Novel Low-Power Wireless Implantable Continuous Blood Calcium Monitor

EE303 Research Proposal

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***Abstract*—Continuous calcium monitoring has potential uses therapeutics and diagnostics. However, there is no current method for doing so. Instead, clinicians rely on blood tests that may include a considerable amount of error. In this paper we propose a novel implantable device that can wirelessly transmit ionized calcium concentration measurements continuously. This device has the potential to improve existing therapies, enable new ones, and reduce healthcare costs.**

I. Introduction

Calcium is one of the most important minerals for humans: responsible for maintaining heart rhythm, facilitating muscle movement, maintaining bone health, supporting brain function, clotting blood, and more. In the short term hypocalcemia can lead to uncontrolled muscle movements, heart arrhythmias, impaired cognitive function, and numbness – made worse in the long term. Hypercalcemia can lead to many of the same symptoms in addition to weakness, excessive urination, nausea, and depression. As an ion calcium, it is a relatively simple molecule to measure, and clearly, calcium imbalance lends itself to a number of pathologies. Yet, there is no current method to monitor an individual's calcium levels. Therefore, there we investigated the potential benefits of a low-cost, low-power, small implantable blood calcium device.

II. Motivation

A. Hemodialysis Therapy

Currently more than 557,000 Americans (roughly 1/500) are currently undergoing dialysis treatments [3]. Regional citrate anticoagulation (RCA) is common practice for renal replacement therapies: citrates are added to extracorporeal blood, binding to calcium ions to inhibit coagulation cascade. This is done to prevent clogging of dialysis filters, however this has the effect of depleting blood of ionized calcium (iCa) [27]. To mitigate this, calcium is reintroduced to extracorporeal blood post filtration. Therefore, it is important for practitioners in dialysis clinics to monitor patient's iCa levels to prevent hypocalcemia. Currently, patient blood calcium levels are checked every 4-6 hours during therapy, which makes for a slow feedback loop [10]. Procuring and testing blood samples are an additional cost and add time to an already time-consuming therapy. Furthermore, as we will discuss below, accuracy of such measurements are drawn in to question. We believe that a cheap continuous monitor can reduce costs and improve care for dialysis patients.

B. Hypoparathyroidism Therapy

Hypoparathyroidism, a disease affecting over 100,000 (around 30/100,000 Americans) patients in the United States alone, occurs when the parathyroid gland produces a low amount of PTH [23]. It is one of the few remaining hormonal insufficiencies not treated with replacement of its missing hormone. Recent research has looked into the continuous infusion of PTH(1-34) into the body through an insulin pump, a common method for insulin delivery in diabetic patients [19]. PTH, allows for both the secretion of calcitriol as well as allows for calcium resorption to happen in the kidneys.

In patients with hypoparathyroidism, treatment with calcium supplements does not adequately treat the disease. PTH is necessary for the excretion of phosphate out of the serum into urine; for those with low PTH, serum phosphate concentration is high. Sodium phosphate has a much higher solubility than calcium phosphate, so when calcium supplements are introduced (with activated vitamin D to facilitate absorption), calcium phosphate precipitates out of the serum, resulting in calcification in the kidney [6]. Furthermore, treatment with bolus PTH has sometimes resulted in hypercalcemia, which has detrimental effects, especially toward brain function. In the case of Lindsay et al.'s study, continuous infusion of PTH via insulin pump leaves open the possibility of unregulated hyperparathyroidism, which can also lead to osteoporosis.

The parathyroid system is fairly simple, with tractable downstream effects, making an artificial feedback-controlled system a feasible option (similar to that closed-loop insulin systems). We believe that a closed-loop PTH system is a logical next step in the treatment of hypoparathyroidism, which can only be facilitadted by continuously measuring serum iCa levels.

C. Additional Diagnostic and Therapeutic Needs

Hypertension, or high blood pressure, is a chronic medical condition commonly characterized by elevated blood pressure levels in the arteries [8]. It often goes unnoticed due to a lack of noticeable systems leading it to termed "the silent killer". Because hypertension can be detected through monitoring blood pressure, continuous calcium sensing can help in the early detection of changes in blood pressure [26]. Arrythmias, on the other hand, are disorders of heart rhythm where the heart either beats too fast (tachycardia) or too slow (bradycardia) [16]. This disorder is typically caused by abnormalities in the electrical impulses that coordinate heartbeats. Calcium ions are typically key players in this electric signaling, meaning that continuous calcium sensing can detect early signs of abnormal calcium handling [14].

Alzheimer's disease (AD) is a neurodegenerative disorder commonly characterized by memory loss, cognitive decline, and behavioral changes. Calcium dysregularion within neurons is an important factor in the patogenesis of AD [18]. Continuous calcium monitoring can help with early detection of the neurodegenerative changes associated with AD [5] as well as allow researchers to better monitor the progression of the disease more accurately. Muscular dystrophy (MD) is a group of genetic disorders commonly characterized by progressive muscle weakness and degeneration. This deficiency leads to disrupted calcium homeostasis, leading to muscle fiber damage and necrosis [4]. Similarly to AD, continuous calcium sensing can help provide insights into the pathophysiological changes in muscle cells [11]. Understanding these underlying mechanisms can help researchers develop new treatments for AD.

Osteoporosis is a condition commonly characterized by reduced bone density and increased fracture risk due to the deterioration of bone tissue. Calcium plays a major role in maintaining bone health, as it is a primary component of bone mineral. Continuous calcium sensing in the blood can help detect abnormalities that may indicate bone resorption or impaired calcium absorption [15]. This data can allow for more prompt interventions to prevent further bone loss.

III. Background and Previous Research

A. ISE Principals and Nernst Equation

Ion selective electrodes (ISE) have two components: a reference electrode, to be placed openly in solution, and an ion-selective electrode. The ion selective electrode has a membrane that is selective just to the ion of interest. On the inside the the membrane is a solid contact material that facilitates electron transfers from the ion of interest. High stability of the solid contact of the ion selective electrode implies that the concentration of the ion of interest inside the membrane is effectively constant (i.e. there is ideally no net movement of ions across the membrane).

$$\begin{aligned} E &= E^0 + \frac{RT}{zF} \ln \frac{[\mathrm{Ca}^{2+}]_{\text{out}}}{[\mathrm{Ca}^{2+}]_{\text{in}}} \\ &= E^0 + \frac{RT}{zF} (\ln [\mathrm{Ca}^{2+}]_{\text{out}} - C) \\ &= U + S \log [\mathrm{Ca}^{2+}]_{\text{out}} \end{aligned} \tag{1}$$

Equation (1) demonstrates how we can derive the concentration of the ion in solution from a measured potential because $[\mathrm{Ca}^{2+}]_{\text{in}}$ is effectively constant. The ISE can then be characterized experimentally by a linear curve on a log scale.

B. Current iCa Measurement Techniques

Fluorescent calcium indicators, such as Fura-2 and Fluo-4, are widely used for measuring intracellular calcium concentrations. These dyes bind to calcium and emit fluorescence in response to this calcium binding [12]. This fluorescence allows for real-time visualization of calcium levels using fluorescence microscopy or flow cytometry. This method is useful for studying calcium dynamics in living cells.

Calcium sensitive electrodes, aka ion-selective electrodes (ISEs), are another popular technique used for measuring calcium levels. These electrodes consist of a membrane that selectively binds to calcium ions, generating a voltage that can be measured and correlated to calcium concentration. ISEs allow for both direct and continuous measurement of calcium activity, making them very popular in laboratory settings [25]. The accuracy of these electrodes can be compromised by the presence of other ions meaning that precise and frequent calibrations are necessary.

Atomic absorption spectroscopy (AAS) is a sensitive method for quantifying calcium concentrations in various biological samples. In this method, the sample is vaporized, and the absorption of light by calcium atoms at specific wavelenghts [28]. AAS is extremely accurate making it a favorable technique for calcium measurement in labs. However, the instrumentation is complex and expensive as well as time consuming.

C. Previous Studies

Luo et. al investigates the role of continuous calcium monitoring in cardiovascular diseases such as heart failure [21]. The researchers used genetically encoded calcium indicators (GECIs) in mice to continuously monitor calcium transients in cardiac cells. This study showed that abnormalities in calcium handling could contribute to the progession of heart failure, ultimately highlighting the importance of calcium homeostatsis in cardiac function. Continuous calcium monitoring, within this setting, allowed for real-time analysis of calcium dynamics, and provided insights that lead to the development of therapies for heart failure.

Kuchibhotla et. al looked at how continuous calcium monitoring could be impactful for patients with AD [17]. Using two-photon calcium imaging, the researchers were able to observe calcium dynamics in the neurons of mouse models. In this study, the authors concluded that calcium dysregulation

occurs early in AD disease progression. This early calcium dysregulation was linked to synaptic deficits and neuronal dysfunction [17]. Continuous calcium monitoring provided crucial data, underscoring the potential of targeting calcium homeostasis as a strategy for fighting early stages of AD.

Haux et. al investigated the feasibility of continuous monitoring of serum ionized calcium lebels in dogs [13]. In this study, the authors employed an extracorporeal blood shunt system to continuously measure ionized calcium in the bloodstream. Sodium citrate was infused to induce hypocalcemia, and the real-time system was used to measure changes in calcium levels. These results showed that the measurement system could accurately detect fluctuations in serum ionized calcium levels induced by sodium citrate infusion. Briggs et. al also explores the development of a novel technique for continuous monitoring of ionized calcium levels [7]. The authors designed a specialized calcium-selective electrode system that could be implanted into animals to measure ionized calcium in real time. The study found that this measurement system could precisely and consistently measure plasma ionized calcium.

D. Miniaturization of ISEs

Miniaturization of ISEs has been of interest in the research community for some time. Miniaturizing ISEs allows for their integration into compact and portable devices, facilitating point of care testing and continuous monitoring of ion concentrations in real time [9]. Cosofret et. al attempted to miniaturize ISEs through using advanced microfabrication techniques. Through silicon micromachining processes, the authors developed miniature ISEs which allowed for the integration of multiple electrodes onto a single chip [9]. This sensor exhibited high selectivity and sensitivity for various ions, including calcium. This study highlighted the potential of microfabricated ISEs to provide continuous monitoring in clinical and research settings.

Liu et. al focused on developing flexible miniature ISEs suitable for wearable devices [20]. The authors developed flexible, thin-film ISEs using conductive polymers and screen-printing techniques. The flexible sensors were capable of conforming to the contours of the skin, enabling non-invasive and continuous monitoring of electrolytes, including calcium, in sweat [20]. These flexible ISEs demonstrated excellent sensitivity, stability, and durability underscoring the potential for flexible, miniature ISEs that could be useful for continuous monitoring of electrolyte levels.

IV. Proposed System Design

A. System Overview

Our system consists of two components: a wireless implantable device and an external power source and receiver. As seen in Fig. 1, the implantable device takes a voltage from ion-selective electrodes, amplifies the signal, and sends it through an ADC. The ADC output will directly modulate the load to transmit data to the receiver (discussed below). The entire circuit will be around a cubic centimeter, with the winding for the inductive couple being the limiting factor.

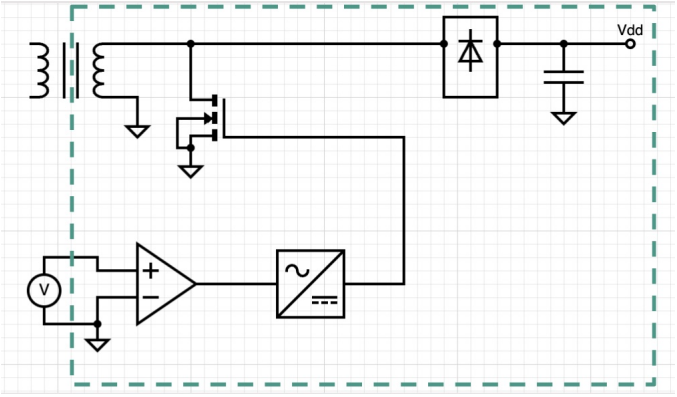

Fig. 1. Block diagram of system, with voltage source representing ion-selective electrode leads and a transformer as coupled inductive link. Dashed line represents boundaries of wireless device.

B. Power and Communication

Through load-modulation, our power and communication can be facilitated by a single inductive link. We can provide wireless power to our device through a pair of coupled inductors. With a power converter topology such as a flyback converter (modeled in LTspice in Fig. 2), we can generate indirect power delivery through a transformer that is independent of load in steady state (assuming a large magnetizing inductance).

To relay data from the secondary (our device) to the primary (power transmitter, data receiver), we modulate the load. This can be done by via a pair of MOSFETs and current limiting resistors. As seen in Fig. 2, this has the effect of increasing the current required from the load. However, in our simulation, we can see that a spike in current corresponds with a drop in voltage, rising as the converter brings the circuit back to steady state.

Therefore, we can send digital signals at a baud rate of around 2 order of magnitude less than our switching frequency, while still keeping supply voltage ripple to around 1%. For the sake of measurement accuracy, we would likely also want to include an LDO to ensure further smoothing of voltage ripple.

Our circuit requires relatively few active components that can all operate on relatively low power requirements. For our ADC a low power, low sample rate ADC's such as TI's ADS7046 requires $\tilde{1}00\ \mu$W [1]. With the inclusion of a switch, rectifier, and LDO, we expect a power consumption of $\tilde{1}$ mW for the receive circuit. We can see in Fig. 2 that large amount of transient current may be required from the transmitter, when the load is varied, but we do not anticipate this exceeding $\tilde{2}0$ mW.

Maintaining low power is important not for sake of energy efficiency – as we power our device externally. Instead, it is important so as not to accumulate heat that could damage surrounding tissue. Thermal resistance of the human body is around $50°\text{CW}^{-1}$ [24]. With our product, we would expect to see a heat rise of less than $1°$C locally. Based on FDA recommendations, these numbers prompts very little worry and

nominal affects on the tissue [2].

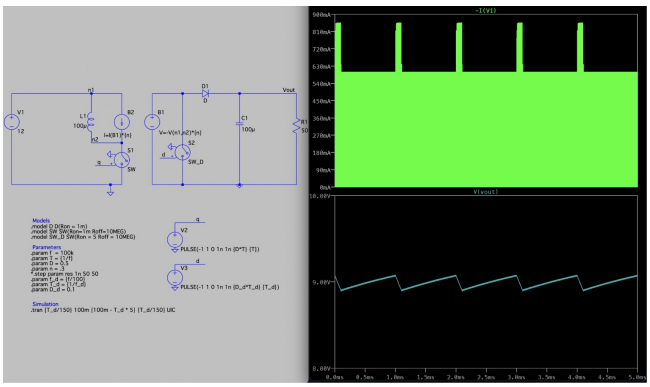

Fig. 2. LTspice simulation of flyback converter, with a periodic load change facilitated by shunt switch with series resistance. Load modulation can be seen at source current (green), and voltage at load is plotted (blue).

C. Implant Locations of Interest

Our study is interested in the potential for two implant locations. A venous implant, where ISEs can be inserted directly in the blood stream will provide the most direct measurement of iCa. However this would be much more invasive and likely require surgery. The ultimate idea is to make blood calcium measurements less invasive than blood tests and cheaper, which would lead us to a transcutaneous solution. Much like continuous glucose monitors (CGMs), a transcutaneous device would extrapolate measurements from interstitial fluid to determine blood iCa concentrations. These devices are low-invasive and able to be ”implanted” at home, eliminating complications, costs, etc. associated with surgeries. This solution has the added benefit of being easily replaced ISEs prove to have poor longevity (due to corrosion or scarring).

a) Venous Implant: To choose where to place the implant, we considered preferred locations for vascular access ports, as ports are similarly semi-permanent implants that require access to large vasculature. Two of the most common locations practitioners choose for ports are the cephalic and subclavicular veins. We will choose the cephalic vein, as evidence suggest that ports placed there are most mechanically stable and least likely to fall out [29].

b) Transcutaneous Monitor: Much like CGM's we will choose to have our device sit on top of the patient's skin, while the electrodes are inserted subcutaneously. For the sake of simplicity, we will reuse the same circuit topology and also power the device wirelessly, unlike current CGMs. CGMs are placed either on the back of the arm or on the abdomen mainly for mechanical reasons (skin does not move as much; patient is less likely to bump the sensor; and the surface is relatively large and flat, making it good for adhesion). This is where we will also choose to place our transcutaneous monitor.

V. Research Design, Timeline, and Funding Estimates

A. Device Verification Study

To verify the operation of our proposed device design, we would begin by characterizing all the device's electrical performance under controlled electrical conditions. Figure 2 shows a LTSpice simulation of the voltage changes of our proposed design under a periodic load change. We would generate a multitude of these LTSpice simulations to verify that the electric performance we observe align with what we have simulated. Additionally, calibration procedures would be performed to ensure that the device operates within specified tolerances. Environmental testing, including temperature, would also be conducted to determine the device's robustness and reliability under different conditions.

After the lab tests were complete, the study would transition to real-world testing to evaluate our device's performance in practical conditions. This phase would require deploying the device in relevant environments and monitoring its operation over an extended period. As we are proposing a continuous monitoring system that will be partially located inside the body, we will start with the device in mice. After multiple tests, we would eventually move towards testing on a group of volunteers to test how the device works in everyday scenarios. The device will be evaluated based on its usability, durability, and accuracy during these real life conditions. User feedback would be heavily considered, along with the results, before deploying the device.

B. Patient Study

The patient study that will be used to analyze the feasibilty and effectiveness of the proposed design is heavily motivated by the study outlined by O'Connell et al [22]. 100 participants, representing a diverse group of individuals, will be split into a CCM group and a control group. Each member of the CCM group will be given the continuous calcium monitor that they will wear during the duration of the study. Each member will also be given a calcium monitoring kit that they can use to verify the results from the calcium monitor if they doubt the results at any time.

The control group will be given calcium monitoring kits, rather than the continuous calcium monitor. Each member of the control group will be required to check their calcium levels, manually, at least four times a day. During the midpoint and final week of the study, each member of the control group will be given a continuous calcium monitor without a corresponding LED screen. The monitor will continuously monitor the calcium levels of the individuals, however they will not be able to see the readings from the monitor. This allows us to get at least 96 hours of consistent calcium data from the control group during these periods without compromising the study.

Each of the participants will meet with us every other week to answer questions and to analyze the results thus far. At the end of the study, conclusions will be made about the effectiveness of the continuous calcium monitor.

C. Timeline

Our timeline for this work is approximately 5 years. We breakdown this work into 3 keys steps: device design and verification, an in vitro study, a research study. We anticipate that it will take about 2-3 years for us to develop a working prototype and verify that it works. From there, we estimate that it will take another year to run a successful in-vitro study. Finally, we will spend the final year running the patient study outlined above.

D. Funding Estimates

Table I shows the estimated budget for the proposed device design. We have a budget of about 200k that we will allocate towards hiring researchers that can help us with the device design and running the in vitro study. We estimate that the two studies will cost approximately 50k. We have plans to set up a course on campus as a means to reduce the costs of the patient study.

Reason	Cost Estimate
Device Development	20k
In Vitro Study	15k
Patient Study	35k
Researchers	200k
Total	320k

TABLE I
DEVICE DESIGN BUDGET

VI. CONCLUSIONS

A. Potential Positive Conclusions

After our study, we hope to see that measurements made from our device are statistically valid compared to samples sent to blood-gas analyzers. This would inform us that our device can perform as well as clinical standards.

We also hope that we are able to reliably extrapolate measurements from our patients' transcutaneous implant to accurately represent their iCa levels measured in their venous implant. This would mean that we can indeed rely on data from a less invasive transcutaneous device to calculate a patient's iCa level at any given time.

B. Limitations

As discussed earlier, we are relying on an already imperfect control: blood-gas analysis of serum that is at a different temperature and pH than the blood. We will be careful to try to limit the amount of time between taking the sample and testing, but we must be aware of this inherent error function.

Furthermore, it may be difficult to corroborate continuous measurements, as we will only be able to take blood samples at discrete intervals of time.

C. Future Areas of Research

If our findings indicate a promising future for the technology, the next area to investigate is the longevity of the device. Electrodes tend to have limited useful life-spans, as they will corrode and become covered in scar tissue with time. This is especially important for venous implants that would have to remain the body for longer periods of time.

Next, for a commercial product, we would ultimately likely want to provide an on-board power supply with the ability to communicate with a mobile app for user convenience.

Finnaly, future research can work off of this product to streamline dialysis treatment; to create a closed-loop hypoparathyroidism therapy; and to monitor and diagnose a number of other diseases.

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