MATERIALS AND DESIGNS FOR 3D CONFORMAL ELECTRONICS WITH
CAPABILITIES IN CARDIAC MAPPING AND STIMULATION

BY

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DISSERTATION

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ABSTRACT

Developments in materials and mechanics for flexible electronics create opportunities for building novel electronic devices that physically interface with the human body, its organs and various tissues. Among the wide variety of application scenarios, integration with the heart represents a case that is both promising and challenging. Conformal electronic systems for monitoring physiological activity and for delivering therapies are critically important for both basic and clinical cardiology. The complex 3D geometry and time-dynamic deformations of the heart, however, create difficulties in establishing intimate, non-constraining interfaces between medical electronics and cardiac structures. Here we present advanced materials, mechanical designs and fabrication approaches that yield classes of 3D conformal electronic platforms with novel capabilities in cardiac physiological mapping and stimulation. Designs for both individual sensors/actuators components and overall device platforms are involved. The materials selections for sensors/actuators components include conductive composite for tactile sensors, silicon nanomembranes for strain gauges, iridium oxide for pH sensors, gallium nitride and gallium arsenide for optoelectronics, metal thin films for temperature sensing, and nanotextured electrode coatings for characterizing electrical activities. Careful mechanical design and fractal concepts enable device characteristics that are compatible with the intrinsic cardiac physiology. Novel device platforms, including multifunctional balloon catheters and 3D multifunctional integumentary membranes, are developed to allow integration of these components in systems that yield critical functionalities for biomedical applications. Animal experiments demonstrate the operational capabilities. The results
suggest routes for fabricating advanced electronic materials and devices with 3D formats and create methodological possibilities for both basic physiological research and clinical medicine.
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CHAPTER 1

INTRODUCTION

1.1 Stretchable Electronic Materials and Devices for Biomedical Applications

Conventional high performance electronics are mostly based on rigid inorganic semiconductor materials in a 2D planar format, e.g. silicon chips. The developments of silicon electronics are predicted by Moore’s Law: the number of transistors per unit area on the chip doubles every two years. Over the past 50 years, technology advancements were remarkably consistent with this prediction, resulting in dramatic improvements in the computing speeds, device miniaturization as well as energy efficiency. These revolutionary technology advancements have greatly changed the style of people’s life. In the area of medical and biological applications, automated, digitized tools, including X-ray computed tomography (CT), magnetic resonance imaging (MRI) and implanted cardiac pacemakers, were enabled with high-performance electronics, offering new means for diagnosis and therapy. Further development for establishing conformal biotic/abiotic interfaces by directly integrating electronic devices with large area of human body, and its various organs and tissues will open up new opportunities for basic studies in life science and for improving human health. However, there is fundamental mismatch in physical formats that create challenges for developing bio-integrated electronics: silicon wafers are rigid, planar, and brittle, but biology is soft, curved and elastic.

Recent developments in materials and mechanics concepts enable various devices in flexible and stretchable formats\textsuperscript{1-6}, suggesting routes to overcome this challenge. The most recent efforts for active electronic components in flexible and stretchable devices are
mainly focused on two types of materials: conductive/semiconducting organic compound and unconventional format of inorganic electronic materials. The former class of materials, including small molecules such as pentacene, anthracene, and rubrene, polymers such as poly(3-hexylthiophene), poly(p-phenylene vinylene), polyacetylene, and their derivatives, provide mechanical flexibility (Young’s modulus of ~ \(10^0\) GPa) that are more favorable than inorganic semiconductors (Young’s modulus of ~ \(10^2\) GPa). But most of the organic materials suffer from lower electrical performance (charge carrier mobility of ~\(10^0\) cm\(\cdot\)V\(^{-1}\)\(\cdot\)s\(^{-1}\)) comparing to conventional inorganic semiconductors (charge carrier mobility of ~\(10^3\) cm\(\cdot\)V\(^{-1}\)\(\cdot\)s\(^{-1}\)) and difficulties in processing with conventional electronics industry.\(^7,^8\) The latter class of materials exploits novel fabrication techniques to yield inorganic semiconductor materials in non-conventional physical formats that offer both good electrical properties and favorable mechanical characteristics (Figure 1.1).\(^9\) A typical example of such scheme is using inorganic semiconductor nano-membranes as building blocks for active components in flexible/stretchable electronics.\(^10\) Because the reduction in thickness has dramatic impact on the mechanical behavior (Figure 1.2), the semiconductor nano-membranes can withstand large bending deformation without reaching fracture limit of the materials.\(^11\) The use of transfer printing techniques allows heterogeneous integration of dissimilar materials with different processing requirements.\(^12\) The high temperature doping and oxidation processes for semiconductors can be performed on the source wafers, while transfer printing technique can serve as a versatile means to deliver semiconductor nano-membranes to flexible and stretchable substrate. Careful mechanical design at micro/nano scale can minimize the strain in the inorganic materials under deformation of the devices and therefore, enable mechanical flexibility/stretchability while maintaining optimum
electrical performance. At the device scale, the inorganic materials components can be placed at the neutral mechanical plane so that they experience minimal strain associated with bending (Figure 1.3). Figure 1.4 shows that the device can be patterned with serpentine geometry, which allows the device to accommodate large amount of applied strain by buckling of the wavy features. Based on these schemes, this group has previously developed classes of conformal electronic systems that can potentially interface with the human body and provide novel capabilities with physiological and medical interest (Figure 1.5). These technical approaches set a foundation for developing conformal bio-integrated electronics with capabilities in cardiac applications.

1.2 Basics of Cardiac Physiology

Heart is the central organ in circulatory system of humans and other vertebrates. It has hollow, muscular structures and pumps blood to various parts of the body by repeated, rhythmic contractions. The adjective “cardiac” means “related to the heart” and “cardiology” is the medical specialty that deals with cardiac diseases and abnormalities. Human heart is located in the thoracic cavity and has four chambers: left atrium, left ventricle, right atrium and right ventricle (Figure 1.6). The superior atria act as receiving chambers and are connected to the veins, while inferior ventricles act as discharging chambers and are connected to the arteries. These chambers form two pumps to control the systemic and pulmonary circulations, respectively. By contraction of the cardiac muscle, the left ventricle expels the oxygenated blood to the body via aorta. At the meantime, the right ventricle expels deoxygenated blood to the lung via pulmonary arteries. By relaxing the heart muscle, the oxygenated blood is collected into left atrium via pulmonary vein,
and deoxygenated blood are collected into right atrium via vena cavae. Then the blood is transfer to the ventricles, completing the cardiac cycle. The valves located at the junctions make sure that the blood flows are unidirectional.

The heart muscle, i.e. myocardium, is controlled by electrical signal propagating over the whole heart. Some of the myocardium is self-excitable. A region of the human heart called the sinoatrial (SA) node, or pacemaker, generates the normal electrical impulse and sets the rate and timing at which all cardiac muscle cells contract. The electrical conduction is carried out through propagation of action potential in the myocardium. The cardiac activities cause potential changes at the surface of the body and can be captured by electrocardiography (ECG), a standard testing technique for cardiac diagnosis\textsuperscript{19}. ECG is commonly recorded with 10 electrodes placed on different positions over the surface of the body. These electrodes form 12 leads, giving different viewing angles on the cardiac electrical activities. A typical ECG waveform is illustrated in Figure 1.7. The baseline is at 0 mV, indicating the period in cardiac cycle that there is no current flowing towards the electrodes. There key wave components in the ECG include P wave, QRS complex and T wave. P wave represents depolarization of the atria. QRS complex represents the fast depolarization of the ventricles. T wave represents the repolarization of the ventricles. 12 leads ECG recording can give spatial information of the electrical activities, which is indicative of heart conditions and is useful in clinical diagnosis. Abnormality in the cardiac electrical system can cause disorder of cardiac rhythm, namely arrhythmia. Pathological arrhythmias include tachycardia (beating too fast), bradycardia (beating too slowly) and fibrillation (loosing rhythmic contractions). The cardiac muscle is fed by coronary arteries, which are branched from the aorta. The coronary arteries carry oxygenated blood to supply
the respiration of the myocardium. Narrowing or blockage of coronary arteries causes ischemia to the myocardium and have severe impact on the cardiac functions.

A healthy heart is indispensable to life. According to the statistics from World Health Organization, cardiovascular diseases have become the number one cause of death globally.\textsuperscript{20} Estimated 17 million people died from cardiovascular diseases annually, representing about 30% of all global deaths. Diagnosis, treatment and prevention of heart diseases have become one of the most urgent needs for improving human health.

\section*{1.3 Tools for High Density Cardiac Mapping and Stimulation}

Tools for high density cardiac physiological mapping and stimulation are critically important for basic and clinical cardiology. These tools can provide means for identification and understanding of mechanisms of excitation-contraction coupling, metabolic dysfunction and arrhythmias, and for delivering precise electrical stimulation to restore the normal cardiac functions with minimal side effects. The heart is a delicate organ that has 3D curvilinear surfaces and time-dynamic deformations, and is surrounded with bio-fluids. Developing conformal electronic tools that interface with the heart is both challenging and promising. Devices developed in the 1980s attempted to address this need by using synthetic fabrics sewn to loosely resemble the shape of the ventricle, with bulk electrodes manually assembled and woven into this platform (Figure 1.8).\textsuperscript{21-24} Although such schemes captured spatial patterns of wave front propagation, they do not enable uniform quality of contact across the heart, practical deployment in clinical settings, high-density mapping capabilities, provision for multifunctional, precision measurement/stimulation or deployment as chronic implants. As a result, alternative
strategies based on serial mapping and stimulation with point-contact catheters/leads or on imaging techniques that use fluorescence, nuclear magnetic resonance or ultrasound have emerged, even though each has significant shortcomings (Figure 1.9).\textsuperscript{25-28}

The ideal scenario remains one in which device functionality integrates directly and non-invasively with the heart, suitable for long-term use. The essential challenge is that the heart is a complex electromechanical syncytium with numerous elements working in synchrony to reliably pump blood and respond to changing metabolic demands. Although much has been gained from isolated cellular studies, the integral functional behavior on the organ level and the interaction between the electrical, metabolic and mechanical remodeling in disease states, especially in vivo, remain poorly explored due to paucity of adequate tools. Thus there is an unmet need for multiparametric mapping capabilities inclusive but far beyond electrical sensing in a conformal, high-resolution manner, which cannot be realized using conventional materials, device technologies or imaging modalities.

Two types of conformal electronic systems that can physically integrate with the heart have recently emerged. One is a flexible, high density electrodes array with integrated silicon transistors for cardiac electrophysiological mapping (Figure 1.10).\textsuperscript{29} This device can provide high density spatiotemporal mapping of epicardial activities, however, the substrate of this type of device (polyimide film) provides little stretchability, which can cause relative motion between cardiac tissues and the electrodes during cardiac cycles. It can cover only a small area of the epicardium, and the signal quality can be affected by motion artifact. Another type of device is a stretchable electronic system in serpentine mesh geometry (Figure 1.11).\textsuperscript{30} It provides significantly improved physical conformability and can integrate over larger fraction on the epicardium. Various sensors and actuators are
incorporated to provide multifunctional mapping capabilities. These two systems represent significant advances on developing conformal electronics for cardiac applications. However, their physical embodiment as 2D sheets limit the possibilities of integrating over the full 3D structures of the heart, or stable contact without sutures or adhesives suitable for chronic applications.

1.4 In This Thesis

This thesis describes advanced fabrication techniques to generate novel 3D conformal electronic platforms for cardiac applications. Careful selection and optimization of materials and device architectures yield various multifunctional components including electrical, pH, thermal, mechanical and optical sensors and actuators, to provide advanced sensing and stimulation capabilities. The research involves interdisciplinary collaborations with theoretical and bio-medical specialists. The results demonstrate advanced methodological possibilities for developing conformal electronic tools for cardiac and other bio-medical applications.

Chapter 1 provides introduction and background information for conformal electronics as well as cardiac physiology and technical needs.

Chapter 2 describes materials and designs for multifunctional balloon catheters with capabilities in cardiac electrophysiological mapping and ablation therapies.

Chapter 3 describes 3D multifunctional integumentary membranes for spatiotemporal cardiac measurements and stimulation across the entire epicardium.

Chapter 4 describes optimized materials and fractal designs for 3D multifunctional integumentary membranes with capabilities in cardiac electrotherapy.
Chapter 5 provides a summary of the research presented here and a discussion of directions for future work.

1.5 References


1.6 Figures

Figure 1.1. Schematic illustration of a printed semiconductor nanomaterials–based approach to flexible electronics. The process involves transfer printing of collections of nanotubes, nanowires, nanoribbons, or other active nanomaterials, separately formed on source substrates, to a common device substrate to generate interconnected electronics in ultrathin, multilayer stack geometries. HGI, heterogeneous integration. (Reproduced from reference 9)
Figure 1.2. Unique physical properties in nano-membranes (NMs). NMs have exceptionally high degrees of bendability, as illustrated in the scanning electron microscope (SEM) image. The flexural rigidity of a 2-nm-thick, silicon NM is $\sim 10^{15}$ times smaller than that of its bulk wafer counterpart (200 μm thick), as illustrated in the red curve of the graph (dashed line at 2 nm). Related mechanics allows bonding of NMs to nearly any surface. Here energy release rates associated with opening of interfaces between NMs and supporting substrates decrease linearly with thickness. The blue line represents calculations for silicon NMs bonded to sheets of polyimide at room temperature, and then heated to 300 °C. (Reproduced from reference 11)
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(Reproduced from reference 21)
Figure 1.9. Schematics of a typical optical mapping system. (Reproduced from reference 25)
Figure 1.10. A flexible multiplexed electrodes array for cardiac electrophysiological mapping. (Reproduced from reference 29)
Figure 1.11. An optical image of a stretchable cardiac device with web like structures.

(Reproduced from reference 30)
CHAPTER 2
MULTIFUNCTIONAL BALLOON CATHETERS WITH CAPABILITIES IN CARDIAC ELECTROPHYSIOLOGICAL MAPPING AND ABLATION THERAPY

Significant portions in this chapter were published on *Nature Materials* **10**, 316 (2011). Reproduced with permission from the journal. My specific role in this project was to develop micro tactile sensors and to integrate with the balloon catheters. The following materials describe the context of the research and my contributions.

2.1 Introduction

Inflatable balloon catheters constitute an extremely simple, yet powerful class of medical instrument that can deliver therapy or facilitate diagnosis of biological tissues and intraluminal surfaces through direct, soft mechanical contact. In peripheral or coronary angioplasty, inflation of such a device in a stenotic blood vessel can eliminate blockage and, at the same time, affect the expansion of a stent to maintain an open configuration.\(^1\) In a different procedure, known as septostomy, the balloon plays a related but more forceful role, as an instrument that creates large passages between the right and left atria, to enable shunting for increased blood flow.\(^2,3\) The balloon catheter device is attractive for these and other procedures because (1) it allows minimally invasive insertion into lumens or other organs of the body through small incisions, due to the miniaturized, cylindrical form of its deflated state, and (2) it can be configured, through controlled inflation, to match requirements on size and shape for its interaction with the tissue, where contact occurs in a soft, conformal manner, capable of accommodating complex, curvilinear and time...
dynamic surfaces in a completely non-destructive manner. The main disadvantage is that conventional balloons offer minimal utility, due to their construction from uniform sheets of electronically and optically inactive materials, such as polyurethane or silicone.

In this work, we exploit the balloon catheter as a platform for heterogeneous collections of high performance semiconductor devices, sensors, actuators and other components. The result is a new type of minimally invasive surgical tool that can provide versatile modes of operation inclusive of but far beyond the simple mechanical manipulations involved in angioplasty, septostomy and other standard procedures. Here, we focus on implementation in cardiac ablation therapy, with several modes of sensory feedback control, designed for the treatment of various types of sustained arrhythmias of the heart, like atrial fibrillation. Current procedures use closed or open irrigation layouts with single, point source ablation electrodes that offer limited sensing functionality or array capabilities. The time-intensive nature of surgical work performed with such devices increases the rate of morbidity, and also demands advanced technical skills from the operator. The systems reported here overcome these limitations and eliminate the need for additional catheters by providing the ability to sense electrical, tactile, optical, temperature and flow properties at the tissue-balloon interface, in real time as the procedure is performed.

2.2 Overall Device Platform

Commercially available catheters (8~18 Fr, BARD) serve as platforms for the devices. Components that integrate with the balloons are formed on semiconductor wafers using adapted versions of planar processing techniques and methods of transfer printing.
Wrapping the resulting collections of interconnected devices on the balloon in its deflated state completes the process. Encapsulating layers serve as moisture barriers to enable the entire system to operate when completely immersed in bio-fluids. These devices sense physiological signals and stimulate tissue. They are connected and powered through a thin ribbon cable based on an anisotropic conductive film (ACF) that bonds to the base of the shaft that connects to the balloon, and wraps along the length of the flexible tubing of the catheter. These procedures add functionality to balloons without significantly altering their mechanical properties or levels of expansion that they can accommodate. These specific mesh layouts can tolerate tensile strains of up to 200% without fracture, due to optimized configurations guided by quantitative mechanics modelling.

Figures 2.1a-c provide images of a balloon catheter device with a passive, uniform network mesh, to illustrate the overall construction and mechanics. The strain distributions obtained through analytical and computational modelling capture, quantitatively, the nature of these deformations (inset of Fig. 2.1c). Active and/or passive devices integrate at the nodes of the mesh, minimizing their mechanical coupling to the strains associated with inflation/deflation of the balloon. Demands on layouts and interconnections for functional systems force local modifications of the simple serpentine geometry of Fig. 2.1a-c, as illustrated in Fig. 2.1d. This micrograph corresponds to part of a multifunctional balloon catheter that supports a temperature sensor and an exposed sensing electrode pad. Active semiconductor devices can also be incorporated. Figure 2.1e shows a completed system, with microscale light-emitting diodes, sensor electrodes, temperature detectors and other components. After multiple inflation and deflation cycles exceeding 100% strain levels, all devices and interconnects undergo little or no performance degradation.
2.3 Materials and Designs for Integrated Tactile Sensors

My contribution to the specific sensors on this platform is a micro-tactile sensor for detecting dynamic mechanical forces exerted on heart tissue. These devices are important for monitoring mechanical interactions during surgery or diagnosis; they must satisfy, simultaneously, two demanding requirements: (1) minimal sensitivity to in-plane forces, to decouple their operation from inflation/deflation or other deformations of the balloon, and (2) high sensitivity to normal forces, in a soft mechanical construction, to enable nondestructive measurements against low-modulus tissue. Existing sensor technologies are unsuitable for integration on highly stretchable substrates such as balloons. More recent tactile sensors based on electrically conducting rubbers or elastomeric dielectrics cannot be used either because responses to in-plane strains conflate with those from normal strains.

To address the aforementioned requirements, we exploit two ideas in mechanics. First, as highlighted in Fig. 2.1, non-coplanar serpentine mesh layouts with devices located at planar nodes experience small strains (<1%), even for large deformations of the substrate. Strains at these locations can be reduced further by decreasing the size of the nodes, and by increasing their thickness and modulus. To exploit these features, we locate our tactile sensors at small nodes on thick (5 µm) layers of a high-modulus (~4 GPa), photo-definable epoxy (SU8, Microchem). For the second requirement, the stiffness of the sensor in the normal direction must be low and its sensitivity to compression must be high. To this end, we use a pressure-sensitive, electrically conductive silicone rubber (PSR; Elastosil LR 3162, Wacker Silicones) with low stiffness (~1.8 MPa), configured in a bridge shape,
overlying a rectangular feature of a low-modulus formulation of poly(dimethylsiloxane) (PDMS; ~650 kPa). This structure forces current to flow through the narrow, top layer of the PSR bridge. The soft, underlying PDMS imposes little constraint on compression-induced lateral expansion of the PSR, thereby facilitating associated resistance changes. A thin coating of polyimide (PI) cured at 300 °C for an hour encapsulates the entire structure to avoid leakage current. This process does not cause device degradation, thereby suggesting that the system is compatible with temperatures used for sterilization.

Figure 2.2a presents a cross-sectional schematic drawing of the sensor (left). The in-plane results of finite-element modelling (right panel) illustrate the ability of the epoxy to reduce strains in the PSR induced by expansion of the supporting balloon substrate. The extent of reduction increases with thickness of the epoxy (Fig. 2.2a). Figure 2.2b presents calculated lateral strains in the PSR induced by applying a uniform pressure (1 MPa). With the soft PDMS layer, the bottom of the PSR bridge can expand laterally (orange dotted box). This lateral tensile strain (ε11) increases the resistance of the PSR. Without PDMS, the stiff underlying layer of epoxy constrains motion of the PSR, thereby minimizing the lateral expansion strain ε11 near the interface (pink dotted box). Figure 2.2c shows optical micrographs at two stages of the process for fabricating sensors with these designs. To test these structures, we used a custom-made micro-compression stage with precision load cell. The measured percentage change in resistance (ΔR%) as a function of normal load appears in Fig. 2.2d, for sensors with three different thicknesses of PDMS and a fixed total thickness. The sensitivity increases with PDMS thickness (h), qualitatively consistent with trends in computed values of strain in the PSR bridge (Fig. 2.3b). We also evaluated
changes in resistance associated with full inflation of the balloon substrate (similar to images of Fig. 2.1; up to 130%), as shown in Fig. 2.2e.

These tactile sensors can be used to monitor balloon-inflation levels and electrical contact. In in vivo experiment on rabbit model, these sensors provide accurate feedback about the contact between the heart and the devices (Fig. 2.4a, b). Figure 2.4b shows that the tactile sensors can be used to track clean contact from detachment on a cycle-by-cycle basis without significant hysteresis. In Fig. 2.4b, the percentage change of resistance recorded from the tactile sensor (blue) clearly correlates with the electrogram signal (red). When the balloon was in good contact, high-quality electrical activation signals were measured, whereas noisy signals were obtained when the balloon was detached from the heart surface. Because these sensors have sufficient sensitivity for tracking normal sinus rhythm at ~240 bpm, we expect that they can be used to detect onset of tachycardia in humans to evaluate the mechanical heart rhythm.

2.4 Fabrication and Compression Test of Tactile Sensors

After patterning serpentine interconnects and electrodes (Cr/Au, 5/150 nm) on a uniform thin sheet of PI (1.2 μm thick), casting procedures form a rectangular feature of PDMS (160 μm ×220 μm) between two adjacent Au electrode pads (150 nm thick; left frame, Fig. 2.2c). Similar steps define a bridge-shaped structure of PSR (160 μm×430 μm) that passes over the PDMS and covers the pads on both sides. Patterned casting procedures form the required features of PDMS and PSR. Here, photolithography first creates trenches in a thick layer of photoresist (AZ P4620, AZ Electronic Materials). Spin coating PDMS (20:1 mixture of base to curing agent; Sylgard 184, Dow Corning) on top of this resist,
curing it at 70 °C for 1 h and then etching back the PDMS removes any residual material from the top surface of the resist. Rinsing with acetone washes away the resist. Next, similarly patterned AZ P4620 defines a structure for the required features of PSR (Elastosil LR 3162, Wacker Silicones). In this case, placing an excess of this material on top of the resist and then scraping with a razor blade forces it into the trenches and removes it from adjacent areas. Curing at 70 °C for 1 h and then removing the resist yields the desired PSR structure. The tactile sensor is completed by spin-casting a layer of PI for encapsulation. To calibrate the response, the entire structure is transfer printed onto a 1-mm-thick slab of PDMS (30:1 mixture of base to curing agent). A multimeter (SMU2055, Signametrics) measures the change in resistance during compression using a custom assembly of stages and a 25-g-force GSO load cell (Transducer Techniques) fixed on a vibration-isolation table, as shown in Supplementary Fig. 2.5. The indentation head mounts on a support designed to cover a single tactile sensor. The tactile sensor attaches to a glass slide that attaches to a vertical translation stage with positioning accuracy of 1 μm. A microscope above the stage facilitates manual alignment. After bringing the device into slight contact with the indentation head, the sample stage moves downward by 30 μm at a speed of 1 μm s⁻¹. For cyclic fatigue testing, speeds were 120 μm s⁻¹. Slight drift in the baseline response can be significantly reduced by several cycles of compression before testing.¹⁵

2.5 Conclusion

The materials and mechanics concepts introduced here represent a technology foundation for advanced, minimally invasive surgical and diagnostic tools, with
demonstrated examples in diagnosing and resolving complex arrhythmogenic disease states of the heart. These devices constitute significant advances over existing balloon and multielectrode catheters in the number of sensing modalities and the spatial density of sensors. Related ideas should also be valuable in other contexts, including atherosclerosis, oesophageal and gastro-intestinal diseases, and endometrial and bladder dysfunction, all of which can be addressed using multifunctional, instrumented balloon-catheter systems.

2.6 References


2.7 Figures

**Figure 2.1. Multifunctional inflatable balloon catheters.** (a) Optical image of a stretchable, interconnected passive network mesh integrated on a balloon catheter (deflated). (b) Optical image of the balloon inflated by ~130% relative to its deflated state (inset). (c) Magnified view of non-coplanar serpentine interconnects on the balloon in its inflated state. This region corresponds to the area defined by the green dotted line in b. The spacing between the islands and the configurations of the serpentine interconnects compare well with simulation results (inset). (d) Magnified image of a temperature sensor and gold lines used to apply positive and negative bias voltages. Electrodes for simultaneous electrogram mapping are also shown. (e) Optical image of a multifunctional balloon catheter in deflated and inflated states. The image shows arrays of temperature sensors (anterior), microscale light-emitting diodes (posterior) and tactile sensors (facing downward).
Figure 2.2. Fabrication, characterization and analysis of tactile sensors for multifunctional balloon-catheter devices. (a) Schematic cross-sectional drawing of a tactile sensor (left) and calculated distributions of strain (right) at the base of the PSR due to inflation of the balloon substrate, for cases with and without an underlying layer of epoxy. (b) Calculated deformations and distributions of strain in the PSR across the cross-section of a sensor with the layout illustrated in a, induced by uniform compression (black arrows). The top two frames show cases with (above) and without (below) a PDMS layer (white). The bottom two frames show magnified views of the strains in the top part of the PSR.
(Figure 2.2 cont.) bridge. (c) Optical images of a rectangular feature of PDMS between two electrode pads (left) and a fully integrated tactile sensor (right) containing a PSR layer formed on top of the PDMS. The red dashed line indicates the position of the cross-sectional view depicted in a. (d) Percentage change in resistance versus applied pressure for sensors with three different PDMS thicknesses (h). (e) Percentage change in resistance as a function of time during several cycles of inflating and deflating the balloon substrate.

**Figure 2.3. Characteristics of the tactile sensors.** (a) Calculated maximum strain in PSR layers of tactile sensors with different thickness layers of epoxy. (b) Percentage change in resistance per 100 kPa change in pressure, and average lateral expansion strain in the PSR bridge $\varepsilon_{11}$ (Fig. 4b) as a function of PDMS thickness.
Figure 2.4. Animal experiments for the tactile sensors. (a) Optical image of an instrumented balloon catheter in its inflated state, showing an array of tactile (white dashed boxes) and electrogram sensors. (b) Simultaneous recordings of electrical activation and mechanical contact measured on the surface of the beating heart.
Figure 2.5. Custom micro-compression stage for evaluating the tactile sensors.
CHAPTER 3

3D MULTIFUNCTIONAL INTEGUMENTARY MEMBRANES FOR SPATIOTEMPORAL CARDIAC MEASUREMENT AND STIMULATION ACROSS THE ENTIRE EPICARDIUM

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3.1 Introduction

Means for high-density multiparametric physiological mapping and stimulation are critically important in both basic and clinical cardiology. Recent developments in materials and mechanics concepts for stretchable electronics\textsuperscript{1-6} create an opportunity to meet this challenge of direct integration of devices with the epicardial surface. Current conformal electronic systems, however, are essentially 2D sheets, which cannot cover the full epicardial surface or maintain reliable contact for chronic use without sutures or adhesives. Here we create 3D elastic membranes shaped precisely to match the epicardium of the heart via the use of 3D printing, as a platform for deformable arrays of multifunctional sensors, electronic and optoelectronic components. Such integumentary devices completely envelop the heart, in a form-fitting manner, and possess inherent elasticity, providing a mechanically stable biot/-abiotic interface during normal cardiac cycles. Component examples range from actuators for electrical, thermal and optical stimulation, to sensors for pH, temperature and mechanical strain. The semiconductor materials include silicon, gallium arsenide and gallium nitride, co-integrated with metals, metal oxides and polymers, to provide these and other operational capabilities. The physical format resembles that of
the naturally occurring membrane that surrounds the heart, i.e. the pericardium. These systems, which we refer to as 3D multifunctional integumentary membranes (3D-MIMs) provide conformal interfaces to all points on the heart, with robust but non-invasive contacts enabled by the soft elasticity of the membrane itself, throughout dynamic cardiac cycles, even when completely immersed in fluid media. Measurements on isolated perfused rabbit hearts demonstrate the utility of these ideas as a general platform for multifunctional, high-density epicardial mapping/stimulation, and create advanced methodological possibilities for cardiac research and therapy.

3.2 Device Design and Fabrication

The fabrication begins with the creation of a thin, 3D elastic membrane shaped to the heart. As shown in Fig. 3.1a, optical segmentation techniques first capture the full 3D geometry of a heart of interest. A commercial 3D printer (ZPrinter 450, Z-Corporation) then renders a solid model of the heart in a proportionally scaled form, as described later, to serve as a substrate for mounting ultrathin electronic/optoelectronic and sensor systems, separately prefabricated on planar substrates. Casting and curing a thin layer of silicone elastomer on top of the heart model with these multifunctional devices on its surface defines the overall format. The front faces of the device components contact the model while the back faces bond to the elastomer. Removing the system (i.e. 3D membrane with integrated device components) from the model prepares it for installation around a living heart, as a type of ‘instrumented’, artificial pericardium.

Figure 3.1b shows a representative 3D-MIM that includes microscale, inorganic light emitting diodes (µ-ILEDs) based on indium gallium nitride (InGaN) for optical mapping,
silicon (Si) nanomembranes for strain gauges, gold (Au) electrodes for electrical sensing/stimulation, iridium oxide (IrOx) pads for pH sensors and Au serpentine resistors for temperature sensors/heaters. The methods for creating these components exploit modern integrated circuit technologies and achieve spatial resolution far beyond that possible with manually assembled arrays. A thin, flexible heat-seal conductive cable (Elform, HST-9805-210) provides connection to external hardware for data acquisition, power supply and control. The 3D-MIM is engineered with overall dimensions slightly smaller than those of the real heart, to provide adequate elasticity and mechanical support for robust contact with the epicardium during diastole and systole, but with sufficiently small pressures to avoid disruption of natural behaviors of the cardiac tissue. The serpentine mesh that interconnects the device components covers the ventricle and conforms to the contours of the epicardium. Although this example is designed for research applications on rabbit hearts, the same strategies are applicable to human hearts, or even other organ systems. Here, the 3D geometries can be obtained using similar 3D printed substrates with patient specific MRI or CT organ segmentation.

3.3 Mechanical Analysis

A critical feature of this type of device is that it can be designed to maintain a stable mechanical interface to the tissue while exerting minimal force on the contracting and relaxing heart muscle. In the cardiac anatomy of humans and other vertebrates, the myocardium is enclosed in a space sealed by the pericardium, which allows reversible volume change within a certain range. When a pathophysiological condition leads to inflammation, the pericardium exerts pressure to constrain the motions of the heart.
chambers. Quantitative analysis allows a comparative assessment of the pressure associated with our 3D device membrane on the epicardium, as well as the dependence of this pressure on materials properties and design parameters. Figure 3.2a shows results for a 3D-MIM with a membrane thickness of 150 μm and effective Young’s modulus of ~60 kPa (Ecoflex, Smooth-on) at various states of volume expansion $(1 + \varepsilon)^3$ of a heart geometry, calculated using 3D finite element methods (FEM), where $\varepsilon$ is the linear expansion factor. The thickness of the membrane is uniform in the analysis; the nonuniformity due to the electronic devices results in local increase of the effective Young's modulus to ~80 kPa and adds <50% of the approximate pressure, as discussed in details in Methods section and Fig. 3.6. The form of the undeformed membrane follows that of a 3D model, proportionally size-reduced (~30% volume reduction comparing to the diastolic state of the real heart) to ensure a baseline level of pressure upon application on the real heart. Computations correspond to the heart at its contracted volume (3D model), and at systolic (120% of the contracted volume) and diastolic (145% of the contracted volume) conditions. The calculated average pressures are similar to those of pericardium under normal physiological conditions, and only ~20% of these pressures under conditions of pericardial constraint8-13. The results suggest that the device is unlikely to cause restrictive impact, as confirmed by ex vivo studies described subsequently. FEM and analytic modeling also establish general relationships between the pressure and the design parameters. Figure 3.2b shows the average pressure as a function of the volume expansion, the thickness of the membrane and its Young’s modulus. The analytic model uses a partial ellipsoid to approximate the geometry of the heart. Details appear in Methods section and Fig. 3.6. The following
expression connects the average pressure, the membrane geometry, mechanical properties and expansion factor:

\[
P_{\text{average}} = C \times \frac{Et\varepsilon}{(1-\nu)(1+\varepsilon)^2}
\]  

(1)

where \( t \) is the thickness of the membrane, \( E \) and \( \nu \) are the effective Young’s modulus and the Poisson's ratio, respectively. The constant \( C \) decreases as the heart size increases, and \( C \) also depends on the shape of the heart (~0.2 mm\(^{-1}\) for a rabbit heart). Decreases in membrane thicknesses and Young’s moduli both linearly reduce the pressure. This scaling allows designs that provide pressures sufficiently large to maintain good contact between the sensor/actuator network and the epicardial surface, but sufficiently small to avoid impact on the intrinsic physiology. Monitoring the time course of several electrophysiological parameters that indicate ischemia in an isolated pressure loaded, working rabbit heart model\(^{14}\) with and without a 3D-MIM reveals the effects. The results, based on control (N=3) and experimental (N=3) hearts (Fig. 3.7), suggest that there is no additional ischemia caused by the devices, as measured by ST elevation and the amplitude of the LV pressure waveform.

3.4 Spatiotemporal Cardiac Measurements and Stimulation

To demonstrate the various functional modes of operation we begin with high precision mapping of epicardial electrical activity. These experiments, and all of those that follow, used explanted Langendorff-perfused rabbit hearts. The 3D geometrical information was obtained from a representative rabbit heart. A single 3D-MIM can accommodate some range in specific sizes and shapes associated with a single type of
animal model, due to its soft, elastic construction. The device here incorporates 68 Au electrodes (1 mm² surface area and spacing of 3.5 mm), distributed across both the anterior and posterior surfaces of the epicardium (Fig. 3.3a, d, and Fig. 3.8). The electrochemical impedances of individual electrodes are \( \sim 2 \text{ k}\Omega \) at frequency of 1 kHz, measured in phosphate buffered saline (Fig. 3.9). The transparency of the membrane allows simultaneous optical mapping through voltage dependent fluorescence, as a means for validating the electrical measurements\(^{15}\). Experiments involved signals acquired from 4 hearts for a variety of conditions: normal sinus rhythms, and paced at a range of frequencies and from a range of electrode pairs to increase the variability of the propagation patterns in the spatial activation maps. The surface electrograms captured various key morphologies associated with the QRS and T waves (Fig. 3.3a). Representative maps and correlations between electrical and optical activation times appear in Fig. 3.3c and 3.3b, respectively. The overall linear correlations between optical and electrical activation times were 0.957 for sinus data and 0.943 for paced data. These studies indicate that this configuration of measurement electrodes can replicate patterns of activation to a resolution that captures the spatial variations observed optically. Analyses for additional electrophysiological parameters are summarized in Fig. 3.11. Figure 3.3d presents a 3D map derived from signals recorded from both anterior and posterior surface of the heart. Unlike optical mapping where motion artifacts dramatically impact the measurement quality and static heart geometries are required, electrophysiological mapping with 3D-MIMs can be applied under normal beating condition. As shown in Supplementary Video, the integrated sensors move synchronously with the underlying cardiac tissue. Although it is practically difficult to avoid relative lateral motion between the sensors and the epicardium during beating.
cycles, due to the engineered geometries of 3D-MIMs, the displacement can be minimized to be less than the characteristic sizes of the sensors and to have negligible impact to the signal quality (Fig. 3.10). This feature is necessary for extending the mapping capabilities beyond laboratory studies and implementing in clinical electrophysiology.

Mapping of changes in pH provides useful information on the metabolic state of the heart. Here, iridium oxide (IrO₃), a well-established material for pH sensing, enables the measurement. Electrodeposited IrO₃ on Au electrodes provides pH sensors with average open circuit potential (OCP) responses of 68.9 mV/pH with standard deviation of 8.6 mV/pH for 32 sensors over the array at 37 °C in Tyrode’s solution (Fig. 3.12). The temperature dependence of the pH sensors is $-1.6 \pm 0.02$ mV/° C ($\mu \pm \sigma$), which corresponds to $-0.02$ pH for a 1 ° C change in temperature. Temperature variations over a physiologically relevant range will, therefore, have a small effect on the pH measurement. For cases where large changes in temperature are externally introduced, the temperature dependence of the pH sensor must be accounted for explicitly. Such pH sensors, along with optical mapping techniques, enable acquisition of maps of pH, transmembrane potential ($V_m$), and calcium transient (CaT) signals during global no-flow ischemia-reperfusion. The pH sensors cover the left anterior and posterior surface of the rabbit heart (Fig. 3.4a). At baseline, all pH sensors record values between 7.34 and 7.40. The responses of two pH sensors (highlighted by grey and charcoal colors) are plotted (Fig. 3.4b.) throughout the protocol. Complete spatial pH maps at time points $t_1$ (baseline), $t_2$ (10 minutes into ischemia), and $t_3$ (20 minutes into reperfusion) appear in Fig. 3.4d-e (left). Turning off the perfusion pump immediately reduced coronary pressure to 0 mmHg and led to an approximately linear decrease in pH to minimum values of 6.40 (grey) and 6.22 (charcoal).
Upon reperfusion, the pH rapidly increased until initiation of ventricular tachycardia (VT) where the pH stabilized at levels somewhat below baseline values. A sample far-field ECG of reperfusion-induced VT appears in Fig. 3.4c. After spontaneous conversion back to sinus rhythm, the pH values increased again to pre-ischemic values. Figure 3.4d-f shows pH maps (left), representative optical signals (V_m—black and CaT—grey; middle) and side-by-side action potential duration at 70% repolarization (APD70) and calcium transient duration at 70% return to baseline (CaT70) maps. At the baseline, pH, APD70, and CaT70 maps highlight that the pH and electrophysiological parameters were initially uniform over the surface of the heart. After 10 minutes of ischemia, pH, APD70, CaT70 changed, though not in a spatially uniform manner. CaT alternans (short and long duration) were observed during ischemia and here we show a short CaT70 in Figure 3.4e. After 20 minutes of reperfusion, parameters returned to values close to the baseline levels. This experiment demonstrates possibilities in multiparametric mapping during ischemia/reperfusion. The information establishes anatomical relationships between metabolism and excitation-contraction coupling.

A 3D-MIM with arrays of temperature sensors illustrates capabilities in monitoring spatial distributions of cardiac temperature. The temperature sensor elements use designs established previously, consisting of serpentine traces of gold (20 μm wide, 50 nm thick) (Fig. 3.13) in which changes in resistance correlate to changes in temperature\(^\text{17}\). The temperature sensors exhibit linear responses over physiological range, with a measurement precision of \(~23\, \text{mK}\) when sampled at 2 Hz in typical hospital settings. Figure 3.5a shows a 3D-MIM with 16 integrated temperature sensors during use on a beating heart. The sensors are calibrated in temperature controlled water bath before the animal experiments,
exhibiting average responses of $1.23 \, \Omega/^{\circ} \text{C}$ with standard deviation of $0.05 \, \Omega/^{\circ} \text{C}$ over 16 sensors across the array (Fig. 3.14). In one experiment, the temperature of the heart was changed by altering the temperature of the perfusion. As shown in Fig. 3.5a, the measured epicardial temperature gradually decreased by ~7 $^{\circ} \text{C}$ during cooling of the perfusate, with a uniform distribution of temperature across the heart. The heart rate, determined from the far-field electrogram, decreased with decreasing temperature and recovered to the original value as the temperature returned to physiological levels, indicating temperature controlled rate of myocardial metabolism. In a second experiment, a cautery pen was used to acutely burn a small region of the epicardium, simulating clinical ablation. The associated temperature map (Fig. 3.5b) shows localized elevation of temperature near the point of ablation. Such information can be used as feedback for clinical control of ablation time and size of affected area. In combination with electrical sensors, such device could provide real-time relation between temperature and excitation.

In addition to electrical and chemical evaluation, mechanical characteristics can be determined. Here, strain sensors based on piezoresistive effects in nanomembranes of Si allow monitoring of the mechanics of contractions of the heart during a variety of propagation states. Careful mechanical design of the serpentine interconnect structures allow accurate measurement in spite of the fact that typical epicardial strains greatly exceed the fracture threshold of Si, as described in previously reported small-scale 2D devices. In the present design, the 3D-MIM strain sensors include three p-doped Si piezoresistors in a rosette configuration (Fig. 3.15). Two of the piezoresistors, with longitudinal axes perpendicular to each other, are aligned to the $<110>$ crystalline directions of the Si, offering effective longitudinal gauge factor of ~0.33 and effective
transverse gauge factor of \( \sim 0.06 \) for each piezoresistor (Fig. 3.16). The other piezoresistor is aligned to the \(<100>\) crystalline direction and exhibit relatively small changes in resistance under strain, due to the intrinsic sensitivity associated with the crystalline direction as well as the overall device geometry. The piezoresistors aligned to the \(<110>\) directions provide maximum sensitivity for characterization of mechanical rhythms of the heart while the piezoresistor aligned to the \(<100>\) direction can be used to calibrate for effects of temperature. Experiments revealed the mechanical behaviors during sinus rhythm, ventricular pacing, and pharmacologically induced ventricular fibrillation (VF) with Pinacidil (30\( \mu \)M bulk dose). The use of Pinacidil significantly reduces the action potential duration and subsequently increases the vulnerability to reentrant arrhythmias when stimulated with 50Hz A/C burst pacing. Bath electrodes simultaneously recorded a far-field ECG to establish the temporal correlation between the electrical and mechanical behavior. Figure 3.5c shows the response of a representative piezoresistor aligned to the \(<110>\) direction. The measurements reveal mechanical rhythms of the cardiac cycles, with consistent cycling with ECG recordings. During VF condition, both the strain gauges and ECG show that the waveform lost normal rhythm and displayed a random pattern typical for VF.

A final demonstration exploits arrays of \( \mu \)-ILEDs\textsuperscript{20, 21} to illustrate the capacity for advanced semiconductor integration and optical mapping/stimulation. Here, nine ultrathin (3 \( \mu \)m), microscale (300x300 \( \mu \)m\(^2\)) light emitting diodes (LEDs) based on aluminum indium gallium phosphide (AlInGaP) with peak emission wavelengths of 670 nm (Fig. 3.17 and 3.18) served as local light sources for excitation of voltage sensitive dyes. Changes in fluorescence associated with these dyes allowed measurement of the cardiac
action potential. Figure 3.5d compares signals obtained with an external light source (Prizmatix, 630nm) and with the integrated \( \mu \)-ILEDs. In spite of their small sizes, the LEDs enable recording of clear action potentials, with waveform shapes consistent with external light. The signal to noise ratio of the \( \mu \)-ILED excited action potentials is lower than the externally excited action potentials due to a necessary decrease in light intensity to minimize the power delivered to the device. The results demonstrate the future possibility of an in vivo optical mapping using either externally applied dyes or internal fluorescent indicators and/or stimulation system in a 3D integration format.

3.5 Discussion

The results presented here suggest routes for integrating active electronic materials and sensors in 3D, organ—specific designs, with potential utility in both biomedical research and clinical applications. With attention to materials, engineering mechanics and functional devices, these systems can establish conformal interfaces with the epicardium, and perform a variety of high density physiological multiparametric mapping and stimulation. The use of transfer printing and the reported scheme for integration onto the printed 3D heart structure allows diverse sensor/actuator devices on a single platform. Separate electrical connection, with a single trigger channel to synchronize the timing, eliminates effects of crosstalk. The devices can provide local information on the metabolic, excitable, ionic, contractile, and thermal state for investigations of both the spatial and temporal responses to a variety of insults, diseases, and therapies. The devices could be used to identify critical regions that indicate the origin of pathophysiological conditions such as arrhythmias, ischemia, or heart failure. These regions could then be used to guide
therapeutic interventions. The techniques in microfabrication, transfer printing and 3D shape definition are scalable to larger sizes and smaller, denser arrays of sensors. To increase the resolution and numbers of sensors, it may be necessary to incorporate transistors into the device to allow multiplexed addressing. Remaining challenges for use as a chronic implant include means for power supply, control/communication, and encapsulation. However, these approaches present a promising opportunity to design and implement high definition implantable devices for diagnostics and therapy of lethal heart diseases.

3.6 Methods

Fabrication of 3D-MIMs. The process, detailed in Supplementary Methods, starts with standard planar processing of inorganic semiconductor materials (Si, InGaN or AlInGaP) followed by transfer printing onto substrates coated either with a bilayer of polyimide (PI) on poly(methyl methacrylate) (PMMA) or poly(ethylene terephthalate) (PET) on poly(dimethylsiloxane) (PDMS). Dissolution of the PMMA or delamination from the PDMS allows release of the devices. Metal layers (Cr/Au) are vacuum deposited and patterned to form interconnects, resistors and electrodes. Application and patterning of a polymer encapsulation layer (PI or a photosensitive epoxy, SU8) on top of the devices completes their fabrication. Transfer printing delivers the resulting structures to a thin film of a low modulus silicone elastomer (Ecoflex, Smooth-on). A flexible conductive cable (Elform) bonded to contact pads at the periphery provides an interface to external hardware. A lamination process attaches the devices to a desired 3D printed model of the heart, with the sensors in direct contact with the surface. Casting and curing another layer of the same
type of elastomer defines the overall 3D geometry of the system. In some cases, elastomer straps molded enhanced the maneuverability for use in Langendorff-perfused heart experiments (Fig. 3.19). Additional openings in the membrane can be included to prevent fluid build-up associated with flow in the supporting bath. Removal from the model allows electrodeposition of IrOx on to yield pristine surfaces for precision pH sensing.

Mechanical analysis. Numerical analysis by 3D FEM: The 3D FEM is used to study the pressure between the 3D-MIM and the heart for a wide range of device parameters and the expansion of the heart. The 3D geometric model of the heart is reconstructed from the data obtained with optical segmentation. The geometric model is imported into the pre-processor in the ABAQUS finite element program\textsuperscript{32}. The heart and the 3D-MIM are modeled by the 4-node, linear tetrahedron solid element C3D4 and the 4-node quadrilateral membrane element M3D4 in ABAQUS, respectively. The total number of elements exceeds 60,000, and mesh refinement ensures the accuracy of the numerical results. For the prescribed expansion of the heart, FEM gives the pressure distribution at the interface between the 3D-MIM and the heart. The average pressure is then obtained over the contact area between the 3D-MIM and the heart, i.e. the ventricles of the heart as in the experiment, as shown in Fig. 3.2a.

The pressure: The part of the heart that is covered by the 3D-MIM (Fig. 3.2a) is approximately a partial axisymmetric ellipsoid with the lengths $a$ and $b$ of semi-principal axes, as shown in Fig. 3.6. The 3D-MIM on the heart surface is modeled as a membrane, which deforms from $Z^2/a^2 + R^2/b^2 = 1$ when being fabricated on the model to $z^2/[z^2 + r^2] = 1$ due to the linear expansion $\varepsilon$ of the heart, where ($Z,$
R) and \((z, r) = [(1 + \varepsilon)Z, (1 + \varepsilon)R]\) are axial and radial coordinates of the 3D-MIM without and with expansion in the axisymmetric coordinates, respectively. The plane stress state of the 3D-MIM with biaxial linear strain \(\varepsilon\) gives the biaxial stress as \(E \varepsilon/(1 - \nu)\), where \(E\) and \(\nu\) are the Young’s modulus and the Poisson’s ratio of the 3D-MIM, respectively. The membrane force, accounting for the change of length due to linear expansion, is

\[
T = \frac{Et \varepsilon}{(1 - \nu)(1 + \varepsilon)},
\]

where \(t\) is the thickness of the 3D-MIM. For a planar curve \(r = r(z)\), the principal curvature along the meridional direction is

\[
-\left(\frac{dr^2}{dz^2}\right)\left[1 + \left(\frac{dr}{dz}\right)^2\right]^{\frac{3}{2}}
\]

at any point \((z, r)\) on the surface. The other principal curvature along the circumferential direction is given by

\[
r \sqrt{1 + \left(\frac{dr}{dz}\right)^2}.
\]

For \(z = (1 + \varepsilon)Z\) and \(r = (1 + \varepsilon)R\), the two principal curvatures are given by

\[
\begin{align*}
\kappa_1 &= \frac{a^4 b}{(1 + \varepsilon)(a^4 - a^2 X^2 + b^2 X^2)^{\frac{3}{2}}} \\
\kappa_2 &= \frac{a^2}{(1 + \varepsilon)b\sqrt{a^4 - a^2 X^2 + b^2 X^2}}
\end{align*}
\]

The pressure on the heart is obtained in terms of the membrane tension and curvatures as in Ref. 33.

\[
P = T (\kappa_1 + \kappa_2).
\]

Its average over the part of \((Z_o \leq Z \leq a, \text{ Fig. 3.6a})\) of the ellipsoid surface that is in contact with the heart is by
\[ P_{\text{average}} = \frac{\int_{z_{0}}^{a} P \cdot 2\pi R \sqrt{1 + \left( \frac{dR}{dZ} \right)^2} dZ}{\int_{z_{0}}^{a} 2\pi R \sqrt{1 + \left( \frac{dR}{dZ} \right)^2} dZ} . \quad (5) \]

This gives Eq. (1) in the main text, and

\[ C = \frac{\int_{z_{0}}^{a} \frac{a^2 \left[ (a^2 + b^2) a^2 - (a^2 - b^2) Z^2 \right]}{b \left( a^4 - a^2 Z^2 + b^2 Z^2 \right)^{3/2}} R \sqrt{1 + \left( \frac{dR}{dZ} \right)^2} dZ}{\int_{z_{0}}^{a} R \sqrt{1 + \left( \frac{dR}{dZ} \right)^2} dZ} . \quad (6) \]

For \( a = 15 \text{ mm}, \ b = 10 \text{ mm} \) and \( X_0 = -5.5 \text{ mm} \), which best fit the geometric model of the heart, the average pressure in Eq. (1) agrees well with the 3D FEM results, as shown in Fig. 3.2b.

The analysis above does not account for the effect of electronic devices on the pressure between the 3D-MIM and heart. Such an effect can be estimated from Eq. (1) by replacing the tensile stiffness \( E_t \) of the 3D-MIM with the effective tensile stiffness of the 3D-MIM with the electronic devices. The inset in Fig. 3.6b shows an electronic device on a sheet of the membrane material (62.8x24.3x0.15 mm\(^3\)), consisting of the interconnects and electrodes. All of the interconnects consist of the Au: 120nm /Cr: 2nm composite layer sandwiched by 1.2 µm-thick polyimide (PI) layers on each side. The cross section of the electrodes is similar to that of interconnects but without the top 1.2µm-thick PI layer to expose Au. The sheet is modeled by the 8-node solid element C3D8R, and interconnects and electrodes are modeled by the 4-node shell element S4R in ABAQUS, respectively. FEM gives its tensile stiffness to be approximately 1.5 times that without the electronic devices, as shown in Fig. 3.6b.
Animal Experiments. Experiments were conducted in accordance with the ethical guidelines of the National Institutes of Health and with the approval of the Institutional Animal Care and Use Committee of Washington University in St Louis. Briefly the heart is removed via a thoracotomy and a cannula is placed in the aorta to allow retrograde perfusion of oxygenated Tyrode’s solution. The perfusion mimics the electrolyte balance within the animal and provides an energy substrate for the heart to continue to function normally from an electrical perspective. The heart is submerged in a perfusion chamber maintained at 37°C with a pH in the range of 7.35-7.45, controlled by oxygen flow. The optical signals of transmembrane potential (V_m) and calcium transients (CaT) rely on the collection of fluorescent signals from a potentiometric dye (di-4 ANEPPS or RH-237) or calcium indicator (Rhod-2a) added to the perfusate with a CMOS camera; when needed to avoid motion artifacts an excitation-contraction uncoupler (Blebbistatin) is also added to the perfusate. Fig. 3.20 illustrates representative experimental settings.

Data acquisition and processing. Electrophysiology: The electrical signals are recorded from the Au electrodes on the 3D-MIMs with a 240-channel unipolar electrogram acquisition system (Astrocard, Boston) and a custom-built interface. Both the optical and electrical signals are collected at a sampling frequency of 1 kHz, aligned with a trigger TTL pulse and post-processed separately in custom MATLAB software. Post-processing: The electrical signals acquired from the 3D-MIMs are first filtered with a 60 Hz notch filter internal to the acquisition software, then the electrophysiological parameter of interest activation time is calculated (Fig. 3.3c) and aligned to the spatial coordinates of the electrodes based on the optical background file. The optical signals are binned, filtered and normalized as previously described. A spatial 3x3 binning filter is applied, as well as a
100 Hz low pass digital filter, and the amplitude of the fractional fluorescence is normalized to between 0 and 1 for each pixel’s temporal sequence. The electrophysiological parameters are calculated for the complete field of view. To create the spatial maps, the activation times are interpolated using MATLAB’s internal function for cubic interpolation of scattered data. The optical map is also sampled at the coordinates of the electrodes and the same interpolation method is applied to compare the full resolution optical pattern with the sampled optical map and the electrical map.

pH data: pH data were acquired using measurement of open circuit potential of each sensor reference to an Ag/AgCl electrode, using Gamry Reference 600 potentiostat. A custom made relay system was used for multiplexing.

Temperature and strain: Data for temperature and strain sensors is acquired with measurements of resistance of each sensor using a custom built system based on National Instruments PXI-6289 board. The resistance of each of the 16 sensors is recorded simultaneously with a 160 μA probe current, a 16-bit A/D converter and a 15 ms sampling period at each sensor.

3.7 References


3.8 Figures

Figure 3.1. 3D-MIMs for spatiotemporal measurement and stimulation across the entire epicardial surface. (a) Graphical depiction of the key steps in device design and fabrication. Scale bar: 2 cm. (b) Images of a representative 3D multifunctional
(Figure 3.1 cont.) integumentary membrane (3D-MIM) integrated on a Langendorff-perfused rabbit heart. The white arrows highlight various function elements in this system. The electronics can cover both anterior and posterior surfaces of the heart (inset). Scale bars: 6 mm. (c) Magnified views of the functional elements in conformal contact with the epicardium. The images are recorded from the back side of the devices. Scale bars: 500 μm.
Figure 3.2. Analysis of pressures on the epicardium associated with integration of a 3D-MIM. (a) Calculated pressure distribution induced by a device with total thickness of 150 μm and effective Young’s modulus of 60 kPa under various conditions of volume expansion of a heart geometry. (b) FEM and analytical results of average pressure as functions of volume expansion (left), thickness (middle) and Young’s modulus (right) of the membrane.
Figure 3.3. High-density electrical mapping. (a) Representative optical and electrical signals acquired simultaneously from the corresponding numbered electrode locations on a Langendorff-perfused rabbit heart. Scale bar: 7 mm. (b) Top: schematic illustration of a
(Figure 3.3 cont.) representative optical action potential (OAP), unipolar electrogram (EG) and position of the activation time. Bottom: correlation of electrical and optical activation times for hearts tested in a variety of states. (c) Interpolated spatial activation maps determined from the electrical and optical measurements. Top: heart paced by the red pair of electrodes on the membrane. Bottom: sinus rhythm. (d) 3D mapping of electrical signaling from both the anterior and posterior surfaces of the heart. Interpolated spatial maps of electrical activation time are projected on a representative rabbit heart geometry, for purposes of visualization. Scale bar: 7 mm.
Figure 3.4. High-density pH and optical mapping of transmembrane potential and calcium transients. (a) 3D-MIM with pH sensors array integrated on a Langendorff-perfused rabbit heart with 2 pH sensors highlighted and values displayed in (b). Scale bar: 7 mm. (b) Temporal change in pH during 30 minutes of no-flow ischemia followed by 30
Three times starred as $t_1$, $t_2$, and $t_3$ correspond to spatial pH maps in (d-f). (c) Representative far-field ECG during baseline and reperfusion induced VT. (d-f) pH map of 32 sensors (left), representative transmembrane potential and calcium transient signals (middle), and APD70—CaT70 maps (right) at baseline (d), 10 minutes of no-flow ischemia (e), and 20 minutes of reperfusion (f). The results provide maps of the anterior-posterior LV. The $V_m$ and CaT are taken from the same pixel, but the location may vary slightly due to shrinkage of the heart during no-flow ischemia. White circles denote pH sensors positions. VT, ventricular tachycardia; $V_m$, transmembrane potential; CaT, calcium transient; APD70, action potential duration at 70% repolarization; CaT70, calcium transient duration at 70% relaxation.
Figure 3.5. Temperature and strain sensing combined with imaging using integrated μ-ILEDs. (a) Application of a 3D-MIM for temperature monitoring during cold perfusion. Left: image of a 3D-MIM with 4 x 4 temperature sensors array integrated on a Langendorff-
(Figure 3.5 cont.) Perfused rabbit heart. Middle: temperature recordings from a representative sensor illustrated in the left inset. Right: temperature maps at representative time points in the middle inset with corresponding heart rate calculated from ECG. Each pixel in the color map corresponds to recording from one temperature sensor. Scale bar: 1 cm. (b) Temperature measurements during an ablation experiment. Positions of the sensors array and cautery pen are shown in the left inset. Temperature map during ablation (upper right) and recordings from representative sensors (bottom right) are shown respectively. Scale bar: 7 mm. (c) Responses of a Si strain sensor under representative physiological conditions, compared with simultaneous ECG recordings. (d) Left: image of a 3D-MIM with μ-ILEDs array in optical mapping experiments. Inset shows a magnified view of area around a representative μ-ILED. Right: comparison of optical signals from a representative pixel (blue dot on the left inset) recorded during excitation using μ-ILEDs on 3D-MIM and external optical excitation, respectively. Scale bar: 3 mm.
Figure 3.6. Mechanical analysis of the devices. (a) Schematic illustration of the partial axisymmetric ellipsoid with the lengths $a$ and $b$ of semi-principal axes for the analytic
(Figure 3.6 cont.) model. (b) The comparison of the stiffness of the 3D-MIM with and without electronic devices along two directions.
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(Figure 3.7 cont.) need to be investigated further. Error bars denote standard deviations. 

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CHAPTER 4

MATERIALS AND FRACTAL DESIGNS FOR 3D MULTIFUNCTIONAL INTEGUMENTARY MEMBRANES WITH CAPABILITIES IN CARDIAC ELECTROOTHERAPY

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4.1 Introduction

Cardiac electrotherapy involves application of electrical potentials or currents to treat arrhythmias. Various modes range from use of electrical pulses to initiate synchronous beating, known as pacing, strong electrical shocks to reset fibrillatory conduction, known as defibrillation, and radio frequency (RF) electric currents to ablate cardiac tissue to disrupt abnormal focal sources or circuits of propagation. Such electrotherapies can be delivered using intravenous leads or catheters placed directly on the cardiac tissue, subcutaneous leads implanted under the skin, or using electrode patches externally mounted on the skin. These systems play critically important roles as clinical delivery paths for the therapeutic current. Physical constraints, however, limit the nature of the interfaces between the cardiac structures and the electrodes. A trade-off exists, however, between spatial control of the electrode location with respect to the local anatomy and large simultaneous coverage of the tissue. An RF catheter provides precise access to anatomical regions but can only make a single point of contact and burn a small mass of tissue at a time. Defibrillation vectors simultaneously excite a large mass of tissue but there is limited flexibility in their position with respect to the anatomy. Additionally, no currently available
clinical method can provide simultaneous electrotherapy with spatiotemporal mapping of physiological parameters for feedback control. One consequence is that defibrillation strategies have remained relatively stagnant in terms of versatility in the way in which energy is delivered. The high voltage shocks that are used in conventional procedures can be extremely painful and they limit the battery life of implantable systems.\textsuperscript{1} A promising direction for advanced low energy cardiac electrotherapy couples feedback-controlled, targeted defibrillation techniques with greatly reduced voltage and energy requirements.\textsuperscript{2-5} Multifunctional, conformal platforms of electrodes that can integrate over large areas of cardiac structures enable unusual schemes toward this goal, otherwise inhibited by traditional implantable lead-based delivery paths.

Emerging classes of materials and mechanics concepts in the field of stretchable electronics create new opportunities for integrating high performance electronics with the human body, its organs and various tissues.\textsuperscript{6-12} Recently described devices, referred to as 3D multifunctional integumentary membranes (3D-MIM), provide conformal electronic platforms that interface with the full 3D geometry of the epicardium.\textsuperscript{13} Here, 3D imaging and printing techniques enable organ-specific geometric designs in the supporting membranes. High performance electronic materials, interconnect structures and sensors mount on this platform to yield various spatio-temporal mapping and stimulation capabilities. The results presented in the following expand on these concepts to demonstrate 3D-MIM devices configured for cardiac electrotherapy. Here, ideas in fractal geometry yield compliant, large area low impedance electrodes for electrical stimulation in designs that do not compromise the physical stretchability or the low effective modulus of the overall system. Advanced electrodes materials, including nanotextured platinum-
iridium (Pt-Ir) alloys and poly(3,4-ethylenedioxythiophene): poly(styrene sulfonate) (PEDOT:PSS) integrate naturally, to enable low impedance interfaces that are well suited both for delivering electrical pulses and for sensing intrinsic electrophysiology. These constructs, particularly when co-integrated with high performance sensors, yield versatile platforms for cardiac electrotherapy, of relevance to both basic research and clinical applications. Experiments on in vitro Langendorff-perfused rabbit hearts demonstrate the operational capabilities of these systems.

4.2 Results and Discussion

The core component of the devices reported here is an array of 8 electrodes distributed around the circumference of the heart (Figure 4.1(a) and (b)). These electrodes provide direct interfaces for delivering spatially and temporally programmed electrical stimulation across a large area of the epicardium. A conformal interface follows from the use of a thin, low modulus, 3D membrane that is formed in a geometry that matches the epicardial surface, using techniques reported recently.\textsuperscript{13} Briefly, 3D imaging and printing techniques render solid models that correspond to the targeted heart. Components for sensors and actuators, prefabricated in ultrathin configurations and interconnected by filamentary serpentine traces on planar substrates, are then transferred and temporarily mounted onto the surface of the 3D model. A thin, soft silicone elastomer (~100 µm) cast and cured on this model serves as the 3D substrate for the active components. A flexible cable (Elform) provides electrical connection to external hardware. Electrochemical approaches can be employed after these fabrication steps to modify the surfaces of the electrodes. Figure 4.1(a) and (b) show a representative device integrated on a Langendorff-perfused rabbit heart.
The active and passive components maintain conformal contact with the cardiac tissue across the entire surface of the epicardium (Figure 4.1(b)), throughout the natural cycles of beating.

Figure 4.1(c) shows the materials components and illustrates a general integration scheme for functional elements of the device. A silicone elastomer (Ecoflex, Smooth-on) with low elastic modulus (~60 kPa) serves as the mechanical support for the active components. This non-conductive substrate may also help contain the electrotherapy to within the boundaries of the membrane, which could potentially reduce pain associated with high-voltage shocks and improve the efficiency of defibrillation. A co-integrated array of resistive temperature sensors based on Au traces (15 µm in width and 70 nm in thickness) yields information useful for monitoring ablation therapy. Depending on application requirements, various microfabricated sensors and actuators including high performance semiconductor devices can be included as well, integrated using the methods of transfer printing.13 Thin layers of Au (300 nm) and Ti (5 nm) serve as interconnects as well as conductive surfaces for electrode deposition and processing described next. Polyimide (PI) layers (1.2 µm) provide electrical insulation. Low-impedance coatings of nanotextured Pt-Ir alloys or PEDOT:PSS can be electrodeposited to yield high quality electrical interfaces.

Fractal design concepts for the electrodes enable large area coverage and high filling fraction for electrically active surfaces, suitable for generating electric fields across cardiac tissue, but without compromising stretchability and compliance.14 Here, the pattern for each electrode exploits a 2nd order iteration of the Greek cross fractal motif, with serpentine traces that fill a rectangular area with dimension of 14.5 mm x 2.5 mm. Serpentines with widths of 100 µm result in a filling fraction of 44%, thereby providing 14 mm² of
geometrical surface area for each electrode. By comparison to previously reported 3D-MIM electrodes, the present configuration increases the surface area by a factor of ~14 and increases the overall dimension (defined by the area of the perimeter of the electrode structure) by a factor of ~36. The Greek cross involves a high degree of geometrical connectivity, to reduce the electrical resistance and provide a high degree of tolerance to defects. An additional benefit of this design relates to the non-uniform distribution of current on the electrode surfaces, where additional charge distributes at the electrode edges. The unique layouts of these fractal geometries increases the ratio of the electrode-insulation edge length to the geometric surface area of the electrode, when compared to a conventional electrode of equivalent geometric area. It is well understood that current at an electrochemical electrode interface is preferentially distributed at the electrode-insulation edges.\textsuperscript{15-17} This observation suggests that a fractal electrode of equivalent geometric area to a conventional electrode design should transfer current more efficiently from the electrode to the tissue. These improvements are particularly beneficial to the development of low power systems.

The mechanics of these structures are also critically important. Finite element analysis (FEA) illuminates the response of the fractal electrodes to applied strains, throughout a range associated with 3D integration and operation on the surface of a beating heart. As shown in Supplementary Figure 4.5, the effective modulus of the fractal electrode element is ~120 kPa, and it can accommodate 15% stretching in either the vertical or horizontal direction before reaching a regime of plastic deformation. By comparison, the intrinsic modulus and yield strain of the constituent metals are ~100 GPa and ~0.3%, respectively. The overall mechanical behavior of the integrated device must meet two
requirements: (a) sufficient stretchability for the device to allow deformations associated with contraction and relaxing of the heart muscle, and (b) minimal force exerted by the device on structures of the epicardial surface. Finite element analysis (FEA) in combination with uniaxial and biaxial stretching experiments reveal the geometry change, strain distribution, and effective modulus of the device, as parameters that determine the ability to meet these two requirements. Figure 4.2(a-c) display the device geometry and strain distribution in the undeformed state, with 20% uniaxial stretching and with 15% biaxial stretching, respectively. The uniaxial stretch is in the horizontal direction, corresponding to the atrioventricular plane, which makes the largest contribution to total heart volume change associated with diastole/systole cardiac cycles. As shown in Figure 4.2(b), the resulting strain is accommodated by deformation of the soft elastomer substrate and buckling of the serpentine features. The maximum principal strain obtained by FEA, shown in Figure 4.2(b) (also Figure 4.6), is less than 0.3%, which is within the elastic regime for the metal and is far less than the fracture strain for all constituent materials (Ti, Au, Pt-Ir, polymer). Figure 4.2(c) and Figure 4.7 display similar characteristics for 15% biaxial stretching. These results suggest that the device can withstand the mounting process as well as the contraction and relaxation of the heart muscles, which result in 10%-15% of tensile deformation.

The second requirement demands minimal constraint on the heart, which is equivalent to minimizing the effective modulus of the device to reduce the average pressure that it exerts on the heart. Figure 4.2(d) shows the linear relationship between the stress and strain for the elastomer membrane and the 3D-MIM (i.e. membrane with interconnected devices). The effective modulus (slope in Figure 4.2(d)) is dominated by
the silicone membrane (~150 µm in thickness, with modulus ~60 kPa). The modulus for the 3D-MIM is only slightly larger, i.e. 71 kPa (horizontal stretching) and 74 kPa (vertical stretching). The calculated average pressure associated with integration of the device on the heart in its diastolic state (145% of the contracted volume) is ~273 Pa (Figure 4.8), which is similar to the pericardial pressure under normal physiological states and well below the values associated with pericardial constraint.19-21 These results indicate that the device is unlikely to cause restrictive impact on the intrinsic cardiac cycles, consistent with all of our experimental observations.

Reducing the electrochemical impedance associated with the interface between the electrodes and the cardiac tissue improves the signal-to-noise ratio (SNR) for recording biopotentials and lowers the power consumption for electrical stimulation.17 Lowering the impedance also enables reductions in electrode size without compromising charge capacitance, thereby allowing improved current focusing and reduced probability of pain or other side effects caused by aberrant current, high-voltage and high-energy electrical shocks. Pt-Ir alloys with nanoscale surface textures and PEDOT:PSS films represent two attractive options that are compatible with the platforms and fabrication procedures reported here. The former exploits recently reported electrochemical deposition methods22 to yield electrodes with enhanced mechanical and electrical properties compared to more conventional alternatives such as Pt, Pt black or standard Pt-Ir alloys. We implemented this technology as a surface modification to the previously described fractal electrodes. The morphology of the electrochemically modified electrodes appears in high-resolution scanning electron microscope (SEM) (Hitachi S4800) images in Figure 4.3(a) and (b). Characterization by electrochemical impedance spectroscopy (EIS) involves
measurements in phosphate buffered saline, using a commercial potentiostat (Gamry Reference 600) with integrated frequency analyzer (EIS 300). EIS data from fractal electrodes with and without the nano-textured Pt-Ir coating appear in Figure 4.3(d) and (f) in the form of Bode plots. Compared to the base Au electrode, the nano-textured Pt-Ir reduces the electrochemical impedance, |Z|, by $10^1$ at a frequency of 100 Hz. In addition to traditional metals, conducting polymers, such PEDOT:PSS and polypyrrole (PPy), can be considered.$^{23-25}$ Such materials exhibit low electrochemical impedance, mechanical flexibility and good bio-compatibility. Electro-polymerization provides a convenient method to form coatings of PEDOT:PSS on Au electrode surfaces. The deposition uses constant voltage mode (1.1 V with respect to Ag/AgCl reference electrode) in an aqueous solution containing 3,4-ethylenedioxythiophene (EDOT) (0.1 wt.%) and poly(sodium 4-styrenesulfonate) (PSSNa) (0.2 wt.%). The SEM image and EIS data of the coated electrode appear in Figure 4.3(c), (e) and (f). Similar to the nano-textured Pt-Ir alloy coating, the PEDOT:PSS reduces the electrochemical impedance dramatically in the low frequency range (1-1000 Hz), with a impedance magnitude of ~100 Ohm at 100 Hz. Impedances at high frequency for both the bare Au electrodes and the modified electrodes arise mostly from resistance of the solution and the series resistance of the interconnects. These selections for electrode materials are representative; many others can be considered, including Pt, Pt black and IrOx.$^{26-28}$

Animal experiments on Langendorff-perfused rabbit hearts demonstrate the multifunctional operation of the devices. Epicardial electrograms recorded with a PEDOT:PSS electrode (Figure 4.4(a)) display clear signals expected from the QRS and T features of the waveforms. To simulate defibrillation therapy, 50 V electrical shocks were
applied through each pair of electrodes (with Pt coated surfaces) integrated on the epicardium to form vectors that traverse the ventricles. Optically imaged action potentials from the epicardium demonstrate an immediate tissue response to the applied electrotherapy. Supporting Video shows the potential during a sinus beat followed by a shock induced beat to illustrate effective capture with a single vector. Figure 4.4(b) compares the activation pattern of the sinus beat with the shock-induced activation. The varying spatial response in activation time confirms effective capture. The virtual electrode pattern (VEP) induced by high voltage shocks is an important feature that determines the mechanism of successful electrotherapy.1 Figure 4.4(b) illustrates this characteristic pattern following a 50V shock delivered from the electrode highlighted in white. This simple demonstration establishes feasibility of creating stretchable thin film electrodes that can carry high voltage and large current shocks to the cardiac tissue. Repeated high-voltage shocks has the potential to induce corrosive degradation of the thin metal layers used in these electrodes. Further investigation will be necessary for chronic operation of this type of high-voltage electrotherapy.

A co-integrated array of 9 temperature sensors/heaters interfaces with the epicardial surface (Figure 4.1(a)) can be useful for monitoring ablation procedures. As an example, the center resistor in the array can act as a Joule heating element to elevate the surface temperature to 70.8 °C from a baseline of 38 °C, as a mimic of point contact ablation. The surrounding resistors then serve as sensors to measure the spatial distribution of the resulting rise in temperature. The experiments indeed show local temperature increases around the heater (Figure 4.4(d)), in agreement with the temperature field obtained by FEA (Supplementary Note and Table S1). The increase of temperature decays rapidly with
distance from the heater. The temperature change is \( \sim 1.7\,^\circ\text{C} \) at locations 4 mm from the heater, and only \( \sim 0.2\,^\circ\text{C} \) at 8.7 mm. This capability for characterizing spatial distributions of temperature can be helpful for guiding precise delivery of cardiac ablation therapy.

In summary, advanced designs and materials approaches provide capabilities for cardiac electrotherapy in an advanced 3D-MIM platform. Concepts in fractal geometry allow large area, conformal electrodes suitable for delivering cardiac electrical stimulation and for sensing cardiac electrical activity. Surface coating materials improve the electrochemical characteristics of the electrodes, in ways that are naturally compatible with the platform and its fabrication. Integrated arrays of sensors can be used to precisely monitor the electrotherapy and other forms of intervention. Animal experiments demonstrate the multifunctional operation of the devices. These results suggest routes for developing advanced tools with utility in both fundamental research and clinical application of cardiac electrotherapy.

4.3 Methods

*Processing for electrode coatings:* (1) Pt-Ir alloy with nanoscale surface textures: Electrochemical deposition of Pt-Ir used a mixed plating bath of ammonium hexachloroplatinate and hexachloroirridate. The details of the plating solution and deposition processes appear elsewhere.\(^{22}\) Immersing bare electrode surfaces in the plating bath followed by application of a controlled electrochemical potential (Gamry Reference 600 in a 3-electrode system) caused chemical reduction of metal ions in solution to metal alloys on the electrode surfaces. The deposition conditions define the morphology and composition of the resulting coatings. (2) PEDOT:PSS coatings: 0.2g of EDOT (Sigma-
Aldrich) added to 200 mL deionized water, stirred overnight for complete dissolution, followed by 0.4 g of PSSNa (Sigma-Aldrich) yielded the solution for electropolymerization. A potentiostat (Gamry Reference 600) controlled the electropolymerization processes in a 3-electrode configuration. Immersing the selected electrodes on the 3D-MIM into the solution and applying a constant voltage (1.1 V to Ag/AgCl reference electrode) for 10 minutes, formed the desired coating, as evidence by a change in the color of the electrode surface from gold to dark blue/black.

**Animal Experiments:** The animal study was approved by the Institutional Animal Care and Use Committee of Washington University School of Medicine. The heart was obtained from a New Zealand white rabbit, anesthetized with an intravenous injection of 80mg/kg of sodium pentobarbital and 400 USP units/kg of heparin before the heart was surgical explanted. The heart was then transferred to a tissue bath that maintained the temperature (37 ± 1 °C) and pH (7.4 ± 0.05) to mimic physiological conditions. The heart was retrogradely perfused under a constant pressure of 60-80 mm Hg with oxygenated Tyrode's solution (95%O₂/5%CO₂, NaCl 128.2 mM, CaCl 1.3 mM, KCl 4.7 mM, MgCl₂ 1.05 mM, NaH₂PO₄ 1.19 mM, NaHCO₃ 20.0 mM, Glucose 11.1 mM). The heart was mechanically uncoupled with 15 μM Blebbistatin (Cayman Chemical, Ann Arbor, MI) and perfused with a bolus injection of di-4 ANEPPS (Life Technologies, Grand Island, NY). The 3D-MIM was placed over the heart, positioned with 4 electrodes across the anterior surface and 4 electrodes on the posterior surface. The electrodes were connected in pairs to a custom defibrillator (Cardialen, Inc, St Louis, MO) that delivered 50-100 V biphasic truncated exponential pulses (phase 1 duration 6 ms, phase 2 duration 4 ms, phase 2 voltage was half the peak amplitude and opposite polarity voltage of phase 1). Optical action potentials were
recorded before, during, and after delivery of the shock from two CMOS cameras (SciMedia Ltd, Costa Mesa, Ca) with 520 nm excitation light through a long pass emission filter with a 650 nm cutoff. The data was then processed with custom Matlab software. The VEP was determined by evaluating the sign of the optical action potential derivative from the time of the shock until 10 ms past the shock.

**FEA simulation:** ABAQUS commercial software was used to study the elastic modulus and the stretchability of the device. The silicone elastomer (Ecoflex, ~150 µm in thickness, with modulus ~60 kPa) was modeled by the hexahedron element (C3D8R), while the device is modeled by the composite shell element (S4R). A submodel was established for the fractal electrode to obtain its effective mechanical properties. Figure 4.5 shows the stress-strain relation of the silicone elastomer with and without the fractal electrode. The modulus of silicone elastomer with the fractal electrode increases to 130 kPa for vertical stretching and 114 kPa for horizontal stretching. Figure 4.6 and Figure 4.7 show the deformation and strain distribution of the overall device subject to (0%, 5%, 10%, 15% and 20%) horizontal stretching and (0%, 5%, 10% and 15%) biaxial stretching, respectively. The optical image in Figure 4.6(a) agrees well with that obtained by FEA in Figure 4.6(b) for horizontal stretching. The maximum strain in the interconnect (Figure 4.6(c)), fractal electrode (Figure 4.6(d)) and sensor (Figure 4.6(e)) are all <0.3%. Figure 4.7 displays similar characteristics of the device subject to biaxial stretching.

FEA was used to study the distribution of contact pressure for a 3D-MIM (~150 µm thickness, and modulus ~74kPa from Figure 4.2d) wrapped around a heart. The volume change associated with integration of 3D-MIM was modeled by the thermally coupled shell
element (S3T). Figure 4.8 shows the contact pressure (a) in the unexpanded state and (b) 145% volume of the unexpanded state, which corresponds to the diastolic state of the heart.

FEA was used to study the temperature field associated with the operation of heater #5. The substrate (myocardium, ~4 mm in thickness, with thermal conductivity ~0.5 W/mK)\(^3\) was modeled by the heat transfer brick element (DC3D8), while the device was modeled by the heat transfer shell element (DS4). The ambient temperature is 38 °C, and the heater 5 was heated to 70.8 °C. Table S1 shows the average temperature for each of the 9 temperature sensor/heater array.

### 4.4 References


4.5 Figures

(a) Image of a representative device integrated on a Langendorff-perfused rabbit heart. White arrows highlight functional components. (b) Side view image. (c) Schematic exploded view illustration of device structures and functional components.

Figure 4.1. (a) Image of a representative device integrated on a Langendorff-perfused rabbit heart. White arrows highlight functional components. (b) Side view image. (c) Schematic exploded view illustration of device structures and functional components.
Figure 4.2. (a–c) Optical images (left) and FEA results of the distribution of maximum principal strain (right) of a representative device (a) in the undeformed state, (b) with 20% uniaxial stretching in the horizontal direction, and (c) with 15% biaxial stretching. The insets show magnified views of the fractal electrode. (d) FEA results of the stress-strain relation of the elastomer membrane and the 3D-MIM.
Figure 4.3. (a) SEM image of a fractal electrode. (b) SEM image of the surface of Pt-Ir alloy coating. (c) SEM image of the surface of PEDOT:PSS coating. (d) Bode magnitude plot of electrochemical impedance spectroscopy (EIS) data for Au base electrode and nano-textured Pt-Ir alloy coated electrode. (e) Bode magnitude plot of EIS data for Au base electrode and PEDOT:PSS coated electrode. (f) Bode phase plot of EIS data for Au base electrode, nano-textured Pt-Ir alloy coated electrode and PEDOT:PSS coated electrode.
Figure 4.4. (a) A representative epicardial electrogram recorded with a PEDOT:PSS electrode. (b) Activation maps created from optical signals on one side of the epicardium during a sinus beat (left) and immediately following a 50V shock (right) from a Langendorff-perfused rabbit heart. (c) Virtual electrode pattern and representative traces from the virtual anode and the virtual cathode illustrating the effect of a 50V shock applied across the heart from the device. The electrode used shown in the field of view is highlighted in white. (d) Left: Positions of the temperature sensors/heater (white boxes) and the steady-state temperature distribution on the epicardium obtained by FEA. Right: steady-state temperature recordings from each of the temperature sensors/heater by experiment.
Figure 4.5. FEA results for the stress-strain relation of the silicone elastomer with and without integrated fractal electrodes.
Figure 4.6. (a) Optical images and (b) FEA results for the device with up to 20% horizontal strain. The corresponding strain distribution in (c) interconnect, (d) fractal electrode and (e) sensor.
Figure 4.7. (a) Optical images and (b) FEA results for the device with up to 15% biaxial strain. The corresponding strain distribution in (c) interconnect, (d) fractal electrode and (e) sensor.
Figure 4.8. The contact pressure exerted on the heart by 3D-MIM for 145% of the contracted volume, which corresponds to the diastolic state of the heart.
Figure 4.9. Calibration data for the temperature sensors array.

Table 4.1. The average temperature on the 9 temperature sensor/heater array by FEA.

<table>
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<td>Sensor 3: 38.4°C</td>
<td>Sensor 6: 39.6°C</td>
<td>Sensor 9: 38.4°C</td>
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CHAPTER 5

CONCLUSIONS AND OUTLOOK

We presented a collection of materials and design concepts that enable 3D conformal electronic devices with advanced capabilities for multifunctional cardiac sensing and stimulation. Ideas for 3D fabrication and careful mechanical designs yield classes of devices with organ-specific geometries that can establish conformal biotic/abiotic interfaces without causing restrictive impact to the cardiac tissues. A wide variety of electronic materials, ranging from semiconductor nanomembranes, electroactive polymers, soft conductive composite and nanotextured metallic coatings, are co-integrated in these platforms to generate multifunctional devices for electrical, thermal, mechanical, chemical and optical sensing and actuation. Development in fabrication techniques and optimization of device architectures allow systematic processing schemes to generate variety of multifunctional platforms. We theoretically illuminated the underlying mechanics associated with design and operation of these types of devices. Animal experiments demonstrated the operational capabilities.

The efforts describe in this thesis suggest routes for fabricating active and passive electronic materials in 3D conformal format, suitable for biomedical applications. The resulting device platforms represent a significant step forward towards building advanced electronic tools for diagnosis and therapies, which are of broad interest for fundamental research in life sciences, physiology and technological innovation in bioengineering and medicine. It should be noted that, however, that the current versions have not been ready for real clinical applications. Further developments in several critical aspects, including wireless data communication and power transmission, long-term operation efficacy,
optimization of physical format for surgical maneuverability, will be necessary to fully exploit the possibilities of 3D conformal electronics in clinical medicine. On the other hand, new materials and mechanics concept can be also helpful to extend the capabilities for 3D conformal electronics. One promising direction is related to recent development in physically transient electronics. By using novel biodegradable electronic materials and structures, we can create new operational modes that are enabled by dissolution of the constituent device structures, which can be important for implantable medical devices. Overall, the works reported here represent a promising start for developing advanced 3D conformal electronic tools for biomedical applications.