

Special Session Title:

Micro- and Nano-Sensors and Actuators for Cellular and Molecular Biology

Special Session Organizer Name & Affiliation:

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Gerd Grau, York University

Special Session Speaker Name & Affiliation 6:

Theme:

- 01. Biomedical Signal Processing
- 02. Biomedical Imaging and Image Processing
- 03. Micro/Nano-bioengineering; Cellular/Tissue Engineering & ...
- 04. Computational Systems & Synthetic Biology; Multiscale
- 05. Cardiovascular and Respiratory Systems Engineering
- 06. Neural and Rehabilitation Engineering
- 07. Biomedical Sensors and Wearable Systems
- 08. Biorobotics and Biomechanics
- 09. Therapeutic & Diagnostic Systems and Technologies
- 10. Biomedical & Health Informatics
- 11. Biomedical Engineering Education and Society
- 12. Translational Engineering for Healthcare Innovation and

Special Session Synopsis— Max 2000 Characters

Recent advances in micro-and nanotechnologies have attracted the attentions for the development of highly accurate sensors and actuators suitable for bioengineering applications. In this session, three talks (third and second) will be focused on micro/nano sensing modalities for detection of biomarkers and DNA molecules. Three other talks will be focused on actuation/manufacturing methods dedicated on bioengineering applications. The details can be seen in the following pages.

Development of a Mist-based Ionic Crosslinking Printhead for 3D Bioprinting

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Abstract— This presentation describes a 3D bioprinting system that enables improved printability of alginate scaffolds by introducing calcium chloride (CaCl_2) as a controlled flow of fine mist droplets. With this method, the filament size can be easily controlled by modifying certain printing parameters. This system produces constructs that exhibit excellent layer adhesion and that are compatible with living cells.

I. INTRODUCTION

Three-dimensional constructs, known as scaffolds, mimic the characteristics of a natural extracellular matrix to provide a foundation for tissue regeneration [1]. Scaffolds are commonly constructed using hydrogels for their high biocompatibility; however, the printability of hydrogels is typically inadequate for producing quality 3D scaffolds. Sodium alginate is a popular hydrogel used for 3D bioprinting; it must, however, be crosslinked with CaCl_2 to form a solid, printable filament.

In previous developments, CaCl_2 is introduced as a liquid sheath flow, which has proven challenging to remove without disrupting the printed structure [2]. Moreover, excess liquid CaCl_2 results in over-gelation of the filament and poor layer adhesion. This development introduces CaCl_2 as a flow of fine mist droplets to crosslink sodium alginate within a novel printhead attachment. In comparison to previous developments, this system offers an improved level of printability of biocompatible hydrogel scaffolds.

II. METHODS

Fine CaCl_2 mist droplets are generated using an ultrasonic atomizer and then delivered to a printhead attachment fitted onto a syringe. The printhead directs the mist flow such that it surrounds the extruded stream of sodium alginate; furthermore, it features a channel to remove excess mist after crosslinking (Figure 1a). A pair of pneumatic pumps (750 mL/min, 3 L/min) enable the delivery and removal, respectively, of mist droplets to and from the printhead. A commercial 3D bioprinter (Inkredible+, Cellink) supports this system: the dispensing syringe is mounted on the printer and is positioned along the x - and y -axes, while a deposition stage below is positioned in the z -direction (Figure 1b).

III. RESULTS AND DISCUSSION

The mist flow rate affects the gelation rate of the filament. Increasing the flowrate results in the over-gelated, non-uniform filament, while decreasing the flowrate

provides little to no crosslinking. Several multi-layer structures are fabricated with high levels of printability and layer adhesion (Figures 2a and 2b) by adjusting the mist flowrate properly through trial and error. The results of a cytotoxicity assay show that scaffolds printed with three sodium alginate concentrations are compatible with living neuron cells.

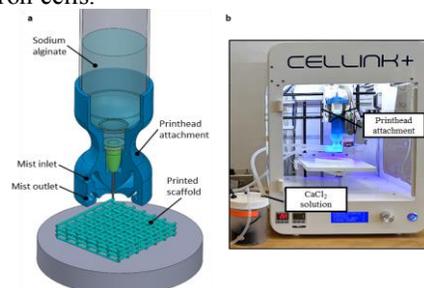


Figure 1. a) Printhead attachment mounted upon syringe barrel containing sodium alginate solution. b) 3D bioprinter with printhead attachment and mist generation and delivery system attached.

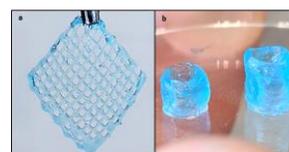


Figure 2. a) A sample of 2-layer scaffold printed with 5 wt% sodium alginate. b) Two cylindrical constructs printed with 7 wt% sodium alginate.

IV. CONCLUSION

The described 3D bioprinting development successfully prints multi-layer alginate constructs that exhibit excellent layer adhesion and that are shown to be biocompatible. With this system, the printability of 3D scaffolds for tissue regeneration or drug discovery is improved.

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First-Principles Modeling for DNA Bases via Monolayer MoS₂ Sensor with a Nanopore

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Abstract— Based on density functional theory and non-equilibrium Green's function, we present a novel monolayer MoS₂ sensor with gold electrodes where a nanopore is placed in the middle of the MoS₂ sheet which enables quick, selective, and sensitive DNA nucleobase detection.

I. INTRODUCTION

MoS₂ monolayer has intense photoluminescence (PL) emission due to the transition from the bulk material form with indirect bandgap to single-layer form with direct bandgap. Monolayer MoS₂ can be utilized to detect DNA bases sequence due to its wide surface area enabling biomolecules adsorption. Currently, nanomaterials such as graphene and MoS₂ are utilized to develop novel sensors for DNA and biomolecular detection. Haung et al. developed a novel sensor of a monolayer of MoS₂ sheets to detect DNA [1]. Loan et al. designed a sensor of graphene/ MoS₂ heterostructural films to detect DNA hybridization [2]. Ke et al. fabricated a single layer of MoS₂ modified with gold (Au) nanoparticles for DNA hybridization detection [3].

II. METHODS

The MoS₂ sensor is composed of three regions: the right and left gold electrodes and the central MoS₂ channel where 13.25 Å nanopore is placed in the middle of the channel. The gold electrodes are metallic while the MoS₂ channel is semiconducting. The finite bias voltage is fixed among the left and right electrodes as 0.5 V and - 0.5 V. The width of the MoS₂ channel is 18.96 Å while the channel length is 38.32 Å. The gold electrodes length is 14.2 Å. The sensor geometry optimization is performed using density functional theory (ATK-DFT). The exchange-correlation functional is evaluated by the density functional theory within the local density approximation (LDA) limits. The DNA nucleobases and the MoS₂ sensor are relaxed until the maximum atomic force is lower than 0.05 eV/Å. A grid mesh cut off the energy of 75 Hartree and 9×9×1 k-points are selected for the Brillouin zone integration.

Note that the equation is centered using a center tab stop. Be sure that the symbols in your equation have been defined before or immediately following the equation.

III. RESULTS

The MoS₂ sensor transmission spectrum is generated by 200 sampling points in the energy range 2 to -2 eV and 1, 1, 50 sampling points in the Brillouin zone integration. Fig. 1. is produced by NEGF+DFT simulations where each of the DNA nucleobases is placed within the MoS₂ nanopore

and the transverse current is measured at 1 V bias voltage at room temperature (300 K).

Each DNA nucleobase has a unique chemical and electronic structure leading to a unique electronic signature for each base. Fig. 1. shows that the different DNA bases (A, G, C, T) produce different currents and that pyrimidine bases including Cytosine and Thymine results in lower current than purine bases including Adenine and Guanine.

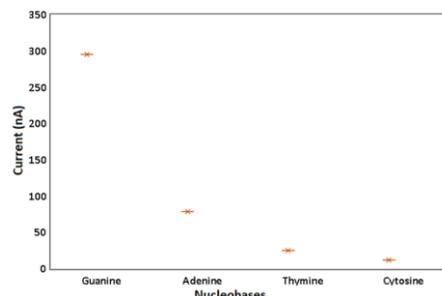


Fig. 1. The room temperature current of the MoS₂ sensor when each of the four DNA bases (A, C, G, T) is placed within the 13.25 Å nanopore.

Moreover, our simulation results show that each DNA nucleobase has a unique chemical and electronic structure leading to a unique electronic signature for each base.

IV. DISCUSSION & CONCLUSION

In this work, a novel monolayer MoS₂ sensor with gold electrodes, where a nanopore is placed in the middle of the MoS₂ sheet, has been presented and investigated as a DNA sequencer. It was found that each of the DNA bases results in a unique current signature due to its unique electronic and chemical structure. Moreover, it was noticed that purine bases have a higher current than pyrimidine bases. This work would lead to an inexpensive and efficient DNA sequencer.

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Continuous, multiplexed monitoring of biomarkers in live animal

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I. INTRODUCTION

Molecular detection methods are the techniques used in clinical diagnostics to detect a molecule that is a marker of disease or risk in a sample taken from a patient. The methods use diverse *in-vitro* biological assays, such as PCR (polymerase chain reaction)¹ to detect nucleic acids and ELISA (enzyme-linked immunosorbent assay)² to quantify small concentrations of proteins and antibodies. Over the past decade, many lab-on-a-chip (LOC) devices have emerged with the aim of simplifying and improving the performance of molecular diagnostics. These biosensor platforms are capable of sensitive, specific, and fast detection of biomolecules; however, a major limitation of most of these sensors is that they generally only perform single and end time-point measurements and phlebotomy (blood withdraw) and testing must be repeated for additional measurements. A continuous monitoring device that can constantly measure the biomolecule levels and report on the individual patient's medical condition will address this issue. Such technology would enable early disease diagnosis for example, continuous monitoring of cardiac markers could predict an oncoming heart attack³ and measurements of chemokines could provide early warning for infection or autoimmune flare-ups⁴, thus leading to more effective treatment. It would also facilitate truly personalized medicine through continuous monitoring of individual patient conditions. It also allows physicians to tailor specific drug and medical treatments to an individuals' unique molecular and/or genetic profile.

II. METHODS

Real-time, continuous monitoring faces exceptional requirements and challenges (Table 1) and, to date, it has only been realized for a handful of biomarkers, such as glucose⁵, lactate⁶, heart rate variability (HRV)⁷, and electrolytes⁸ in the sweat. Unfortunately, the current technologies have not been successful in addressing the main limitations as listed in Table 2.

In response, we have developed a real-time biosensor in a miniaturized, microfluidic device platform that enables

Table 1. Main challenges facing real-time monitoring

1	• Constantly perform several analytical tasks with very small sample volume .
2	• Exhibit adequate sensitivity, specificity, and dynamic range in short timescale (minutes).
3	• Generalizable to various analytes.
4	• Perform multiplexed measurements.
5	• Implement as a point-of-care and bed-side platform.

Table 2. Review of current real-time biosensors

Marker	Detection mechanism	Comment	Challenge
Glucose	Electrochemical	• Enzyme catalysed	2, 3, 4
Lactate	Electrochemical	• Enzyme catalysed	2, 3, 4
Electrolyte	Electrical	• Flexible sweat sensor • (H ⁺ , Na ⁺ , K ⁺ , Cl ⁻) are measured.	1, 2, 3
HRV	Optical monitoring	• Based on optical properties of blood. • Connected to finger.	1, 2, 3, 4
Drug	Electrochemical	• Based on structural changes of a capture probe.	2, 4, 5

individual patient condition tracking. As a clinically relevant model, we showed that our platform enables continuous tracking of glucose and insulin in a live, diabetic rat model.

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Hybrid Microfluidic Electroporation Device: A Novel Platform for Oocyte Maturation's Studies

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INTRODUCTION AND METHODOLOGY AND RESULTS

The zebrafish is an excellent model organism due to its low maintenance cost, experimental versatility, and a similar genetic structure to humans, which includes genes related to human diseases (Howe et al. 2013). Moreover, the zebrafish follicle experiences rapid, extrauterine folliculogenesis and can be readily used as a target for genetic manipulation. The follicles are comprised of oocytes surrounded by follicular cell layers, which develop during growth and maturation stages (Clelland et al. 2009). These stages are largely regulated by the function of gonadotropins similarly to that of the human reproductive regulation system. Thus, the zebrafish serves as an attractive model for studying oogenesis and folliculogenesis (Elkouby et al. 2017; Zhao et al. 2015). Up to now, the role of regulatory hormones such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in oocyte development have been studied through exposure in a hormone-rich medium (Silva et al. 2018). Protein complexes (e.g. activin and inhibin) and gene inhibitors can also be delivered through injection of the zebrafish or microinjection into the follicle (Tan et al. 2009, Wu et al. 2000). In another attempt, the gonadotropin hormones added into the medium of extracted follicle cells and oocyte revealed their involvement in the regulation of oocyte maturation (Abramov et al. 2013). Despite the advantages of the above-mentioned molecular delivery methods, novel non-invasive technologies should be sought to deliver any dye, gene or hormone directly into zebrafish follicle. Indeed, the gene delivery into either the oocyte or follicular cells extracted from the follicle (e.g. Abramov et al. 2013) does not allow to study the interaction between the follicular cells and the oocyte during follicle development, and oocyte maturation cannot be observed. In this multidisciplinary research, we propose an efficient non-invasive, precise and controllable method to deliver various molecules into follicular cell layers or oocyte using electroporation and microfluidic techniques.

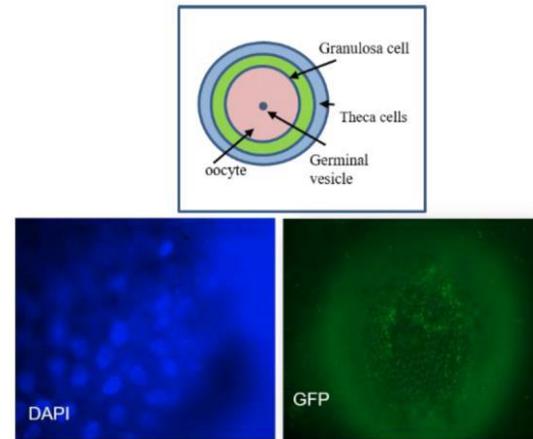


Fig. 1. (a) illustration of the follicle, fluorescent microscope image of follicular cells after the delivery of (a) DAPI, (b) GFP using electroporation.

Next Generation Sensory Systems for Medicine and Biology

Title: Molecular Detection of Nanopore
Signals

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Nanopore sensors provide exciting opportunities for the fine measurement of molecules at large scales and in minute platforms. They are already present in marketed DNA sequencing machines whose applicability spans both mobile and high-throughput measurement scenarios. But the quality of the raw measured signal is still greatly obscured by sensor and measurement apparatus limits. As a result, advanced measurement machinery and intense computing need to be applied in order to adequately reconstruct the interaction of nanopore sensors with their molecules-under-test. This talk outlines the current state of the art in this field, sensor behaviours, limits, and measurement techniques and the nonidealities associated therein. It then discusses means by which measured signals may be analyzed and organized into coherent information on molecular structure.

Fabrication of stretchable low-cost conductors for wearable electronics

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In order to create truly wearable biomedical sensors, electronics needs to conform to changes in the shape of the human body and become stretchable. A number of different stretchable conductors have been reported in the past; however, they often involve expensive nanomaterials or complex fabrication methods. Here, we will discuss our recent progress towards low-cost stretchable conductors for wearable applications. Dispenser printing is used to deposit and pattern a silver paste. Printed electronics does not require complex vacuum processes, high temperatures or photolithography and is well-suited to low-cost, large-area electronics on flexible substrates. Dispenser printing in particular is a relatively simple printing technique that requires low investment compared with other printing techniques. It is a digital printing method where patterns can be redesigned on the fly. We have studied the dispenser printing process to optimize pattern definition. Well-defined serpentine traces were printed to increase stretchability. They were embedded in stretchable PDMS substrates. The paste contains silver flakes, a polymer binder and a solvent. The flakes are micron-scale, which is significantly lower in cost than alternatives such as nanoparticles or nanowires. After curing, silver traces exhibit stretchability up to about 50% before cracks form. This can be further improved by optimizing the curing conditions. Lines that are cured at lower temperatures exhibit larger

stretchability exceeding 100%. There exists a trade-off between stretchability and resistivity as curing temperature is decreased. This trade-off can be alleviated by creating a hybrid double-layer structure of fully cured and partially cured silver where the fully cured layer carries the majority of the current and the partially cured layer bridges cracks in the fully cured layer. In summary, we will present a method to fabricate stretchable conductors in a simple and low-cost fashion.