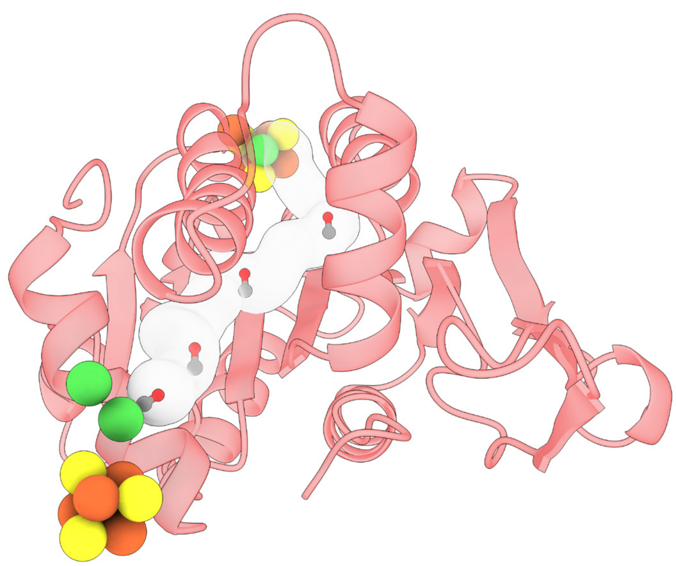
Life Science & Semiconductors, Medical Devices & Biotechnology

Capturing Methanogenic Carbon Monoxide Dehydrogenase/Acetyl-CoA Synthase Complexes via Cryogenic-Electron Microscopy

A. Biester, C. L. Drennan
Sponsorship: Howard Hughes Medical Institute, National Institutes of Health

Carbon monoxide dehydrogenases (CODHs) and acetyl-CoA synthases (ACSs) are major players in the global carbon cycle. Approximately two-thirds of the estimated one-billion metric tons of methane produced annually by methanogens on Earth is derived from the ACS-catalyzed cleavage of acetate. A nickel-iron-sulfur (Ni-Fe-S)-containing ACS cleaves acetyl-CoA into a methyl group, carbon monoxide (CO), and coenzyme-A (CoA). The methyl group goes on to form the greenhouse gas methane, and the CO is oxidized to form the greenhouse gas CO2. The latter reaction is catalyzed by a Ni-Fe-S-containing CODH. The reactions of CODH and ACS are reversible; acetogenic bacteria, like *Moorella thermoacetica* and *Clostridium autoethanogenum*, employ CODH/ACSs to synthesize acetyl-CoA from one-carbon units derived from CO_2.

Although our lab determined the first structure of an acetogenic CODH/ACS over twenty years ago, the structure of the methanogenic enzyme has been elusive. Methanogenic CODHs cannot be recombinantly expressed, and the protein as isolated from native methanogens exists as a massive 2.2 MDa acetyl-CoA decarbonylase/synthase (ACDS) complex—a size that has precluded crystallography. Due to the cryogenic electron microscopy (cryo-EM) "resolution revolution" and the amazing cryo-EM facility run by Sarah Sterling in MIT.nano, it is now possible to obtain structures at atomic resolution of methanogenic CODH/ACS enzyme complexes. We visualize the Ni-Fe-S metal cluster that is responsible for the first step in the biological production of methane from acetate. This research is timely, as metabolic engineering efforts are underway to employ acetogens and methanogens and their CODH/ACS enzymes in producing biofuels from greenhouse gases. *Clostridium autoethanogenum* is already being used by LanzaTech in the conversion of CO_2 to ethanol.



▲ Figure 1: Cryo-EM has allowed us to visualize a methanogenic CODH/ACS complex that contains an internal gas channel. This channel provides a route for CO to travel between a Ni-Fe-S cluster (green, orange, and yellow spheres) that produces CO from acetate and one that converts the CO to CO_2.

FURTHER READING

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Ultrasound-based System for Emboli Detection and Sizing

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Sponsorship: Boston Children's Hospital Anaesthesia Foundation

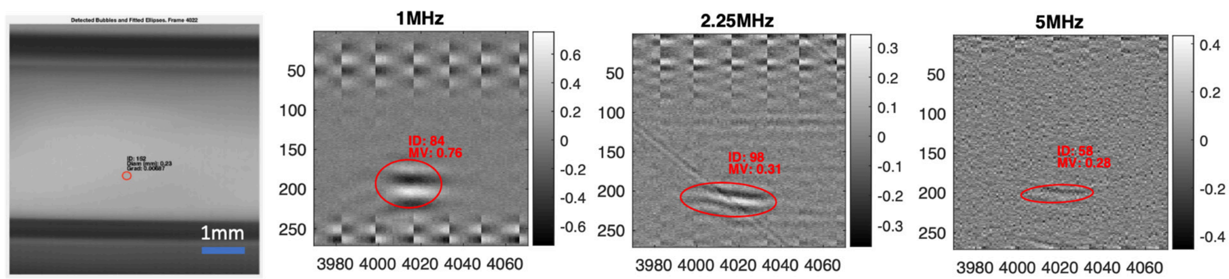
Extracorporeal membrane oxygenation (ECMO) is a life-support mechanism designed to aid individuals whose lungs and/or hearts are failing. It continuously pumps blood through an external system that adds oxygen and removes carbon dioxide. However, ECMO carries risks, including the potential formation of emboli–either solid, such as blood clots, or gaseous, such as air bubbles. In a study involving 1,095 ECMO-patients, 53% developed deep vein thrombosis. Emboli in the micrometer range, when entering the body, can cause tissue damage through ischemia and may lead to stroke or pulmonary obstruction. Detecting, counting, and differentiating (solid vs. gaseous) such emboli remain major technological challenges.

Ultrasound-based methods seem ideally suited to fill this technological gap, but current research methods face limitations. These include the need for a reliable base-line power measurement to accurately detect emboli, the lack of ground truth data, and reliance on small datasets of embolic signals.

In ultrasound signals, emboli appear as high intensity transient signals, and there is a relationship between air bubble size, for example, and the received backscatter intensity. The proposed solution is an ultrasound system–in collaboration with colleagues from Boston Children's Hospital–for the detection, differentiation, counting, and sizing of emboli in ECMO.

Some of our key achievements include 1) the development of a lab-based flow phantom system; 2) acquisition of ground truth data using a high-speed camera; 3) controlled experiments varying parameters such as bubble size and flow rate; 4) implementation of a tracking algorithm for video analysis and a detection algorithm for ultrasound signals; and 5) establishment of an initial relationship between the ultrasound signal and the bubble size.

Future work will extend to solid emboli and physiological fluid mimicking blood's acoustic properties. Expanding this technology to other extracorporeal support systems will be a priority, broadening its impact across different critical care domains.



▲ Figure 1: A 150-micrometer bubble detected in high-speed camera videos. Corresponding M-mode ultrasound signals from the same bubble are shown at 1, 2.25, and 5 MHz, with object detection and maximum voltage extraction highlighted.

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Towards Scalable Screening for the Early Detection of Parkinson's Disease: Validation of an iPad-based Eye Movement Assessment System Against a Clinical-grade Eye Tracker

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Sponsorship: Analog Devices, Inc., MIT Aging Brain Initiative, the Northwestern University Department of Physical Therapy and Human Movement Sciences, the Northwestern Medicine Enterprise Data Warehouse

Early detection and monitoring of Parkinson's disease (PD) remain challenging, underscoring the need for accessible and cost-effective methods. Abnormalities in saccadic eye movements have emerged as promising noninvasive biomarkers for early PD detection and disease progression tracking. Although clinical-grade eye tracking devices provide high accuracy and precision, their clinical adoption is constrained by cost and complexity. Here, we introduce and validate a cost-effective and accessible iPad-based system for assessing saccadic eye movements, benchmarking it directly against the clinical-grade EyeLink 1000 Plus eye tracker. Our approach utilizes the iPad's front-facing camera combined with a deep learning algorithm for gaze estimation. Validation involved 25 participants (10 with PD, 15 healthy controls) performing standardized pro-saccade (PS), anti-saccade (AS), memory-guided-saccade (MGS), and self-generated saccade (SGS) tasks. The iPad system demonstrated subject-level error magnitudes averaging 2 ms (SD = 2 ms) for latency and 0.7° (SD = 0.6°) for amplitude in the PS, AS, and MGS tasks and 0.003 s^{-1} (SD = 0.004 s^{-1}) for instantaneous primary saccade rate and 1.6° (SD = 1.5°) for amplitude in the SGS task. To contextualize our findings, we reviewed studies reporting saccadic impairments in PD relative to healthy individuals. By compiling data from studies that included PD participants at varying stages of disease severity, we established benchmarks for clinically meaningful changes in saccade metrics. Our results indicate that the iPad system achieves accuracy and precision—particularly in temporal measurements—that meet or exceed these benchmarks, supporting its potential use in clinical screening and longitudinal monitoring of PD. Our findings underscore the iPad-based system's potential as an accessible, cost-effective, and scalable solution for routine clinical screening and longitudinal monitoring of PD.

Miniaturized Ingestible Temperature Sensing System with Enhanced Safety and Versatility for Continuous Internal Monitoring

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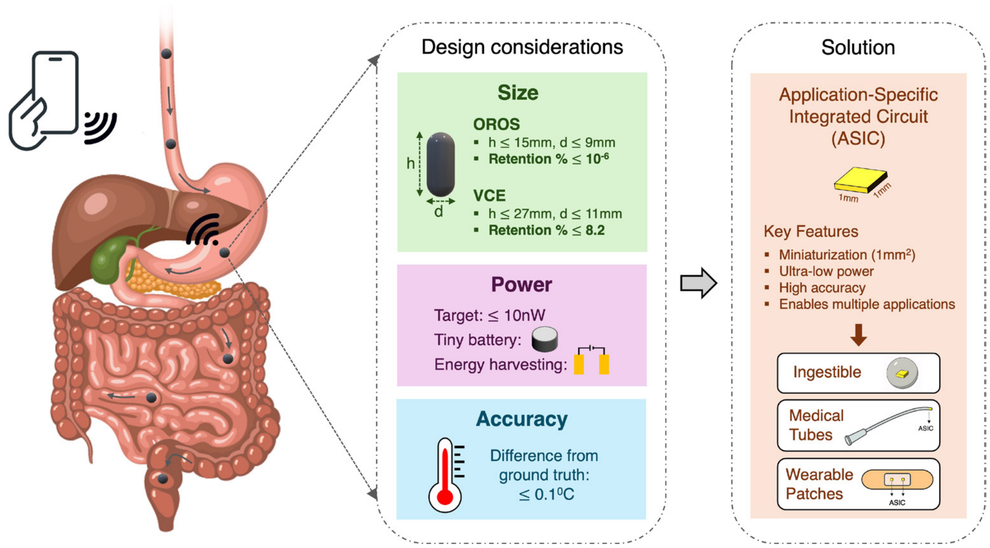
Sponsorship: Defense Advanced Research Project Agency, Advanced Research Projects Agency for Health

Ingestible electronic systems provide a minimally invasive approach for continuous monitoring of core body temperature, offering critical insights into gastrointestinal (GI) physiology and pathophysiological conditions. Despite significant progress, existing ingestible temperature sensors typically exceed dimensions that restrict universal applicability, particularly in pediatric populations. Here, we introduce the Miniaturized Ingestible Temperature Sensing (MITS) system, a compact temperature monitoring device comprising a highly miniaturized (1 mm x 1 mm) and ultra-low power (10 nW) integrated circuit chip, coupled with a custom-designed and miniaturized antenna (5 mm x 5 mm) for wireless communication through backscattering, and a tiny coin-cell battery for power (Figure 1).

The completely assembled system with encapsulation measures 6 mm in diameter and 4 mm in height, which aligns with the established safety dimensions validated by clinically successful OROS® systems and presents minimal risk for GI retention as indicated by clinical experiences with video capsule endoscopy. Preclinical evaluation in swine across diverse physiological conditions—including induced inflammation, variable GI transit times, alterations in circulation, and multi-day monitoring—demonstrate the system's broad potential applicability. These findings underscore how significant size reduction of ingestible devices enhances safety, facilitates pediatric use, and expands monitoring applications across various clinical scenarios.



▲ Figure 1: Overview: The MITS device is designed for continuous, real-time, and wireless monitoring of core body temperature. MITS can be orally ingested and can measure the temperature inside the GI tract, serving as an important tool both inside and outside the clinic.

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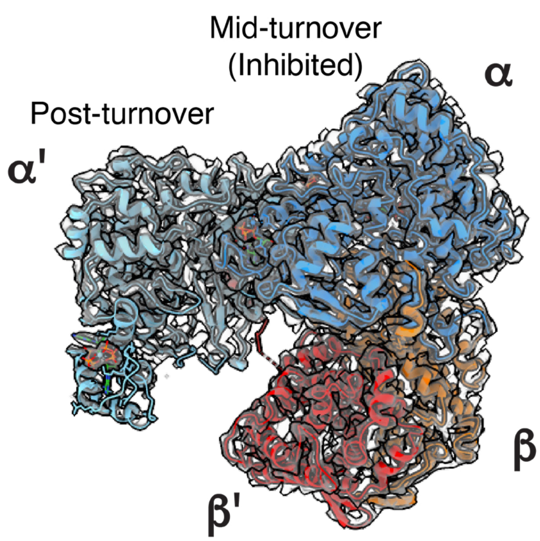
Structural Mechanisms of Catalysis in Ribonucleotide Reductase by Cryogenic-Electron Microscopy

D. E. Westmoreland, C. L. Drennan
Sponsorship: Howard Hughes Medical Institute, National Institutes of Health

Antibiotic resistance is anticipated to be a major challenge of the 21st century. To address this concern, we are studying class Ia ribonucleotide reductases (RNRs), which are present in a number of pathogenic organisms and are responsible for catalyzing the only known de novo biosynthetic route to deoxyribonucleotides from the corresponding RNs. As such, class Ia RNRs represent a promising target for novel antibacterial drugs. The active state of this enzyme—a heterodimer of two homodimeric subunits, α2 and β2—however, is transiently associated and has only been observed using cryogenic electron microscopy (cryo-EM) and either mutations or substrate analogs as inhibitors (Figure 1).

Our work focuses, therefore, on the use of cryo-EM to understand how the class Ia RNR from *Escherichia coli* structurally regulates its catalysis in an effort to design antibiotics that inhibit the active state of RNR. In particular, the C-terminal tails of both the α2 and β2 subunits are known to play critical roles in the catalytic mechanism of RNR, but the tail regions of these subunits are conformationally dynamic and have not yet been resolved by any structural method, including cryo-EM.

Here, we use high-resolution cryo-EM data sets in combination with machine learning-based data processing techniques (cryoDRGN, developed by the Davis Lab in the Department of Biology) to curate particle stacks of tens of thousands of particles with increased resolution for both the α2 and β2 tail regions. This work helps explain how the conformational dynamics of these tail regions function within the larger catalytic mechanism of RNR. Further work in this area will compare the human RNR, also a class Ia RNR, with the E. coli RNR to design novel antibiotics with reduced cytotoxicity in humans.



▲ Figure 1: Active state structure of E. coli class Ia RNR in which one side of the enzyme has already undergone catalysis (post-turnover) and one side has not yet completed catalysis (mid-turnover). The α2 subunit is shown in light and dark blue; the β2 subunit is shown in red and orange).

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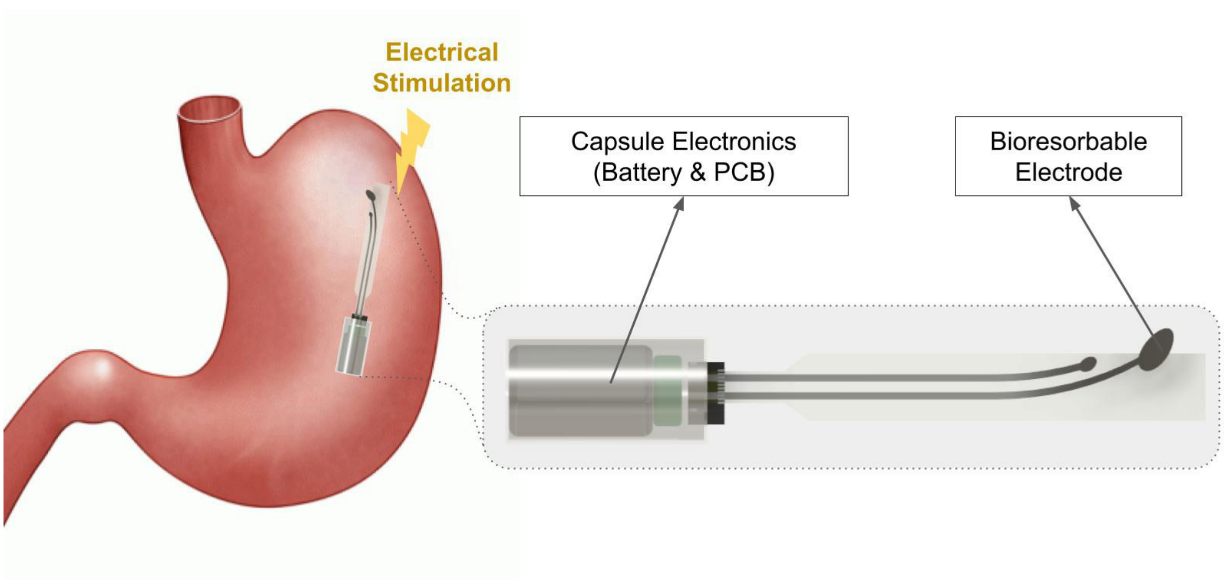
Ingestible Gastric Electrical Stimulation System Using Bioresorbable Electromechanical Systems

A. O. Erus, M. G. Say, I. Moon, G. Traverso
Sponsorship: ARPA-H

The gut-brain axis, a bidirectional communication network between the gastrointestinal (GI) tract and the central nervous system, regulates various physiological functions via neurohormonal signaling. Electrical stimulation of the GI tract can modulate hormone release, offering therapeutic potential. However, current gastric electrical stimulation (GES) systems require invasive surgery for implantation and removal. To address this limitation, we developed an ingestible GES system composed of a bioresorbable electrode array integrated with capsule-based electronics. The bioresorbable substrate and thin film metal are chosen for their low dissolution rate and high mechanical strength. The electrodes are fabricated using laser systems, offering a faster, cost-effective alternative to traditional photolithography. In vitro testing, including dissolution, stress-strain, and impedance assessments, demonstrates the system's viability, supporting its potential for non-invasive GES.



▲ Figure 1: Simplified schematic of gastric electrical stimulation system (not to scale) in the stomach.

Highly Integrated Graphene-based Chemical Sensing Platform for Structural Monitoring Applications

C. Lopez Angeles, T. Palacios
Sponsorship: Ferrovial

Two-dimensional materials, such as graphene, hold promise for sensing applications. Graphene's remarkable surface-to-volume ratio, when employed as a transducer, enables the sensor channel to be readily modulated in response to chemical changes in proximity to its surface, effectively converting chemical signals into the electrical domain. However, their utilization has been constrained due to variations in device-to-device performance arising from synthesis and fabrication processes.

To address this challenge, we employ Graphene Field Effect Transistors (GFETs) in developing a robust and multiplexed chemical sensing array comprising tens of sensing units. This array is coupled with custom-designed high-speed readout electronics for structural monitoring applications.

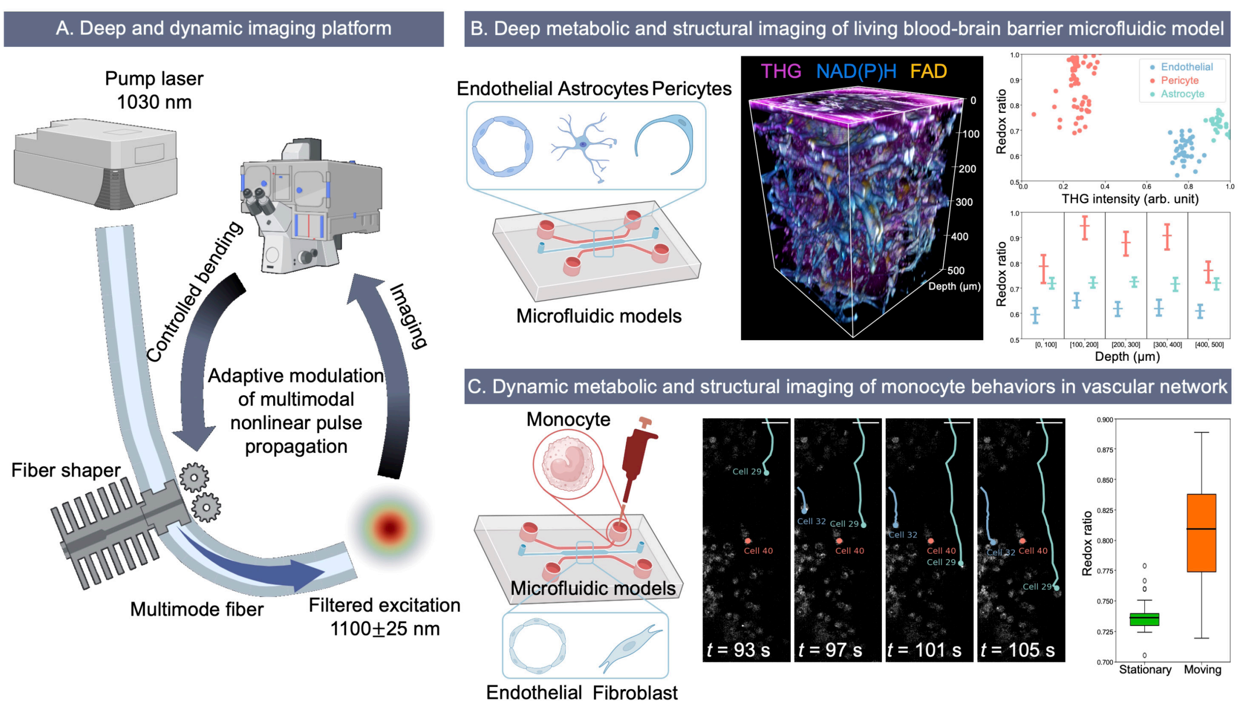
For example, in harsh environmental conditions, structures constructed from reinforced concrete may experience degradation due to corrosion, a chemical process initiated by carbonation and significant fluctuations in temperature and humidity. Under normal conditions, concrete maintains a pH level within the alkaline range of 13 to 14. However, when subjected to carbonation, its pH decreases to values between 8 and 9.

Our platform excels in real-time pH monitoring. By conducting I-V sweep measurements in the sensor channel, we have established a correlation between [H+] concentration and the gate-source voltage (Vgs) at graphene's Dirac point with an accuracy of roughly 98%. This system and correlation allows for the prompt detection of any deviations induced by corrosion within a concrete environment.

Deep and Dynamic Metabolic and Structural Imaging in Living Tissues

K. Liu, H. Cao, R. Kamm, L. Griffith, F. Wang, T. Qiu, S. You
Sponsorship: Mathworks Fellowship

Label-free imaging through two-photon autofluorescence (2PAF) of NAD(P)H allows for non-destructive and high-resolution visualization of cellular activities in living systems. However, its application to thick tissues and organoids has been restricted by its limited penetration depth, largely due to tissue scattering at the typical excitation wavelength required for NAD(P)H. Here, we demonstrate that the imaging depth for NAD(P)H can be extended to over 700 μm in living engineered human multicellular microtissues by adopting multimode fiber (MMF)-based low-repetition-rate high peak-power three-photon (3P) excitation of NAD(P)H at 1100 nm. This is achieved by having over 0.5 MW peak power at the band of 1100±25 nm through adaptively modulating multimodal nonlinear pulse propagation with a compact fiber shaper. Moreover, the 8-fold increase in pulse energy enables faster imaging of monocyte behaviors in the living multicellular models. These results represent an advance for deep and dynamic imaging of intact living biosystems. The modular design is anticipated to allow wide adoption for demanding in vivo and in vitro imaging applications, including cancer research, autoimmune diseases, and tissue engineering.



▲Figure 1: (a) Deep and dynamic imaging platform. (b) Deep imaging over the entire depth of 500 μm in the living human blood-brain barrier microfluidic model. (c) Dynamic imaging of monocyte trafficking in vascular network.

New NMR Probe Configurations for Spectroscopy and Relaxometry of Moving Fluids

H. Gaensbauer, A. Bevacqua, D. H. Park, J. Han
Sponsorship: Singapore MIT Alliance for Research and Technology, CAMP IRG

Nuclear Magnetic Resonance (NMR) spectroscopy and relaxometry are widely used and well-established techniques that can detect and identify chemical compounds in samples with significant background. Because NMR measurements are nondestructive, they have many applications in industrial process control, where they can be used to track reaction progress, detect contaminants, and provide insight into the quality of the product being produced. However, movement of the sample through the NMR system during the experiment reduces the resolution of NMR spectroscopy and confounds NMR relaxometry measurements. This makes it difficult or impossible to use NMR to continuously monitor flowing fluids in industrial settings, especially when the flow rate is variable or unknown. In this work, we present an RF coil geometry that produces NMR measurements that are completely insensitive to the flow behavior of the sample. We show that these coils can be designed for different ranges of flow rates and demonstrate in-line monitoring of a commercial dairy sample over a period of several hours. These coils enable in-line high resolution spectroscopy and relaxometry for process monitoring applications without needing to control or even know the flow rate, making it possible to retrofit state-of-the-art NMR systems for continuous quality control on a wide range of biomanufacturing and industrial processes that would traditionally require regular invasive sampling.

Surface Patch Coils and Pulse Sequences for Noninvasive Blood Tests Using Magnetic Resonance

A. Huang, H. Gaensbauer, J. Han
Sponsorship: MIT Research and Innovation Scholars Program, MIT Lincoln Labs

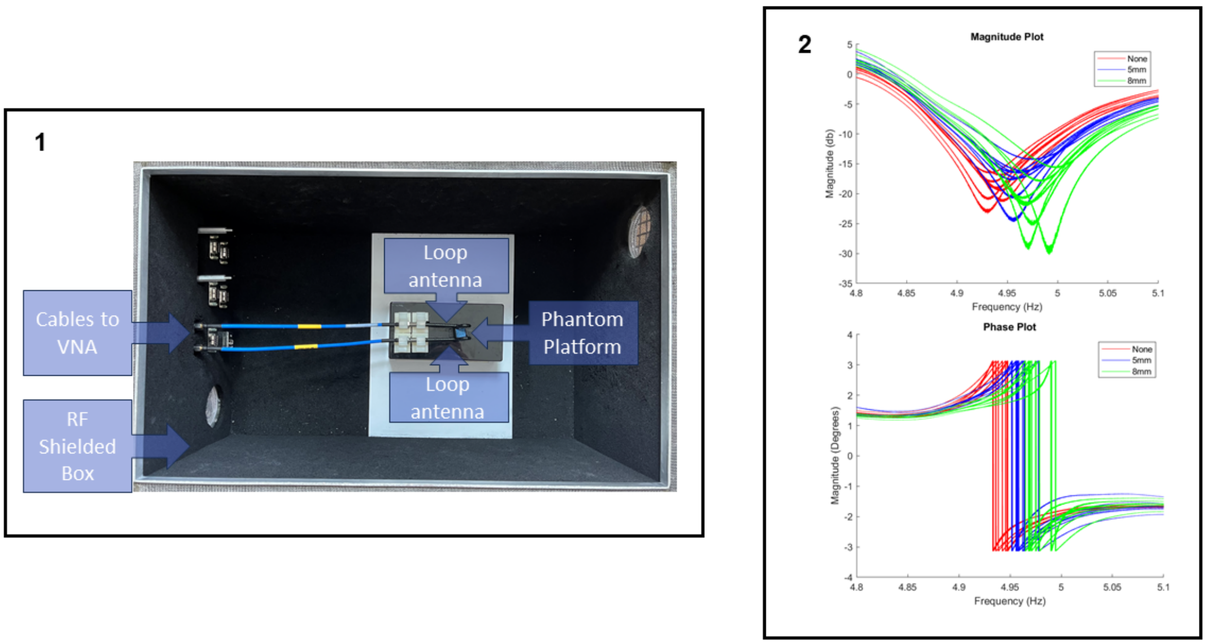
Traditional blood tests for diseases such as malaria and diabetes require drawing blood, which is painful and time-consuming. Our lab has shown that magnetic resonance (MR) relaxometry can be used to perform these blood tests electromagnetically, opening the door to contact-free, noninvasive diagnostic blood tests. While our low-cost, gradient-free MR systems have been demonstrated in vitro, they have not yet been demonstrated in vivo, due to the movement of blood in the body and the chaotic tissue signal background. In this work, we demonstrate the use of custom surface coils designed for blood signal detection with standard time-of-flight MR pulse sequences to isolate signals from blood and compensate for the blood flow velocity. We go on to perform relaxometry measurements in a model of a human arm. This brings us one step closer to noninvasive blood monitoring with low-cost equipment.

System Prototype for Electromagnetic Breast Cancer Detection

M. St. Cyr, S. Sabouri

Breast cancer detection is ideally quick, accurate, and comfortable. An emerging technology to fill the gaps in current diagnostic methods is microwave imaging, which sends and receives microwave signals through the breast in order to detect tumors of various sizes. This method has potential for a more comfortable patient experience at a lower cost than the current standards in breast cancer imaging [1].

In this work, a prototype system is developed for determining tumor size in breast tissue by utilizing microwave imaging techniques. The system consists of RF shielding components, custom loop antennas, and a vector network analyzer for signal generation and data collection. Additionally, post processing is completed by a ML algorithm to classify tumor sizes. By sending and receiving signals in the GHz range, this system can detect and distinguish between tumors of varying sizes on the millimeter scale within breast phantoms.



▲ Figure 1: (1) System overview (2) Transmission coefficient of various tumor sizes.

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