Cell adhesion quantification by transmission surface plasmon resonance using nanostructured biosensing chips

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Abstract— **Tumor metastasis and the associated implications cause the major mortality of cancer patients. Moreover, the capability of cell adhesion onto the cellular matrix or endothelial cell is a good parameter for evaluating tumor metastasis potency. Nevertheless, there is no simple and rapid approach to assess the effects of compounds or proteins on the tumor cell adhesion or detachment. We have developed a label-free optical method based on surface plasmon resonance (SPR) on metal (Gold, Au, or Aluminum, Al) nanoslit array film for studying the influence of an anti-cancer drug or shear stress on cell adhesion, detachment, and mortality. The method is implemented using a microfluidic biochip capable of cell culturing and cell adhesion observation/quantification. The devices were used to evaluate the correlation between metastatic potency and adhesion of lung cancer and melanoma cell lines. Cell adhesion was determined by the metal nanoslit's transmission spectra bearing Fano resonance signals, which exhibited spectral changes when the cells bind to the nanoslit. The peak and dip of the Fano resonance spectrum reflected long- and short-range cellular changes, respectively, allowing us to detect and distinguish between focal adhesion and cell spreading simultaneously. The nanoslit-based biosensor chips were further used to evaluate the inhibitory effects of drugs on cancer cell spreading. We think the method will become a powerful tool for discovering anti-metastasis drugs.**

Solution-based facile antibiofouling coatings for biomedical implants and biosensors

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***Abstract*— Foreign body reaction and bacterial infection following biomaterial insertion can cause serious complications or signal loss for biomedical implants and biosensors. Antibiofouling coatings have received great attention as a solution to the problems, however, complicated and expensive coating methods hindered their practical applications. Herein, we developed super-antibiofouling surface easily applicable on complex structure and different materials used in medical devices via liquid-phase deposition of Lubricated Polydopamine/Perfluoropolymer (LPP) surface coating.**

I. INTRODUCTION

Implantable biomedical devices and biosensors have been widely adopted and developed for clinical for continuous monitoring of patients' health status. When the biomedical devices and biosensors are implanted, foreign body reaction occurs diminishing immune system, and the body becomes highly vulnerable to bacterial infection and complications. When bacteria adhere to the implants and forming impenetrable biofilm to antibiotics, removal and treatment require reoperation accompanied by pain and economic burden [1]. Also, fibrotic capsule due to immune response surrounds the implant hindering detection of bio-signals. Hence, anti-biofouling coating which could prevent adhesion of bacteria and immune-related proteins has been of great interest. However, the durability, and the complex fabrication systems limited its usage. Herein, we developed versatile anti-biofouling coating for biomedical devices including orthopedic implants, urethral catheter, and neural probe. The developed coating exhibits excellent durability and anti-biofouling property while being facile to be coated on any materials with complex shapes.

II. RESULTS

Briefly, the developed coating consists of 3 different layers. The first layer is polydopamine (PDA), which act as an adhesive between substrate and the perfluoropolymer (PFP) layer. The second layer is PFP, which makes its surface energy low, and have high chemical affinity to the lubricant. Then the medical grade slippery lubricant was infused to make surface highly repellent to biomolecules. All the fabrication process was done via liquid phase deposition allowing even 3D complex structures with different materials. In this study, Lubricant-infused Polydopamine-Perfluoropolymer (LPP) coating was applied on medical implants composed of different types of materials (i.e., orthopedic implants, urethral catheter, neural probe). Then, its contact angle was characterized after each deposition step to demonstrate the change in surface. Next, the cell adhesion was tested *in vitro* using NIH-3T3, and RAW-264.7 cells. Due to superior antibiofouling property of LPP coating, great difference in cell adhere was observed where almost no cells were adhered on LPP-coated surface. In the same manner, immune-response related proteins including fibrinogen and albumin was tested exhibiting the same results as cell adhesion test. Then, the developed coating was applied in biomedical implants such as orthopedic implant, Foley catheter, and neural probe in which is frequently exposed to the biomolecules, and anti-biofouling

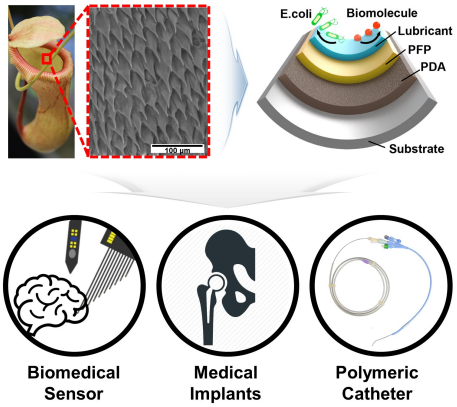

Figure 1: Schematics of the LPP coating, and its applications

is beneficial. Despite the coated implants being exposed to bacteria solution for three days, the biofilm was not found on its surface. The results demonstrate that the developed coating can be easily applied on complex shapes while exhibiting super antibiofouling, and antibacterial property.

III. DISCUSSION & CONCLUSION

The results demonstrate its great potential for clinical purposes, and biomedical biosensors where anti-biofouling coating is highly demanded to prevent biomolecule adhesion, and bacterial infection. It will be important to determine the functional lifetime of the coating in representative physiological conditions to validate it further. We hope this initial work will promote research in antibiofouling, and infection reducing coating not only for clinical usage, but also for biomedical biosensors where biofouling matters.

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Disposable Electrofluidic Pressure Sensor-Embedded Microfluidic Viscometer for Biomedical Applications

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***Abstract*— This paper reports a novel fully disposable electrofluidic pressure sensor-embedded microfluidic device for viscosity samples. The electrofluidic pressure sensor is constructed using ionic liquid-filled microfluidic channels, which can be seamlessly integrated with the microfluidic device for sample handling. The device possess great sensing linearity, temperature stability, and disposability to prevent cross contamination between biomedical samples. In this paper, the device is exploited to measure Newtonian, non-Newtonian, and blood samples for demonstration.**

I. INTRODUCTION

Viscosity is one of the most essential fluidic properties regulating fluidic behaviors, and it is a crucial factor for various biomedical applications. A number of microfluidic viscometer designs have been constructed in previous studies; however, many drawbacks, including: limitations for Newtonian fluids, limited shear rate ranges, temperature sensitivity, incapability for real-time monitoring, and complicated setup, make the devices impractical for routine measurements. In this paper, we develop a fully disposable and optically transparent microfluidic viscometer for biomedical applications. The device can be used for Newtonian and non-Newtonian fluid measurement under different temperatures and shear rates.

II. METHODS

The microfluidic viscometer developed in this paper consists of a glass substrate, a polydimethylsiloxane (PDMS)-made bottom microfluidic layer and top electrofluidic channel layer. An elastic PDMS membrane is sandwiched between the two layers. In the bottom microfluidic layer, hydrostatic pressure at the upstream is built up during the fluidic sample injection due to viscous force. By measuring the hydrostatic pressure at the upstream with the known flow rate and geometry of the channel, sample viscosity can be estimated at a specific shear rate.

In order to precisely measure the hydrostatic pressure, an embedded electrofluidic pressure sensor is designed in the top layer. A pressure transduction hole is fabricated near the inlet of the microfluidic channel, which is exploited to transfer hydrostatic pressure from bottom layer to top layer. Once the hydrostatic pressure deforms the elastic membrane through the pressure transduction hole, electrical resistance of an electrofluidic resistor aligned to the hole will be changed due to its cross-sectional area variation. To precisely measure the resistance change, Wheatstone bridge circuit architecture is exploited. The Wheatstone bridge circuit provides the sensor great sensing linearity and temperature stability [1]. Consequently, the hydrostatic pressure can be estimated by measuring the electrical voltage across the circuit, and the viscosity can be calculated based on fluid mechanics theories.

In the experiments, four types of fluids are analyzed. Water and glycerol solutions of different concentrations are exploited to demonstrate the viscosity measurement of Newtonian fluids. To demonstrate shear thinning property of non-Newtonian fluids, 1000 ppm xanthan gum solution is tested. In order to further demonstrate usage of the device for real biological samples, human whole blood with EDTA is tested under different temperatures.

III. RESULTS & DISCUSSION

The results successfully demonstrate that the developed microfluidic viscometer can successfully measurement the viscosities of Newtonian and non-Newtonian fluidic samples with relatively small volume (< 1 ml). The results also confirm the great disposability and different temperature operation capability of the viscometer for practical biomedical applications.

IV. CONCLUSION

A fully disposable microfluidic viscometer based on an embedded ionic liquid electrofluidic circuit pressure sensor is sdeveloped in this research. The device can be applied widely in biomedical applications where long-term and various temperature operations are required.

ACKNOWLEDGMENT

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High-Efficiency Light-Induced Circulating Tumor Cells Screening Biochip Prepared by 40.68 MHz VHFPECVD

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***Abstract*— In this study, the high-efficiency circulating tumor cells screening biochip using the nanocrystalline silicon (nc-Si:H) thin film prepared by 40.68-MHz very high-frequency plasma-enhanced chemical vapor deposition (VHFPECVD) is proposed. The quality, uniformity, and electrical properties of the prepared nc-Si:H thin films affect the performance parameters.**

I. INTRODUCTION

The use of dielectrophoresis (DEP)-based biochip technologies is rapidly increasing because DEP-based biochip technologies are fast, antibody free, highly accurate, label free, and cost efficient. Pohl et al. (1951) used a DEP-based technology to move particles for the first time [1].

The VHFPECVD has the following: such as a high deposition rate, low ion bombardment in a plasma chamber, reduced intrinsic stress of silicon films, and high thin film surface density, which subsequently provide a high-performance light-induced circulating tumor cells screening biochip.

II. METHODS

Fig. 1 shows the three-dimensional (3D) configuration of the proposed circulating tumor cells screening biochip. The biochip comprised an inlet for injecting a cell suspension and two outlets for collecting cancer cells and leukemia. Furthermore, two indium tin oxide (ITO) glass substrates were used as a base for producing an alternative-current (AC) electricity field in the biochip.

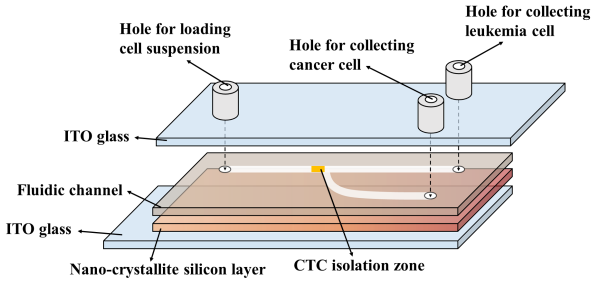

Figure 1. 3-D configuration of the proposed circulating tumor cells screening biochip.

III. RESULTS

Samples 1 (600 mTorr) and 2 (800 mTorr) had higher purities of 82% and 62% than sample 3, which was attributed to the low-light soaking resistivity and increased the photoelectric effect of silicon films [2]. Therefore, the reduction in the chamber pressure during VHFPECVD eliminated THP-1 leukocytes, which was helpful for improving the cancer-cell purity of the sample. High-purity cancer-cell isolation is crucial for the subsequent gene expression and biochemistry analyses. Moreover, the flow rate (1 μl min^{-1}) of the isolation process was higher than the currently available rate.

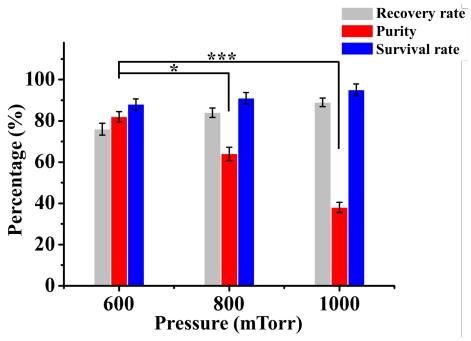

Figure 2. Biochips prepared by different chamber pressures (600, 800, and 1000 mTorr) have different effects on recovery rate, purity and survival rate of the circulating tumor cells screening.

IV. DISCUSSION & CONCLUSION

This study provides a potential study on the fields of circulating tumor cells screening, particularly for the circulating tumor cells in clinical trials.

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Impedimetric Measurement of 3D Cancer Cell Invasion Process

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***Abstract*— Quantitative analysis of cancer cell invasion process under tested condition is important to precisely study the cellular invasion capability. In this study, a microfluidic device was developed and electrodes were embedded in the microchannel for the impedimetric measurement of cell invasion. Cancer cells were stimulated by interleukin-6 cytokine and invaded along the hydrogel-filled microchannel. The three-dimensional (3D) cell invasion process was monitored by measuring the impedance across the electrodes.**

I. Introduction

Cancer metastasis is a process that cancer cells leave the primary site of the tumor mass and disseminate to distant sites. When the cancer cells reach the distant sites, they proliferate and form other tumors. Cancer metastasis is induced by a complex molecular cascade. It is the most usual cause of death in cancer patients and recognized as a very serious clinical problem. For the study of cancer metastasis, Transwell system is usually used in the current biological laboratory. This is a commonly used assay to study the cancer cell invasion ability under the tested condition. However, the cell invasion process cannot be visualized and the quantification of invaded cells is subjective.

In the current work, a microfluidic device was developed and consisted of two reservoirs connected with a microchannel. Before the cancer cell invasion experiment, the microchannel was filled with hydrogel working as the extracellular matrix for mimicking the physiological microenvironment. Cancer cells were then loaded into one of the reservoirs and cellular stimulation was prepared. In order to measure the invasion process, five electrodes were fabricated on the bottom surface of the microchannel. Impedimetric measurement was conducted to estimate the cell invasion process. This device can be fully automated in conjunction with impedance analyzer and microscopic imaging instruments.

II. Results

Illustration of the microfluidic device is shown in Figure 1(a). Before the cell invasion experiment, the microchannel was filled with Matrigel (354234, Corning® Matrigel® Matrix, USA) that was diluted 50 times by culture medium. Then, the Matrigel was dried and solidified overnight for constructing a 3D cell invasion microenvironment. Afterward, 20 µl cell suspension, i.e., 3×10^3 cells suspended in culture medium containing with different concentrations of IL-6 (550071; BD Pharmingen, USA), was loaded to one of the reservoirs. The IL-6 is a kind of cytokines and the cell invasion capability could be stimulated. 20 µl culture medium was loaded to another reservoir. The microfluidic device was then transferred to the incubator. The cells were guided, entered and invaded along the microchannel. The cell invasion process was continuously recorded by the impedance analyzer for the next 24 h.

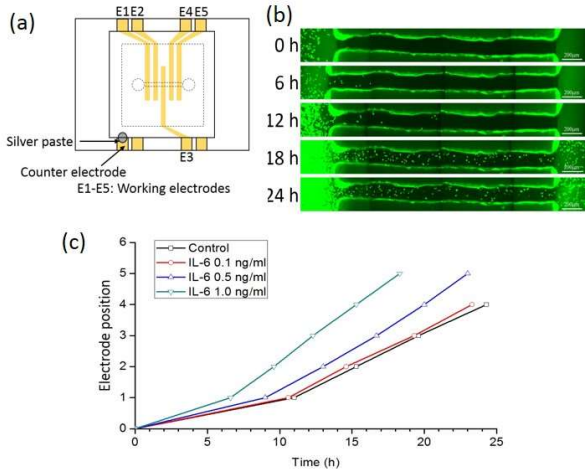

Figure 1. Illustration of the microfluidic device embedded with electrodes for impedance measurement. (b) A sequence of microscopic images showing 3D cell invasion process. (c) Invasive speed quantified by impedance measurement.

The cell invasion under tested condition could be investigated in the microfluidic device. After cell application, the cells were stimulated by IL-6 cytokine in different concentrations, i.e., 0 (control), 0.1, 0.5, and 1.0 ng/ml. A sequence of microscopic images showing cell invasion process is shown in Figure 1(b). The invasion speed quantified by impedance measurement is shown in Figure 1(c). Obviously, higher concentration of IL-6 can stimulate the cells more and enhance the cell invasion capability.

III. Conclusion

In this study, the microfluidic device provides a promising and quantitative tool for cell invasion assay. It is an automatic, real-time, and non-invasive analytical equipment for high-throughput screening.

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MXG – Accelerometer-based Location Specific Inertial Motion Sensing for Health-care Applications *

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***Abstract*— Accelerometers have been widely used in many fields of applications, especially for the health-care related in these days. In this study, we introduce a concept of on-body location specific accelerometer-based inertial motion sensing technique, abbreviated as MXG, to detect mechanical motion signals from different locations of the body. The 'X' in "MXG" represents detected physiological motion signals from different body locations. For example, signal related with: muscle contraction is MMG, physical activity is MAG, heart or cardiac activity is MCG, respiratory function is MRG, snoring detection is MSG, and cuffless blood pressure measurement is MPG. This review study gives a general introduction on how these sensing technologies can be applied in their respective health-care applications.**

I. Introduction

Nowadays, MEMS-based accelerometers are very popular not only in industrial and automobile applications but in health-care applications too. In this review study, we classified different accelerometer-based sensing techniques by their sensing locations on the body as well as their respective types of health-care applications and then named them as "MXG". In this, 'M' is the abbreviation for "Mechano-", which is a prefix in the nomenclature of compound terminologies. And, 'G' is abbreviated for "-Gram" or "-Graphy", which means recording, describing, etc. of physiological signals from inertial motion behaviors.

II. Mechano-X-Gram (MXG)

As illustrated in Fig. 1, the character 'X' in "MXG" represents the specific locations and types of applications in health-care.

- MMG: MechanoMyoGram use accelerometer to measure the tiny vibration signals due to muscle contraction. It has been found that MMG is highly correlated with Electromyogram (EMG) and can be used in applications for detecting fatigue, monitoring lower back pain, etc.
- MCG: MechanoCardioGram is the technique to monitor the mechanical behavior of cardiac activity with sensors attached on the chest around heart area. It can be used as an alternative or auxiliary system for cardiac diagnosis when conventionally used Echocardiography equipment is not available.

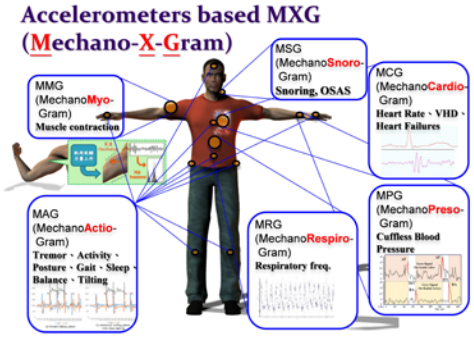

Figure 1. Accelerometer-based MXG.

- MAG: MechanoActioGram is a compound technique to monitor physical activities in daily living with accelerometers. With sensors attached on the wrist, body trunk, waists, limbs, head, etc., these can be used for health-care applications, like tremor detection, posture monitoring, gait analysis, sleep quality monitoring, etc.
- MSG: MechanoSnoroGram can be used to monitor the snoring in sleep as vibration signals of the hyoid bone in the neck. After MSG data analysis, subjects can be stratified for snoring, hypopnea, or even Obstructive Sleep Apnea Syndrome (OSAS).
- MRG: MechanoRespiroGram uses accelerometer to detect the diaphragm movement causing from respiration. After signal analysis, the respiratory frequency can be obtained.
- MPG: MechanoPresoGram can detect the pulse flow time (PFT) as the time duration from the trans-aortic peak flow event of the heart in MCG to the pulse wave peak of the radial artery (RA) on the wrist. With the information and conversions through proper modeling, blood pressure (BP) without cuff used can be obtained. This technique is very useful for continuous blood pressure monitoring.

III. Final Remark

Researchers investigating accelerometer based inertial motion sensing for health-care applications tend to use the prefix "Mechano-" for the developed techniques because it does measure the mechanical or physical motion signals of the body. However, few other researchers who have applied accelerometer for some specific field of applications might be using different terminologies. For example, the MCG technology mentioned in this article is also known as Seismocardiography (SCG) in other research studies.

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