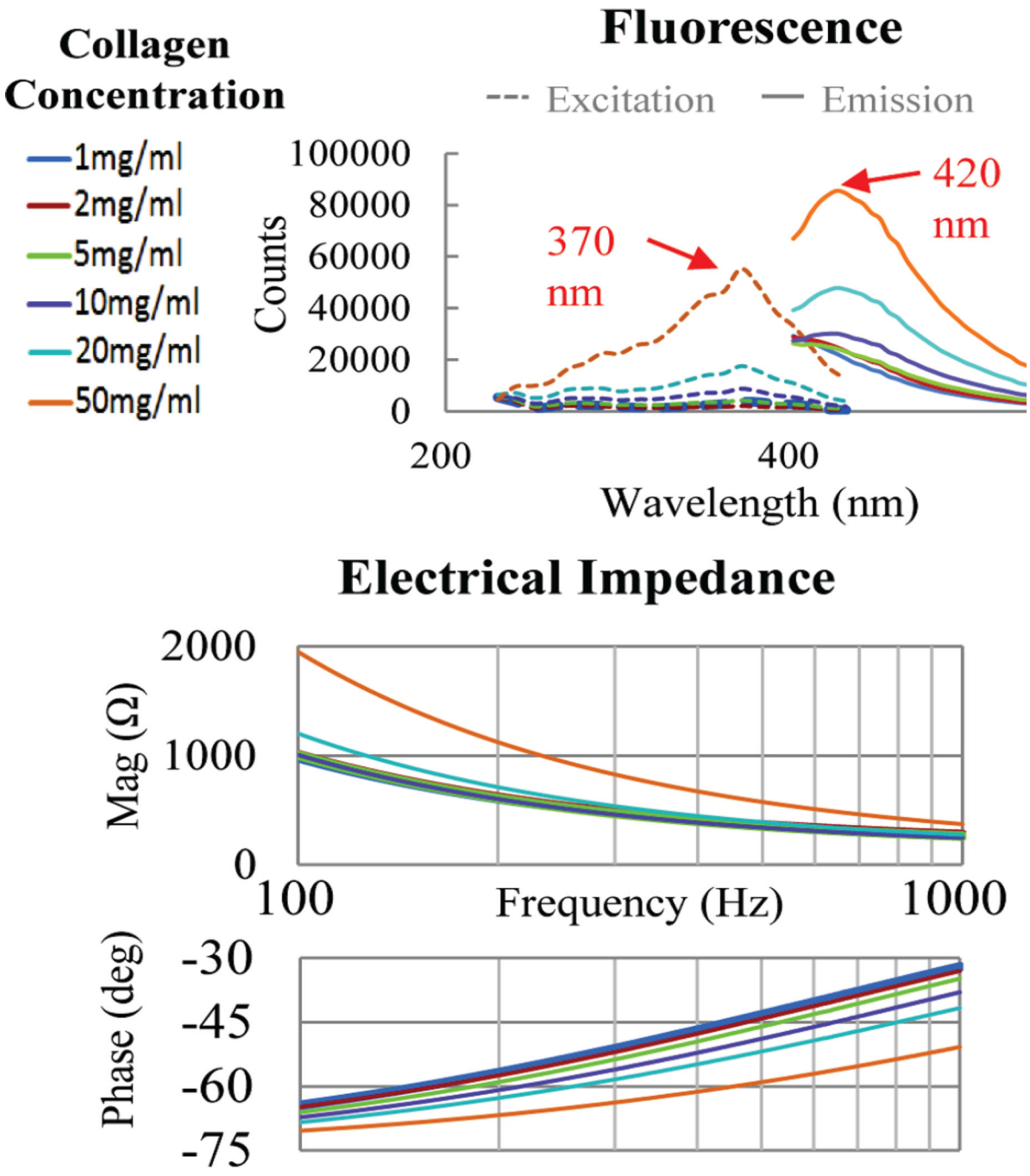

Figure 2.
In vitro collagen measurements made with gold-standard benchtop equipment.

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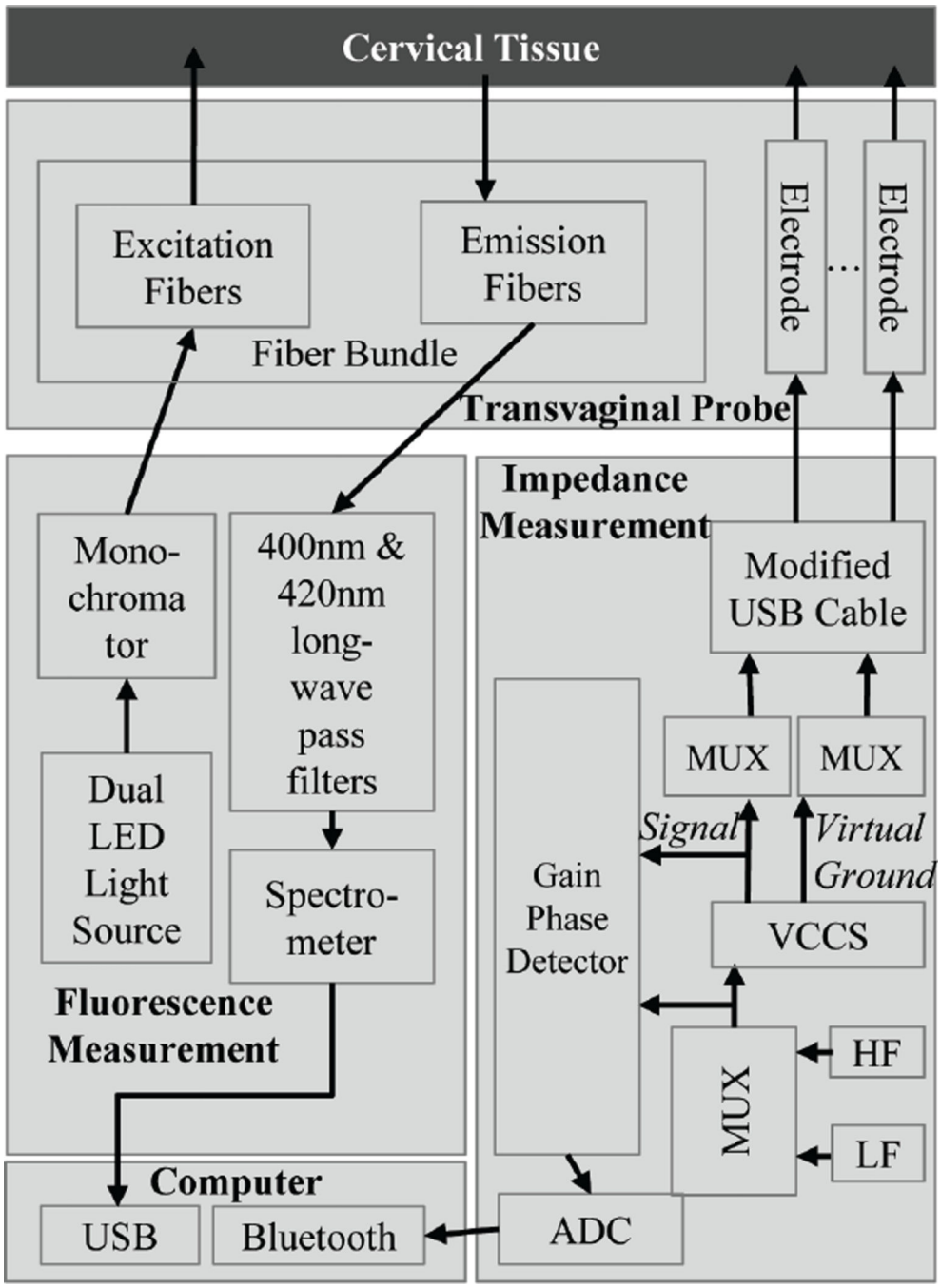

Figure 3.
Block diagram of combination fluorescence and impedance cervical interrogation system.

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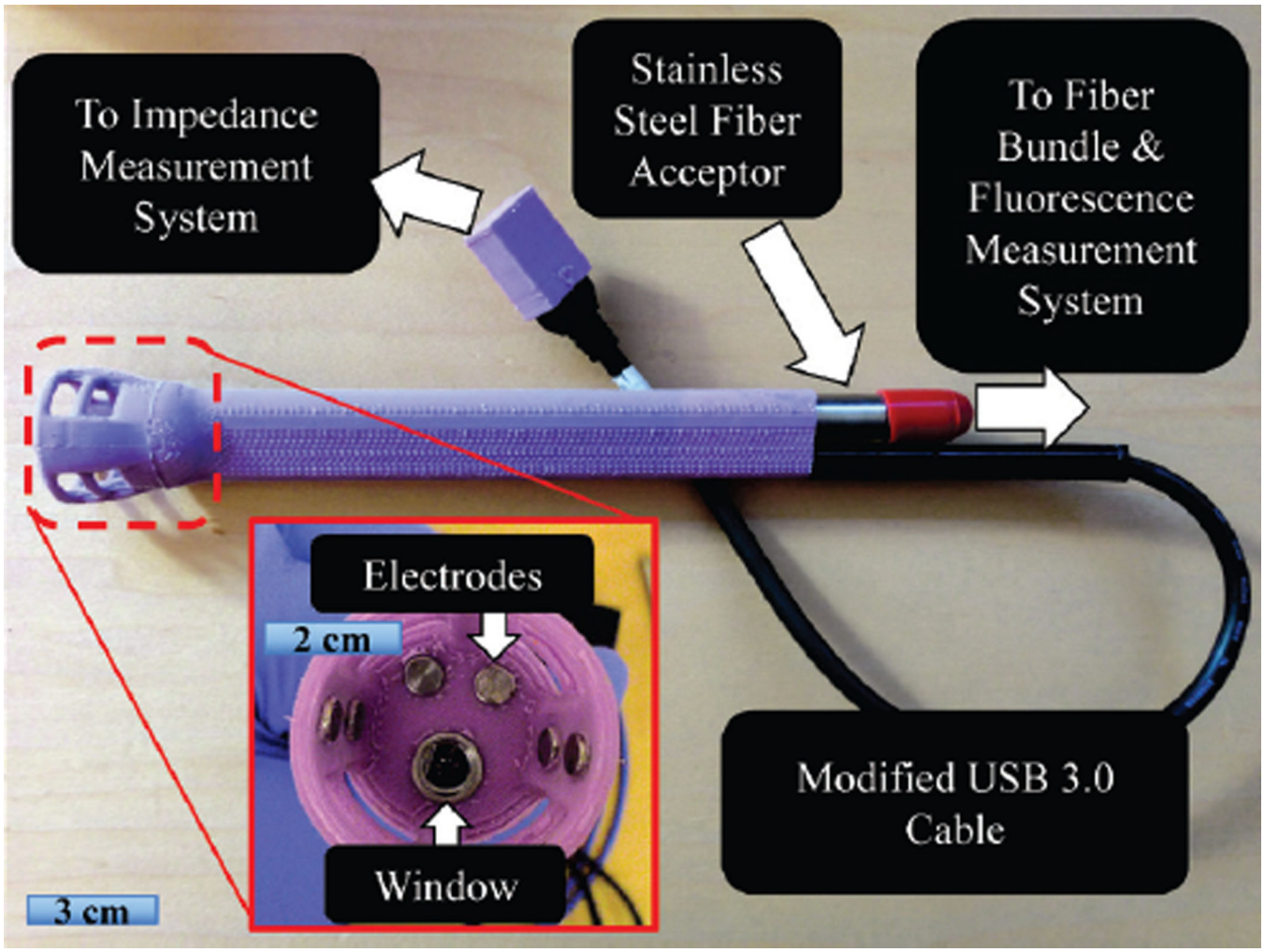

Figure 4.
Photograph of novel cervical measurement device used in a clinical feasibility study at our institution. The cup shaped portion of the device is brought into contact with the cervix through a speculum.

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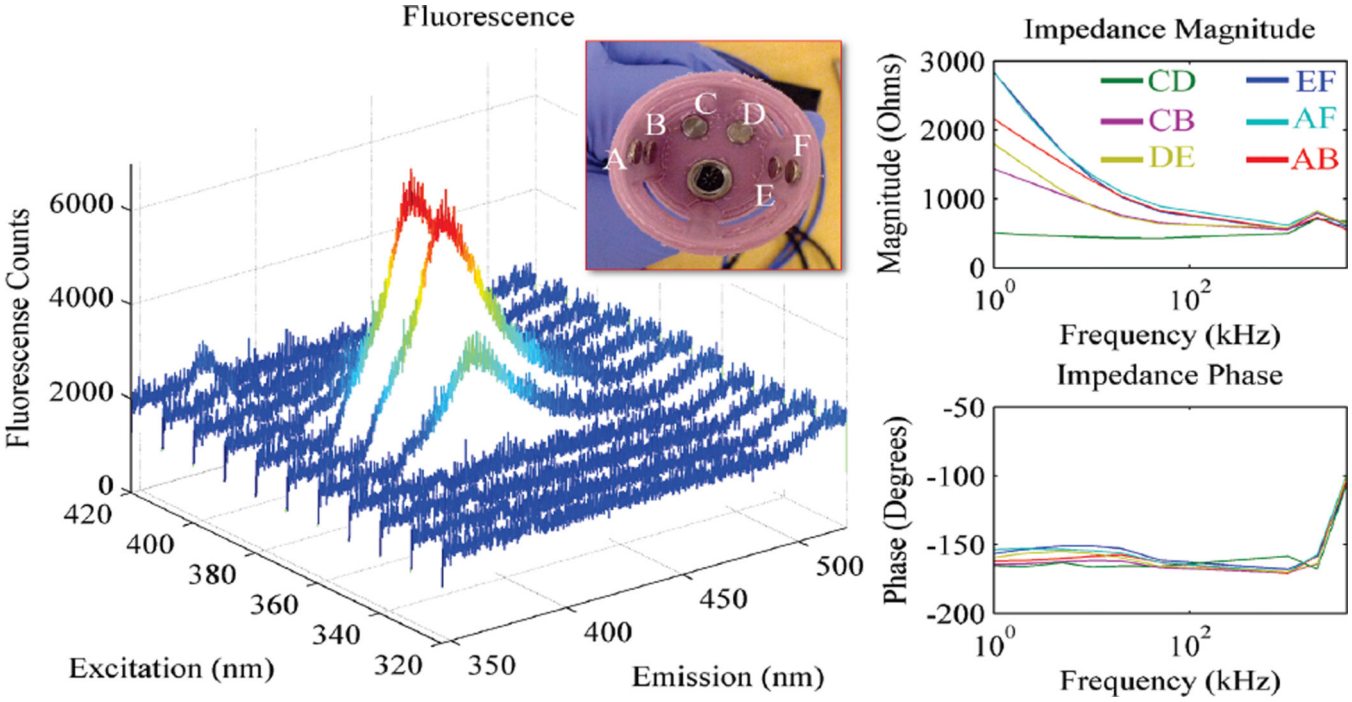

Figure 5.

Preliminary impedance and fluorescence data from one pregnant patient at one time point. Fluorescence is acquired at excitation wavelengths of every 10 nm between 320nm–420nm. Six combinations of electrode pairs used to acquire impedance include face of external os, lateral sides of the cervix, and a combination of face and side electrodes. Future work will trend this data over the course of pregnancy.