Norman Beischer Early to Mid-career Clinical Research Fellowship Application for Funding for 3 years (2021-2023)

Grant recipient: Dr Fiona Brownfoot

PROGRESS REPORT May 2021 (5 months into Fellowship)

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SYNOPSIS OF GRANT

I am a clinician scientist with a focus on translational research. With the generous funding provided through the Norman Beischer Early to Mid-career Research Fellowship I have been able to start my own lab at the University of Melbourne, Mercy Hospital for Women. This funding has allowed me to further research across my three research streams including:

1) Developing a novel device to reduce stillbirth
2) Developing a pH sensor to better detect fetal hypoxia in labour
3) Developing treatments for preeclampsia

I am pleased to report my progress.

Stream 1: Developing a novel device to reduce stillbirth

We are developing a comfortable device that can detect the baby's heart beat and alert the mother if the baby is distressed and at risk of stillbirth. Our device is as thin as glad-wrap and will stick on the mother's abdomen and continuously monitor the baby's heart rate. It will alert the mother if the baby is distressed and at risk of stillbirth.

Stillbirth is a devastating complication affecting 1 in 130 pregnancies. Disappointingly the staggering rates of stillbirth in Australia have remained unchanged for decades. Perhaps this is due to inadequate fetal monitoring during pregnancy. Currently, all technologies that can detect fetal distress, just before stillbirth, are intermittent. Therefore, we often miss the critical moment of fetal distress where a life-saving delivery could be performed.

The optimal way to detect fetal distress in pregnancy would be to use a small device that could be placed on the mother's abdomen and detect the baby's heartbeat. **Excitingly we are developing a device that can reliably measure the fetal heartbeat and detect fetal distress.**

Progress to date:

We are very pleased to report that we have developed algorithms to better extract the fetal heart rate. We have also developed the first iteration of the electronic hardware to obtain a fetal heart rate. We will be ready to embark on a clinical trial with our new device in 2022.

Part 1: Complete

Validating and refining algorithms to accurately extract the fetal ECG

We have optimised the number of sensors and algorithms required to best detect the fetal ECG. We recruited patients at term and placed a number of sensors across their abdomen. This allowed us to determine the optimal number of sensors required to extract a fetal heartbeat. Furthermore, we developed algorithms to remove noise from the signal and obtain an accurate fetal heart rate.

Exciting we published this work in March this year in the prestigious engineering journal IEEE Transactions on instrumentation and measurement. We also submitted an abstract to the Perinatal Society of Australia and New Zealand 2021 and were selected to give an oral presentation which was very well received. Importantly we have acknowledged the Norman Beischer Research Foundation in the manuscript and in our presentation.

We have also explored the possibility of better detecting abnormal fetal heart rates and have shown our algorithms are superior. We have also published this work and ensured we acknowledged the foundation.

Outputs this year:

Publications:

1. Keenan E, Karmakar C, Brownfoot F, Palaniswami M. Personalized Anatomic Modeling for Noninvasive Fetal ECG: Methodology and Applications. IEEE Transactions on Instrumentation and Measurement. 2021, 70:1-12
2. Keenan E, Udhayakumar RK, Karmakar CK, Brownfoot FC, Palaniswami M. Entropy profiling for detection of fetal arrhythmias in short length fetal heart rate recordings. Annu Int Conf IEEE Eng Med Biol Soc. 2020 Jul;2020:621-624

Presentations:

1. Brownfoot. Fetal monitoring in complex pregnancies, RANZCOG ASM 2021
2. Keenan, Brownfoot. PSANZ 2021.
3. Keenan, Brownfoot IEEE 2021.

Impact of this work:

This work has allowed us to develop the software for our long term fetal ECG device. It has also informed the design of our hardware.

Part 2: Completing

Developing an electronic device for long-term detection of the fetal ECG.

We are really excited to let you know that we have developed the first iteration of our long-term fetal ECG device.

Part 3: To embark on once our hardware is complete.

Integrating an electronic skin sensor and software to ensure our device accurately detects the non-invasive fetal ECG in pregnant women.

Once our hardware is complete (we anticipate completion by the end of 2021) we will embark on our 24 hour clinical trial. We anticipate we will start this clinical trial at the end of 2021 or in 2022.

Stream 2: Developing a device to better detect fetal hypoxia in labour

Currently we use a heart rate monitor to determine whether the baby is coping with labour. The CTG is often difficult to interpret. We propose to develop a device that accurately detects fetal distress in labour.

Our progress

The Norman Beischer Medical Research Foundation supported this research with a project grant and with my fellowship I have been able to continue to build on this work.

We have developed a sensor to better detect markers of fetal distress in labour. We are now in the process of optimising this sensor.

Stream 3: Developing treatments for preeclampsia

With the support of the Norman Beischer Medical Research Foundation in the past I identified two possible treatments for preeclampsia, metformin (Brownfoot et al 2016) and sulfasalazine (Brownfoot et al 2019). In partnership with Prof Walker and Prof Tong we are collaborating with a team from South Africa headed by Associate Professor Cathy Cluver. She has conducted a randomised clinical trial assessing metformin as a treatment of preeclampsia and has very promising results. As a result of this we will further investigate its mechanism of action in the placenta in an attempt to develop more targeted therapies. This involves examining its effect on cellular metabolism and the mitochondria. Furthermore we have concluded a phase 1 pharmacokinetics study examining sulfasalazine as a possible treatment for preeclampsia. We are currently performing the analysis of this clinical trial. I hope to report more detail on the exciting progress of this stream in 2022.

Conclusion

With the Norman Beischer Early to Mid-career Clinical Research Fellowship I have been given the exciting opportunity to expand my lab. This has allowed me to further develop diagnostics and treatments to better detect fetal distress in pregnancy and labour and explore therapies for preeclampsia. I am really grateful to the foundation for giving me this exciting opportunity. Hopefully together we can improve outcomes for our mothers and babies.

Further reading

1. Keenan E, Karmakar C, Brownfoot F, Palaniswami M. Personalized Anatomic Modeling for Noninvasive Fetal ECG: Methodology and Applications. IEEE Transactions on Instrumentation and Measurement. 2021, 70:1-12

Abstract - Fetal cardiac monitoring is one of the cornerstones of modern obstetric care. Non-invasive fetal electrocardiography (NI-FECG) is an emerging modality for monitoring fetal well-being using electrical signals recorded from the maternal abdomen. However, the reliability of NI-FECG extraction techniques remains highly variable due to a range of technical and clinical factors, such as sensor placement and inter individual anatomic variations. In this work, we propose, develop, and validate an open-source method for modelling these variations, including changes in maternal body structure and fetal position using two clinical NI-FECG databases. To validate our model's accuracy, we first assess its performance in characterizing the fetal QRS (fQRS) complex amplitude in six private NI-FECG recordings with detailed anatomic information. To demonstrate its clinical utility, we next apply our model to predict an optimal sensor placement in a separate open-access database of 60 24-channel NI-FECG recordings. The optimal six sensor positions predicted by our model achieve similar reliability for fetal heart rate (FHR) monitoring compared to the entire 24-sensor array. The presented results indicate our model provides a suitable method for estimating the influence of anatomic variations on NI-FECG signals and optimizing sensor placement in a simulated setting. The code for the developed model has been made available under an open-source GPL license and contributed to the *fecgsyn* toolbox.

2. Keenan E, Udhayakumar RK, Karmakar CK, Brownfoot FC, Palaniswami M. Entropy profiling for detection of fetal arrhythmias in short length fetal heart rate recordings. Annu Int Conf IEEE Eng Med Biol Soc. 2020 Jul;2020:621-624

Abstract - The use of fetal heart rate (FHR) recordings for assessing fetal wellbeing is an integral component of obstetric care. Recently, non-invasive fetal electrocardiography (NI-FECG) has demonstrated utility for accurately diagnosing fetal arrhythmias via clinician interpretation. In this work, we introduce the use of data-driven entropy profiling to automatically detect fetal arrhythmias in short length FHR recordings obtained via NI-FECG. Using an open access dataset of 11 normal and 11 arrhythmic fetuses, our method (TotalSampEn) achieves excellent classification performance (AUC = 0.98) for detecting fetal arrhythmias in a short time window (i.e. under 10 minutes). We demonstrate that our method outperforms SampEn (AUC = 0.72) and FuzzyEn (AUC = 0.74) based estimates, proving its effectiveness for this task. The rapid detection provided by our approach may enable efficient triage of concerning FHR recordings for clinician review.