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**NANYANG
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**ENGINEERING FUNCTIONAL NANOMATERIALS FOR
BIOPHOTONICS AND NANOMEDICINE APPLICATIONS**

OUYANG QINGLING

**SCHOOL OF ELECTRICAL & ELECTRONIC
ENGINEERING**

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ENGINEERING FUNCTIONAL NANOMATERIALS FOR BIOPHOTONICS AND NANOMEDICINE APPLICATIONS

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School of Electrical & Electronic Engineering

A thesis submitted to the Nanyang Technological University
in partial fulfillment of the requirement for the degree of
Doctor of Philosophy

2019

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- Prof. Yong and Dr. Zeng Shuwen suggested the research area and edited the manuscript drafts.
- I wrote the drafts of the manuscript. The manuscript was revised together with Dr. Zeng Shuwen and Dr. Jiang Li.
- I completed the calculations and figures for the simulation, and Dr. Zeng Shuwen, Dr. Jiang Li provided help.
- Prof. Dinh, Prof. Qian, Prof. He, Prof. Qu, and Prof. Coquet provided suggestions in the manuscript preparations.

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- I and Dr. Feng Xueling performed the drug release experiments, acquired data, analyzed data, and wrote the manuscript.
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Summary

To date, functional nanomaterials have been commonly synthesized and applied for various biomedical applications such as sensing, imaging, drug delivery, and tissue engineering due to their unique optical, electronic, and biocompatible property. In this Ph.D. work, different types of nanomaterials/nanodevices have been engineered, characterized, and studied for biophotonic sensing and nanodrug delivery therapy, namely, two-dimensional (2D) transition metal dichalcogenides (TMDCs), nanoporous polymers and triboelectric nanogenerator (TENG). The engineered solutions presented in the Thesis aims at addressing current limitations in healthcare diagnostics and therapeutics fields, particularly the low detection sensitivity of optical biosensors and the large footprint of stimuli-controlled drug delivery systems. The presentation of this Thesis work was divided into two parts.

In the first part of Thesis, we studied the physical and optical property of a series of 2D TMDCs including molybdenum disulfide (MoS_2), tungsten disulfide (WS_2), molybdenum diselenide (MoSe_2) and tungsten diselenide (WSe_2), to develop and optimize next generation of plasmonic biosensors with high sensitivity for small molecules. The sensing performance is affected by types of 2D materials, thickness and incident wavelength. In theoretical studies, a monolayer WS_2 based plasmonic biosensor was demonstrated to achieve a 200% increment in the detection sensitivity in the visible wavelength. In the experimental studies, the phase sensitivity of the WS_2 sensing film reaches 15,000 deg/RIU in detecting low concentration analytes, which represents an enhancement of 151% over the conventional bare gold SPR sensing film.

In addition, the enhanced SPR biosensor exhibits fast and accurate feedback in real-time monitoring of small molecules.

In the second part of the work, we designed and studied the triboelectric nanogenerator (TENG) in creating a miniaturized, self-powered drug delivery device for transdermal patch application. TENG system can effectively convert various mechanical energies into electricity. It has many advantages such as the large output of power, low cost, simple fabrication, and high conversion efficiency. The designed transdermal patch mainly composed of an electric-responsive polymer and TENG. The drugs embedded in the polymer matrix were released upon receiving electric-stimuli from TENG. Such a mechanism can allow one to achieve precise control in programming the drug delivery profile by tailoring the appropriate TENG action time. The release rate can be tuned from ~ 0.05 to $0.25 \mu\text{g}/\text{cm}^2$. More importantly, the drug delivery efficiency in dermis was noted to improve by $\sim 100\%$ when compared with the absence of TENG triggered reaction.

In conclusion, this Ph.D. work has generated reliable and emerging engineering solutions to overcome challenges we faced in the current healthcare diagnostic and therapeutic technology especially in the areas of optical plasmonic sensors and skin patch drug delivery devices. Such solutions can be further integrated into other sensing and drug delivery systems for personalized healthcare applications.

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Nomenclature

2D	Two-dimensional
SPR	Surface plasmon resonance
TMDCs	Transition metal dichalcogenides
WS₂	Tungsten disulfide
WSe₂	Tungsten diselenide
MoS₂	Molybdenum disulfide
MoSe₂	Molybdenum diselenide
WO₃	Tungsten trioxide
S	Sulfur
CVD	Chemical vapor deposition
TIR	Total internal reflection
ATR	Attenuated total reflection
FWHM	Full width at half maximum
SPW	Surface plasmon wave
UHP	Ultra-high purity
sccm	Standard cubic centimeters per minute
rpm	Revolutions per minute
ssDNA	Single-stranded deoxyribonucleic acid

DI water	Deionized water
TENG	Triboelectric Nanogenerator
PMMA	Poly(methylmethacrylate)
PMDS	Polydimethylsiloxane
PTFE	Polytetrafluoroethylene
HF	Hydrofluoric acid
PCB	Printed circuit board
SPE	Screen printed electrode
ICP	Inductively coupled plasma
PPy	Polypyrrole
DEX	Dexamethasone Sodium Phosphate
DEX⁻	Anionic state of Dexamethasone Sodium Phosphate
FLU	6-carboxyfluorescein
PBS	Phosphate-buffered saline; Polarized Beam Splitter
BS	Beam Splitter
ELISA	Enzyme-linked immunosorbent assay
DMEM	Dulbecco's modified Eagles medium
LPS	Lipopolysaccharide
IL-1β	Interleukin 1 β
RAW 264.7	Mouse Macrophage Cell Line
HPLC	High-performance liquid chromatography

Chapter 1 Introduction

1.1 Motivations and objectives

The term “nanomaterials” refers to materials with dimensions on the order of approximately 1-100 nm which exhibit properties distinct from their bulk counterparts. Depending on the specific dimension of their constituent nanostructures, nanomaterials can be divided into zero-dimensional (0D), one-dimensional (1D), two-dimensional (2D) and three-dimensional (3D), as shown in Figure 1-1. Such nanoscale materials provide scientists a promising route to control the physiochemical properties of materials, which are determined by their size, rather than by their composition [1]. Owing to their unique properties, such as conductivity, photothermal effect, fluorescence, and biocompatibility, functional nanomaterials have been widely

Figure 1-1 The nanostructures of zero-dimensional (0D), one-dimensional (1D), two-dimensional (2D) and three-dimensional (3D) nanomaterials. Figure reproduced from ref. [75] © 2010 Massachusetts Medical Society.

investigated in biomedical fields with a collaborative effort by chemists, biologists, physicists, clinicians, and engineers [2]. In the last 20 years, such nanomaterials have been enabling breakthroughs in various biomedical applications such as biosensing, imaging, drug delivery, and tissue engineering. For instance, in biophotonics 2D materials can be engineered into sensing platforms to enhance the sensitivity of optical sensors [3], quantum dots can be designed as labels for *in vivo* fluorescence imaging [4], and metallic nanoparticles can be used to perform photothermal therapy for target tissues [5]. In nanomedicine, nanostructured polymers or liposomes can be engineered as nanocarriers for a series of therapeutic agents such as drugs, antibodies, and peptides [6]. They can achieve controllable release *in vivo* [7], targeting release to cancer cells [8] and active implantation [9]. These achievements are attributable to the nanoscale dimensions of the functional nanomaterials, which allow them to interact with matter (i.e., pharmaceutical compounds or/and biomolecules) at molecular level, which is not possible with conventional bulk metals or compounds [10, 11]. The success of these biomedical applications demonstrates that nanomaterials enable effective improvement in diagnostic precision, enhance the therapeutic efficacy, and reduce toxic side effects, greatly benefitting the development of healthcare.

In recent years, another developing trend has been that of personalized healthcare, which aims not only to improve the quality of care but also to save medical resources and thus reduce costs; thus, it has been regarded as the next generation of healthcare by many experts [12-14]. Personalized healthcare is a broad platform that mainly includes:

- i) Predicting risk for disease or patients' response to treatments at the molecular or genetic level, thus identifying appropriate treatment options [15].

- ii) Providing individuals with tools to understand, monitor their health and self-treat on their own terms, while receiving doctor input through telemedicine [16].

Therefore, we can extract at least two main directions to support the development of personalized healthcare: namely, to develop fast and precise diagnostic technologies at the molecular level, and to build individual therapeutic tools/systems for at-home treatment.

Therefore, in this Thesis, we aim to explore novel and effective technologies and tools from biophotonics and nanomedicine with the aid of functional nanomaterials for pushing forward the possibilities of personalized healthcare. The detailed studies presented in this Thesis are divided into two parts, namely, optical biosensing and controllable drug delivery respectively.

1.1.1 Biophotonic applications

Background. Biophotonics is an emerging multidisciplinary research area that involves a fusion of biomedical science and photonics, dealing with interactions between light and biological matters [17]. In biophotonics, light can be used as a controllable tool for both analytical purpose or treatment in life sciences and medicine. One significant reason is that light allows observation and study on cellular structures with utmost sensitivity and precision with little damage to cells or tissues [18]. For example, optical imaging can achieve detailed quantitative molecular profiling for individual cells with the aid of fluorescent nanomaterials, e.g., quantum dots [19]. In optical biosensing, it can realize label-free and real-time detection of chemical or biological species [17] and immunoassays [20]. In addition, biophotonics has also been applied in optical diagnostics [21], optical tracking [4], light-based tissue engineering

[22], light-activated therapy [23], and light-guided therapy [17]. Therefore, modern healthcare benefits greatly from biophotonic applications both in the diagnosis and in the therapy of disease.

In this Thesis, we mainly discuss the optical biosensing aspect of biophotonics, which has emerged as an attractive application due to the high demand for such tools in medical diagnostics. Biosensors are analytical tools that are used to detect a microorganism or a biochemical species. They are usually applied to monitor the presences changes in the concentrations of biomolecules such as glucose, proteins, DNA, and enzymes, whose presence is indicative of physiological changes induced internally [24]. Furthermore, some biosensors have also been developed to detect and identify bacteria, viruses, and toxins directly [17]. Therefore, biosensors are significant tools in disease diagnostics. There are two essential components of biosensors: the biorecognition element to identify the specific analyte, and the transducer to convert the physical or chemical response of biorecognition into a detectable signal. The general workflow of a biosensing system is shown in Figure 1-2.

The sample is introduced to the biorecognition element (e.g., antigen or ligand) that will capture or react with the specific analyte. The stimulation unit, at the same time, will provide optical, electric or chemical stimuli to the biorecognition unit and excite the corresponding physical or chemical response. Such a response can be converted into a signal in the transduction process and is finally detected by a detection

Figure 1-2 The general scheme of biosensing. Figure reproduced from ref. [17]

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unit. According to the different stimulation and transduction mechanisms, biosensors can be divided into different types, such as optical, electrochemical, thermal and of other types [25, 26]. Optical biosensors are one of the most commonly used type, generally having optical stimulation and detection via changes in, e.g., the intensity or phase of the input light as a result of biorecognition. Benefitting from photonics technologies, optical biosensors have many distinct advantages over other types, including fast or even real-time measurement, high selectivity and specificity, remoting sensing, minimal invasiveness and multi-channel detection [17].

The surface plasmon resonance (SPR) biosensors are currently attracting a lot of attention, due to the unique advantages of label-free detection, small sample size, and reusability [27]. The SPR biosensors rely on the SPR phenomenon that occurs at the interface of two materials with opposite permittivity, e.g., metal and dielectric, when it is illuminated by polarized light at a specific angle. Therefore, in SPR biosensors, the metal (generally gold or silver) is regarded as the sensing platform/surface, while the dielectric refers to the analyte. The refractive index change of the analyte results in changes of the resonance condition between the surface plasmons and the incident light, which can induce changes in characteristics (phase, angle, intensity) of the reflected light. In this way, SPR can realize label-free and real-time sensing [28].

Limitations. The detection limit of existing SPR biosensors with gold sensing platform is mainly in the range 10^{-4} - 10^{-6} refractive index (RIU) [24, 29-35], which enables to detect large biomolecules, such as proteins and DNA. However, this sensitivity is insufficient to detect small molecules (molar weight < 8 kDa), such as hormones and metabolites [36].

The state-of-the-art. In recent years, various methods for increasing the sensitivity have been suggested and implemented. For example, colloidal gold

nanoparticles are applied onto the bare gold sensing surface to enhance the sensitivity. The electric field of the gold nanoparticles can couple with that of the surface plasmon wave of the gold film, thus enhance the localized electric field generated by the SPR wave onto the sensing surface [37]. Generally, the higher electric field contributes to a higher sensitivity to refractive index changes of the surroundings [38, 39]. The size of the nanoparticles directly affects the strength of the localized electric field and thus, affects the sensitivity enhancement [36]. Other nanostructured materials, such as metallic nanoholes [40, 41] and nanoslits [42], have also been employed to modify the performance of the surface plasmon wave and enhance the sensitivity. However, all methods above suffer from a common problem: great difficulties to achieve precise control over the geometry and the optical properties of nanostructures makes reproducible performance of such sensors very challenging. Therefore, it is not easy to achieve the desired sensitivity exactly in large batch of mass produced sensors. An alternative method is to coat the gold sensing surface with a 2D material, such as graphene. The graphene monolayers can be easily obtained by mechanical exfoliation [43]. Different from nanoparticles, the geometry (especially the thickness) and the optical properties of graphene coating can be easily and precisely controlled by tuning the number of graphene monolayers (0.34 nm per layer) [44]. The reasons for sensitivity enhancement are two-fold: First, the hexagonal structure of graphene significantly improves the surface adsorption of biomolecules with carbon-based ring structures. Second, graphene modifies the surface plasmon resonance condition of the sensing surface. However, the drawback of this method is that the sensitivity enhancement ratio is too low, only 25% for ten layers of graphene [3]. This is likely due to the relatively low light absorption of graphene ($\sim 2.3\%$) [45].

Objective. In this Thesis, we propose the use of other emerging 2D materials, 2D transition metal dichalcogenides (TMDCs), i.e., tungsten disulfide (WS_2), tungsten diselenide (WSe_2), molybdenum disulfide (MoS_2), and molybdenum diselenide (MoSe_2) as coatings to enhance the sensitivity of SPR biosensors. These 2D TMDCs have similar structures with that of graphene, with the chalcogen atoms in two hexagonal planes separated by a plane of metal atoms. It is noted they exhibit similarly strong adsorption as graphene for biomolecules with aromatic rings [46, 47]. More importantly, they have the salient optical property of higher light absorption (above 5%, up to 30%) [48, 49], much higher than that of monolayer graphene (2.3%), even in ultra-thin layers less than 1 nm thick [50]. When 2D TMDCs are coated onto the gold SPR sensing surface, they can increase the light absorption of the SPR sensing surface, thus enhancing the electric field and the sensitivity. The light-matter interactions of the 2D TMDCs are dependent on the number of layers [50, 51]; in other words, the sensitivity of the biosensors can be precisely controlled by tuning the number of layers. Fortunately, current synthesis technologies allow both monolayer and multi-layer TMDCs to be easily obtained, providing a high likelihood of successful fabrication of such TMDC-enhanced biosensors [52]. It is noted that the SPR performance is affected by many factors, including incident wavelength, the refractive index of TMDCs, the thickness of gold film, and the number of TMDCs layers. Therefore, it is necessary to systematically study the theoretical modeling of the TMDC-based SPR biosensors to determine the performant materials and optimized parameters, which can guide the engineering work. The objectives in this part can be grouped into two main tasks as follows:

- i) Develop the theoretical model of the TMDC-based SPR biosensor and investigate how the refractive index of TMDCs, the thicknesses of the gold film

and of the TMDCs, and incident wavelength affect the sensing performance.

Determine the optimized geometry of the TMDC-enhanced biosensor, as well as the optimized detection sensitivity, accuracy, and the detected concentration range (Chapter 3).

- ii) Fabricate the optimal TMDC-enhanced SPR sensing chip by chemical vapor deposition (CVD) and related film-transfer techniques. Build the optical setups to verify the sensitivity enhancement of the 2D TMDC film. Measure the SPR signals involved in angular and phase modes and conduct real-time monitoring of small molecules (Chapter 4).

1.1.2 Nanomedicine application

Background. Nanomedicine is an emerging field that has developed from nanotechnology over the past three decades [53, 54]. One of the internationally accepted definitions of nanomedicine formulated by the European Science Foundation (ESF2004), is “the science and technology of diagnosing, treating, and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body”[54-56]. Furthermore, five main sub-disciplines of nanomedicine have been defined, namely: nanomaterials and nanodevices; novel therapeutics and drug delivery systems; analytical tools; nanoimaging; and clinical, regulatory, and toxicological issues [55]. Nanomedicine has provided various advanced technologies for medicine development, such as novel drug delivery, tissue engineering, *in vitro* diagnostics, *in vivo* imaging, and active implants [55-58]. This Thesis mainly explores two disciplines within nanomedicine: “nanomaterials and nanodevices” and “novel therapeutics and drug delivery systems.”

Improving therapeutic efficacy has always been a significant goal in the field of medicine. In recent decades, scientists and clinicians have begun to realize that therapeutic efficacy is correlated not only with the potency of a drug but also with the method of drug formulation and delivery process in the body [6, 59, 60]. When drugs enter the body, their pharmacological activity is likely damaged due to environmental changes such as pH, temperature, and moisture [61]. Furthermore, the drug delivery mode affects various factors influencing therapeutic efficacy, including distribution, pharmacokinetics, cellular uptake, metabolism, toxicity, excretion, and clearance [62]. Therefore, it is critical to improve the knowledge of how drug delivery affects the therapeutic efficacy and safety, and thus to explore novel delivery technologies.

The oral and injectable drug administrations are two most common used drug administration approaches in our daily life, which require repeated dosing to keep the circulating drug concentrations in the body within effective therapeutic window during the treatment period [63]. Upon each administration, the drug concentration in the body increases rapidly to reach the therapeutic concentration, but this process may also cause undesired side effects when the drug level exceeds the maximum safe concentration [6, 60]. Furthermore, as the drugs are transported in the body, the concentration decreases rapidly below the minimum effective level due to metabolism, degradation, and transport away from the area of interest [60]. Therefore, frequent dosing is needed to retain the therapeutic efficacy. Such conventional administration results in two major problems: the high potential of toxic side effects, and a waste of drug and relevant materials [6]. In order to solve this problem, the “sustained release” approach was developed aiming to slow down the drug release rate by using specific compounds, such as slowly dissolving drug coatings, substances that would decrease drug solubility, compressed tablets, and the employment of emulsions or suspensions [64-66]. However,

such methods can only prolong the sustained time of efficient drug potency to a certain extent but are unable to realize controllable release rate, thus still requiring repeated dosages [67].

Afterwards, research began to concentrate on “zero-order release”, which refers to drug release at a constant rate, independent of time [68] (detailed in Chapter 2, Section 2.2.1). Thus zero-order release offers several advantages including reduced frequency of administration, maintaining release within the therapeutic window, less potential of side-effects, and improved patient compliance. Therefore, numerous technologies and systems have developed to control the drug release rate and amount, aiming to achieve the zero-order release [69-71]. Although it is unquestionable that zero-order transdermal delivery has unique advantages. However, it should be noted that there is no perfect delivery method for all diseases. On the other hand, zero-order release is not necessarily the optimal method for all diseases. For example, for diabetic patients, the level of insulin must correlate with the blood glucose level, which fluctuates throughout the day. Therefore, there are many other types of controlled drug release method, such as target drug release to specific tissues and cells, thus to further reduce the harm to healthy ones [72-74]. The choice of delivery methods depends on the pathophysiological features of the disease and the nature and pharmacodynamics of therapeutic agents. In this Thesis, we mainly focus on the zero-order release with the transdermal drug administration.

The state-of-the-art. In order to achieve controlled drug release, various nanomaterials have been designed as drug nanocarriers, including polymeric nanospheres, inorganic nanomaterials (e.g., gold, silicon, metal, iron oxide), dendrimers, and micelles [75, 76]. Such materials have improved the therapeutic efficacy and reduced the side effects of drug administrations such as oral and injectable

for a range of therapeutic agents, such as drugs, antibodies, enzymes, and peptides [77]. Additionally, these nanomaterials have been tailored to develop other drug delivery modes, including transdermal, ocular, nasal, pulmonary, and others, aiming to maximize therapeutic benefits and patient compliance [6, 78-80] (detailed in Chapter 2). Among various nanomaterials, the responsive polymers (or “triggerable” polymers) are the most extensively developed and applied in controlled drug delivery systems, since they can respond to both exogenous stimuli (e.g., electric field, temperature, light, ultrasound, and magnetic fields) and endogenous stimuli (e.g., enzymes, glucose, and pH) for actuating drug release. Upon the presence of the stimulus, the stimuli-responsive materials would release the loaded drug molecules (or other therapeutic compounds) to the environment due to chemical or physical reactions such as redox reactions, degradation, or swelling [6, 76, 81]. Each type of stimuli-responsive polymer has its advantages and disadvantages (Table 1-1) and can be tailored for the intended controllable drug release applications. Generally, the endogenous stimuli response-based nanocarriers can be injected or implanted in the body for localized and targeted drug release, since the targeted areas (e.g., tumors and infected or inflamed tissues) are generally accompanied by changes in pH or/and enzymes [82-84]. On the other hand, the exogenous stimuli based nanocarriers are usually used to realize the remotely triggered drug release. The release rate and amount can be controlled by an auxiliary equipment such as a laser, potentiostat, or oscillator [85-88]. The diversity of the exogenous and endogenous stimuli-responsive nanomaterials allows the design of novel controlled drug delivery system with great flexibility to meet various therapeutic requirements [76].

Table 1-1 The various exogenous and endogenous stimuli of the controllable drug release, and their applications, advantages/disadvantages, and corresponding nanomaterials.

Type of stimulus	Applications/advantages	Disadvantages	Nanomaterials (examples)
Exogenous stimuli			
Electricity (voltage, current)	Nucleic acid delivery, insulin delivery. Significant freedom in the design of the device.	Low tissue penetration depth, bulky power supply	Polypyrrole nanoparticles [89], carbon nanotubes [90], silica nanoparticles [91], PLGA nanoparticles [9]
Light (radiation)	Cancer therapy, DNA release. Remote spatiotemporal control.	Low penetration depth. The safety and biodegradability of the nanocarriers are still questionable.	Gold nanorods [92], azobenzene and o-nitro benzyl derivatives [76], mesoporous silica [93]
Temperature	Cancer therapy, Localized drug delivery, Specific targeting drug delivery	Complex operation (need to associate with photothermal therapy)	Poly (N-isopropyl acrylamide) [94], silica nanoparticle [95], liposome hybrids [96]
Endogenous stimuli			
pH	Drug delivery in specific organs, targeting drug release, cancer therapy, inflammation therapy	Disruption of the lysosomal membranes, Possibility of autophagy and cell death.	PEG-poly (β -amino ester) micelles [97], Chitosan [98], Albumin [99]
Enzyme	Intracellular, extracellular compartment drug delivery, siRNA delivery, targeting drug release, cancer therapy, inflammation therapy	Lack of precise information of the target enzyme levels at the desired site.	TAT-functionalized liposomes [100], dextran-coated iron oxide nanoparticles [101]
Glucose	Drug release of insulin,	Low responsiveness sensitivity, Stay in proof of concept stage, no strong clinical evidence	poly(ethylene glycol)-b-poly(styrene boroxole) polymersomes [102], polypeptide-based micelles [103] and PBA-functionalized MSNPs [104].
Multi-stimuli	Improved drug release activation by dual responsiveness (e.g., pH and temperature, light and magnetic)	Complicated system, remain as proof of concept	Ionic self-assembled nanoparticles [105] and liposomes [106]

Limitations. Although these various stimuli-responsive nanomaterials have provided advanced and effective solutions for developing novel drug delivery systems, there remain prominent challenges in translating the stimuli-responsive drug delivery systems from experimental models to clinical applications. These challenges include controllability of drug release, the large footprint (e.g., auxiliary equipment), and the manufacturing process [71, 107].

Specifically, the endogenous stimuli in the body (e.g., the pH, enzyme of a tumor, or glucose in circulating blood) are influenced strongly by patient-to-patient variability. Therefore it is difficult to give precise triggers to control the drug release [108]. From this point of view, the systems based on exogenous stimuli generally have higher controllability of drug release, since the external stimuli can be precisely controlled by operating the auxiliary equipment, such as tuning the wavelength of laser light [109, 110], the voltage/current of power supply [111, 112], and the frequency of oscillators [113-115]. This may explain why only the exogenous stimuli-responsive systems have reached the clinical stage (detailed in Chapter 2). However, the bulky auxiliary equipment (i.e., laser, potentiostat, and oscillators) used to provide the exogenous stimuli have brought significant limitations to the design flexibility and further development for personalized healthcare systems: i) Limited therapeutic environment and space; ii) Low potential for prolonged treatment; iii) Increased patient inconvenience and discomfort (reduced patient compliance); iv) Sophisticated designs of the therapeutic system.

Objective. In order to create a controlled drug delivery systems with both high controllability on drug release rate and small footprint, we propose a novel self-powered, electric-stimulated drug delivery system. Here, a miniaturized triboelectric nanogenerator (TENG) was designed to generate the specific exogenous stimuli (i.e.,

electric voltage) for the drug carrier, and an electric-stimuli responsive polymer (i.e., polypyrrole) was engineered as the drug nanocarrier for drug release.

TENG is an emerging nanodevice that enables to harvest and convert mechanical energy to electric energy [116]. It can harvest all kinds of mechanical energy, from micro-scale (e.g., human motion, walking) to macro-scale (e.g., wind, water). TENG was invented in 2012 and has been extensively investigated and applied in various self-powered sensors/systems and micro/nano power source, due to their unique advantages of simple structure and high output [117, 118]. TENG mainly consists of two materials with different tribological properties. When these materials rub against each other, an electric potential difference can be established between them due to contact electrification and electrostatic induction [116, 119]. The surface of materials can be functionalized with nanostructures (e.g., nanowire, nanoparticle) that can significantly increase the contact area and the generated surface charge density [120], thus enhancing the electric output (up to 313 W/m² [116]). TENG can use a wide range of materials, from metals and polymers to textiles. Therefore, it can be easily made portable, flexible, or even wearable [120-123]. In addition to small footprint and high yield, there are two important reasons to incorporate TENG into a drug delivery system. First, compared with other types of exogenous stimuli such as optical and thermal energy, electricity allows more flexibility in design, control and storage, and it can be easily converted into optical or thermal energy if necessary. Also, the electricity from TENG can be further utilized to enhance the drug delivery efficiency through, for example, iontophoresis treatment (a specific transdermal drug administration by use of a voltage gradient on the skin [124, 125]). The operation of TENG is completely immune to environmental and spatial disturbances. Finally, it is convenient and easy

for patients to operate the TENG (e.g., rotate, tap or rub) to control the exogenous stimuli and the drug delivery profile [120].

The electric-stimuli responsive polymer, polypyrrole, was chosen as the drug carrier due to its prominent advantages of high conductivity, simple synthesis, and biocompatibility [89, 111, 126]. Furthermore, it gives great freedom in the morphology design of the system. For example, it can be engineered as a nanoporous structure with the help of nanobeads to achieve large drug loading capacity [127-129]. In addition to the TENG and the nanocarrier, a power management circuit is also required in this controlled drug delivery system, which is used to store/adjust the original AC output to the effective DC level required for the electric-stimulated drug release action.

With the aid of TENG, this self-powered, electric-responsive drug release system aims to achieve high controllability on drug release and small footprint, moving forward to individual drug delivery tools for personalized healthcare. The objectives in this part can be grouped into the two main tasks as follows:

- i) To develop a TENG triggered electric-responsive drug release platform. The TENG is required to provide controllable, sustainable, and self-powered electric triggers to realize the zero-order release profile (Chapter 5).
- ii) To develop a novel self-powered, controllable transdermal drug delivery system based on the above platform. The electricity from the TENG is to be utilized in two actions: first, to trigger the electric-responsive polypyrrole for controllable release; second, to actuate the iontophoresis treatment for enhanced drug delivery efficiency (Chapter 6).

In summary, there are two urgent challenges that must be addressed to improve the level of diagnostics and therapeutics for pushing the possibilities of personalized

healthcare forward. First, current SPR biosensing technology has limited sensitivity for small molecules detection, which affects the precision of diagnostics. To meet this challenge, the 2D TMDC-enhanced SPR biosensor is proposed. The 2D TMDC films coated on the gold substrate act as the sensing platform, and they can enhance the sensitivity by improving the light coupling condition, thus enhance the SPW. Also, the detection sensitivity can be precisely controlled by tuning the number of TMDCs layers. Second, current stimuli-responsive drug delivery systems have either low controllability of drug release or large footprint, limiting the therapeutic environment and reducing patient compliance. To address this problem, a novel self-powered, electric-responsive drug delivery system is developed for efficient and precise drug dosing. In the system, a triboelectric nanogenerator is designed as a miniaturized power supply to provide the electric stimulus by harvesting small-scale mechanical energy; a conductive nanocomposite, polypyrrole, is engineered as the drug nanocarrier for controllable drug release.

1.2 Contributions

The main contributions of this Thesis are providing effective solutions by engineering functional nanomaterials for current problems in healthcare diagnostic and therapeutic fields. Specifically, in the first part of the Thesis, a high sensitivity 2D TMDC-based SPR biosensor is developed, enabling detection of small molar weight molecules. The detection sensitivity of monolayer WS₂-enhanced SPR biosensor is found to be as high as 1.5×10^4 deg/RIU, representing an improvement by ~151% compared with the conventional gold sensing surface. Furthermore, a 5-layered MoSe₂-based SPR biosensor under near-infrared wavelength is estimated to achieve an ultra-high sensitivity improved by three orders of magnitude compared with that of

conventional SPR sensors. These results demonstrate that the 2D TMDCs coatings can effectively enhance the sensitivity due to by improving the coupling condition between the incident light and the SPW. Also, the sensitivity can be easily tuned by the TMDC type and geometry. This novel method has a high potential for SPR biosensors to detect small molecules, which is promising to improve the precision of disease diagnostics.

In the second part of the Thesis, a self-powered, electric-responsive drug delivery system is engineered by use of a triboelectric nanogenerator as power source and nanoporous polypyrrole (PPy) as the drug delivery carrier. It is capable of achieving high controllability of drug release and has a small footprint (diameter = 15 cm). Rotating the TENG manually for 1.5 min can release $3 \mu\text{g}/\text{cm}^2$ of the drug. The release rate and amount can be precisely controlled by tuning the TENG operation time. In addition, the drug delivery efficiency is enhanced by $\sim 100\%$ through the iontophoresis triggered by TENG. Such a novel system has overcome many limitations of the existing stimuli-responsive systems, allowing precise controllability, unlimited therapeutic environment, prolonged treatment, and improved patient compliance. Therefore, it has a high likelihood of being an individual treatment tool for personalized healthcare.

The detailed contributions of the Thesis are as follows:

- 1) The 2D TMDC sensitivity-enhanced SPR biosensor is presented. To determine the material with the best sensitivity enhancement, we investigated four types of 2D TMDC-based SPR configurations, namely WS_2 , WSe_2 , MoS_2 , and MoSe_2 . Each was systematically analyzed with theoretical models under both angular and phase modulation. For angular modulation, the best performance was provided by monolayer WS_2 , with a sensitivity as high as $155.68 \text{ deg}/\text{RIU}$ at 633 nm , which was three times that of conventional SPR biosensors. As for phase modulation, an ultrahigh sensitivity of $1.1 \times 10^7 \text{ deg}/\text{RIU}$ was achieved

at 1024 nm, which was three orders of magnitude higher than those with bare gold sensing substrates (Chapter 3).

- 2) A novel two-dimensional (2D) TMDC enhanced SPR sensing chip was fabricated. The monolayer tungsten disulfide (WS_2) was first deposited onto a SiO_2/Si substrate by a chemical vapor deposition method and then transferred onto the gold substrate. Characterization of the fabricated TMDC flakes revealed the average length of the single crystal WS_2 to be $\sim 35 \mu\text{m}$ with the area estimated to be $\sim 550 \mu\text{m}^2$, and the coverage was $\sim 20\%$ (Chapter 4).
- 3) To achieve both angular and phase modulation measurement, a home-made optical setup for testing the sensitivity of the 2D TMDC-enhanced SPR sensing chip was built. A PDMS sample chamber was fabricated which allowed the sample solution to flow above the WS_2 sensing surface to conduct real-time monitoring. Glycerin solutions with gradient concentrations were measured, respectively. Also, the results showed that the detection sensitivity was different for different analytes concentration ranges. Compared with the conventional bare gold substrate chip, the WS_2 -based sensing chip showed generally higher sensitivity, especially at low concentrations. The sensitivity reached 15000 deg/RIU for 1% glycerin solution, which is ~ 2.5 times that of the bare gold sensing substrates used in conventional SPR biosensors (Chapter 4).
- 4) A radial-arrayed rotary triboelectric nanogenerator (TENG) which could produce a high instantaneous voltage reaching up to 250 V (ascribed to the nanostructured triboelectric films) was fabricated to power the drug delivery device. A planar screen-printed electrode (SPE) covered with the electrically-excitable drug nanocarrier PPy was connected to the TENG via a management circuit. The special design of PPy-coated SPE allowed the drug carriers not only

to receive sufficient electricity but also to realize a tunable drug release volume, as the volume can be increased simply by increasing the coverage area of PPy. This controllable drug release platform can achieve efficient and precise drug release: lightly rotating the TENG manually for 1.5 min can release $3\text{ }\mu\text{g}/\text{cm}^2$ of the drug from the PPy (Chapter 5).

- 5) A home-made power management circuit was designed, achieving two significant functions. First, the circuit was able to store and adjust the irregular output from TENG into a continuous and stable DC voltage. Second, its output could be easily tuned using an external resistor to a suitable DC voltage for efficiently powering the drug delivery device (Chapter 5). With the help of the circuit, the drug release rate of the system could be controlled in two ways, by changing the TENG operation duration or by changing the circuit resistance. Both methods provide a tunable range from $\sim 0.05\text{ }\mu\text{g}/\text{cm}^2$ to $\sim 0.25\text{ }\mu\text{g}/\text{cm}^2$ per minute (Chapter 6).
- 6) A self-powered and high-efficient transdermal drug delivery system was built. The electricity from the TENG was utilized in two medical processes, namely, stimulating drug release and activating iontophoresis treatment. As a result, this therapeutic system not only achieved controllable release rate but also enhanced drug delivery efficiency through skin when compared with conventional transdermal patches. The system was tested on the porcine skin *ex vivo*. Manually rotating the TENG for 10 min induced a delivery of $30.7\text{ ng}/\text{cm}^2$ of the drug in the dermis. In addition, the TENG-triggered drug delivery efficiency in dermis was $\sim 100\%$ higher than that obtained with conventional transdermal administration (Chapter 6).

1.3 Thesis organization

This Thesis demonstrates the design, fabrication and characterization of two types of functional nanomaterials for biophotonic and nanomedicine applications, and it is broadly divided into two parts each detailing the work and results for different but related topics. The first part describes the 2D TMDCs-based SPR optical biosensors for sensitivity enhancement. It discusses the sensitivity limitations for current SPR biosensors and their further influence on healthcare diagnostic applications. The theoretical modeling study for optimizing the 2D TMDCs-enhanced SPR configurations is presented. In addition, the techniques for synthesis and characterization of 2D TMDCs are demonstrated in detail. Finally, the experimental detection process, as well as the optical setups for measuring the sensitivity enhancement effect, are presented in detail. The second part demonstrates TENG-coupled skin patch devices for controllable drug delivery. It highlights the lack of solutions for current controlled drug delivery therapy and the challenges faced in the field of healthcare therapeutics. Furthermore, systematic solutions for precise and on-demand drug dosing by using TENG and nanostructured polymers are presented. The fabrication and characterization of a high output TENG are demonstrated in detail. Finally, the performance of controllable drug delivery tested on *ex vivo* porcine skin is presented.

This Thesis is divided into 7 chapters. Chapter 1 is the introduction of this Ph.D. Thesis, which mainly discusses its motivation, objectives, and significant contributions. In the motivation section, we give a brief introduction to the characteristics and applications of functional nanomaterials; we also discuss some of the major problems faced in biomedical fields. Besides, we discuss the unique advantages of the functional

nanomaterials chosen to solve these problems in certain applications. In the “Objective” section of the Thesis, we illustrate the key targets aimed to be achieved by the research work intended to solve the presented problems. In the “Contribution” section of the Thesis, we conclude by outlining the significant results and innovations in this Ph.D. Thesis.

Chapter 2 is the literature review. It discusses the background and current state of functional nanomaterials for biomedical applications and is divided into two parts, biophotonic and nanomedicine applications. The first part mainly introduces the biophotonics engineering strategies, such as the synthesis and characterization of two-dimensional materials. Moreover, their optical properties for biophotonic applications are also discussed. The second part mainly focuses on the engineering strategies for different types of stimuli-responsive polymers and triboelectric generators. It also discusses various functional properties of such nanomaterials and their applications in nanomedicine field.

Chapters 3 to 6 detail specific applications of functional nanomaterials: Chapters 3 and 4 focus on 2D TMDCs-based optical biosensors (first part topic), while Chapters 5 and 6 present the TENG-based drug delivery system (second part topic). The detailed description is as follows:

In Chapter 3, the theoretical study of the sensitivity enhancement of 2D TMDCs-based SPR biosensors is demonstrated. The key parameters that affect the detection sensitivity, such as incident wavelength, refractive indices of the used materials, and thickness of the 2D TMDCs are discussed. Then a theoretical model is developed using both equations and computational methods (e.g., transfer matrix method, finite element method). The optical properties of several 2D TMDCs, including WS₂, MoS₂, MoSe₂, and WSe₂ were measured and used in the model to

optimize the SPR sensor's sensitivity enhancement. Furthermore, the theoretical sensitivities to gradient analyte concentrations of each 2D TMDC-enhanced biosensor are discussed. Finally, the optimized configuration of 2D TMDCs-enhanced SPR biosensor and the corresponding sensitivity are demonstrated.

In Chapter 4, a 2D tungsten disulfide- (WS_2 -) based SPR biosensor with high sensitivity is presented. The deposition and the characterization of monolayer WS_2 are demonstrated. The design and fabrication of the WS_2 -coated SPR sensing chip are described in detail. The optical setups and the detection process of the WS_2 -enhanced chip, in both angular and phase modulation modalities, are then presented. Additionally, the results of real-time monitoring for the small molecules on the WS_2 sensing surface are presented.

In Chapter 5, a triboelectric nanogenerator (TENG)-based controllable drug release platform is presented. The operation mechanisms of the TENG and the drug release unit realized using functional nanomaterials are explained. The fabrication of the radial-arrayed rotary TENG and its output characterization are demonstrated in detail. The synthesis and engineering of the electric-stimulated drug nanocarrier are also presented. Next, the design of the home-made power management circuit used for regulating the TENG's original output for drug release action is discussed. The tests for accuracy and stability of the on-demand drug delivery are demonstrated. Finally, two simple methods for tuning the drug release rate, namely changing the TENG operating time and circuit resistance, are described.

In Chapter 6, a novel self-powered and high-efficiency transdermal drug delivery system created with nanocomposite materials and triboelectric nanogenerator (TENG) is demonstrated. The working principle of the system is described, whereby the electricity generated by TENG is utilized for both controlling the stimuli-responsive

drug release and enhancing the efficiency of drug delivery via iontophoresis treatment. The precise and efficient drug delivery process in porcine skins *ex vivo* is demonstrated in detail. The commonly used anti-inflammatory drug dexamethasone sodium phosphate (DEX) was employed in the *ex vivo* experiment. The quantitative determination of the amount of released DEX that penetrated into the porcine skin is presented. Next, DEX was replaced by fluorescein in an *ex vivo* experiment to give a visual demonstration of drug delivery profiles in the skin when treated with the proposed system. Finally, an *in vitro* experiment on RAW 264.7 cells was conducted to demonstrate that the drug bioactivity is not affected after release from the drug nanocarriers.

Lastly, Chapter 7 summarizes the main contributions of this Thesis and provides a broad outlook of possible further developments and applications for these contributions in the future.

Chapter 2 Literature Review

This Thesis focuses on the engineering of nanomaterials for biophotonic and nanomedicine applications, and it mainly consists of two parts: the use the 2D TMDCs to enhance the sensitivity of SPR biosensors for improving diagnostic precision, and the use of a nanostructured polymer and TENG to create a novel controlled drug delivery system for improving the drug's therapeutic efficacy. Therefore, to preface the work of this Thesis, this chapter provides a literature review for optical biosensors and controlled drug delivery, as well as for the relevant nanomaterials/nanodevices. It is broadly divided into two sections. In the first section, we give a brief introduction to the healthcare applications of biophotonics, highlighting the significance of optical biosensors for disease diagnostics. Next, we discuss the four main types of optical biosensors, comparing their detection limits and emphasizing the importance of SPR biosensors. Furthermore, we discussed the challenges of current SPR biosensors, namely, the limited sensitivity for the detection of small molecules. As a proposed solution, the two-dimensional materials, especially the TMDCs, are introduced in detail, showing their high potential for use in SPR sensing platforms to enhance the sensitivity. In the second section, we introduce the healthcare applications of nanomedicine and discuss the importance of controlled drug delivery for improving the therapeutic efficacy. Afterwards, we describe the current status of controlled drug delivery systems and highlight the role of the stimuli-responsive nanomaterials as the drug carriers. Here, the limitations of low controllability and large footprint of the existing stimuli-responsive delivery systems are discussed. Regarded as a promising solution for these limitations, an emerging nanodevice, the triboelectric nanogenerator (TENG), is

subsequently introduced, showing the potential to act as a self-powered supply to provide the exogenous stimuli for the drug delivery system.

2.1 Biophotonic applications

Biophotonics involves a combination of biology and photonics, which deals with the interactions between light and biological matters or/and systems. The ultimate goal of biophotonics is to reveal life, processes within cells, tissues, and even whole organs by using optical methods. Therefore, biophotonics combines various optical approaches to study the structural, chemical and functional properties of biological materials or systems, seeking to provide a multi-dimensional and comprehensive understanding of biological processes occurring in organisms. This information can be obtained from various optical phenomena, namely, interactions between electromagnetic radiations and living organisms or organic materials, including emission, absorption, scattering and reflection [17]. There are three major benefits of using optical techniques to study biological matters: i) The optical measures without direct contact to target analytes, i.e., the study of light-matter interactions taking place within living organisms allows minimum disturbance to their natural properties and activities. ii) Precise measurement, i.e., the optical methods are able to achieve ultra-sensitive detections, down to single molecular level, which is desired for the life science studies. iii) Fast measurement and instantaneous feedback [130]. Therefore, the biophotonics has been widely applied in the development of healthcare, especially in optical diagnostics and light-based therapeutics.

For the disease diagnostics, biosensors are significant analytical tools that are used to detect microorganisms and chemical or biological species. Furthermore, they are also used to monitor the changes in the concentrations of analytes as a function of

physiological changes *in vivo* [17]. The biosensors generally utilize the biological recognition elements to sense the presence of analytes, and create physical or chemical responses, that can be converted into a detectable signal by a transducer. According to the different types of stimulation and transduction, the biosensors can be divided into different categories, including optical, electrochemical, thermal biosensor and other types [131]. Compared with other biosensors, the optical biosensors have attracted great attention because they are capable of performing remote sensing, are immune to electromagnetic interferences, and can provide multiple channels detection within a single device [24].

2.1.1 Optical biosensors

Biosensor can be classified based on their detection principle, such as indirect detection, i.e. fluorescence, luminescence or radioactive interaction [132-134] and direct (label free) [135-137]. It can also be classified based on the physical working principle such as interferometry, diffraction grating and SPR, as shown in Table 2-1.

In fluorescence-based biosensors, either the biological recognition elements or the target molecules are labeled with fluorescent tags, e.g., dyes. The presence of the target molecules, as well as the interaction strength between target and recognition element can be indicated by the fluorescence intensity. Although the fluorescence-based detection can achieve ultra-high sensitivity with the detection limit down to single molecular level [23], it suffers from laborious labeling processes, in which is also possible to further affect the properties of the desired biomolecules. In addition, the bias of the fluorescence signals result in challenges in quantitative analysis, since it is difficult to control the number of fluorophores on each molecule precisely [27]. To overcome these problems, label-free detections have been developed, where the target

Table 2-1 Comparison of detection limits of four typical optical label-free biosensors, namely, surface plasmon resonance (SPR)-based biosensors, optical waveguide-based biosensors, optical ring resonator-based biosensors, and optical fiber-based biosensors. Table reproduced from ref. [24] © 2008 Elsevier B.V.

Technology platform	Optical structures	Analyte	Detection limit
Surface plasmon resonance	Surface plasmon resonance	Bulk solution	10^{-5} - 10^{-8} RIU [24]
	Surface plasmon resonance imaging (SPRI)	Bulk solution	10^{-5} - 10^{-7} RIU [24]
	SPRI	Protein	1nM [138]
	Optical heterodyne SPR	Protein	0.2 nM [139]
	Angle modulated SPR	Protein (PSA)	0.15 ngmL ⁻¹ [140]
Waveguide	Resonant mirror	Protein	~0.1 pgmm ⁻² [141]
	Symmetrical metal-clad waveguide	Bulk solution	2×10^{-7} RIU[142]
	Reverse symmetry waveguide	Cell	60 cells mm ⁻² [143]
Ring resonator	Ring on a chip	Bulk solution DNA Protein	10^{-4} to 10^{-7} RIU [144] ~100nM [145] 0.1nM [146]
Optical fiber	Fiber Bragg grating	Bulk solution	~ 10^{-6} RIU[147]
	Long-period grating	Bulk solution	10^{-4} RIU[148]
		Protein	2μg mL ⁻¹ [149]

molecules are detected in their original form instead of being labeled with fluorescent tags. This type of detection not only has the advantages of low-cost and easy operation, but also allows kinetic and quantitative measurements of molecular interaction. The label-free detection can be further divided into refractive index (RI) detection, absorption detection, and Raman spectroscopic detection, according to the different detected parameters of analytes. In this chapter, we mainly focus on the optical label-free biosensors that are based on RI detection. A more detailed introduction of optical

absorption and Raman-based biosensors can be found in literature [25, 26]. Here, we will discuss the structures and performances of four typical optical label-free biosensors, namely, surface plasmon resonance (SPR)-based biosensors, optical waveguide-based biosensors, optical ring resonator-based biosensors, and optical fiber-based biosensors.

Surface plasmon resonance-based biosensors. The surface plasmon resonance (SPR) refers to the resonant oscillations of conduction electrons stimulated by polarized incident light at a so-called resonance angle at the interface between a positive and a negative permittivity materials [150]. Such oscillations can be regarded as resonant surface plasmon waves that propagate along the interface with an evanescent electric field decaying exponentially into the surrounding media. The evanescent electric field is extremely sensitive to the refractive index of the medium making SPR-based biosensors able to monitor the tiny variations of the refractive index of the analytes [38]. The best known configuration of SPR biosensors is the Kretschmann coupling configuration, which mainly consists of a prism, metal layer (e.g. gold or silver) and the dielectric layer, as shown in Figure 2-1a. The prism is used to couple the incident light with the surface plasmon to excite the resonance, based on the principle of attenuated total reflection. The metal and dielectric layers create the interface of the negative and positive permittivity materials [151].

Optical fiber based biosensors. The optical fiber generally consists of a cylindrical core and a surrounding cladding, where the refractive index of core is higher than that of the cladding. Therefore, light rays propagate in the optical fibers along the core by the principle of total internal reflection (TIR), with negligible energy loss. For the optical fiber-based biosensors, the fibers serve as the transduction element; and the biosensing process is based on the transmission of the light along the fibers to the site of detection, as shown in Figure 2-1b. According to the different interaction sites, the

optical fiber based biosensors can be classified into intrinsic sensor and extrinsic sensor. For the former, the interactions of the light and analytes occur within the fiber; while for the latter, the fiber is usually used to couple light to the target detection region [152]. Due to the advantages of low-cost and easy fabrication, such biosensors can be further combined with different types of spectroscopy techniques, such as absorbance, refraction and luminescence [153].

Optical ring resonator based biosensors. The optical ring resonator can be regarded as a ring-shaped waveguide, where a resonant optical mode forms at the

Figure 2-1 (a) The basic Kretschmann configuration of the surface plasmon resonance based sensor. Figure reproduced from Ref. [356] © 2013 Optical Society of America. (b) The structure of optical fiber based sensor. Figure reproduced from Ref. [357] © 2016 Society of Photo-Optical Instrumentation Engineers. (c) The structure of the optical resonator based biosensors. Figure from Ref. [358] © 2015 Elsevier B.V. (d) The basic configuration of waveguide based sensor. Figure from Ref. [359] © 2012 Optical Society of America.

curved boundary between the high and low refractive index media due to the total internal reflection of light, as shown in Figure 2-1c. The resonant wavelength is expressed as: $\lambda = 2\pi r n_{eff} / m$, where the r indicates the radius of the ring resonator, n_{eff} represents the effective refractive index of the resonant mode, and the m is an integer number. The resonant light propagated in the ring resonator generates an evanescent wave, which is sensitive to the refractive index change of the medium, and is able to penetrate into the surrounding medium with a depth of hundreds nanometers [154]. Therefore, in the optical ring resonator based biosensors, the resonant evanescent wave can be utilized to sense the refractive index changes of the analytes that near the resonator surface. In contrast to the linear waveguide- or optical fiber-based biosensors where the interaction length of light-analyte is determined by the physical size of the sensor, the effective interaction length L_{eff} of the optical resonator based biosensors is determined by the resonator quality factor Q [155], as $L_{eff} = Q\lambda / 2\pi n$. The λ indicates the resonant wavelength and n is the refractive index of the ring resonator. This property allows smaller footprint of the biosensors and less volume of analytes [24].

Optical waveguide based biosensors. The optical waveguide is a physical structure that used to guide the electromagnetic wave within the optical spectrum. It can be classified according to the geometry (i.e., strip, planar or optical fiber), the refractive index distribution, and the materials (e.g., metal, glass, semiconductor and polymer) [156, 157]. In the optical waveguide based biosensors (Figure 2-1d), the incident light is coupled into the waveguide at the resonance angle, and generates evanescent wave outside the waveguide, resulting in the resonance angle sensitive to the refractive index change of medium near the waveguide [24]. In this way, the waveguide based biosensors can be used to detect the refractive index of the analytes.

The sensing performance, especially the detection limit (DL) of four optical biosensors above are compared as shown in Table 2-1. It is obvious that all of them can be used to detect different types of analyte including bulk solution, protein and DNA. Generally, SPR based biosensors exhibit the lower detection limit than other ones. This is likely because the SPR sensing mainly relies on strength of the electric field of the surface plasmon wave, which is extremely sensitive to the refractive index changes of the surrounding medium. Attributed to the sensing mechanism, SPR biosensors can also realize real-time and low-cost detection. These remarkable properties allow SPR biosensors been widely used in the monitoring of binding kinetics and affinity and detection of biomolecules for disease diagnostics. However, in these applications, SPR biosensors are found unable to detect small analytes (normally, molar weight < 8 kDa), such as ssDNA, hormones and cytokine [158]. There needs an improvement of 1-2 orders of magnitude of sensitivity to overcome this limitation. To address this problem, some nanomaterials have been employed to functionalize the sensing surface of the SPR biosensor to modify the SPR electric field [38]. In the following sections, we will introduce the two-dimensional materials, especially the transition metal dichalcogenides (TMDCs) as a solution to improve the sensitivity.

2.1.2 Two-dimensional materials

Layered materials form one of the most familiar material types for human beings as they have been utilized for more than a thousand years. The first application of layered materials can date back to 400 C.E when layered clays were used to make dyes [159]. However, the great potential of layered materials had not been fully realized until 2004, when graphene was first extracted from graphite [160]. Graphene is an allotrope of carbon, comprising of a monolayer of carbon atoms arranged in a

hexagonal lattice. Graphene is a semi-metal with zero bandgap, and it has unique material properties potentially useful in many applications including electronics, optics and materials science. It is reported that graphene exhibits remarkable electron mobility of more than $15000 \text{ cm}^2 \cdot \text{V}^{-1} \cdot \text{s}^{-1}$ at room temperature. The scattering of graphene acoustic phonons limits the mobility to $2 \times 10^5 \text{ cm}^2 \cdot \text{V}^{-1} \cdot \text{s}^{-1}$ at room temperature, which is 4.5×10^3 times higher than that of copper [161, 162]. These prominent properties make graphene an ideal candidate for potential usage in various devices and applications, such as solar cells [163], gas/liquid sensors [164], photodetectors [165], and light-emitting diodes [166]. The outstanding performance of graphene has attracted researchers' attention and stimulated them to search for more such graphene-like materials. Therefore, traditional layered materials including hexagonal boron nitride, TMDCs (e.g., tungsten disulfide, molybdenum disulfide, tungsten diselenide) and black phosphorus have revived researchers' interest. The 2D atomic layers of such materials have been successfully exfoliated from their bulk counterparts and investigated. The results have shown that the properties of all these single-layer materials are significantly different from those of their bulk crystals. For example, the emission efficiency of the 2D TMDCs are reported to be four orders of magnitude higher than that of the in corresponding bulk crystals, due to the difference in bandgap [167]. Also, for the surface enhanced Raman spectroscopy (SERS) peaks of atomic hexagonal boron nitride (h-BN) are much stronger than those from bulk h-BN crystals, attributed to their greater surface adsorption capability [168, 169].

In recent years, with the discoveries of ever more interesting and unusual 2D materials, systematic studies including basic theory and synthesis techniques as well as applications have been widely carried out throughout the world. Among various 2D

materials, the TMDCs monolayers have received special attention due to their unique properties:

- 1) TMDC monolayers have direct bandgap, which makes TMDCs useful in optoelectronic and electronic applications such as photodetectors, light-emitting devices, transistors, etc.
- 2) Ultra-high light absorption more than 5%, which is more than 2.2 times that of graphene [51].
- 3) Through van der Waals forces, they can be used to create novel heterostructured three-dimensional (3D) materials along with other 2D materials such as graphene and h-BN [170].

These exciting properties make TMDC extremely useful in optoelectronic applications, with virtually unlimited possibilities for their usage. The chemical elements that can be used to form TMDCs are shown in Figure 2-2; their combinations would allow for about 40 TMDCs existing in nature. Their specific properties, synthesis methods and characteristic properties are described in detail below.

2.1.2.1 Synthesis of 2D TMDCs

Developing effective and reliable synthesis methods is the first step to characterize and investigate the intrinsic physical properties of the 2D TMDC materials. According to literature, various methods have been investigated to synthesize 2D TMDCs. Here we introduce and discuss the advantages and disadvantages for the three most common methods, namely, mechanical exfoliation, chemical vapor deposition, and wet chemical synthesis.

Exfoliation. This is the most direct method to obtain the 2D layers, and it refers to peeling atomically thin flakes from a bulk layered crystal. This method can be further divided into mechanical and liquid exfoliation.

For mechanical exfoliation, a simple and commonly used approach is micromechanical cleavage, which has been developed from graphene synthesis methods and has proven to be effective and suitable for a variety of other 2D materials, including TMDCs and boron nitride [171-174]. It can be realized either by rubbing two layered crystals or by using an adhesive tape. After rubbing two layered crystal against each other, a variety of flakes can be obtained, and the monolayers are identified among these flakes with the aid of an optical microscope [175]. When using the adhesive tape, the monolayers are obtained by sticking the tape onto the surface of the layered crystal and then repeatedly folding/unfolding the tape until thin flakes are isolated [176]. The biggest advantages for mechanical exfoliation are simplicity and production of the highest-quality 2D materials [177]. However, the drawbacks of low production efficiency and yield have hindered its widespread adoption. Another solution, liquid

H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg	3	4	5	6	7	8	9	10	11	12	Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	La-Lu	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	Ac-Lr	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Cn	Uut	Fl	Uup	Lv	Uus	Uuo

Figure 2-2 The transition metal dichalcogenides in the periodic table of element.

From Ref. [327] © 2013 Macmillan Publishers Limited

exfoliation, has therefore been developed, aiming to cleave the atomic flakes from the bulk crystal in liquids with chemical techniques.

Here, we introduce two specific approaches: ion intercalation and sonication. For the ion intercalation process, we give the following example. The lithium ion, for example, is induced into the bulk MoS₂ crystal by immersing the natural crystal into butyl-lithium solution for two days. The lithium intercalation can weaken the adhesion between the MoS₂ interlayers and reduce the relevant energy barriers, resulting in an increase in the spacing between atomic layers [178]. The exfoliation is finally completed with the subsequent treatment of ultrasonication or thermal shock [179]. However, the disadvantage of this approach is that the ion intercalation likely causes deformation of the original TMD layers. For instance, the exfoliated monolayers may become Li_xMoS₂ instead of MoS₂.

In the second approach, sonication, the basic mechanism is to use high-energy jets formed by cavitation bubbles to break up the out-of-plane chemical bonds [180]. Such bubbles are generated by ultrasonic waves in a specific solvent such as N-methylpyrrolidone. A variety of 2D TMDCs layers including WS₂, MoS₂, MoSe₂ are produced efficiently with this method [181]. Although this exfoliation method is an easy and swift way to obtain TMDCs nanosheets, it also has some limitations, such as the inability to control the size and thickness of the nanolayers.

CVD. In order to develop systematic synthesis methods that can realize sizable, uniform, and scalable TMDCs monolayers, chemical vapor deposition (CVD) was widely investigated and demonstrated. The summary of CVD-based TMDC growth methods is shown in Table 2-2. Molybdenum disulfide (MoS₂) is one of the first 2D TMDCs materials to be investigated; therefore, there are a variety of CVD synthesis

methods developed based on MoS₂. Here, we take MoS₂ as an example to introduce three commonly used methods.

1) The sulfurization of transition metal/metal oxide: In this method, the MoS₂ flakes are obtained directly by sulfuring the transition metal or its oxide with sulfur vapor [182, 183]. It is reported that the Mo films deposited on a SiO₂/Si substrate were placed in the center of the tube furnace at a temperature of 750 °C, while the pure sulfur was placed at a low-temperature (slightly above 113 °C) and upwind zone of a quartz tube. By controlling the temperature, the MoS₂ flake can be obtained by subsequent thermal annealing in the sulfur vapor. Since the Mo thin film was deposited on the substrate in advance, the size and thickness of the produced MoS₂ are dependent on that of the original Mo film. Similarly, the MoSe₂ flakes were also obtained efficiently by using such a method [184]. Besides the advantage of simple operation and the high production rate, this method provides a promising approach to realize large-area TMDC

Table 2-1 Summary of chemical vapor deposition based TMDCs growth conditions. Ref. [327] © 2013 Macmillan Publishers Limited

TMD	Precursor	Growth condition	Morphology
MoS ₂	(NH ₄) ₂ MoS ₄ in DMF by bubbling with Ar	200 mTorr to 2 Torr at 400 °C	Hexagonal flake with 2 to 5 nm thickness
MoSe ₂	MoCl ₅ (heating at 255 °C) C ₈ H ₁₈ Se (70 °C) or C ₄ H ₁₀ Se (90 °C)	Atmosphere at 450 ~ 600 °C	Thin film for C ₈ H ₁₈ Se Needle-like structures for C ₄ H ₁₀ Se
WS ₂	WOCl ₄ (heating at 176 °C) HS(CH ₂) ₂ SH (heating at 63 °C)	Atmosphere at 250 ~ 600 °C	Thin film
WSe ₂	WOCl ₆ (heating at 260 °C) C ₄ H ₁₀ Se (heating at 70 °C)	Atmosphere at 450 ~ 600 °C	Plate-like crystallites mixed with needle-like crystal
VSe ₂	V(NMe ₂) ₄ (heating at 130 °C) C ₈ H ₁₈ Se (heating at 90 °C)	Atmosphere at 250 ~ 500 °C	Thin hexagonal platelets
TiS ₂	Ti(NMe ₂) ₄ (heating at 150 °C) Bu ^t SH (57 °C) or Bu ₂ S ₂ (115 °C)	Atmosphere at 300 ~ 600 °C	Thin film

flakes. However, the drawback is that the synthesized MoS₂ (monolayer or multiple layers) are combined on the substrate, and it is difficult to separate them [185]. This method can be employed in the applications requiring high yield but low surface uniformity.

2) Vapor phase reaction with chalcogen precursors: In this method, to grow the TMDC layers, the transition metal oxide is usually regarded as the metal precursor, while pure sulfur powder is used to provide the sulfur element. This method is almost the most common one, since it can produce not only crystalline TMDCs layers efficiently, but also can achieve high surface uniformity [186-189]. In the report by Ling *et al.*, used oxide MoO₃ powder placed in a crucible at the center of a quartz tube chamber, with the sulfur powder put in another crucible and placed upstream of the tube. The target substrate was placed facing the MoO₃ contained crucible. Ultra-high purity argon gas was induced into the reaction chamber before/during the growth procedure. The temperatures for MoO₃ and sulfur were controlled separately, with the MoO₃ at 650°C and the sulfur at 180°C [187]. This method was demonstrated by many researchers to be suitable and effective for a variety of TMDC flakes, such as MoSe₂, WS₂, and WSe₂ [190-192]. For example, it is reported that WS₂ monolayers can be produced by WO₃ powder and sulfur power, with a deposition temperature of 700-850°C and 200°C respectively[190]. Besides the solid-phase chalcogen precursors, the gas-phase alternative was explored to further improve the surface uniformity of the atomic TMDC layers [188]. Chen *et al.* reports that WS₂ flakes were synthesized from tungsten chloride (WCl₆) and hydrogen sulfide (H₂S) gas. In this growth procedure, the SiO₂/Si substrate was placed at the middle of the tube furnace and the gas-phase WCl₆ was induced into the chamber with pure argon Argon (Ar) as carrier gas at 100 °C. When

the target substrate was heated to 700°C, the WCl₆/Ar (Ar at 20 sccm) and the hydrogen sulfide (H₂S) were injected into the furnace at a pressure of 0.27 Torr.

3) Thermal decomposition: In contrast to the conventional vapor-phase chemical reaction deposition, a thermal decomposition approach has been reported using a two-step thermolysis process [193]. Liu *et al.* immersed a pre-cleaned sapphire substrate in ammonium thiomolybdates [(NH₄)₂MoS₄] solution and baked it at 120°C for 30 min, resulting in a [(NH₄)₂MoS₄] thin film deposited onto the substrate. The substrate was subsequently annealed in flowing Ar/H₂ gas (1 Torr, flow rate=4:1) at 500°C for 6 min. In this step the MoS₂ layers were produced due to the thermal decomposition, as shown in the following chemical equation: $(\text{NH}_4)_2\text{MoS}_4 + \text{H}_2 \rightarrow 2\text{NH}_3 + 2\text{H}_2\text{S} + \text{MoS}_2$. Afterwards, a second annealing was conducted in Ar (500 Torr) with the sulfur at 1000 °C. The addition of sulfur contributed to the improvement of the crystallinity and the electrical performance of the atomic MoS₂ layers. This method proved to be simple, scalable, and also translatable for other TMDC flake synthesis [182, 183, 194-196].

2.1.2.2 Characterization methods

Characterizing the morphology and the molecular structure of the two-dimensional TMDCs is essential to investigate their intrinsic physical properties in electronics, optics and structure. Therefore, it is significant to develop effective and accurate characterization methods. Here, we discuss two commonly used ones.

Raman spectroscopy. Raman spectroscopy is one of the most popular methods for characterizing TMDC flakes since it can provide a range of important physical information, such as the presence of defects, stacking, monolayers, and number of layers, without any damage or deformation to the sample materials. The mechanism is

based on the Raman scattering theory, where the absorbed laser light interacts with the vibrations, i.e. phonons, of the sample's material, resulting in an energy shift of the re-emitted photons. Such an energy shift can be regarded as a specific signal that reflects relevant information of the vibrations and other excitations. Specifically, the electromagnetic wave emitted from the illuminated spot can be collected by a lens and spectrally analyzed using a monochromator. In this way, materials with different vibrational or rotational modes can be identified.

Take the four 2D TMDCs (MoS_2 , WS_2 , MoSe_2 , WSe_2) for example. They share the same trigonal prismatic structure, but they have different symmorphic space group dependent on the number of monolayers (odd or even) [183]. Therefore, the point group symmetry can be used to estimate the number of layers. In addition, three active first order modes are observed, namely E_{1g} , E_{2g}^1 , and A_{1g} , when such four 2D TMDCs are excited with high frequencies. The E_{1g} and E_{2g}^1 belong to the in-plane modes, while A_{1g} is the out-of-plane mode. For samples with an odd number of layer, the three modes are E'' , E' and A'_1 , while becoming E_{2g}^2 , E_{2g}^1 , and A_{1g} for even number of layers [197]. With the number of layers increase, the frequencies decrease for the in-plane modes while the increase for out-of-plane mode [176]. Furthermore, a second order Raman mode is observed in the WS_2 monolayer with 514.5 nm excitation wavelength [198]. This mode is involved in the longitudinal acoustic (LA) mode at the M point of the Brillouin zone, usually labeled as LA(M). It can accurately distinguish the monolayer from a few layers, which has been used as a fingerprint for the WS_2 monolayer.

There are various types of Raman spectroscopy, including polarized Raman [199], resonant Raman [200], surface enhanced Raman [201] and so on.

Photoluminescence spectroscopy. Photoluminescence (PL) refers to the light emission from an analyzed substance after absorption of photons or other

electromagnetic waves. The basic instrumentation consists of a radiation source (e.g., laser), a filter for selecting the radiation band, and a detector. PL is usually used to detect the bandgap, defects, and impurity levels of the sample. For example, the direct and indirect bandgap semiconductors can be easily and accurately distinguished by PL. It is noted that only direct-gap semiconductors exhibit PL since indirect-gap materials cannot emit photons directly. Currently, PL spectroscopy is one of the most common characterization methods for TMDC monolayers. This approach appeared in 2010 when molybdenum disulfide (MoS_2) monolayers were first demonstrated to have different photoluminescence characteristics than their bulk counterpart [202]. The original MoS_2 crystal is a typical indirect-gap semiconductor with negligible photoluminescence. However, as the thickness decreases to the nanoscale, the bandgap of MoS_2 changes from indirect to direct, leading to a gradual increase in the photoluminescence intensity. Similar results were observed in other atomically thin TMDCs [203]. Moreover, the peak emission wavelength can be utilized to identify different TMDC materials. When excited with a wavelength of 532 nm, the peak emission wavelengths for MoSe_2 , WSe_2 , MoS_2 , and WS_2 are located at 795 nm, 755 nm, 620 nm, and 625 nm, respectively [202, 204, 205]. PL spectroscopy, therefore, has been developed as an effective tool to determine TMDC types as well as their number of layers.

In addition to the Raman and PL spectroscopy methods mentioned above, there are many other characterization methods, such as optical microscopy, atomic force microscopy (AFM) and transmission electron microscopy (TEM) [183, 206]. Optical microscopy can be used to observe the triangular shape typical for the TMDC crystals. AFM is a scanning microscopy which has a high resolution that is three orders of

magnitude larger than the optical diffraction limit of an optical microscope. It can be used to determine the exact thickness of atomically thin TMDCs.

2.1.2.3 Optical properties and applications

Direct bandgap. Strong PL is the most special optical property of TMDC monolayers, because such property has not been observed in their bulk counterpart. Specifically, the bulk TMDCs (MoS_2 , WS_2 , MoSe_2 , WSe_2) are typical indirect-gap semiconductors like silicon, and they are unable to emit photons after absorbing radiation. Interestingly, such TMDC bulk crystals can become direct-gap semiconductors when they are thinned to monolayers, demonstrated in both theoretical and experimental studies [172, 207-209]. Tongay *et al.*, when measuring and comparing the bulk crystal and atomically thin MoS_2 , found that the PL intensity increased as the thickness decreased, with the strongest PL intensity observed for monolayers [202]. This phenomenon indicates that the luminescence quantum efficiency of MoS_2 monolayers is much higher than that of the bulk crystal, which is further verified by the experimental measurements. This characteristic has been reported in other nanoscale semiconductors as well. For direct-gap semiconductors, such as InAs and GaAs [210], both the bulk crystal and their nanosheets monolayers display obvious photoluminescence. The atomic films of indirect-gap semiconductors like silicon, also exhibits stronger luminescence compared with the bulk counterpart, but the underlying physics is profoundly different from that in MoS_2 . For silicon nanocrystals, the enhanced luminescence arises from quantum confined electronic states involved in increased emission energy [211]. Most importantly, the silicon nanosheet remains an indirect-gap semiconductor and displays a low radiative transition rate after scaling down from the bulk crystal [212]. However, the enhanced luminescence of MoS_2 monolayers is attributed to direct electronic transitions and a

dramatically slow electronic relaxation. Furthermore, it shows a high radiative recombination rate [202].

Optical dielectric function. The optical dielectric function is significant to describe the light-matter interactions of materials [213-215]. The dielectric function is denoted as $\varepsilon(\omega)$, which refers to the complex permittivity ε as a function of angular frequency ω . It indicates that the optical dielectric function of materials is dependent on the excitation wavelength. The commonly used method to study the optical dielectric function is to measure the reflectance and absorption spectra and to use Kramers-Kronig constrained analysis. Heinz's group has conducted such measurements and

Figure 2-3 The measured reflectance (a)-(d) of the TMDCs monolayers and the corresponding real part (e)-(h) and imaginary part (i)-(l) of their optical dielectric functions. Ref. [50] ©2014 American Physical Society

investigations of optical dielectric function for four TMDCs (i.e., WS₂, MoS₂, MoSe₂, WSe₂) [50]. Figure 2-3 presents the dielectric functions of TMDC monolayers resulted from these measurements [216, 217].

Applications. In recent years, the atomically thin TMDCs have been widely employed in various electric and photoelectric applications including photodetectors, solar cells, and light-emitting devices [51, 218, 219]. Pospischil *et al.* realized a WSe₂-monolayer based *p-n* junction, which was used as solar cell, photodiode and light-emitting diode, with a light-power conversion up to ~0.5% and a luminescence efficiency of ~0.1% [220]. Ultra-efficient and flexible photovoltaic devices were developed by Novoselov's group, demonstrating a high photoresponsivity of above 0.1 A/W with an enhanced quantum efficiency exceeding 30%. Such results are attributed to the enhanced light-matter interactions and photon absorption caused by the atomically TMDCs thin films [51]. In addition, the biomedical applications of TMDCs were rapidly developed in recent years, since TMDCs have been demonstrated to be nontoxic and have good biocompatibility [221-223]. The TMDC nanosheets have been engineered as a sensing platform, owing to the planar structure and large surface area (large surface area to volume ratio). Combined with various current biosensing technologies, TMDCs thin film-based biosensors have been investigated, including electrochemical, gas and fluorescence sensors [223]. Xia and co-workers demonstrated a MoS₂ nanosheet-based H₂O₂ biosensor with a detection limit of 0.26 μ M [224]. Polyethylene glycol functionalized MoS₂ nanosheets have been reported by Liu *et al.* for use in a drug delivery system capable of realizing anti-tumor effects through photothermal therapy, due to the strong absorbance in near-infrared [225]. Cheng *et al.* reported a WS₂ nanosheet-enhanced multifunctional photothermal therapy system

capable of both ultra-efficient cancer cell ablation and accurate *in vivo* bioimaging of target tissue [221].

2.2 Nanomedicine

Nanomedicine is a field which has emerged in recent decades, whose breadth is captured by two generally accepted definitions. The one from ESF2004 that has been presented in Chapter 1, Section 1.1.2. The applications of nanomedicine are shown in Table 2-3. Other experts defined nanomedicine as the use of nanoscale or nanostructured materials in medicine that according to their structure have unique medical effects” [53, 226]. Both concepts mentioned that nanomedicine is developed from nanotechnology, which generally refers to the creation or/and use of materials at the level of molecules and atoms (with sizes generally less than 100 nm) [54]. With the rapid development of nanotechnology and nanomaterials in the last two decades, nanomedicine has also garnered prominent achievements in healthcare applications, including novel drug delivery, tissue engineering, *in vitro* diagnostics, *in vivo* imaging, and active implants [3-6], as detailed in Table 2-3.

In particular, drug delivery is the dominant research field in nanomedicine, with a share of 76% of scientific articles and 59% of the patents according to the Science Citation Index and European patent office (EPO) database [53], as shown in Figure 2-4. The dominance of drug delivery in nanomedicine is likely due to two reasons: First, the therapeutic benefit to patients has been found to be correlated to the method of drug formulation and delivery within the body more than the potency of a drug. This is because the delivery mode affects various factors that contribute to the therapeutic benefit, including distribution, cellular uptake, pharmacokinetics, metabolism, excretion and clearance, and toxicity [6]. Therefore, it is necessary and critical to

improve the fundamental knowledge of how drug delivery affects efficacy and safety, as well as to develop novel drug delivery technologies [61]. Second, a variety of

Table 2-2 Brief description of the six main healthcare applications of nanomedicine, and their corresponding definitions and examples. Table adapted from ref. [53] © 2006 Nature Publishing Group

Healthcare applications	Definition and examples
Drug delivery	Nanoscale particles/molecules developed to improve the bioavailability and pharmacokinetics of therapeutics. Examples are polymer nanoparticles, liposomes (and virosomes), nanosuspensions and polymer therapeutics. Drugs in which a protein is combined with a polymer nanoparticle or chemical nanostructure to improve its pharmacokinetic properties would be classified as nanomedicine-based drug delivery.
Drugs and therapy	Nanoscale particles/molecules used in the treatment of diseases that according to their structure have unique medical effects and as such differ from traditional small-molecule drugs. Examples include drugs based on fullerenes or dendrimers.
Biomaterials (Functional nanomaterials)	Self-assembling particles or other types of nanomaterial that improve the mechanical properties and the biocompatibility of biomaterials for medical implants. Examples include nanocomposite materials used as dental fillers and nanohydroxyapatite used for implant coatings and bone substitutes. Also, decoration of implant materials with biologically active signal molecules that stimulate, for example, cell growth or differentiation.
In vitro diagnostics	Novel sensor concepts based on nanotubes, nanowires, cantilevers or atomic force microscopy applied to diagnostic devices/sensors. These sensors aim to improve the sensitivity, reduce production costs or measure novel analytes. For example, Bioforce's Virichip uses atomic force microscopy for the detection of whole viruses for early diagnosis of viral infections.
In vivo imaging	Nanoparticle contrast agents, particularly for MRI and ultrasound that provide improved contrast and favorable biodistribution. For example, superparamagnetic iron oxide nanoparticles for use as MRI contrast agents.
Active implants	Particles/materials that improve electrode surfaces and biocompatibility of device housings. Examples include Biophan's magnetic nanoparticle-based coating that makes medical implants safe for use with MRI imaging and nanomaterials used for retina implants to improve the charge transfer at the electrode tissue interface.

Figure 2-4 (a) Breakdown-of the main areas of activity in nanomedicine as reflected by: a) Journal publications. Source: Science Citation Index, 1984–2004, VDI Technologiezentrum GmbH, Düsseldorf, Germany. (b) Patent filings worldwide. Source: EPODOC database, 1993–2003, European Patent Office, Rijswijk, The Netherlands. Figure adapted from Ref. [53] © 2006 Nature Publishing Group

functional nanomaterials such as polymer nanoparticles [227] and liposome hybrids [228], can be synthesized, designed, and combined with therapeutic agents to realize ideal treatments, such as controllable drug delivery and targeted drug release to enhance the therapeutic efficacy [73, 229-231]. In the following sections, controlled drug delivery and related functional nanomaterials and assisting nanodevices are described in detail.

2.2.1 Controlled drug delivery

The motivations for controlled drug release initially arose from the problems associated with conventional drug delivery modes. Oral and injectable drug administrations are the most common modes [78] since they are easy to operate and

have high patient compliance. Generally, upon drug administration, the drugs will be delivered into the systemic circulation and diluted into the fluids, bound to plasma protein, whereupon they associate with body tissues [232]. The variation in time of the drug concentration in plasma for different drug administration methods is shown in Figure 2-5. In the required treatment time, the ideal drug plasma level should remain approximately in the middle of the therapeutic window, which is above a minimum effective concentration (MEC) and below a minimum toxic concentration (MTC) [233]. However, upon the conventional administrations of tablet or injection, the drug plasma concentration increases rapidly to therapeutic concentrations but also decreases quickly due to the distribution, metabolism, and excretion [62], resulting in little time spent inside the therapeutic window. Therefore, in order to prolong the effective therapeutic time, the frequent and repeated dose is commonly required [6]. This drug delivery mode results in two major problems:

Figure 2-5 Comparing plasma concentration variations in the time for the three types of administration. Figure reproduced from Ref. [360] © Controlled Release Society 2012

- 1) Increased possibility of side effects and toxicity. Upon each drug administration, drug levels increase to effective concentrations, but they likely rise above the minimum toxic level. The repeated doses therefore significantly increase the likelihood of unwanted side effects.
- 2) Increased therapeutic cost. The drug plasma level decreases rapidly due to body fluid circulation, which is a significant waste of drugs and relevant materials [6, 63].

To address this problem, other drug administration methods [234-236] (detailed in Section 2.2.2) and novel drug delivery technologies including, stimuli-responsive drug nanocarriers [76, 83], and functional nanodevices [237-239] have been extensively developed. They aim to achieve superior control of drug exposure over time, to enable precise control of drug release rate, to shield drugs from premature elimination, or to assist the drug in crossing physiological barriers. Additionally, some systems also perform targeted drug release, meaning to shepherd the drug to the desired site of action while minimizing drug exposure elsewhere in the body [232].

2.2.2 Other drug delivery routes

Besides the most common used oral and injectable drug administration routes, a variety of delivery modes such as transdermal, pulmonary, nasal, and ocular routes, as well as surgical implantation have also been widely developed, as shown in Figure 2-6, some of them have even been created with the aid of functional materials/nanomaterials [6]. The intended tissues, the applied materials, and the advantages/disadvantages of each drug delivery mode have been listed in Table 2-4. These various drug delivery modes can be tailored for different therapeutic requirements of patients. For example, the surgically implanted drugs can directly access diseased tissues, which improves the

drug delivery efficacy but at the same time increases the potential of infection due to

Table 2-3 The advantages, disadvantages, the target organs or tissues and the materials examples of a variety of drug delivery routes. Table adapted from ref. [6] © 2018 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

Drug delivery routes	Advantages/Disadvantages, Targets, Examples
Injections: intravenous (IV), intramuscular (IM), subcutaneous (SQ), depot	Advantages: applied to a large number of drugs, rapid onset (IV), 100% bioavailability Disadvantages: rapidly cleared from the body (IV), frequent injections required (IV), liver toxicity (IV) Targets: tissues with blood, access (IV), systemic muscle (IM) Examples: chemotherapy (IV), vaccines (IM), insulin (SQ), hormones (Depot)
oral	Advantages: high patient compliance, ease of use Disadvantages: low bioavailability, variable absorption, lack of targeted systems Targets: systemic Examples: liquid medications, capsules, pills
Transdermal	Advantages: painless administration, sustained and controlled release, active control of continuing and discontinuing administration, reduced side effects, high patient compliance Disadvantages: low bioavailability, expensive, bulky (materials) Targets: systemic skin Examples: patches, microneedles, creams
Pulmonary (i.e., inhalation)	Advantages: ease of use, high bioavailability, rapid absorption and systemic uptake, direct access to lungs. Disadvantages: administration devices are large, bulky, inconsistent delivery due to variation in patient technique, local lung toxicity and immunogenicity Targets: lungs, systemic, brain, Examples: aerosols, dry powders, nanoparticles, microparticles
Surgical implantation	Advantages: direct access to a range of diseased tissues, reduced off target toxicity Disadvantages: potential infection due to surgery, foreign body response and rejection, materials can be large, bulky, requires surgical intervention, potentially requires anesthetics, potentially requires immunosuppressing drugs. Targets: local, to a range of diseased tissue. Examples: polymer implants, microparticles, hydrogels
Mucosal routes: vaginal, nasal, buccal	Advantages: ease of use, noninvasive, self-administrable Disadvantages: low bioavailability, variable absorption Targets: systemic, brain (nasal), the local nervous system (nasal) Examples: films, sprays, gels

Figure 2-6 The examples of new drug delivery routes in addition to pills and injections. Figure adapted from Ref. [6] © 2018 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

the surgery [229, 240]. Transdermal delivery is a painless and low side effect drug administration method, but it has relatively low drug delivery efficacy due to the barrier of skin [241]. Although the utilization of microneedles can improve the efficacy, it is expensive for clinical applications [242, 243].

2.2.3 Transdermal drug delivery

Among the above-mentioned routes of drug delivery, transdermal delivery is one of the most popular modes that has been widely used, due to its unique advantages. Compared with hypodermic injections, it is painless. In addition, it reduces the risk of dangerous medical waste such as needles and the spread of diseases caused by needle re-use (especially in underdeveloped areas). Compared to oral administration, they can

achieve prolonged drug release (up to one week), which greatly improves patient compliance [241, 244-246].

The use of transdermal delivery can be traced back thousands of years, and people can get treatment by putting drugs on the skin. As the development of medical technologies, a variety of drugs can be delivered by transdermal delivery systems. In 1979, the first transdermal system for systemic delivery-a three-day patch that delivers scopolamine to treat motion sickness-was approved in the United States. Ten years later, nicotine patches became the first transdermal blockbuster, making transdermal delivery a popular drug delivery mode for the public. Nowadays, the transdermal delivery systems are able to delivery various drugs, such as lidocaine, estradiol, testosterone, fentanyl, etc [241, 247].

However, compared with oral and injective administrations, transdermal delivery is significantly limited by the skin permeability [248]. Therefore, many researchers are aiming to increase the skin permeability by reversibly disrupting stratum corneum structure, or to provide an extra driving force for transport into the skin [249]. There are various methods including, iontophoresis, chemical enhancers, and non-cavitation ultrasound, and so on, which are proved to have good performance in clinical applications [250].

2.2.4 Stimuli-responsive nanocarriers

In order to achieve the controlled drug release, stimuli-responsive nanomaterials have been developed which enable loading of drugs (or therapeutic agents) and respond to specific stimuli for actuating drug release [76]. These stimuli are generally divided into exogenous and endogenous stimuli. The nanomaterials based on exogenous stimuli (e.g. electric current/voltage, temperature, light, ultrasound, and magnetic fields) can

be used to achieve remotely controlled drug delivery for on-demand and pulsatile drug delivery [109, 112, 113], while those sensitive to endogenous stimuli (e.g., pH, enzymes and glucose) can be injected or implanted in the body for the targeted drug release. The targeted regions, such as tumors and infected/inflamed tissues are generally accompanied by different pH or/and enzyme levels compared with healthy ones, which can trigger the drug release [82-84]. Therefore, such “smart” functional nanomaterials have been widely used as the drug nanocarriers in controlled delivery systems. The detailed descriptions of the six types of commonly used stimuli-responsive nanomaterials are as follows.

Electric-responsive nanomaterials. Electric-responsive materials can be used to achieve sustained or pulsed drug release triggered by weak electric fields generated by low voltages (~ 1 V). The materials can be obtained from a variety of compounds, including polymer nanoparticles, carbon nanotubes, and nanohydrogels. For example, the conductive polypyrrole nanoparticle has been exploited for tailored drug release of charged drug molecules, due to the reduction-oxidation reaction. The backbone of polypyrrole (PPy) is positively charged. Therefore, the positive charges can be balanced by loading negatively charged drug molecules, and this process is oxidation reaction to PPy. When the drug-loaded PPy is given proper negative voltages (or negative charges), the anionic drug molecules that doped within the oxidized PPy backbone will be released to the local environment as the positive charges on the backbone were neutralized by the extra negative charges, and this process is the reduction reaction to PPy. Its wide use is attributable to several reasons. First, it has a simple and low-cost synthesis process: polypyrrole can be easily synthesized by oxidation of the pyrrole either by commonly used oxidants such as H_2O_2 and FeCl_3 or by electrochemical reactions [251-254]. Second, polypyrrole has good of biocompatibility, flexibility, and

responsivity to proper negative voltages [126, 255, 256]. In addition to polypyrrole, montmorillonite, formulated in the chitosan nano-hydrogel, enables tuning of the drug release profile by electrostimulation, and it still maintains good reversibility and responsiveness after consecutive operations [257]. Multiwalled carbon nanotubes have also been employed as conductive nanocarriers to conduct for electric-stimulated drug delivery [90].

Temperature-responsive nanomaterials. These nanomaterials exhibit sharp nonlinear changes of their properties when temperature changes, causing the drug release [258]. Generally, when such materials are used as nanocarriers, they will remain stable in body temperature ($\sim 37^\circ\text{C}$), and release the drug molecule immediately at a certain higher temperature (e.g., $\sim 40\text{-}42^\circ\text{C}$, a locally heated tumor) [111, 259]. Such nanocarriers usually including polymer micelles [260], nanoparticles (usually poly(N-isopropyl acrylamide), PNIPAM) [261, 262], and liposomes [263]. The temperature triggers are usually obtained by using radiofrequency oscillators [263], temperature-controlled water sacks [264], or miniature microwave applicators [265].

Light-responsive nanomaterials. Such materials can respond to specific a wavelength of light, or a range of wavelengths to release the drugs. Different materials are sensitive to different wavelengths, including ultraviolet (UV), near-infrared (NIR), and visible (VIS) regions [76]. For example, the azobenzene group can realize the controlled release of DNA by using 350 nm ultraviolet light [110], while hollow gold nanospheres enable drug release when irradiated with NIR light (at 808 nm) [266]. A key drawback of using UV-responsive nanomaterials is that the light penetration depth in the tissue of these short wavelengths is very low (less than 200 μm) due to strong scattering in DNA and organic molecules [267]. Therefore, these materials are only applicable to regions that can be directly illuminated (e.g., skin or eyes). This problem

can be solved by using NIR light-responsive nanomaterials: NIR light, on the one hand, can achieve deeper penetration depth. On the other hands, NIR radiation is less harmful to tissue, allowing NIR-responsive drug nanocarriers to have higher potential in clinical applications [93, 266].

pH-responsive nanomaterials. The pH-responsive drug nanocarriers release the drug upon pH changes. Such materials are usually obtained from polymers (such as polybases and poly-acids) with ionizable groups or silica nanoparticles that exhibit increased solubility or conformational changes in response to pH variations [82, 230]. They are mainly employed in two routes: achieving the controlled drug delivery for specific organs or compartments, including vagina [268], gastrointestinal tract [269], lysosomes and endosomes [269]; and triggering the drug release in the target regions, where subtle pH changes are associated with pathological situations, such as tumors and inflamed tissues [270].

Enzyme nanomaterials. Similar to the pH-responsive materials, the enzyme-responsive materials have been exploited to achieve enzyme-mediated drug release. Such materials can respond to specific enzymes, such as glycosidases, proteases, and phospholipases, which can be observed in pathological conditions, such as cancer, inflammation, and infected tissues [271, 272]. The materials can be obtained from short peptide sequences, functionalized liposomes, or dextran-coated iron oxide nanoparticles [100, 273].

Redox-sensitive nanomaterials. The redox-sensitive nanomaterials can response to the disulfide bonds cleaved from glutathione (GSH) for actuating drug release. Therefore, different concentrations of GSH in the extracellular and intracellular compartments between the diseased region (e.g., tumor tissues) and healthy ones can be used to trigger the drug release [76]. Such materials are developed from micelles of

amphiphilic copolymers containing a single disulfide bond between two polymer blocks [274, 275], or the disulfide links in the hydrophobic backbone [276].

In summary, the literatures demonstrated both the exogenous and endogenous stimuli-triggered nanomaterials have provided effective solutions of developing novel drug delivery systems for various diseases; however, it also implied that the controllability on drug release of the endogenous stimuli-responsive nanomaterials are generally lower than that of the exogenous ones. This is because the endogenous stimuli (e.g., the pH, enzyme of tumor) cannot give identical triggers to control the drug release, since they are significantly influenced by patient-to-patient variability thus exhibiting poor reproducibility [108]. In contrast, the controlled drug delivery systems triggered by exogenous stimuli through the auxiliary equipment generally possess higher controllability of drug release. For example, the electric-responsive release can be precisely controlled by the voltage/current of power supply [111, 112]; the light-responsive release can be tuned by the wavelength of laser light [109, 110]; temperature-responsive release can be changed by the frequency of oscillators [113-115]. It should be noted that such auxiliary equipment is usually bulky and thus brings limitations to further developments, including limited therapeutic environment and space and increased patient inconvenience and discomfort (reduced patient's compliance). Therefore, miniaturized and effective nanodevices such as nanogenerators are required to provide precise exogenous stimuli for novel controlled drug delivery system.

2.2.5 Triboelectric nanogenerator

The triboelectric nanogenerator (TENG) is an emerging nanodevice used to harvest and convert mechanical energy into electric energy using the triboelectric effect

[116, 119, 120]. Owing to the advantages of high output, broad materials selection, simple configuration, and low cost, TENGs have been realized and widely applied in various fields, including self-powered devices/systems, micro/nano power source generation, and blue energy (Figure 2-7). In this section, the fundamental mechanism, the operation modes, the nanomaterials design of TENGs, as well as the feasibility of the TENG to be engineered as a portable (even wearable) electric-stimuli generator for the novel controlled drug delivery system will all be demonstrated in detail.

Figure 2-7 The various applications of triboelectric nanogenerator: wind/hydraulic electrogenerating, micro-electromechanical systems (MEMS), biosensors, robotics, electronic skin, information safety and air purification.

Figure adapted from Ref. [120] ©2016 Springer Link

2.2.5.1 Fundamental mechanism and modes

The triboelectric effect is one of the most common physical phenomena in people's daily lives; for example, combing one's hair with a plastic comb can easily give rise to the triboelectricity: when two different materials rub against each other, one of them will become positively charged, while the other will be negatively charged. The charge will remain on the outer surface of the subjects for a duration of seconds to minutes, depending on the materials. The underlying physical mechanism of the triboelectric effect is known as contact electrification. When two different materials are in contact, weak chemical bonds may form between their surfaces, which is known as adhesion. When two metal surfaces come into contact (or rubbed with each other), electrons are transferred from the material with the lower work function (or higher Fermi level) to the material with the higher work function (or lower Fermi level) in order to the electrochemical potential between the two materials [277]. Here, "electrochemical potential", ξ , refers to the energy which must be given to an electron to take it from the Fermi level to infinity, and is defined as $\xi = \Phi + eV_s$, where Φ and V_s is the work function and surface potential of the metal respectively, and e is the electron charge [277, 278]. As for the contact/friction between the metal and insulator, the electrons are generally transferred from the valance band of metal to the defect or 'trap' states in the band gap of practical isolators [120, 277]. The triboelectric effect appears everywhere in our daily lives but has not really been utilized until 2012, when the first triboelectric nanogenerator (TENG) was invented. The essential components of the TENG are two different materials/nanomaterials such as metal and polymer (as long as they have different triboelectric properties). Currently, TENGs have four basic modes, namely contact-separation, contact-sliding, single-electrode, and free-standing triboelectric-layer modes, as shown in Figure 2-8.

Generally, when two materials contact-separate or contact-slide with one another, an electric potential can be generated between two electrodes (linked with the materials), due to the contact charging and electrostatic induction [116]. The surfaces of the materials can be functionalized by using various nanostructures (e.g., nanotubes, nanowires or nanoparticles) to increase the contact area and charge density, thus enhancing the triboelectrification effect and contributing significantly to the high electric output of the TENG [120, 122]. The four basic modes and their corresponding mechanism are as follows:

Figure 2-8 The four fundamental modes of triboelectric nanogenerators: (a) vertical contact-separation mode; (b) in-plane contact-sliding mode; (c) single-electrode mode; and (d) freestanding triboelectric-layer mode. The yellow region in a-c indicates the electrodes, while the green region in d indicates electrodes. Figure adapted from Ref. [120] © Springer International Publishing Switzerland 2016.

Vertical Contact-Separation Mode. In this mode, the TENG consists of two different tribological materials, e.g., Nylon top and Polytetrafluoroethylene (PTFE) bottom, with the surfaces facing each other [237, 279]. Two electrodes are deposited

on the bottom and top surfaces of the materials respectively, as shown in Figure 2-8a. In the original state, there is no electric potential difference (EPD) between the electrodes. When the two materials are brought into contact with each other under an external force, the surface charge transfer will take place at the contacted area due to the triboelectrification, leading to oppositely charged surfaces. Once the two contacted surfaces separate, the EPD will be established between the two electrodes, resulting in a current flowing through the load. Therefore, alternating current will be produced between the electrodes if the two materials repeat the vertical contacted-separated motion. When the electric potential of the bottom electrode (U_{BE}) is defined to be zero, the electric potential of the top electrode can be expressed by

$$U_{TE} = -\frac{\sigma d'}{\varepsilon_0}, \quad (2-1)$$

where the d' indicates the distance between the two surfaces, σ is the triboelectric charge density, and ε_0 represents the vacuum permittivity.

Lateral sliding mode (or contact-sliding mode). The configuration of this mode is similar to that of the vertical contact-separation mode, as shown in Figure 2-8b. In the original state, the surfaces of the two materials fully overlap and contact one another, and there is no EPD between the two electrodes. When the two materials have a relative sliding lateral motion that cause friction between their surfaces, opposite charges will be generated on the two surfaces, resulting in an EPD between the electrodes. Similarly, the alternating current will be generated if the two surfaces have periodic contact-sliding motion [280, 281], hence it can be used whenever a lateral sliding is presented, e.g. a planar motion or cylindrical rotation.

Single-electrode mode. Unlike the two modes above, this mode of TENG has only one electrode on one of the materials, as shown in Figure 2-8c. This mode is used

when one of the triboelectric objects is mobile and cannot be electrically connected to the load, such as a human walking on the floor. For example, assume the top material is PTFE, and the bottom electrode is copper [282]. In the original state, when the surface of PTFE is fully in contact with the electrode, the electrons from the electrode will transfer to PTFE (since PTFE is more triboelectrically negative than copper) due to the contact electrification. Once the PTFE and the electrode separate (vertical contact-separated mode), the negative charges of the PTFE surface will induce positive charges on the electrode, resulting in free electrons flowing from electrode to the ground [283]. If the PTFE slides outward (lateral sliding mode), the positive charges on the electrode will decrease, resulting in the electrons flowing from ground to electrode [282]. Therefore, both contact-separation and contact sliding motions can be used for energy harvesting in this example.

Freestanding triboelectric-layered mode. This mode consists of a rotator and a stator: the stator (e.g., Polydimethylsiloxane (PDMS)), to which are stuck two symmetric electrodes (e.g., copper film), is placed at the bottom, while the rotator (e.g., copper) is placed at the top and slides on the surface of the PDMS. The structure is shown in Fig 2-8d. The size and shape of the rotator are exactly the same as those of the gap between the two electrodes [284]. In the original state the rotator fully overlaps with one of the PDMS surfaces, and the electrons will transfer from copper to the PDMS due to contact electrification. Once the rotator moves to another PDMS piece, an asymmetrical charges distribution of the two surfaces will occur, leading to the flow of free electrons between two electrodes. Such a mode is usually applied in rotational TENG, which has also proved to be one of the most efficient mode of TENG modes [120, 285].

2.2.5.2 Nanostructured materials for triboelectrification

There are many available materials which can be used for triboelectrification ranging from metals to insulators. However, none of them is comparable with nanostructured materials in terms of the efficiency of triboelectrification. Due to the recent advances in nanotechnology, the surface of materials can be easily functionalized with desired nanostructures, such as nanowires, nanoparticles, and nanotubes. In this

Figure 2-9 (a) The detailed fabrication flowchart of the carbon nanotube (CNT) coated and fiber-based nanogenerator. (b) The SEM image of the CNT coated cotton thread and (c) the corresponding magnified image. (d) The SEM image of the polytetrafluoroethylene (PTFE) coated cotton thread (after the CNT coating) and (e) the zoomed-in image. The photograph of the nanostructured thread with (f) linear and (g) bended shapes. (h) The flexible TENG-cloth woven by the proposed thread. Figure adapted from Ref. [287] ©2014 American Chemical Society

section, we will mainly discuss the design, fabrication process, and contributions of nanostructured materials in various TENGs.

An ultra-high surface-to-volume ratio allows a large contact area and high surface charge density, leading to a significant enhancement of the triboelectric generation efficiency. Jiang *et al.* demonstrated a carbon nanotube-based TENG, in which carbon nanotube (CNT)-coated cotton thread, and a thin layer of polytetrafluoroethylene (PTFE) served as triboelectric materials. The fabrication process and images of the nanomaterials are presented in Figure 2-9. The electrode here was made from CNT instead of conventional metal, as CNT not only provided high conductivity but also enhanced the adhesion to the cotton thread due to the mutual strong chemical bonds [286]. These characteristics contributed to higher generating efficiency. Because of the flexibility of the CNTs, such functional nanostructured threads can be woven into a cloth and thus worn on the human body to power a wireless temperature monitor. The instantaneous output of the CNT based TENG reached $\sim 0.9 \mu\text{W}$, with a power density of $\sim 0.1 \mu\text{W}/\text{cm}^2$. In addition, such wearable TENG can also monitor human motion quantitatively with electric sensing signals [287]. A report by Lee *et al.* also demonstrated a wearable textile-based TENG which was fabricated with aluminum nanoparticles and a thin film of polydimethylsiloxane (PDMS), as shown in Figure 2-10. A high output power density of $33.6 \text{ mW}/\text{cm}^2$ was obtained, attributable to the nanostructured surface configuration. Furthermore, commercial LED bulbs were activated by human motion when the proposed TENG was attached to an arm sleeve. These indicate that the TENG can be a simple and reliable power supply for wearable devices [288].

In addition to nanoparticles, nanowire surface modification has also proved to be a reliable engineering strategy [289-292]. Yang *et al.* have demonstrated a rationally

designed triplecantilever-based TENG for harvesting ambient vibration energy. The TENG was based on the contact-separation mode, with the 100 nm ZnO nanowire arrays fabricated onto the surface of the beryllium–copper alloy foil (BCAF). The open-circuit voltage and the short-circuit current reached 101 V and 55.7 μA , respectively,

Figure 2-10 The schematic configuration of the nanostructured and textile-based triboelectric nanogenerator. (a) The fabrication flow-chart for the triboelectric nanogenerator, including the top aluminum nanoparticle coating and bottom PDMS coating. The SEM images of (b) uniform aluminum nanoparticles structured surface, and (c) the nanostructured PDMS bottom plate. Figure adapted from Ref. [288] © 2015 Elsevier Ltd. All rights reserved.

with a peak power density of 253.3 mW/m² [293] which were all attributed to the usage of nanowire arrays. Additionally, the nanowire arrays can also be applied in flexible and wearable TENG. Thus, Wu *et al.* coated a commercial polyester textile with conductive nanowires (Ag NWs), and a graphene film was further coated on top of the Ag NWs, forming a polyester/Ag NWs/graphene structured textile. The coating processes were conducted in Ag NW and graphene oxide (GO) solutions respectively. The random network of Ag NWs allowed them to conform to the shape of the polyester textile; therefore, the Ag NWs remained highly conductive even after being bent or folded. Such textile-based TENGs have been reported to have superb conduction with surface resistivity below 20 Ω /square. Furthermore, it also was shown to be scalable, foldable and washable [121]. Similar to the nanowire, nanorods have also been fabricated on various surfaces and demonstrated excellent triboelectric enhancement. In a freestanding triboelectric-layer mode based TENG, the nanorod was fabricated on the surface of Kapton with the length ranging from 0.4 to 1.1 μ m, leading to a high current output of 117.6 μ A at a rotating rate of 1000 rpm [294].

Compared with other nanostructures, the nanowire and nanorod are more commonly used in TENG devices, since they have easier fabrication process and a wider range of available materials, allowing more customizability for various shapes and modes of TENG [280, 287, 288]. Both nanowires and nanorods can be fabricated e.g., by a one-step inductively coupled plasma (ICP) etching [280, 294, 295]. Fang *et al.* have investigated nanowire growth nanotechnology on a series of commonly used polymers, such as polydimethylsiloxane (PDMS), poly(3,4-ethylene dioxythiophene) poly(styrene sulfonate) (PEDOT/PSS), polyethylene naphthalate (PEN), and so on, as shown in Figure 2-11a. As a result, they have provided an easy approach to fabricate aligned large-scale polymer nanowires after etching with the previously mentioned one-

step ICP process [292, 296]. Briefly, the target polymer was spin-coated onto a substrate followed by coating with a thin layer of gold by direct current sputtering. A

Figure 2-11 (a) Scanning electron microscopy and optical images for various aligned polymer nanowires: a. PMMA, b. PS, c. PDMS, d. PEDOT/PSS, e. PEN, f. PET, g. Durafilm, k. Kaption film, i. optical image of Kapton film covered with nanowire. (b) The relationship between the fabricated nanowire array density and the gold thickness. Figure adapted from Ref. [292] © 2009 American Chemical Society

group of gases (argon, oxygen, tetrafluoromethane) was introduced into the ICP reaction chamber and plasma ions were generated and accelerated towards the polymer surface by two power sources. With this fabrication method, the length and density of the nanowire can be controlled by the thickness of gold film and ICP etching, respectively. Within 30 min, the nanowire length increased linearly with the plasma etching time. The relationship between nanowire density and the gold thickness is presented in Figure 2-11b. Generally, the etching ratio is within 300-400 nm/min with a relatively stable nanowire diameter of 100 nm. In addition, the authors emphasized that such method is suitable and effective for any organic materials.

2.3 Conclusion

This literature review provided the research background of optical biosensors and controlled drug delivery, as well as different types of nanomaterials/nanodevices, namely two-dimensional materials, nanostructured polymers and triboelectric nanogenerator. The development, synthesis, characterization, properties, and corresponding biomedical applications of such nanomaterials were detailed. This chapter was also divided into two parts. In the first part, the healthcare applications of biophotonics and significance of the surface plasmon resonance (SPR) biosensor for optical diagnostics were highlighted. The advantages of SPR biosensors, the ability of real-time and convenient detection, and their challenges in detecting small biomolecules were also discussed. To solve this limitation, the possibility of using 2D transition metal dichalcogenides (TMDCs) as sensitivity-enhancing coatings for SPR biosensors were reviewed. Furthermore, the fabrication details of the 2D TMDCs were also discussed. Specifically, the best way to synthesize functional 2D materials was shown to be by chemical vapor deposition (CVD), because it not only provides high

production efficiency and rate but also allows large-area and uniform nanosheets. Such CVD-grown 2D materials were implemented in various engineering strategies, devices and applications which highlighted that the usage of 2D materials resulted in improved or unique performance characteristics. In addition, photoluminescence and Raman spectroscopy were demonstrated to be efficient and accurate methods to characterize the 2D materials, elucidating properties such as material structure and thickness. Furthermore, the unique optical properties of 2D TMDCs, including direct bandgap and high light absorption, were discussed in detail. Such properties can be utilized to enhance light-matter interaction and photon absorption in optoelectronic applications. Finally, due to their prominent structural (ultrathin, planar) and chemical (biocompatible, nontoxic) properties, the 2D TMDCs have been integrated into a variety of biomedical devices, demonstrating excellent performance compared with conventional devices.

In the second part, the current developments and healthcare applications of nanomedicine were discussed. In particular, the motivation and significance of controlled drug release regimens were illustrated. The controlled release systems have been developed to control the drug exposure time and release rate, to shield the drug from premature elimination, to target drugs at the desired site, and ultimately to enhance the therapeutic efficacy and reduce toxic side effects. Additionally, the state of the art of the controlled drug delivery technology, including new routes of drug release, triggerable drug nanocarriers, and assistant nanodevices were discussed in detail. The advantages/disadvantages and the intended use cases of various new drug release routes, such as transdermal delivery and implantation, have been introduced. The stimuli-responsive nanomaterials have been designed as controllable drug nanocarriers that enable response to both endogenous and exogenous stimuli for actuating drug release.

Compared with endogenous stimuli-based drug release system, the exogenous stimuli-based systems have much higher controllability, since the external stimuli are provided by auxiliary equipment which can be precisely controlled. An emerging class of nanodevices, the triboelectric nanogenerator, was introduced as an ideal alternative of the bulky auxiliary equipment. It can harvest and convert mechanical energy to electric energy with has high energy conversion efficiency and can be designed to be wearable and foldable, increasing its potential for integration into an exogenous stimuli-based drug delivery system.

Chapter 3 The theoretical modeling of atomic transition metal dichalcogenide based plasmonic biosensing

This Thesis is divided into two parts: Chapters 3 and 4 focus on the first part of the work, the 2D transition metal dichalcogenide- (TMDC-) enhanced SPR biosensors, while Chapters 5 and 6 focus on the second part, the electric-stimulated drug delivery system. Chapter 3 & 4 demonstrate the design fabrication and testing of four types of 2D TMDC-based SPR sensing platforms with significant sensitivity improvement. More specifically in this chapter we systematically investigate the theoretical models of four types of 2D TMDC-based SPR biosensors to determine the most performant materials, geometry, and optimized operational parameters, such as detection sensitivity, accuracy, and the detected concentration range. Two sensing modes, angular and phase modulations, are investigated. The tuning of the substrate (TMDCs/Au) thickness on an atomic scale with a nanoscale gradation allows efficient modulation of plasmonic sensing signals. This is because the 2D TMDCs that coated on the gold surface act as the ultrathin lossy materials to adjust the coupling condition (between the incident light and the surface plasmon polaritons), thus tune the enhancement of the SPR wave. All the calculations are based on the transfer matrix method and Fresnel equations. In the angular modulation mode, the sensitivity of our WS₂-enhanced SPR biosensor reaches 155 deg/RIU, an increase of 200% over conventional bare gold substrates. In the phase modulation mode, a very low minimum reflectivity of 3.256×10^{-8} is demonstrated with an excitation wavelength of 1024 nm, showing a complete transfer (~100%) of the light energy into plasmon resonance. The singularity at the resonance dip leads to an ultrahigh plasmonic sensitivity of 1.1×10^7

deg/RIU, which is three orders of magnitude higher than that typically obtained with bare gold sensing substrates used in the conventional plasmonic sensors. These results can indicate both the quality and performance of our novel device and the potential for further study & development of the proposed SPR biosensors in more complex structure and enhanced performance.

3.1 Introduction

Surface plasmon resonance (SPR) is one of the most popular of all optical biosensing technologies due to its benefits of label-free and real-time detection. The devices that excite the SPR are typically constructed based on the Kretschmann coupling configuration which was shown in Fig. 2.1-a. It mainly consists of a dielectric layer, a metal layer, and a prism used for coupling the incident light. Surface plasmon resonance is the resonant oscillation of conduction electrons at the interface between materials with permittivity of opposite signs, typically dielectric ($\epsilon > 0$) and a metal ($\epsilon < 0$). The surface plasmons (SPs) can be considered as electron density waves that propagate at the interface between the metal and dielectric. In order to excite surface plasmon waves (SPW), the incident photons or electrons should oscillate with the conduction electrons on the metal surface. It is noted that only p -polarized light (transverse-magnetic (TM) wave) can excite SPs, while the s -polarized light (transverse-electric (TE) waves) is often used as a reference signal. When the horizontal component of the incident wave vector k_x (i.e., the evanescent wave vector) matches with the surface plasmon wave vector k_{sp} , the surface plasmon resonance phenomenon occurs, expressed as,

$$k_x = k_0 n \sin \theta = k_{sp} , \quad (3-1)$$

where k_0 represents the incident wave vector in free space and θ denotes the incident angle, n is the refractive index of prism. This specific incident angle in such equation is known as the resonance angle or SPR angle θ_{SPR} .

When the excitation wavelength is fixed, the SPR curve can be obtained by scanning the incident angle and monitoring the reflectivity. The minimum reflectivity in the SPR curve corresponds to the resonance angle. When SPR is excited, the incident light couple with the SPs and enhance oscillations of SPs, thus enhance the electromagnetic field of SPW, resulting in a significant decrease in the reflectivity R near the resonance angle. The coupling can be analyzed by calculating the reflectivity R of the light given by

$$R = \left| \frac{\gamma_{13} + \gamma_{13} \exp(i2K_{z1}) d}{1 + \gamma_{13}\gamma_{13} \exp(i2K_{z1}) d} \right|^2, \quad (3-2)$$

$$\gamma_{31} = \frac{\varepsilon_3 K_{z1} - \varepsilon_1 K_{z3}}{\varepsilon_3 K_{z1} + \varepsilon_1 K_{z3}}, \quad (3-3)$$

$$\gamma_{12} = \frac{\varepsilon_1 K_{z2} - \varepsilon_2 K_{z1}}{\varepsilon_1 K_{z2} + \varepsilon_2 K_{z1}}, \quad (3-4)$$

And

$$K_{zj} = \sqrt{\varepsilon_j \frac{\omega^2}{c^2} - K_x^2}, \quad \text{for } j = 1, 2, 3 \quad (3-5)$$

$$K_x = n \frac{\omega}{c} \sin(\theta), \quad (3-6)$$

where the subscripts 1, 2, and 3 designate the quantities in the metal, air, and the prism, respectively; ε_j and K_{zj} are the dielectric constants and the wave-vector components perpendicular to the interface in medium j ; d is the thickness of the metal film, and $\lambda = 2\pi c/\omega$ is the wavelength of light in vacuum. Here $\varepsilon_1 = \varepsilon_1' + \varepsilon_1''$, $\varepsilon_2 = 1$, and $\varepsilon_3 = n^2$.

When θ close to resonance angle θ_{SPR} , the reflectivity R can be approximately expressed as

$$R(\theta) = 1 - \frac{4 \operatorname{Im}(K^0) \operatorname{Im}(K^R)}{[K_x - \operatorname{Re}(K)]^2 + \operatorname{Im}(K)^2}, \quad (3-7)$$

With $K = K^0 + K^R$, where

$$K^0 = \frac{\omega}{c} \sqrt{\frac{\varepsilon_1 \varepsilon_2}{\varepsilon_1 + \varepsilon_2}} = \frac{\omega}{c} \sqrt{\frac{\varepsilon_1' \varepsilon_2}{\varepsilon_1' + \varepsilon_2}} + i \sqrt{\frac{\varepsilon_1' \varepsilon_2}{\varepsilon_1' + \varepsilon_2}} \frac{\varepsilon_1'' \varepsilon_2}{2\varepsilon_1'(\varepsilon_1' + \varepsilon_2)} \frac{\omega}{c}, \quad (3-8)$$

$$K^R = \frac{\omega}{c} (-\gamma_{31})_{K=K^0} \left(\frac{2}{\varepsilon_1 + \varepsilon_2} \right) \left(\frac{\varepsilon_1 \varepsilon_2}{\varepsilon_1 + \varepsilon_2} \right)^{\frac{3}{2}} \times \exp \left(i \frac{4\pi d}{\lambda} \frac{\varepsilon_1}{\sqrt{\varepsilon_1 + \varepsilon_2}} \right), \quad (3-9)$$

Here K is the complex wave vector of the SPW in the Kretschmann configuration, and K^0 is the complex wave vector of the SPW at the metal-vacuum interface in the absence of the prism. K^R is the perturbation to K^0 in the presence of the prism. The imaginary parts of K^0 and K^R are the intrinsic and radiative damping, respectively. The former represents the Joule loss in the metal, and the latter represents the leakage loss of the SPW back into the prism [297, 298]. The reflectivity has a Lorentz dip at θ_{SPR} with a minimum reflectivity R_{min} given by

$$R_{min} = 1 - \frac{4\eta}{(1 + \eta)^2}, \quad (3-10)$$

Where

$$\eta = \frac{\operatorname{Im}(K^0)}{\operatorname{Im}(K^R)}, \quad (3-11)$$

Under SPR, the incident light couples with the SPW and enhances the oscillations of SPP, thus enhances its electromagnetic field. The value of the minimum reflectivity R_{min} implies the extend of the light coupling. The more of the light coupled into the SPs, the lower value of the minimum reflectivity R_{min} . No matter the intrinsic

damping is larger than the radiative damping (under coupling), or the reverse (over coupling), the incident light cannot couple into the SPW completely. Only when the intrinsic damping $\text{Im}(K^0)$ equals the radiation damping $\text{Im}(K^R)$, the optimum coupling (or critical coupling) occurs. Therefore, 100% incident light will be coupled into the SPW, the R_{min} becomes zero, and the electromagnetic field will be maximally enhanced [299].

The SPW is very sensitive to disturbances around the metal/dielectric interface since the refractive index changes at the interface cause a redistribution of the SPW electromagnetic field, leading to changes in some SPR parameters, such as the resonance angle, minimum reflectivity, and phase of reflected light [28, 36, 151, 300]. These exciting properties are therefore utilized as the transducing mechanism in biosensors: the SPR parameters can be used as the sensing signals to detect the refractive index of the analyte adsorbed onto the metal surface. The sensitivity is defined as the ratio between the changes in the SPR sensing parameters to the changes of the reflective index.

The sensitivity of conventional bare gold sensing film based SPR biosensors is insufficient to detect analytes with low molar weight and concentration. It has been demonstrated that low R_{min} induces high detection sensitivity [301, 302]. In this way, the sensitivity enhancement can be realized by adjusting the coupling condition to or close to optimum coupling. In equations (3-2) to (3-11), it is obvious that the optimum coupling is affected by a series of parameters, including permittivity and thickness of metal, the permittivity of dielectric (analyte) and excitation wavelength. Therefore, the optimized parameters of the optimum coupling are different for each different SPR configurations. In order to achieve the optimum coupling or maximally close to it, we applied functional nanomaterials of 2D TMDCs onto the gold film surface as an SPR

enhancement layer, as shown in Figure 3-1. Coating thin films of lossy materials (dielectric) on metal can directly change the effective permittivity of this metal/dielectric layer, whose effective permittivity can be tuned to the desired value (in a certain range) by simply changing the thicknesses of the metal and the lossy material [298, 303]. The emerging 2D TMDCs are reported to have outstanding performance in optical applications [51, 218, 219], one of their most intriguing optical property is they own a high absorption rate (above 5%, up to 30%), while still maintaining a similar atomic thickness of less than 1 nm [48, 49, 51]. In addition, due to the 2D structure, the thickness of TMDCs atomic films can be easily and precisely controlled by tuning the number of layers. Therefore, 2D TMDCs are excellent candidates as the lossy materials coating on the gold surface to improve the light coupling, thus enhance the sensitivity of the SPR biosensor. Besides, 2D TMDCs have also been demonstrated to have strong adsorption to biomolecules with aromatic ring due to the graphene-like structure, which can improve the detection sensitivity as well [46, 47, 304-308].

For selecting the performant materials from four TMDCs and determining the optimized structure, we conducted a systematic theoretical analysis of 2D TMDCs-enhanced SPR models in this chapter. The significant SPR performance parameters including reflectivity, resonance angle, reflected light phase, and electric field were studied first analytically by utilizing the Fresnel equations with the transfer matrix method, and secondly by performing finite element analysis (FEA) simulations and optimizations [309]. The relevant parameters such as incident wavelength, refractive index (RI), permittivity, and thickness of TMDC/Au layers, were all investigated and optimized for the design. The optimized sensitivity was obtained by tuning the number of TMDCs layers and the thickness of gold thin films. Also, the detection accuracy of the enhanced SPR models was estimated by calculating the full width at half maximum

Figure 3-1 Schematic diagram of 2D TMDCs structured on the plasmonic sensing substrate. (a) Antibody binding processes at the TMDC sensing surface. The other drawings illustrate structured plasmonic sensing configurations using a monolayer of (b) WS₂, (c) WSe₂, d) MoS₂ and (e) MoSe₂.

(FWHM) of the SPR curves. As a result, we determined the optimized TMDCs-based SPR models. For angular modulation mode, the sensitivity of a monolayer WS₂-based biosensor achieved 155 deg/RIU, which is 300% of the conventional Kretschmann structure (bare gold substrate); for the phase modulation mode, a sensitivity up to 1.1×10^7 deg/RIU was achieved with a 5-layered MoSe₂-based model, which is 3 orders of magnitude higher than that of conventional SPR biosensors.

3.2 Methods

3.2.1 Theoretical modeling of 2D TMDCs based SPR biosensors

The theoretical model of the SPR biosensor is based on the well-known Kretschmann attenuated total reflection (ATR) structure. The incident light passes through the prism and is reflected at the base of the prism. Most of the light energy is absorbed by the metal and dielectric layers overlying the prism to generate the

evanescent wave, which propagates along the interface and penetrates into the dielectric materials whose RI is to be determined. The reflective coefficient r_p of the interface for p -polarized light is calculated by the Fresnel equation

$$r_p = \frac{E_{rp}}{E_{ip}} = \left| \frac{n_t \cos \theta_i - n_i \cos \theta_t}{n_t \cos \theta_i + n_i \cos \theta_t} \right|. \quad (3-12)$$

while at the same time also applying Snell's Law,

$$n_i \sin \theta_i = n_t \sin \theta_t, \quad (3-13)$$

where n_i and n_t represent the RIs of the incident and transmitted media, respectively, at the interface. The 2D TMDC-enhanced SPR biosensor models consist of 6 component layers: the SF10 prism, a gold thin film, a silicon nanosheet, 2D MX₂ nanolayers (MoS₂/WS₂/MoSe₂/WSe₂), the biomolecular analyte layer, and sensing medium layer. The silicon nanosheet here is used as an extra lossy materials to the metal/dielectric layer. One more type of lossy materials can enlarge the range of effective permittivity of the metal/dielectric layer, thus increasing the opportunities to obtain the optimum light coupling. In order to analyze this multiple-layered model, the transfer matrix method (TMM) was employed. The overall matrix M is the product of the transfer matrices of the individual layer matrices M_k , where k represents the k^{th} layer of the model in the following:

$$M = \prod_{k=2}^{N-1} M_k = \prod_{k=2}^{N-1} \begin{bmatrix} M_{11} & M_{12} \\ M_{21} & M_{22} \end{bmatrix}. \quad (3-14)$$

The layers in our system were stacked horizontally in the z -direction. All layers are defined by the parameters n_k , ε_k and d_k , which represent the refractive index, dielectric constant and thickness of the k^{th} layer, respectively. The angle θ_k denotes the incident angle of the k^{th} layer and λ is the excitation wavelength. In our TMDC-based SPR

configuration, layer 1 is prism, layer 2 is gold film, layer 3 is silicon, layer 4 is TMDC, layer 5 is biomolecular analyte, and the last layer N, i.e. layer 6 is sensing medium (water). The glass substrate of the gold film are seamlessly adhered onto prism with the optical matching oil, also, and they have a similar refractive index, therefore, we regarded them as one layer in the simulation model. According to SPR theory, only the TM (also called *p*-polarized) incident wave can excite SPR waves. Therefore, the TE (*s*-polarized) wave is often used as the reference light beam in experimental work. For the TM incident light, the M_k is given by:

$$M_k = \begin{bmatrix} \cos \beta_k & -\frac{i \sin \beta_k}{q_k} \\ -iq_k \sin \beta_k & \cos \beta_k \end{bmatrix}. \quad (3-15)$$

Here, the four elements M_{11} , M_{12} , M_{21} and M_{22} of the matrix M can be obtained using q_k and β_k defined as

$$q_k = \frac{\sqrt{\varepsilon_k - n_1^2 \sin^2 \theta_1}}{\varepsilon_k} = \frac{\lambda \beta_k}{2\pi d_k \varepsilon_k} \quad (3-16),$$

and

$$\beta_k = \frac{2\pi n_k \cos \theta_k (Z_k - Z_{k-1})}{\lambda} = \frac{2\pi d_k}{\lambda} \sqrt{\varepsilon_k - n_1^2 \sin^2 \theta_1}, \quad (3-17),$$

where θ_1 is the incident angle at the first layer and Z_k represents the impedance boundary condition of the theoretical modeling. The first boundary of the tangential fields is defined as $Z_1 = 0$, and the last boundary Z_{N-1} is given by:

$$\begin{bmatrix} U_1 \\ V_1 \end{bmatrix} = M \begin{bmatrix} U_{N-1} \\ V_{N-1} \end{bmatrix}, \quad (3-18),$$

where U and V represent the tangential components of the electric and magnetic fields at the interface, respectively. Finally, the complex reflection coefficient, r_{pn} , of the n^{th} layer for p -polarized light can be defined as:

$$r_{pn} = \frac{(M_{11} + M_{12}q_N)q_1 - (M_{21} + M_{22}q_N)}{(M_{11} + M_{12}q_N)q_1 + (M_{21} + M_{22}q_N)}. \quad (3-19)$$

Thus the corresponding reflectivity, R_p , can be obtained as the square of the reflection coefficient's modulus:

$$R_p = |r_{pn}|^2. \quad (3-20)$$

The SPR operation can be visualized clearly by plotting the variation of reflectivity as a function of the incidence angle, the so-called SPR plot, which is essential for both angular and phase modulation. The minimum reflectivity R_{min} is defined as the lowest reflectivity in the SPR curve.

3.2.2 Angular modulation

The resonance angle (or SPR angle) is defined as the incidence angle corresponding to the minimum reflectivity R_{min} of the SPR curve. In angular modulation, the sensing signal is the resonance angle. The angular sensitivity is defined as the ratio between the changes in resonance angle to the changes in refractive index (RI variations) of the analyte, as shown in Eq. (3-11)

$$S_{angle} \equiv \frac{d\theta_{SPR}}{dn_{bio}} \quad (3-21),$$

which can be approximated as

$$S_{angle} \cong \frac{\Delta\theta_{SPR}}{\Delta n_{bio}} \quad (3-22),$$

if actual (but small) angular and RI variations are considered. The full width at half maximum (FWHM) and the full width at one tenth of maximum (FWTM) of the SPR curve are often used to describe the accuracy of biosensors.

3.2.3 Phase modulation

Since SPR involves only the TM waves, the TE waves can be used as reference signals. In this way, the environmental noise can be effectively eliminated. To extract the differential phase φ_d from the reflected light, we use Eq. (3-13) below to process the phase signals φ_p and φ_s of TM (p -polarized) and TE (s -polarized) reflected light waves:

$$\varphi_d = |\varphi_p - \varphi_s|. \quad (3-23)$$

For TM polarized (p -polarized) light, the phase shift is dependent on the reflective coefficient r_p , given by:

$$r_p = \frac{E_r}{E_i} = |r_p| e^{j\varphi_d} = \left| \frac{\tan(\theta_i - \theta_t)}{\tan(\theta_i + \theta_t)} \right| e^{j\varphi_d}. \quad (3-24)$$

The phase sensitivity S_{phase} is then defined as the ratio of the changes in differential phase $\Delta\varphi_d$ to the changes in refractive index of the analyte Δn_{bio} , as follows:

$$S_{phase} = \frac{\Delta\varphi_d}{\Delta n_{bio}}. \quad (3-25)$$

3.2.4 The wavelength-dependent refractive index for each layer

From the equations above, it is obvious that the thickness and the RI of each layer significantly influence the reflectivity. In this theoretical modeling, we investigated incident wavelengths in a broad range extending from visible to near-infrared (NIR) range (600 to 1024 nm). Therefore, the wavelength-dependence of the

RI for each of the six layers has to be considered in detail, as follows. The first layer of the multi-layered model is the SF10 prism with the RI given by

$$n_{prism}(\lambda) = \sqrt{\frac{1.62153902\lambda^2}{\lambda^2 - 0.0122241457} + \frac{0.256287842\lambda^2}{\lambda^2 - 0.0595736775} + \frac{1.64447552\lambda^2}{\lambda^2 - 147.468793}}, \quad (3-26)$$

where λ denotes the excitation wavelength of the light source in [μm] (valid from 0.38 μm to 2.5 μm). The dispersion constants in the Eq. (3-16) were obtained from the datasheets provided by the optical glass product company Schott Inc. for N-SF10 prism [310]. The complex refractive index of the second layer-the gold thin film-was obtained from the experimental results of Johnson and Christy [311]. The refractive index of the third layer, the silicon nanosheet, is determined by

$$n_{silicon}(\lambda) = A + A_1 e^{-\frac{\lambda}{t_1}} + A_2 e^{-\frac{\lambda}{t_2}}, \quad (3-27)$$

with $A = 3.44904$, $A_1 = 2271.88813$, $A_2 = 3.39538$, $t_1 = 0.058304$, and $t_2 = 0.30384$. The λ in Equations (3-16) and (3-17) represent the wavelength in micrometer [312]. The refractive index of the fourth layer, 2D TMDCs ($\text{MoS}_2/\text{WS}_2/\text{MoSe}_2/\text{WSe}_2$), from visible to NIR range are provided in Table 3-2 and Table 3-2. The investigation of refractive index data for these emerging 2D TMDC monolayers is an active research area. The complex refractive index used in the manuscript was obtained from two references based on the measurements from reflection spectra and spectroscopic ellipsometry [50, 313]. According to many current plasmonic literature studies, the dielectric constants of the 2D TMDC layers are assumed to be isotropic, such as in references [314-316]. The complex refractive index $\bar{n}$ is defined as $\bar{n} = n + \kappa i$ [317], where the real part n indicates the phase velocity, while the imaginary part κ , known as the extinction coefficient, is proportional to optical loss [36, 216, 217]. It is noted that both expressions of complex refractive index, namely, “ $\bar{n} = n + \kappa i$ ” and “ $\bar{n} = n - \kappa i$ ” are

correct [317-320]. They are derived from two different but conjugated conventions of the electromagnetic field. The former is derived from $E_0 e^{i(kz-wt)}$, while the latter is derived from $E_0^* e^{-i(kz-wt)}$ [319].

3.2.5 Finite element analysis simulations

In order to calculate the electric field enhancement of our multilayer TMDC-based biosensing model, finite element analysis (FEA) was performed using COMSOL Multiphysics 5.0. The three-dimensional multi-layered SPR models were built for studying the excited SPR wave and the electric field. Also, this method can calculate

Table 3-2 RI, excitation coefficient values and thickness for monolayer TMDCs at a few wavelengths in the ‘red’ part of the visible range.

TMDC	T_{MXZ} (nm)	$\lambda = 600$ nm	$\lambda = 633$ nm	$\lambda = 660$ nm
MoS ₂	0.65	$n=4.3934,$	$n=5.0805,$	$n=4.9991,$
		$k=1.2269$	$k=1.1723$	$k=1.2563$
MoSe ₂	0.70	$n=4.7586,$	$n=4.6226,$	$n=4.4963,$
		$k=1.1504$	$k=1.0063$	$k=0.9382$
WS ₂	0.80	$n=3.5202,$	$n=4.8937,$	$n=4.4735,$
		$k=0.6048$	$k=0.3124$	$k=0.2059$
WSe ₂	0.70	$n=4.5039,$	$n=4.5501,$	$n=4.3357,$
		$k=0.9340$	$k=0.4332$	$k=0.2532$

Table 3-2 RI and excitation coefficient values for monolayer TMDCs in NIR.

TMDC	$\lambda = 785$ nm	$\lambda = 904$ nm	$\lambda = 1024$ nm	$\lambda = 1150$ nm	$\lambda = 1319$ nm	$\lambda = 1540$ nm
MoS ₂	$n=4.6348,$	$n=4.7261,$	$n=4.8690,$	$n=4.4317,$	$n=4.3429,$	$n=4.2374,$
	$k=0.1163$	$k=0.1346$	$k=0.2444$	$k=0.0721$	$k=0.0433$	$k=0.0325$
MoSe ₂	$n=4.2984,$	$n=4.0212,$	$n=3.8768,$	$n=3.7965,$	$n=3.6710,$	$n=3.5281,$
	$k=0.8225$	$k=0.4273$	$k=0.3561$	$k=0.2972$	$k=0.2343$	$k=0.1887$
WS ₂	$n=4.0123,$	$n=4.9916,$	$n=4.5660,$	$n=4.7071,$	$n=4.5418,$	$n=4.1715,$
	$k=0.0399$	$k=0.2574$	$k=0.1058$	$k=0.1742$	$k=0.1688$	$k=0.1675$
WSe ₂	$n=4.3655,$	$n=5.1345,$	$n=5.0110,$	$n=4.9163,$	$n=4.7083,$	$n=4.4561,$
	$k=0.0367$	$k=0.2692$	$k=0.2562$	$k=0.2234$	$k=0.1581$	$k=0.1496$

the SPR angle and phase, therefore it could verify the results obtained from the TMM.

The specific process is given in detail as follows:

- 1) Mesh the overall geometry into finite elements.
- 2) Set the properties of the excitation light, e.g., wavelength, polarization, and incidence angle, and then define the frequency domain of the designed geometry.
- 3) Perform the FEA simulation and extract the results of interest.

3.3 Results and Discussion

3.3.1 Angular SPR sensitivity

3.3.1.1 Reflectivity

We plotted the minimum reflectivity R_{min} of the SPR biosensor models as a function of the number of TMDCs for various thicknesses of the gold thin film, i.e., 30 nm, 35 nm, 40 nm, 50 nm. Also, different excitation wavelengths from visible to NIR - 600 nm to 1024 nm were also studied. All calculation results are detailed in Appendix; here, we only selected the structures with the best performance for each excitation wavelength, as shown in Figure 3-2. The four TMDCs are uniformly referred to as “MX₂” in the following description. Two features are observed from the results:

- 1) When the gold thickness is decreased, the curve dips shift with increasing the number of MX₂ layers. This indicates that the MX₂ layers complement the role of the gold films.
- 2) It is worth noting that when the gold thickness is 50 nm (maximum studied), no MX₂ is required to achieve the minimum reflectivity, since 50 nm is the

optimized thickness of the gold thin film according to the conventional Kretschmann ATR configuration [321, 322].

3.3.1.2 The changes in resonance angle

Next, the changes in resonance angle were investigated. The RI variation of analyte Δn_{bio} , which induces the changes in resonance angle, is defined as the RI variation between the media with sample and without sample, e.g. $\Delta n_{bio} = n_{sample\ solution} - n_{solvent\ (water)}$. In our simulations, $n_{solvent\ (water)}$ equals to 1.332 and Δn_{bio} was assumed to equal 0.005. Similar to Figure 3-2, we also plotted the changes of the resonance angle as a function of the number of MX₂ layers as shown in Figure 3-3. The results demonstrated:

Figure 3-2 The minimum reflectivity as a function of the number of MX₂ layers for the best performance at each excitation wavelength: (a) 600 nm, (b) 633 nm, (c) 785 nm and (d) 1024 nm, with various thickness of the gold thin film.

- 1) As the number of MX₂ layers increased, the changes in resonance angle increased until reached a maximum, then decreased rapidly to a very small value.
- 2) The decreasing thickness of gold thin film led to a peak shift to a larger number of MX₂ layers.
- 3) As the excitation wavelength increases, the peak shifted towards a larger number of MX₂ layers. Similar behaviors were also observed in Figure 3-2: As the gold thickness decreased, the curve dips shifted to a larger number of MX₂ layers. As the excitation wavelength increased, a larger number of MX₂ was required to achieve the minimum reflectivity dip.

Figure 3-3 The changes of the resonance angle for a fixed refractive index change in analyte ($\Delta n_{bio} = 0.005$) as a function of the number of layers of MX₂ at excitation wavelength of 600 nm, 633 nm, 785nm and 1024 nm, with various thickness of the gold thin film.

3.3.1.3 FWHM

Besides the reflectivity variations and changes in resonance angle, we also studied the FWHM, which indicates the detection accuracy of the biosensor, as a narrower FWHM corresponds to higher accuracy. All the detailed simulation results of the FWHM, reflectivity, and resonance angles with various gold film thicknesses and excitation wavelengths for the four types of MX₂ models are presented in the Appendix. After balancing these three factors, we finally deduced the parameters which can provide the best performance for each TMDC-based structure (Table 3-4), and the optimized parameters for each excitation wavelength (Table 3-3). It is obvious that for different types of TMDCs-based SPR biosensors, the optimized parameters for achieving the optimum coupling (or to maximally close to the optimum coupling) is different. The light coupling is affected systematically by a series of parameters, including the wavelength of the incident light, thicknesses, and permittivity of Au, TMDCs and Si layers at the same time. The relationship between these parameters to the minimum reflectivity is expressed in equation 3-1 to 3-11, in other words, there does not have an evident linear relationship between them. Among the four TMDCs, the highest sensitivity, 155.68 deg/RIU, was achieved with a 35 nm gold film and a WS₂ monolayer with a 600 nm excitation wavelength. The corresponding minimum reflectivity was 2.5592×10^{-2} , with an FWHM of 17.4644 deg. Similarly, the optimized parameters under different excitation wavelengths are also different. According to our simulation, the highest sensitivity among the five wavelengths is obtained at 600 nm with WS₂ monolayer.

Table 3-4 The optimized parameters for the best performance of the four types of TMDC enhanced models.

Excitation wavelength (nm)	Type of TMDC	Gold thickness (nm)	Silicon thickness (nm)	Number of MX ₂ layers (L)	Minimum Reflectivity	$\Delta\theta_{SPR}$ (Deg) ($\Delta n_{bio}=0.005$)	Sensitivity (Deg/RIU)	FWHM (Deg)
600	WS ₂	35	7	1	2.5592×10^{-2}	0.7784	155.68	17.4644
633	MoS ₂	40	7	1	1.1513×10^{-5}	0.6586	131.70	17.5728
633	WSe ₂	40	7	2	5.3807×10^{-3}	0.7070	141.40	17.2340
633	MoSe ₂	40	7	1	2.0438×10^{-3}	0.6584	131.68	17.0915

Table 3-3 The optimized parameters of TMDC-enhanced models if different excitation wavelengths are to be employed.

Excitation wavelength (nm)	Type of TMDC	Gold thickness (nm)	Silicon thickness (nm)	Number of MX ₂ layers (L)	Minimum Reflectivity	$\Delta\theta_{SPR}$ (Deg) ($\Delta n_{bio}=0.005$)	Sensitivity (Deg/RIU)	FWHM (Deg)
600	WS ₂	35	7	1	2.5592×10^{-2}	0.7784	155.68	17.4644
633	WS ₂	40	7	1	2.4099×10^{-2}	0.7394	147.88	16.2417
660	WS ₂	40	7	3	3.3778×10^{-5}	0.7282	145.64	16.8245
785	WS ₂	40	5	13	2.5767×10^{-3}	0.6395	127.90	15.5232
1024	MoS ₂	40	5	26	1.6573×10^{-6}	0.4499	89.98	17.5445

Figure 3-4 demonstrates the sensitivity of the four MX₂ models as a function of the number of MX₂ layers and gold thickness at their optimized excitation wavelengths. For the WS₂ model, the highest sensitivity was 155.68 Deg/RIU with a 35 nm thick gold layers. For other models, the highest calculated sensitivity seemed to be achieved with 50 nm thick gold thin film and monolayer MX₂. However, their corresponding minimum reflectivities R_{min} were higher than 0.03, leading to low light energy-transfer efficiencies (from a simulation point of view). Therefore, we obtained the highest sensitivity of MoS₂, MoSe₂, and WSe₂ models when using a 40 nm thick gold film.

Figure 3-4 The sensitivities of the four TMDC-enhanced models as a function of gold thin film thickness and number of MX₂ layers. (a) WS₂-enhanced model at 600 nm wavelength; (b) MoS₂-enhanced model at 633 nm wavelength; (c) WSe₂-enhanced model at 633 nm wavelength; (d) MoSe₂-enhanced model at 633 nm wavelength.

From all the above results, we can conclude that the best angular sensitivity enhancement over the four 2D materials and various incident wavelengths were achieved with a WS₂ monolayer, a 35 nm thick gold thin film, and at 600 nm incident wavelength. We further compared this enhanced SPR configuration with the conventional Kretschmann configuration (with a 50 nm gold thin film). As shown in Figure 3-5, the sensitivity of our optimized WS₂ enhanced configuration (155.68 deg/RIU, in solid red line) is 3 times higher than that of Kretschmann (53.40 deg/RIU, in blue dashed line). For the Kretschmann configuration without any dielectric layers, the light coupling can only be affected by the gold film. Conversely, for the WS₂ enhanced structure, both the WS₂ and gold films can be used to adjusting the light

Figure 3-5 Comparison of the SPR sensing performances between the optimized WS₂ enhanced scheme (the red solid line) and the conventional Kretschmann configuration with 50 nm thick Au substrate (the blue dashed line).

coupling condition, allows higher opportunity to achieve optimum coupling, and thus higher SPR enhancement [297, 298, 323].

3.3.2 Phase SPR sensitivity

We have also investigated the phase sensitivity of the 2D TMDC-structured SPR sensing substrates. The phase sensitivity is orders of magnitude higher than the angular sensitivity, since there is a sharp phase jump at the SPR angle. Similar to the calculation methods used in angular modulation section, the reflectivity, the phase changes, and the FWTM in the phase modulation were studied as a function of gold thickness and incident wavelength. Here, the refractive index change of the analytes is assumed to be $\Delta n_{bio} = 0.00012$ RIU, which corresponds to a standard single-stranded DNA binding interaction with a low concentration in the picomolar range [36, 324]. The summarized results are shown in Table 3-5, and all the detailed results are presented in the Appendix. Clearly, the largest phase change ($\Delta\phi_d$) always corresponds to the lowest minimum reflectivity (R_{min}). This phenomenon is consistent for all four types of 2D TMDC layers at all excitation wavelengths. In addition, from the FWTM we found that the coating of MX₂ layers led to a slight broadening of the resonance curves. This is because the additional MX₂ layers may induce the over-coupling, result in energy damping [216, 217]. We selected the optimized parameters giving the highest sensitivity enhancement for visible and NIR wavelengths, respectively. For the visible wavelength, the highest sensitivity was obtained in the WS₂-based model with 41 nm gold (2 nm silicon) at a 600 nm wavelength. For NIR excitation the highest sensitivity was achieved with the MoSe₂ model with 39 nm thick gold (4 nm silicon) at 1024 nm wavelength. The SPR curves for these two optimized MX₂-enhanced

Table 3-5 Changes in differential phase, minimum reflectivity and FWTM at various gold and silicon thickness with different number of TMDC layers. It was assumed that the refractive index change to be detected is $\Delta n_{bio} = 1.2 \times 10^{-4}$ RIU and the incident wavelength $\lambda_{inc} = 1024$ nm.

Type of MX ₂	d_{Si} (nm)	d_{Au} (nm)	MX ₂ (L)	$\Delta\Phi_d$ (Deg) ($\Delta n_{bio}=0.00012$)	R_{min}	FWTM
WS ₂	0	39	6	83.7199	4.57×10^{-7}	0.4777
WS ₂	1	42	1	62.9637	1.15×10^{-5}	0.2357
WS ₂	2	40	4	68.0817	4.03×10^{-6}	0.4163
WS ₂	3	40	4	87.5683	3.91×10^{-7}	0.4546
WS ₂	4	42	1	57.9695	1.53×10^{-5}	0.2970
WS ₂	5	43	0	69.1099	6.28×10^{-6}	0.2663
WS ₂	6	43	0	79.2962	4.34×10^{-7}	0.2874
WS ₂	7	43	0	76.2760	1.82×10^{-6}	0.3104
MoSe ₂	0	42	1	91.8140	1.74×10^{-7}	0.2117
MoSe ₂	1	42	1	86.8287	2.65×10^{-7}	0.2279
MoSe ₂	2	42	1	78.2922	5.00×10^{-7}	0.2456
MoSe ₂	3	42	1	84.0054	9.90×10^{-7}	0.2648
MoSe ₂	4	39	5	106.9330	3.26×10^{-8}	0.4853
MoSe ₂	5	42	1	74.2272	3.75×10^{-6}	0.3088
MoSe ₂	6	43	0	79.2962	4.34×10^{-7}	0.2874
MoSe ₂	7	43	0	76.2760	1.82×10^{-6}	0.3104
MoS ₂	0	42	4	69.2605	4.44×10^{-6}	0.2623
MoS ₂	1	42	4	71.7154	4.61×10^{-6}	0.2839
MoS ₂	2	42	4	70.9399	4.24×10^{-6}	0.3074
MoS ₂	3	42	4	70.5056	3.37×10^{-6}	0.3332
MoS ₂	4	42	4	75.1060	2.09×10^{-6}	0.3618
MoS ₂	5	42	4	76.0397	7.74×10^{-7}	0.3932
MoS ₂	6	43	0	79.2962	4.34×10^{-7}	0.2874
MoS ₂	7	42	4	82.6321	8.40×10^{-7}	0.4669
WSe ₂	0	41	3	44.9583	3.52×10^{-5}	0.2763
WSe ₂	1	40	5	65.5617	5.20×10^{-6}	0.3904
WSe ₂	2	40	5	87.9733	2.66×10^{-7}	0.4259
WSe ₂	3	41	3	71.5747	2.45×10^{-6}	0.3524
WSe ₂	4	41	3	79.6861	1.53×10^{-7}	0.3829
WSe ₂	5	41	3	80.5496	3.66×10^{-7}	0.4167
WSe ₂	6	43	0	79.2962	4.34×10^{-7}	0.2874
WSe ₂	7	43	0	76.2760	1.82×10^{-6}	0.3104

Figure 3-6 The SPR curve comparison of conventional bare gold substrate and TMDC structured models. (a) Visible wavelength of 600 nm; (b) Near infrared wavelength of 1024 nm.

models and the conventional model are shown in Figure 3-6. The minimum reflectivity R_{min} for a Au thin film 50 nm thick (typical thickness in conventional SPR biosensors) under the excitation wavelength of 600 nm and 1024 nm were as large as 0.05 and 0.08, while the values for WS₂ and MoSe₂ enhanced models were 4.92×10^{-8} and 3.26×10^{-8} , respectively. The much lower R_{min} values for the MX₂ models indicated better light coupling, leading to stronger SPR excitation and a more abrupt phase jumps.

Next, we studied another critical parameter: the penetration depth of the surface plasmon resonance. The penetration depth (L_p) is defined as resonance depth where the excited electric field intensity decreased by a factor $1/e$. The electric field (in V/m) and the penetration depth (in nm) for the optimized MX₂ SPR model are shown in Figure 3-7. It is obvious that the strongest electric field occurred at the interface of the TMDCs and the analytes, reaching to 1.4×10^5 V/m. The penetration depth was determined to be

Figure 3-7 Results of Finite Element Analysis (FEA) simulations showing the electric field distribution onto a 2D TMDC structured substrate under the resonance condition ($\lambda_{inc} = 1024$ nm). (a) The y components of the electric field distribution shown in 3D space. (b) The y components of the electric field distribution. (c) The evanescent decay of the excited electric field penetrating into the sample medium. (d) Distribution of the electric field norm (i.e. the intensity of the electric field, $I = |\vec{E}(x, y, z)|$).

~440 nm, as shown in Figure 3-7c. A larger penetration depth contributes to a higher sensitivity of the excited surface plasmon waves to refractive index changes [151, 325].

We further investigated the sensitivity for a large range of analyte concentrations. We selected four optimized MX₂-enhanced SPR models from the above simulated results (i.e., monolayer WS₂ model with 41 nm thick gold, 6-layer MoS₂

Figure 3-8 The differential phase shift $\Delta\phi_d$ as a function of the refractive index change of sample solutions Δn_{bio} of four types of TMDCs enhanced models.

model with 47 nm thick gold, bilayer WSe₂ model with 45 nm thick gold, and 5-layer MoSe₂ model with 39 nm gold). Figure 3-8 illustrates the differential phase changes ($\Delta\phi_d$) over 30 amounts of RI variation (Δn_{bio}), ranging from 0 to 0.0015 RIU. The phase change for all MX₂-enhanced models shows a much sharper change than the conventional ones, because the minimum reflectivity (R_{min}) of MX₂-based models is much lower. Detailed data are shown in the Appendix (Tables A35-36). The MX₂ layers improved the light coupling of SPR, result in more light energy transferred to the SPW and thus increased the sensitivity. Although the added 2D TMDC layers can improve the sensitivity, but excessive TMDC layers will cause the over coupling, which will decrease the sensitivity. Thus, there needs a balance when adjusting the thicknesses of

Table 3-6 Comparison of the plasmonic sensing performances with/without the optimized TMDC layers on a gold thin films, considering reflective index changes of the analyte $\Delta n_{bio} = 2 \times 10^{-6}$. High phase sensitivities always correspond to low minimum reflectivity, showing that the TMDC layers have induced strong and abrupt phase variation.

Enhanced models	Resonance angle (Deg)	Minimum reflectivity	FWTM (deg)	$\Delta\phi_s$ (Deg)	Sensitivity (deg/RIU)
Au(39nm)/Si(4nm)/MoSe₂(5L)	54.7660	3.2560×10^{-8}	0.4853	22.5679	1.128395×10^7
Au (39nm)/Si(4nm)	53.8679	0.0217	0.3109	0.0409	2.043310×10^4
Au (50nm)	53.0390	0.0742	0.1353	0.0255	1.275259×10^4

gold film and MX₂ films during the optimization processes. Among these four optimized 2D TMDC-enhanced SPR models, the 5-layered MoSe₂ with 39 nm thick gold at 1024 nm wavelength exhibited the lowest minimum reflectivity of 3.2560×10^{-8} , and therefore the highest phase sensitivity of 1.128395×10^7 deg/RIU. Comparisons of the sensing performance for enhanced and non-enhanced SPR models have been listed in Table 3-6. The phase sensitivity for the optimized MoSe₂ based SPR model is 3 orders of magnitude higher than that of the conventional SPR with a Au thin film with 50 nm thick, 1.28×10^4 deg/RIU, showing a much more improved sensing performance for a tiny refractive index change (2×10^{-6} RIU), thus making it more sensitive to small molecular interactions.

3.4 Conclusion

In this chapter, we have designed atomically thin 2D TMDC-structured plasmonic sensing substrates for sensitivity enhancement. Fresnel equations, Maxwell's equations and the transfer matrix method were used to analyze and calculated the reflectivity, resonance angle, phase, and the corresponding sensitivity in both angular and phase modulation modes for the optimized structures. To study the influence of the excitation wavelengths on sensing performance, we investigated different incident wavelengths, from 600 nm to 1024 nm. The results showed that 2D TMDC layers can be coated as a lossy material on the gold surface to improve the light coupling and thus significantly improve the sensitivity of the biosensor. At the same time, an excessive number of MX₂ layers result in over coupling and reduced the sensitivity. The highest SPR sensitivity for angular modulation was 155.68 Deg/RIU, achieved with a 35 nm gold films, 7 nm silicon nanolayer and a WS₂ monolayer at 600 nm excitation wavelength, which was 300% that of the conventional structure. For the phase modulation mode, the highest phase sensitivity of 1.1×10^7 deg/RIU was achieved with a 5-layered MoSe₂, 39 nm gold and 4 nm silicon at 1024 nm wavelength. This phase sensitivity was 3 orders of magnitude higher than that of conventional SPR biosensors. These results clearly demonstrate that 2D TMDCs can effectively enhance the sensitivity of SPR biosensors for both angular and phase modulation modes. The sensitivity enhancement depends on the excitation wavelength, TMDC type, and the number of layers. In the visible range, the WS₂ monolayer has the best performance, while for the NIR range, the best results came from multi-layer MoSe₂ which can achieve an ultra-high sensitivity, that is promising for the realization of single molecular detection in diagnostics.

Chapter 4 Sensitivity enhancement of 2D transition metal dichalcogenide-based SPR biosensors

The theoretical modeling study in Chapter 3 demonstrated that transition metal dichalcogenide nanolayers could significantly improve the sensitivity of SPR biosensors. Particularly, among the studied TMDCs the WS₂ monolayer showed the strongest enhancement effect under visible excitation wavelength due to the optimum light coupling. Therefore, in this chapter, we demonstrate a novel two-dimensional WS₂-based SPR biosensor. The monolayer WS₂-structured gold sensing film was fabricated via CVD and wetting transfer techniques. The characterization was performed by photoluminescence, Raman spectroscopy, and atomic force microscopy (AFM). The reflectance and the resonance angle of the proposed biosensor were measured with a home-made angle-sensitive setup with a 632.8 nm laser. The phase sensitivity of the WS₂ sensing film reached 15,000 deg/RIU, which represents an enhancement of 151% over the conventional bare gold SPR sensing film in detecting low concentration analytes.

4.1 Introduction

Improving the sensitivity of SPR biosensors has always been a central goal of SPR technological development. Recently, 2D transition metal dichalcogenides (TMDCs) have attracted great attention from the scientific community and demonstrated their potential for improving the performances of various optoelectronic nanodevices such as photodetectors and solar cells [195, 326]. From a 2D material perspective, one of their most intriguing optical property is their much higher

absorption rate (above 5%, up to 30%) than that of monolayer graphene (2.3%), while still maintaining a similar atomic thickness of less than 1 nm [48, 49, 51]. Moreover, in contrast to graphene, which exhibits zero bandgaps, these 2D TMDCs exhibit tunable bandgaps. The bandgap can be tuned from indirect in their bulk (multiple-layer) forms to direct when the thickness is decreased to the monolayer scale [195, 327]. This makes them ideal candidates for the future generation of integrated flexible electronic devices, by themselves or as complementary material to graphene. The structures of these 2D TMDCs are also similar to that of graphene, where the metal atom M (Mo, W) and the chalcogen atoms X (S, Se) are bonded in the form of X-M-X, with the chalcogen atoms in two hexagonal planes separated by a plane of metal atoms. In bulk TMDCs, they have stacked through van der Waals forces and thus a single layer can be easily obtained through the exfoliation process. Currently, these atomically thin materials are synthesized in large area scale by using chemical vapor deposition (CVD) methods [328]. Previous research has shown that structuring a thin layer of dielectric materials can advantageously change the plasmonic resonance condition, but there remain concerns regarding their integration in the prism-coupling plasmonic sensors [329, 330]. Engineering the SPR sensing film in a low-cost and integration-ready fashion is highly desired for the commercial SPR sensor market. In this chapter, we engineer a single crystal TMDC monolayer-structured SPR biosensor. The WS₂-structured gold sensing film was fabricated using CVD and the poly(methylmethacrylate) (PMMA) wetting transfer technique. The significant performance characteristic of the WS₂-based SPR biosensor, including resonance angle, reflectance and differential phase, were determined by the angle and phase modulation setups. The phase sensitivity for detecting glycerin with different concentrations was demonstrated respectively. For all the detected solutions, the sensitivity of WS₂-based sensing film is generally improved

compared to that of the conventional bare gold sensing film. The sensitivity enhancement, as high as 151%, is most significant at low concentrations. The enhancement is mainly attributed to the improved light coupling induced by WS₂. Acted as a lossy materials (dielectric) on the gold film, WS₂ monolayer can directly change the effective permittivity of this metal/dielectric layer and thus adjust the light coupling between incident light and SPW [14].

4.2 Materials and methods

4.2.1 Fabrication of TMDC based sensing chip

4.2.1.1 The growth of single crystalline WS₂ monolayers

The monolayer WS₂ flake was grown on a SiO₂/Si substrate by chemical vapor deposition (CVD). The 300 nm substrate was pre-cleaned with acetone in an ultrasonic bath for 20 min and dried with ultra-high purity (UHP) nitrogen gas. Commercial WO₃ powder (50 mg, > 99.5%, Sigma Aldrich) and the substrate were placed at the center and downstream of the furnace, respectively, at a temperature of 900°C. At the same time, the sulfur (S) powder (500 mg, Sigma-Aldrich) was loaded upstream in a lower temperature region at 200°C. The temperature of the two regions of the furnace were controlled separately. During the sulfurization, both the WO₃ powder and the S power were heated to the prescribed temperatures within 30 min and kept at those temperatures for 60 min. The entire growth process was performed under ultra-high purity argon gas with the flow rate of 100 sccm at atmospheric pressure. The furnace was cooled down to room temperature naturally with the cover open.

4.2.1.2 Preparation of WS₂ based sensing chip

The monolayer WS₂-based SPR sensing chip was obtained by transferring the WS₂ flake from the SiO₂/Si substrate to a gold thin film substrate via the poly(methylmethacrylate) (PMMA) wetting transfer technique. First, the target gold substrate was prepared. The commercial gold-coated substrate (Platypus Technologies, AU.0500.ALSI) was made from a 50 nm gold film coating on a 0.7 mm aluminosilicate glass slide. There was a 2.5 nm titanium layer sandwiched between the gold film and glass surface for enhancing the adhesion. Before the transfer, the gold slide was diced into ~2 cm² pieces and washed in an ultrasonic bath with acetone for 30s. Next, the PMMA film was spin-coated on the surface of the WS₂-covered SiO₂/Si substrate at 3000 rpm for 30s. The PMMA was used as the supporting film to peel off the WS₂ flake from the silicon substrate. Following this, the entire substrate was soaked into a HF solution to etch the SiO₂/Si substrate for 10 min. The PMMA film encapsulating the WS₂ flake will then float on the liquid surface. The PMMA/WS₂ layers were washed with deionized water several times (~10 s) and lay flat on the surface of the water. Then, it was gently fished up with the pre-cleaned gold substrate. In this way, the PMMA/WS₂ layer was transferred onto the gold film substrate. Finally, the PMMA supporting film was removed with acetone after baking the gold substrate at 80°C for 30 min.

4.2.2 SPR optical setups

The measurements for the SPR sensing parameters, including resonance angle, reflectance and phase, were conducted through the angle modulation and phase modulation setups, respectively. The design of the setups and the measurement process are presented in detail below.

4.2.2.1 The SPR biosensor

Figure 4-1 (a) Photograph of TMDC-enhanced SPR biosensor. The light-coupled prism, the WS₂ sensing film and the sample container are immobilized on the rotation stage with a PMMA mount. (b) The image of individual components: the WS₂ sensing film is sandwiched between the prism and sample chamber bringing the WS₂ sensing surface into full contact with the sample solution.

The SPR biosensor was built based using the well-known Kretschmann configuration. It mainly consisted of a prism, SPR sensing film, and a sample container. The glass substrate of the gold sensing film seamlessly adhered onto the base of a right-angle BK7 prism (with catheti 40 mm long) through optical matching oil (Cargille Labs) as shown in Figure 4-1. The prism was used to couple the incident light onto the sensing film. A sample container was then attached to the sensing film, allowing the sample solution to flow through the WS₂/Au sensing surface. The sample container was fabricated by PDMS (polydimethylsiloxane) through a 3D printed mold. At the center of the PDMS container was a $10 \times 10 \times 1.5 \text{ mm}^3$ sample chamber. Two microtubes (diameter 300 μm) at the bottom of the chamber were designed for injecting and draining the sample solution. The other ends of the microtubes were connected to a syringe for pumping or draining the target sample solution. The injection rate was approximately 50 $\mu\text{L/s}$, controllable by a syringe pump. A PMMA mount was

engineered to immobilize the prism, WS₂/Au sensing film, and sample container on the rotation stage. Thus, the incident angle could be varied by rotating the rotation stage. The scale on the rotation stage was used to determine the incidence angle and thus the resonance angle.

4.2.2.2 Angular modulation setup

The essence of the resonance angle measurement is scanning the incidence angle and plotting the measured reflectance as a function of angle. The specific incidence angle at which the SPR reflectance curve exhibits a minimum is regarded as the resonance angle. To measure this, we built an angular modulation SPR setup, as shown in Figure 4-3, to monitor the reflectance of the WS₂/Au sensing film. The experimental setup began with a light source – a 4 mW 632.8 nm He-Ne laser. The collimated incident light was sent through a polarizer to remove the *s*-polarized light, as only *p*-polarized light can induce SPR. The polarized light beam impinged onto the surface of WS₂/Au film through the prism, and upon reflection, travelled to an optical

Figure 4-2. The optical schematic diagram of the phase sensing setup used for measuring the differential phase changes of the reflected light.

detector. The photodetector (power meter, Newport 2832C) was used to collect and measure the intensity of the reflected light. The incidence angle was generally varied between 30° and 90° to monitor the intensity. The final reflectance was obtained by calculating the ratio between the reflected intensity and the incident intensity.

4.2.2.3 Phase modulation setup

A phase modulation SPR setup was constructed to measure the phase signal of the reflected light from the SPR biosensor, as shown schematically in Figure 4-2. A 4 mW 632.8 nm He-Ne laser with a beam spot size of 1 mm was used as the source. We note that the incident angle should be fixed at the resonance angle during the entire phase measurement. The light beam was split into *p*- and *s*-polarized light by a polarized beam splitter (PBS). The *p*-polarized light was used to excite the SPR effect, while the

Figure 4-3. The optical schematic diagram for measuring the reflectance and the resonance angle for the SPR biosensor. The incident light from a 4 mW 632.8 nm He-Ne laser was polarized, impinged onto the WS₂/Au sensing film through the prism, and then collected by a photodetector. The inset is a photograph of the practical setup.

s-polarized light was regarded as a reference beam. The *p*-polarized light beam passed through the prism and reflected at the sensing film. For the *s*-polarized beam, a Galvo-mirror (Thorlabs, GVS001) was driven by a sine wave signal oscillating at 90 Hz to generate an optical path difference between the two beams of light. Then, the *s*-polarized and *p*-polarized lights were adjusted to the same path by a beam splitter (BS). Through a polarizer, the two light beams interfered with each other, whose intensity was measured by a photodetector and recorded by a data acquisition card (NI PCI-6115). The phase signals were finally obtained using a Labview program to process the acquired data.

Figure 4-4 shows the raw and processed measurement data. The corresponding sine waves of the interfered light can be observed through an oscilloscope (Instek GOS-653G), as seen in the circled region in Figure 4-4a. The oscilloscope diagram shows that there were two symmetric sinusoidal waveforms in the reflected light, which was caused by the rotation of the Galvo-mirror to the left and right. The sinusoidal waveforms can be extracted by using the lowpass filtering through the Labview program as shown in Figure 4-4b. Therefore, the phase data can be obtained from the intensity of the sinusoidal waveforms by a point-wise arcsine algorithm [331, 332].

Figure 4-4. (a) The waveform of the reflected light collected by an oscilloscope. (b) The sinusoidal waveforms of the reflected light after filtering by the Labview program.

Finally, the differential phase was calculated from the phase difference between the *p*-polarized light and the *s*-polarized light.

4.2.2.4 Preparation of sample solutions

Deionized (DI) water, a series of glycerin solutions were used to demonstrate the sensitivity of the WS₂-enhanced SPR biosensor. The glycerin (99%) was purchased from Sigma-Aldrich. Glycerin solutions with various mass ratios of 1%, 1.5%, 2%, 2.5%, 3%, 5% and 10% were prepared by using deionized (DI) water. The refractive index of the DI water and the prepared glycerin solutions were measured by an Abbe refractometer (2WAJ). The refractive index was varied from 1.3326 to 1.3451 with sample solutions from 0% to 10% glycerin solutions in water. Before measuring the glycerin solutions, 1000 μ L of DI water was injected through the microtube and measured. This step served three functions: First, it can be used for the calibration of the setups and the measured results can be regarded as the baseline of the entire measurement. Second, it can be used for checking the leaks and drainage of the chamber and the microtubes. Lastly, it is useful for gently rinsing off tiny impurities on the sensing film surface and a sample chamber, to avoid spurious measurements for the solutions of interest. After this step, the DI water was drawn out from the chamber before injecting the glycerin solutions. The volume of the chamber was approximately 150 μ L; thus, normally 1000 μ L of glycerin solution was injected to concurrently rinse off the DI water residue and fill the chamber. When changing the sample solutions, the same procedure was performed to avoid dilution of the current solution by previous solution residue. Care was taken to fill the chamber completely with liquid and avoid the formation of bubbles after the injection. This is because the bubbles would likely disturb the light beam and cause unwanted refraction and reflection.

4.3 Results and discussion

4.3.1 Characterization of the WS₂ monolayer

An optical microscope image of a monolayer WS₂ flake deposited on the SiO₂/Si substrate is shown in Figure 4-5a. It can be seen that atomically-thin WS₂ flakes grown by the CVD method have perfect triangular shapes and sharp edges. The maximum side length of the triangle was about 35 μm , and the area was estimated to be about 550 μm^2 . The coverage of the SiO₂/Si substrate was approximately 20%. Figure 4-5b presents the atomic force microscopy image of WS₂ monolayer, with the thickness estimated to be 1.2 nm. Figure 4-5c shows the optical image of the WS₂ flake after transfer onto the 50 nm gold film substrate. The WS₂ flake almost retained its original triangular shape after the transfer, which indicates the PMMA wetting transfer technique is a convenient and efficacious method in engineering 2D WS₂. A photograph of the engineered WS₂-based sensing film is shown in Figure 4-5d, where the WS₂ flake was placed at the center of the film.

The WS₂ thin flake was characterized by photoluminescence (PL) spectroscopy and by Raman spectroscopy. Figure 4-6a shows the PL spectra of the WS₂ flake excited by a 532 nm laser source. The peak intensity appeared at 645 nm and was slightly offset from the commonly measured peak at 625 nm of WS₂ on SiO₂/Si substrate. This discrepancy was attributed to the reflection of gold film substrate. Figure 4-6b

Figure 4-5. (a) An optical image of the single crystalline WS₂ monolayer deposited on the SiO₂/Si substrate. (b) The atomic force microscopy image of WS₂ monolayer. The measured thickness of its edge was estimated to be 1.2 nm. (c) The optical microscope image of the WS₂ monolayer transferred onto the 50 nm gold-film-coated 0.7 mm glass substrate. (d) The photograph of the engineered WS₂/Au SPR sensing film.

illustrates the Raman spectrum of the as-grown monolayer WS₂ over the wavenumber ranged from 100 to 700 cm⁻¹ with the 532 nm excitation wavelength at room temperature. The typical Raman modes of WS₂ flakes are presented in the graph as labeled, such as the first order mode of A_{1g} (Γ) and the second order mode of 2LA (M). Particularly, the strongest 2LA (M) mode at a wavenumber of 350.8 cm⁻¹ caused by the

double resonance scattering is regarded as the fingerprint characteristic of the WS₂ monolayer.

Figure 4-6. The spectroscopy characterization of the as-grown WS₂ monolayer on the gold film-coated glass substrate with an excitation wavelength of 532 nm. (a) The PL spectrum of WS₂, with strongest PL peak located at 645 nm. (b) The Raman spectrum of the WS₂ monolayer at room temperature. The strongest mode, 2LA (M), is located at 350.8 cm⁻¹, and the A_{1g} mode is located at 417.9 cm⁻¹.

4.3.2 Sensing measurement of bare gold sensing film

The reflectance and differential phase measurements with a conventional bare gold sensing film was performed first. In the reflectance measurement, the chamber was filled with air, and the incidence angle was varied from 34° to 38°. As the reflectance changed with the incident angle, we plotted the SPR curve and obtained the resonance angle of 36.2° at the minimum reflectance of 0.12, as shown in Figure 4-7a. This value matched well with the simulated value of 36.1° obtained from Fresnel's equation, shown in Figure 4-7b. For the phase measurement, we measured the differential phase for the DI water and glycerin solutions with mass ratios ranging from 1% to 10 %. The refractive index of these solutions changed from 1.3326 (DI water) to

Figure 4-7 The conventional SPR biosensor with 50 nm bare gold sensing film: variation of reflectance in the air, (a) experimental result and (b) simulation result, with respect to incident angle; changes in differential phase, (c) experimental result and (d) simulation result, for various mass ratios of glycerin solutions.

1.3451 (10% glycerin). The differential phase of the DI water was set as the baseline for comparison with the rest of the sample solutions. Figure 4-7c presents the changes in the differential phase as a function of the refractive index of the sample solutions. When the refractive index changed from 1.3326 (DI) to 1.3339 (1% glycerin), the change in differential phase was found to be 11.8 deg. Therefore, the corresponding phase sensitivity was calculated to be 5900 deg/RIU. The experimental results have the same trend as the simulation results (Figure 4-7d), indicating that the proposed theoretical modeling was effective to estimate the sensitivity of SPR biosensors. When comparing the results, it can be seen that the experimental values were ~20% lower

than the simulated ones, which was probably due to two reasons: First, in the measurement, the optical alignment error may affect the final interference fringe detection, which is used to obtain the differential phase. Second, during the measurement of liquid sample, the incident angle may have a tiny drift from the SPR angle.

4.3.3 Sensing measurement of WS₂-based sensing film

We replaced the bare gold sensing film with the engineered WS₂-based sensing film and conducted the measurement of reflectance and differential phase, as shown in Figure 4-8 and 4-9a&b. The measured resonance angle was 36.7° with a minimum

Figure 4-8. The monolayer WS₂-based SPR sensing film: (a) experimental result and (b) simulation result of reflectance variation in air, with respect to angle of incidence; (c) experimental result and (d) simulation result of the changes in differential phase for various mass ratios of glycerin solutions.

Figure 4-9. The experimental results (a) and simulation results (b) of the low concentration of glycerin as a function of different phase changes. (c) The comparison of the phase sensitivity between the conventional SPR bare gold sensing film and the novel WS₂-based SPR sensing film. The refractive indexes of the sample solutions range from 1.3326 (DI water) to 1.3451 (10% glycerin). The inset is the comparison of the corresponding changes in differential phase between these two sensing films.

reflectance of approximately 0.06. This reflectance was about 50% lower than that of the bare gold film, indicating that more incident light energy was coupled into the SPW and thus enhanced its electric field. It has been proved in the theoretical study of Chapter 3 that a lower minimum reflectance leads to a higher phase sensitivity. Here,

in the phase measurement, we also measured the changes in differential phase of the DI water and a series of glycerin solutions with concentration gradient, as shown in Figure 4-8c. It is noted there is a linear relation between the sample RI and the phase changes when the mass ratio of glycerin solution is below 3%, with the corresponding RI of 1.3326 to 1.3368. The equation of fitting linear line is shown on the plot. The changes in differential phase from DI water to 1% glycerin was found to be 29.6° , more than 151% higher than that of the bare gold sensing film. This enhancement attributed to the improved light coupling condition induced by the WS₂ monolayer. Figure 4-8d showed the comparison of the simulated and experimental results. We found that the simulation result (20% coverage) of the phase changes are around $\sim 40\%$ higher than that of the experimental results. This is probably due to four reasons: i) the chemical impurities such as PMMA contaminated the surface quality of WS₂/Au sensing chip; ii) The alignment error of the reflected light to the detector may reduce the collected light intensity, thus affected the phase signals; iii) During the measurement of liquid sample (e.g. glycerin solution), the incident angle may have a tiny drift from the SPR angle due the liquid fluctuation. iv) The coverage of WS₂ to gold film is not exactly uniform, and the 20% coverage ratio of WS₂ to gold film is an averaged value for the whole chip. Therefore, the coverage of the site that hit by the incident light may not be exactly 20%.

Figure 4-9a&b demonstrate the phase changes as a function of lower sample concentrations. The mass ratios here are namely, 0.001%, 0.01%, 0.05%, 0.1%, 0.5%, 1%, 2% and 3%. It is noted that the concentrations of glycerin solution with a mass ratio of 0.001% is approximately equal 10^{-4} M. We can find from Figure 4-9a, the concentration of glycerin solution appears a linear relation to the phase change (by using a log scale). Figure 4-9b demonstrates the simulation results for the glycerin

solutions with even lower concentrations down to 10^{-7} M, which also appears a linear relation between the differential phase changes and the glycerin concentrations.

Table 4-1 The refractive index of each glycerin sample solutions and their corresponding phase sensitivity. The sensitivity enhancement ratio refers to the ratio between the sensitivity of WS₂ based sensing film (S_{WS_2}) to the sensitivity of conventional bare gold sensing film (S_{Au}). The unit of the sensitivity is deg/RIU.

	1%	1.5%	2%	2.5%	3%	5%	10%
	glycerin	glycerin	glycerin	glycerin	glycerin	glycerin	glycerin
n	1.3339	1.3345	1.3351	1.3357	1.3364	1.3389	1.3456
S_{WS_2}	21142.86	18888.89	17083.33	15555.56	14794.52	10894.31	5840
S_{Au}	8428.57	8055.56	7083.33	7301.587	6849.315	5691.057	4240
Ratio	251%	234%	241%	213%	216%	191%	138%

We then compared the sensitivity of the WS₂ sensing film and conventional gold sensing film, as demonstrated in Figure 4-9c and Table 4-1. The results showed that the sensitivity of the WS₂ sensing film was generally higher than that of the conventional film for all detected sample solutions, which matched well with the reflectance results. The highest sensitivity for the WS₂ sensing film was about 15,000 deg/RIU, which was 251% of that of a conventional gold film. As the refractive index of the solution increased, the sensitivity decreased gradually. The sensitivity enhancement ratio (S_{WS_2}/S_{Au}) of the WS₂ sensing film to the conventional film was around 1.9 in 5% glycerin, while decreasing to approximately 1.4 in 10 % glycerin. From these results, we can draw two conclusions. First, the WS₂ monolayer can efficiently improve the sensitivity of the SPR biosensor. Second, the WS₂-enhanced sensing film is ultra-sensitive to low concentration solutions, but it saturates quickly as the analyte concentration increases.

4.3.4 Real-time detection

Next, a real-time detection with WS₂ sensing film surface was conducted to monitor the concentration changes of glycerin solutions by using the differential phase measurement. As shown in Figure 4-10, a series of glycerin solutions with a concentration gradient were detected respectively by the WS₂-based SPR biosensor in a 50 min monitoring window. The DI water was first monitored for 10 min, and a flat differential phase shift baseline was observed. At the 10th min, the DI water in the sample chamber was withdrawn, and 1% glycerin was injected. We immediately observed a significant shift in differential phase from 0 to 29.3°. 10 min later, the 1% glycerin was replaced with 3% glycerin, and we again observed an obvious shift, from 33.5° to 51.9°. Similar performance was observed in the monitoring of 5% and 10%

Figure 4-10 The Real-time monitoring for molecules of glycerin with the novel WS₂-based sensing film. The differential phase measurements were conducted with the phase modulation setup. The glycerin solutions with different mass ratios of 1%, 3%, 5% and 10% were monitored for 10 minutes each. The baseline was obtained with the DI water before measuring the sample solutions.

glycerin with the differential phase reach up to 68.1° and 74.2° respectively. For each 10 min measurement of glycerin solutions, clearly there was a relatively large

fluctuation in the phase signal at the beginning of the sample injection, but the signals tended to stabilize in a short time. The phase signal continued to rise as the increase of analyte concentration, while the phase increasing rate decreased gradually due to the saturation effect [322, 324]. These results demonstrated that the WS₂-based sensing film could give a swift and sensitive response to the RI variations of the liquid analyte.

4.4 Conclusion

In this chapter, a novel transition metal dichalcogenide (TMDC) monolayer-based SPR biosensor was designed, fabricated and tested. The tungsten disulfide (WS₂) monolayer was deposited on a silicon substrate and then transferred onto the gold thin film to fabricate the novel sensing film. The characterization of the WS₂-based sensing film was conducted by PL and Raman spectroscopy. The reflectance and resonance angle of the WS₂ sensing film were measured by the angle modulation setup. The sensitivity performance was demonstrated by detecting glycerin solutions with different concentrations through home-made phase modulation setup. In the detection of low refractive index solutions, the phase sensitivity of the WS₂-based biosensor was strongly enhanced compared with the conventional gold sensing film-based SPR biosensors by 151%. This enhancement attributed to the improving light coupling condition induced by the WS₂ monolayer. Furthermore, the monitoring of the glycerin solutions has shown that the WS₂-based sensing film enables accurate real-time detection for a wide range of detection concentrations. In conclusion, engineered 2D TMDCs can be easily fabricated and integrated into the sensing platform to efficiently enhance the sensitivity of SPR biosensors and realize precise detection for small molecules at low concentration. This achievement can improve the precision of SPR biosensors and broaden their areas of applications. For those clinical applications that

need high selectivity for different analytes, we can functionalize the sensing surface by using specific chemical/biological agents, such as aptamers, ligands, antigens [20, 333-335]. They are considered promising recognition elements with good chemical stability, high selectivity and high affinity toward specific analytes.

Chapter 5 Triboelectric nanogenerator triggered electric-responsive drug release platform

Chapters 5 and 6 focus on the second part of the Thesis, the novel electric-stimulated drug delivery system. The existing stimuli-responsive controlled drug delivery systems are limited, either by low controllability or by a large footprint. In this chapter, we propose a novel self-powered, electric-stimulated drug delivery system, which can not only be portable but also provide high controllability for precise and targeted drug dosing. In the system, a miniaturized triboelectric nanogenerator (TENG) is designed to produce the exogenous stimuli, and the conductive nanocomposite polymer polypyrrole (PPy) was employed as the drug nanocarrier for controllable drug release. The triboelectric nanogenerator designed with nanowire polymer and metallic sheets was used to harvest mechanical energy from human motion and convert it into electric energy. The electricity was utilized to achieve controllable drug release triggered by the conductive nanocomposite PPy. Manually rotating the TENG for 1.5 min can induce the PPy films to release a drug (dexamethasone) dosage of $3\ \mu\text{g}/\text{cm}^2$. In a 60 min measurement, the TENG-triggered released drug dosage reached $35\ \mu\text{g}/\text{cm}^2$. In addition, with the adjustment of a power management circuit, the proposed platform can easily realize accurate and efficient on-demand drug release by operating the TENG.

5.1 Introduction

Nowadays, controllable drug delivery is an important part of advanced healthcare, since it can realize zero-order drug release that ultimately enhances the therapeutic efficacy and reduces the side effect. Some of the most useful tools which can be used for this purpose are the stimuli-responsive drug nanocarriers made of functional nanomaterials, such as nanostructured polymer. The drug molecules are loaded within nanocarriers and can be released into the environment when the nanocarriers are excited/triggered by the stimuli. The polymeric nanocarriers can be designed to have different physicochemical properties in order to become sensitive to both exogenous stimuli (e.g. electricity, light and magnetism) and endogenous stimuli (e.g. pH, enzyme and moisture). The diversity of such stimuli-responsive polymers allows great flexibility in the design of controlled drug delivery systems to meet various therapeutic requirements. However, there are still some serious challenges: it is difficult for nanocarriers responsive to endogenous stimuli to have precise controllability of the release, because such stimuli (e.g. pH, enzyme) have a strong patient-to-patient variability. In contrast, the exogenous stimuli-responsive materials have another problem, namely the need of bulky auxiliary equipment, such as laser or power supply, to generate the stimuli. This would result in a large footprint of the controlled drug delivery system, which directly limits the availability of the therapeutic environment and increases patient's inconvenience. Furthermore, neither of the previous methods is an individual treatment tools suitable for personalized healthcare.

In order to solve this problem, in this chapter we present a triboelectric nanogenerator (TENG)-based drug delivery platform for electric-responsive drug dosing. Instead of using a separate power supply, the TENG itself stimulates the

electrical-sensitive nanocomposite polypyrrole to release drug by harvesting ambient mechanical energy. The rotatory TENG mainly consists of a rotator and stator, which are fabricated with two radial-arrayed copper foils and one thin film of nanowire arrayed polytetrafluoroethylene (PTFE). When the rotator and stator rub against each other under the action of an external force (like human motion), the mechanical energy will be converted to electric energy due to the contact electrification and electrostatic induction [336, 337]. The nanowire arrayed PTFE film increases the contacted area and the electron density thus enhances the output. With the assistance of a power management circuit, the output from TENG can be utilized to control the stimuli-responsive PPy to release the drug. Here, the nanocomposite PPy is used as the nanoporous drug carrier to achieve precise and efficient drug dosing, due to its sensitivity to electric stimuli and its excellent conductivity, biocompatibility and flexibility. For nanomedicine, TENG stands out from other self-charging technologies, including solar cells and thermoelectric generators, due to its advantages of sustainable charging, high efficiency and simple structure. The solar cell charging, for example, is only available in the presence of the sun, while TENG can provide continuous electricity anytime and anywhere since human motion is abundant and easily accessible. In addition, TENG can be easily miniaturized and integrated with wearable medical devices due to its simple structure and easy fabrication process.

The performance of TENG and the controllable drug delivery platform was evaluated. When our fabricated TENG was rotated manually for 1.5 min, the concentration of 3 $\mu\text{g}/\text{cm}^2$ of drug (dexamethasone) was released from the electric-stimulated drug carrier. In a 60 min measurement, the TENG-triggered released drug dosage reached 35 $\mu\text{g}/\text{cm}^2$, and the zero-order release was realized. In addition, an accurate and efficient on-demand drug release was achieved by operating the TENG.

These results demonstrated that the proposed triboelectric nanogenerator based electric-responsive drug release platform could provide patients a comfortable and battery-free approach to achieve customized drug delivery and it can be further employed in different types of drug delivery routes to meet various treatment requirements.

5.2 Materials and methods

5.2.1 Fabrication of TENG

The TENG mainly consisted of a rotator and a stator. Both the rotator and the stator were fabricated on a printed circuit board (PCB).

The rotator comprised a layer of poly(methyl methacrylate) (PMMA) was used as a substrate/holder for the rotator. Deposit a layer of Ti (10 nm) and then a layer of Cu (200 nm) on the rotator in sequence using a DC sputterer and then patterned using wet etching to define the equal-degree and radial-arrayed sector intervals on the copper foil.

Stator comprised a thin glass epoxy layer was prepared as the base material of the laminate panels. A layer of copper was deposited on the glass epoxy to form the electrode layer, and was patterned using the same wet-etching process was used to etch the radial-arrayed pattern of two disconnected and complementary electrodes. Two metallic wires were connected to the two electrodes respectively for outputs. The aligned nanowires of the PTFE polymer were fabricated by inductively coupled plasma (ICP). A commercial PTFE thin film (TS-PTFE, thickness= 90 μm) was cut into a circle with diameter of 15 cm, then put it on a silicon wafer and coated with 5 nm gold by direct current sputtering. Then Ar (15 sccm), O₂ (10 sccm) and CF₄ (30 sccm) were introduced into the ICP chamber at a pressure of 15.0 mTorr and 55°C for a 5 min

etching. The length of the nanowire is around 400 nm. The nanowire arrayed PTFE was finally transferred and adhered onto the stator.

5.2.2 Preparation of nanoporous PPy based drug release electrode

The nanocomposite polymer, polypyrrole (PPy) was employed as the drug carrier. Dexamethasone disodium phosphate (DEX, Sigma) was used as the test drug. A potentiostat (Autolab PGSTAT302N, Metrohm) was used to grow the PPy/DEX film on a planar gold electrode (PalmSens, model 101, inner diameter = 2 mm). Before the electrodeposition, the gold electrode surface was pre-cleaned by the aluminum oxide polishing powder (0.1 μm , 0.3 μm). 2 μL of 1% polystyrene colloid particles solution (Polysciences, diameter 50 nm) was dropped on the surface of the gold electrode to serve as the template of the nanoporous structure. The gold electrode was baked for 1 hour at the temperature of 60 $^{\circ}\text{C}$ to dry and fix the nanobeads. The deposition solution (1 mL) for the DEX-loaded PPy film was prepared with 0.1 M pyrrole (Sigma) and 0.1 M Dexamethasone disodium phosphate (Sigma). The gold electrode and an Ag/AgCl counter electrode were immersed into the deposition solution and applied with a constant positive current of $\sim 50 \mu\text{A}$ for 120s. After the electro-polymerization, the PPy/DEX deposited gold electrode was gently washed with deionized water for 3-4 times to rinse off the remaining solution. After that, the gold electrode was immersed in toluene for 12 hours to remove the nanobeads inside the PPy. Finally, the nanoporous DEX-loaded PPy was obtained.

5.2.3 The power management circuit

The circuit, whose schematic is shown in Fig. 5-5 was built with electrode components including a rectifier, a capacitor (470 μF , 50 V), two Zener diodes (1.7 V),

an external resistance (1 M Ω) and a switch. The rectifier was used to convert AC voltage to DC voltage; the capacitor was used to store the discontinuous electrical energy and convert it to a continuous voltage; the Zener diode was used to maintain the DC voltage due to its current-voltage characteristic; the load was connected in parallel with diode; the resistor was used to divide the voltage with diode.

5.2.4 Measurement

The TENG was driven by hand motion. The voltage and current outputs of the TENG were measured by a low-noise system electrometer (Keithley Model 6514). The UV absorbance of the released DEX solution was measured by a spectrophotometer (Nanodrop 2000a, Thermo Scientific™). The morphology characterization of the PPy nanocomposite and the PTFE nanowire was conducted by using scanning electron microscope (FESEM 6340F).

5.3 Results and discussion

5.3.1 The triboelectric nanogenerator

A radial-arrayed rotary TENG was fabricated, and it mainly consisted of a rotator and a stator; the detailed schematic structures are shown in Figure 5-1. The rotator was a copper film etched with equally spaced and radially-arrayed sector intervals. As for the stator, it contained a copper electrode layer and a PTFE film. The electrode layer was etched in a radially-arrayed pattern to form two disconnected and complementary electrodes 1 and 2 on the same plane. The radial arrayed sectors patterned on the two copper films were symmetrical. This planar-structured design not only leads to a simple structure and fabrication process, but also enhances the

robustness and durability of the TENG. The PTFE film was immobilized on the surface of the copper electrode as an electrification material, which was sandwiched between the two copper films surfaces. The scanning electron microscopy (SEM) images of the fabricated PTFE nanowires array demonstrated that the diameter of the nanowire was ~ 200 nm and the length was ~ 1 μ m. Almost all nanowires were perpendicular to the substrate. It is obvious that the PTFE nanowires have a reasonably uniform distribution and size on the substrate. Besides the above primary components, the glass epoxy and PMMA thin layers were realized as the holder/substrate for the rotator and stator, as shown in the photograph of the actual TENG device in Figure 5-1-b.

Figure 5-1 (a) Overall view of the TENG design; (b) The photograph of the fabricated TENG; (c) The exploded structure of TENG; (d) details of the copper rotator and stator patterns and a the scanning electron microscopy (SEM) image of the fabricated PTFE polymer-nanowires array.

Figure 5-2 (a) The TENG electricity generation process: the TENG can effectively harness slight movement and convert it to alternating-current electricity due to contact electrification and electrostatic induction. (b) The chemical reaction mechanism for drug loading (PPy polymerization) and electric-stimulated drug release. In the first formulation, the PPy's are formed by electro-polymerization while loading the anionic drug Dexamethasone phosphate (DEX⁻) as a dopant. In the second formulation, when the negative voltage applied to PPy's, the drug is released during the reduction reaction.

We use the basic sector of TENG to demonstrate the electricity-generation process as shown in Figure 5-2. As the rotator spins from state 1 to state 2 under external force (such as human motion), the electrons transfer from copper rotator to PTFE layer due to the contact electrification. Thus, the rotator surface is positively charged while the PTFE surface is negatively charged. The charges density of rotator is twice of that

Figure 5-3 The characterization of the radial-arrayed rotary TENG: the open-circuit voltage of TENG driven by a motor at varying rotation rates of (a) 90 rpm, (b) 50 rpm and (c) 10 rpm respectively. (d) The open-circuit voltages of TENG that is rotated manually for 2 s, 6 s, 10 s and 30 s respectively.

of the PTFE surface due to the charge conservation. Under the continuous rotation, an alternating potential difference is built between electrode 1 and 2 due to electrostatic induction. It is noted that the nanowire structure of the PTFE enhances the contacted area and thus increases the triboelectric charge density, leading to an improvement in electric output.

In order to characterize the TENG output, we measured the open-circuit voltage of TENG when it was driven both by a motor and hand, respectively, as shown in Figure 5-3. When the TENG was driven by a motor, the instantaneous voltages can be as high as 250 V (Figure 5-3a-c). If the TENG was gently rotated manually, the voltages can also reach values up to 100 V and above (Figure 5-3d). During our testing TENG was

given various rotation durations by hand, namely, 2 s, 6 s, 10 s and 30 s. For each charging duration, we can observe a swift and high voltage output, which indicates TENG can efficiently harvest mechanical energy from human motions and convert into electrical energy.

5.3.2 The PPy drug release electrode

The next step was to investigate the electric-stimulated drug release electrode. A conductive nanocomposite polymer, polypyrrole (PPy), was chosen as the drug-carrier. For the test drug, a common-used anti-inflammatory drug, Dexamethasone Sodium Phosphate (DEX) was used to demonstrate the controlled drug release performance. It is a phosphorylated prodrug of Dexamethasone, which is generally used in the treatment of varying inflammations, allergic reactions and musculoskeletal injuries [338]. The DEX loaded PPy porous films were electrodeposited on the surface of a gold electrode using a one-step electro-polymerization. During the polymerization of pyrrole, the negatively-charged drug, DEX^- , (in the anionic state) was loaded into the polymer matrix to balance positive charges formed on the backbone of PPy (Figure 5-2b). Prior to electrodeposition, the electrode surface was treated with polystyrene (PS) nano-beads to form a template and thus to obtain the nanoporous PPy films. Compared with conventional bulk planar PPy films, the porous PPy nanostructures (Figure 5-4a,b) possess enhanced surface area, thus exhibiting higher drug loading capacity [339]. When the PPy films are biased with proper negative voltages (or were reduced electrochemically), the anionic DEX^- previously doped within the oxidized PPy backbone will be released to the local environment as the charges on the backbone were neutralized, as shown in the second chemical reaction of Figure 5-2b [340, 341]. The nanoporous structure was deformed after the drug was released from the PPy backbone

Figure 5-4. The SEM images of the electrodeposited polypyrrole (PPy): (a) The images for template-synthesized nanocomposite PPy film with 50 nm nanoporous structure and (b) its magnified image. (c) The image of nanocomposite PPy film after applied with -0.8 V voltages for 15 min to release the drug. (d) The conventional electrodeposited PPy film.

under electric stimulation as shown, in Figure 5-4c. The most efficient voltage applied on the PPy film for the electrochemical reduction is reported to be in the range -0.8 ~ -1.5 V [339, 342, 343].

5.3.3 The power management circuit

Since the AC output of TENG cannot be directly utilized by the PPy drug release electrode, a power management circuit was designed to convert the original output to the desired DC voltage (within 0.8-1.5V). The home-made management

Figure 5-5 (a) The schematic structure of the power management circuit. (b) The volt-ampere characteristics curve of the Zener diode. The negative threshold voltage of the diode was measured to be around -1.7 V. (c) The I-V characteristic curve of the Zener diode under negative voltages. (d) The theoretical relationship between the voltage on the capacitor and that across the Zener diode when the capacitor was charged by the TENG.

circuit shown in Figure 5-5a can accumulate the discontinuous TENG-generated charge output and convert it to sustainable DC voltage source for electrically-responsive drug release action. For example, after manually operating TENG for 3 min, with the adjustment of the circuit, the DC voltage applied to the drug-load PPy can be maintained in 0.8-1.5 V range for around 20 min. In the power management circuit, the Zener diode, was a key factor that allowed to maintain the output voltage in the desired range. It was connected in parallel with the PPy drug release electrode to keep the voltage below 1.2 V and in the range 0.8-1.2 V for a relatively long duration for the

electric-stimulated drug release. The current-voltage (I-V) characteristic curve of the Zener diode was plotted by the measured values of voltages and their corresponding currents, as shown in Figure 5-5b. The reverse bias part of the I-V characteristic of the diode was used to maintain the output voltage in the range 0.8-1.2 V, as shown in Figure 5-5c. According to the circuit diagram, the relationship between the voltage on capacitor V_c and the voltage across the diode V_d can be described as follows:

$$\frac{V_d}{R_d(V) \parallel R_r(V)} = \frac{V_c - V_d}{R_0} . \quad (5-1)$$

Thus,

$$V_c = V_d \times \left(1 + \frac{R_0}{R_d(V)} + \frac{R_0}{R_r(V)} \right), \text{ with } R_d = \frac{V_d}{I_d} \quad (5-2),$$

where R_d , R_r , R_o represent the static resistances of the diode, the drug release electrodes and the external resistor respectively; I_d is the current passing through the diode. The diode resistance R_d can be extracted from its I-V characteristic curve. According to our experimental results, the resistance of the drug release electrode R_r was not a constant value because of the redox reaction taking place on the electrodes surface. Here, we assumed that both R_r and R_o had both values of 1 MΩ. According to the derived equation, we can plot the relationship between the voltage on the capacitor V_c and that across the diode V_d as shown in Figure 5-5d. It is obvious that when TENG charged the capacitor up to 20 V, the voltage on the diode remained at around 1.2 V. It was noted that the most efficient electric-stimulated drug release took place at the voltage range of 0.8-1.5 V. The capacitor discharging profile can be described in followed equations as:

$$V_c = V_0 \times e^{-\frac{t}{\tau}}, \text{ with } \tau = R \times C \quad (5-3),$$

Figure 5-6 The theoretical results of the capacitor discharging profile. (a) The discharging time is 190s when the voltage across the capacitor reduces from 1.2 V to 0.8 V. (b) The capacitor discharging time is 900s when its voltage discharges from 15 V to 2.2 V.

where V_0 is the initial voltage on the capacitor when it starts to discharge, which is fixed in 20 V; t is the discharging time; R is the total resistance connected in parallel with the capacitor and C is the capacitance of the capacitor, with a value of 470 μ F in our circuit. According to the previously derived equations, (5.1) & (5.2) the capacitor discharging graph can be plotted as shown in Figure 5-6. The voltage across the capacitor that remained in the effective voltage range of 0.8-1.2 V can only last for 190 s according to the zoom in discharging graph of the capacitor (see Figure 5-6a). However, the output voltages across the diode can remain in the range 0.8-1.2 V for 900s. This long-lasting time was obtained because when the voltage across the diode remains in 0.8-1.2 V range, the corresponding voltage across the capacitor was in the range 2.2-15 V, as shown in Figure 5-6b. The decrease of the voltage across the capacitor from 15 V to 2.2 V needed around 900s (135 s to 1035 s, see Figure 5-6b). Hence, the time needed for the voltage across the diode for decrease from 1.2 V to 0.8 V was 900s as well. Therefore, when the drug release electrode is connected in parallel with the diode instead of the capacitor, the action time of the voltages (i.e. the time interval during which the output voltage is

Figure 5-7 (a) In this 60 min measurement, the continuous voltage from both TENG and a traditional device (potentiostat) were applied to charge the SPE. **(b)** The released drug (DEX) amount is recorded as per square centimeter of the PPY-coated electrode surface.

in the range 0.8-1.2 V) applied on the drug release electrode can be extended by around five times.

Figure 5-8 (a) The calibration curve for dexamethasone sodium phosphate absorbance at 242 nm of known concentrations of 0.5, 1, 2.5, 5, 10, 20, 30, 40 $\mu\text{g/mL}$, respectively. (b) The UV absorbance at 242 nm of the drug solutions by the TENG when operated for 20, 40 and 60 min., respectively.

The performance of the proposed TENG triggered nanocomposite drug release platform was demonstrated. We first assessed the electro-stimulus drug release with a traditional power supply, a potentiostat device, in continuous applied voltage mode. We immersed the drug-load gold electrode and a Ag/AgCl counter electrode in 100 μL PBS

solution, and applied a voltage of -0.8 V between them for 60 min (Figure 5-7a, the blue line). The blue line in Figure 5-7b demonstrated that the amount of DEX⁻ released from the PPy film was proportional to the duration of the potential applied on the drug-load electrode. Afterwards, the potentiostat was replaced by the TENG to provide sustainable voltages for the electrodes by turning the rotator manually. The Phosphate-buffered saline (PBS) solution was sampled and analyzed by UV absorbance spectroscopy; the amount of released DEX⁻ was quantified with the characteristic absorption at 242 nm (a characteristic band of DEX), as shown in Figure 5-8. By operating the TENG for around 3 min, the voltage applied across the electrodes increased gradually until reached a peak value of ~1.05 V, followed by a slow decrease (Figure 5-7a, red line). The voltage increase was caused by the TENG's charging operation, while the decrease is due to the electrically stimulated drug release process (electrochemical reduction) on the drug-loaded electrode. With the adjustment of the management circuit, the voltage could be maintained in the range a 0.8-1.1 V (the efficient voltage) for around 20 min. When the voltage decreased below 0.8 V, a quick charging (~30 s) could increase the voltage back to the peak value again. As shown in Figure 5-7b, the TENG-triggered release profile approximately matched the potentiostat-triggered release profile in the 60 min drug release process. The amount of released DEX⁻ was nearly linearly proportional with the duration of the efficient voltages, indicating that the proposed platform can achieve zero-order drug release. The cumulative amount released in 60 min was noted to be 35 $\mu\text{g}/\text{cm}^2$, which was higher than that of the potentiostat powered profile (27 $\mu\text{g}/\text{cm}^2$). Also, the release rate of TENG triggered case is higher than that of the potentiostat triggered one, because the average voltages applied to the electrode provided by TENG were higher than those supplied by the potentiostat. Therefore, we can conclude:

Figure 5-9 (a) During a period of 4 hours measurement, the SPE is intermittently charged 3 times by the TENG (20 min. each time followed by a 60 min pause). The applied voltage is greater than -0.8 V during each period of stimulation. **(b)** Drug release is observed in the 20 min. electric-stimulated duration, while no drug release is recorded in the 60 min. pause period.

- 1) the drug released amount was proportional to the duration of time during which effective voltages were applied on the drug-electrodes.

- 2) The drug release rate was positively related to the applied voltage (within effective range).
- 3) TENG can be employed as an effective substitute to power supplies for exogenous stimuli-responsive drug delivery systems.

Furthermore, we evaluated the stability and reliability of the on-demand drug release from the system. During the 4 hours' measurement, TENG was operated to power the system three times, and each time the TENG was charged for 3 min: the efficient voltages (>0.8 V) were applied on the PPy for 20 min followed by a 60 min. duration without applied voltages, as shown in Figure 5-9a. The on-demand release results in Figure 5-9b show that the drug release action was only activated when the efficient voltages were applied on the PPy; once the voltages stop to power the drug-loaded electrode, the release stopped completely. In addition, the nearly same release profile (i.e., rate and amount) of the three times electrically stimulated releases demonstrated that the TENG-triggered drug release performance was repeatable and stable, and it can realize zero-order release. In the control group, negligible drug diffusion from the as-fabricated porous film was observed in the absence of electric-stimuli. These results indicated that the drug-load electrodes displayed a good and stable on-demand release profile.

5.4 Conclusion

In conclusion, a triboelectric nanogenerator- (TENG-) based drug delivery platform for controllable drug dosing was presented for the first time, which demonstrated a proof-of-concept minimized TENG system that can be used to precisely control the zero-order release of a drug. The weak energy from human motion can be harvested and converted to desired DC electricity to power the electrically stimulated

drug release by the TENG and a power management circuit. A rotary TENG was designed and fabricated using nanowire PTFE polymer and metallic sheets, and it can achieve high voltage output of 250 V (where driven by a motor) or 110V (when rotated manually). The conductive nanocomposite polypyrrole was synthesized as a nanoporous drug carrier with which to achieve the electrically stimulated drug release. By manually rotating the TENG for 1.5 min, a dosage of 3 $\mu\text{g}/\text{cm}^2$ can be released from the PPy drug nano-carrier. In a 60 min. measurement, the TENG-controlled drug release reached a precise on-demand drug delivery of 35 $\mu\text{g}/\text{cm}^2$. Furthermore, the TENG-based drug delivery platform has the potential to be engineered into different shapes for various drug delivery modes, such as transdermal and ocular drug administration, since the TENG can be designed as flexible and wearable.

Chapter 6 Self-powered, on-demand transdermal drug delivery system with a triboelectric nanogenerator

In the previous Chapter 5, we demonstrated a triboelectric nanogenerator-based drug release platform, aiming to provide an easy solution for various drug delivery routes to achieve controllable drug delivery. In this chapter, a specific transdermal drug delivery system is developed based on that drug release platform, providing a self-powered, noninvasive and convenient approach for customized treatment. This novel system overcomes many limitations of the state of the art, enabling both tight release rate controllability and increased drug delivery efficiency. In addition, such a system allows unlimited therapeutic environment, prolonged treatment and high patient compliance. The triboelectric nanogenerator is designed to power two biomedical actions in the system, namely, the electric-stimulated drug release and an iontophoresis treatment. In our test, dexamethasone was used as the targeting drug. The rate of drug release of the system could be changed from $\sim 0.05 \mu\text{g}/\text{cm}^2$ to $\sim 0.25 \mu\text{g}/\text{cm}^2$ per minute by either tuning the TENG operation time or the circuit resistance. As a proof of concept, the system was demonstrated on porcine skin *ex vivo*, and $\sim 30.7 \text{ ng}/\text{cm}^2$ of the drug was measured to have been injected in the skin when the TENG was employed for 5 min. Furthermore, drug delivery efficiency was enhanced by $\sim 100\%$ compared with the conventional transdermal patches. Finally, *in vivo* experiments on mouse RAW 264.7 cells indicated that the bioactivity of the drug was not affected after release from the proposed drug delivery system.

6.1 Introduction

With the rapid development of miniaturized and wearable drug delivery devices, the transdermal drug delivery technologies are currently in high demand due to their advantages of continuous delivery of therapeutic agents, less side-effects and being noninvasive. The transdermal drug delivery (TDD) is usually achieved by a medicated transdermal patch that is placed on the skin to deliver a specific dose of the drug through the skin and into the bloodstream. The TDD has many advantages over other drug delivery routes such as oral, nasal and intravenous, because it not only reduces the suffering of the patient but also avoids the first-pass drug-degradation effects. For example, the oral administration of estradiol (a female hormone) was reported to cause liver damage. However, no liver damage was observed in estradiol transdermal patches [344, 345]. Similarly, transdermal patches of many other medications like clonidine (a high blood pressure medication) and dexamethasone (an anti-inflammatory medication) also exhibit fewer side-effects compared with oral formulation [346, 347]. However, the key limitation for the conventional transdermal patch delivery is its inability to perform on-demand drug delivery, because the delivery process depends completely on the passive diffusion effect and thus it is difficult to control the rate, dosage and duration of the drug release. This limitation impedes its further development in personalized therapy applications, which should allow patients to tailor treatments according to individual symptoms.

In this chapter, we present the first triboelectric nanogenerator (TENG)-based on-demand transdermal drug delivery system for effective drug dosing. The system can provide patients with an eco-friendly approach of precise and targeted drug dosing to meet varying needs for transdermal drug delivery, due to the easy operation of TENG.

In this system, the electricity from TENG was utilized in two biomedical actions: electrically stimulated drug release and iontophoresis treatment. The electrically stimulated drug release was used for controlling the release rate and dosage, while the iontophoresis treatment was used to control the efficiency of drug delivery. The working mechanism of the stimulated drug release has been demonstrated in detail in Chapter 5. As for the iontophoresis, it is a process of transdermal drug delivery that applies specific voltages onto the skin to enhance the efficiency of drug delivery (the current should be below 0.5 mA/cm^2 for human safety) [348-350]. When a voltage is applied onto the skin through two patch electrodes, the charged drug molecules can be transported across the stratum corneum by electrophoresis and electroosmosis effects. Besides, the resulting electric field thus established across the skin via the two electrodes can increase the permeability of the skin. Therefore, the drug transport efficiency in the skin is enhanced with the help of the external voltage.

In this chapter, the working performance of the system for precise and efficient on-demand drug delivery was evaluated. Two types of release-rate control modes were designed for the system, namely, tuning the TENG operation time and changing the resistance of the circuit. Both of them can achieve a tunable drug release rate from $\sim 0.05 \mu\text{g/cm}^2$ to $\sim 0.25 \mu\text{g/cm}^2$ per minute. As a proof of concept, the entire drug delivery process was performed on porcine skin *ex vivo*, and $\sim 30.7 \text{ ng/cm}^2$ of drug (dexamethasone) was delivered into the skin after 5 min. of TENG operation. Additional, the drug delivery efficiency was improved by $\sim 100\%$ with the aid of TENG triggering. The *in vitro* experiments with mouse RAW 264.7 cells showed that the bioactivity of the drug remained unaffected after it was released from the proposed drug delivery system. All these results demonstrate that the novel triboelectric nanogenerator based system can provide patients a precise and battery-free method to achieve on-

demand transdermal drug delivery. Furthermore, due to its excellent stability and portability, it is also a very promising system which could be employed in a broad spectrum of biomedical applications, including long-term treatment, sports medicine and personalized healthcare.

6.2 Results and discussion

6.2.1 Working principle of the drug delivery system:

The self-powered transdermal drug delivery system consisted of three components: transdermal patches (drug patch & iontophoresis electrode patch), triboelectric nanogenerator (TENG) and power management circuit, as illustrated in Figure 6-1. The TENG harvested the mechanical energy from human motion into AC electricity, which was then converted by the management circuit into DC voltage with the value required by the transdermal patches. Inside the drug patch, a screen-printed electrode (SPE) covered with a thin film of conductive nanocomposite polymer, polypyrrole (PPy), served as the drug carrier (or reservoir). The round drug-loaded electrode A (covered with PPy films) and the annular counter electrode B were integrated on the SPE. The conjugated polymer PPy was chosen as the drug carrier because of its various advantages, including good conductivity, stability, biocompatibility as well as ease of surface modification [342, 351, 352]. The drug molecules that had been loaded into the PPy film in advance were subsequently released by PPy in response to specific electrical stimulation. Additionally, a phosphate-buffered saline (PBS) soaked sponge was placed between the SPE surface and the skin, which had two functions: first, it served as a conductor between electrodes A and B for the electric-stimulated drug release; second, it temporarily stored the drug molecules

6.2.2 Tunable release rate

To achieve precise on-demand drug delivery, we developed tunable drug release using our fabricated transdermal drug delivery system. Chapter 5 has showed that the TENG triggered stimulated drug release is characterized by a drug release rate which is positively related to the applied voltage. In this case, the system could be operated in two distinct modes that allowed tuning the drug release rate. The first one was to change the TENG operation time. Figure 6-2a presents the voltages that were applied to the SPE under various TENG operation durations, namely 1.5, 2.5 and 5 min, respectively. When the TENG was manually operated, the voltage applied across the SPE increased rapidly, after which it decreased gradually due to the energy consumption of the transdermal patches. From Fig. 6-2 it can be seen that, longer of TENG operation time, the higher the maximum voltage and the longer the effective voltage lasts, because the management circuit has the ability to accumulate and store the electrical energy generated when the TENG was operating. The corresponding drug release profiles are shown in Figure 6-2b. It is apparent that the drug release rate and the cumulative drug amount were proportional to the TENG charging time. Thus, one can easily achieve on-demand drug delivery by simply tuning the TENG charging time.

Another way to control the drug release rate was to change the resistance in the management circuit. The external resistor in the circuit was used to divide the voltage from the load, thus, if its resistance increased, the voltage applied to the load decreased. In this way, we could tune the voltage range applied to the SPE by changing the resistance of the external resistor in the circuit. In Figure 6-3, the voltage applied to the SPE decreased gradually as the resistance increased from 1 M Ω to 3.75 M Ω . As a result, the corresponding release rate decreased as well.

Figure 6-2 The drug release rate mode tuned by the TENG operation time. (a) The Voltages applied onto the SPE for varying TENG charging durations. The resistance of the external resistor is fixed at 1 M Ω . (b) The corresponding drug release profiles for increased TENG charging durations.

Hence, both operational modes can be used to tune the drug release rate from 0.05 $\mu\text{g}/\text{cm}^2$ to 0.25 $\mu\text{g}/\text{cm}^2$ per min, which allowed the proposed system to adapt to various conditions. It is noted that when the voltage decreased below -0.8 V, the drug release did not stop immediately as previously reported in chapter 5 (Figure 5-10). This was because the structure of the PPy films used in Chapter 5 was much looser than that

Figure 6-3 The drug release rate mode controlled by the resistance in the circuit.

(a) Voltages applied onto the SPE for varying resistance values of the external resistor in the management circuit. The TENG charging duration was fixed at 5 min. (b) The corresponding drug release profiles for increased resistance of the external resistor.

of the film used in this Chapter. The PPy films with loose structure allowed a very easy release of the doped drug molecules. Therefore, it has a quicker response to the electrically stimulation and can be utilized to achieve precise and sensitive on-demand drug release. However, this quick-release property of loose PPy films hindered the possibility of a tunable release rate. In contrast, PPy films with compact structures slow

down the transport speed of the drug molecules. Therefore, PPy films with a much more compact structure were also synthesized and used for the device presented in this Chapter. In this way, a prolonged drug release can be observed even after the electric stimulation stopped. This property can be utilized in personalized medicine to achieve a slow drug release rate for extended period of time.

6.2.3 Release of DEX

We tested *ex vivo* the performance of the as-designed TENG-based drug delivery system on porcine skin, with the experimental setup shown in Figure 6-4. The

Figure 6-4 The photograph of the experimental setup. (a) The radial-arrayed rotary TENG. (b) The home-built power management circuit. (c) The drug-loaded PPy deposited on the screen-printed electrode (SPE) and the PBS soaked sponge placed on the SPE. (d) The SPE and the iontophoresis patch electrode placed on the porcine skin for the drug delivery *ex vivo* experiment.

Figure 6-5 HPLC analysis: The calibration for absorbance at 242 nm of the known weight of 0.1, 0.2, 0.5, 1 µg dexamethasone sodium phosphate in 100 µL DI water. (a) Typical HPLC chromatograms for various concentration of dexamethasone sodium phosphate solution. The value besides the peak refers to the area of the peak. (b) The plotted calibration curve for the dexamethasone sodium phosphate.

experiment was divided into two groups: In the experimental group A, the TENG was continuously charged manually for 10 min, while in group B the TENG was charged for around 18 min. (discontinuous charging). In their control groups, the TENG was not operated during the entire process. The amount of DEX⁻ that penetrated into the

porcine skin was investigated by high-performance liquid chromatography (HPLC), an analytical technique which can separate and identify the DEX⁻ from the tissue fluids mixture. The standard DEX solutions were first measured by HPLC to obtain the calibration curve shown in Figure 6-5. The absorbance at 242 nm showed an excellent linear relationship with the amount of released DEX. The HPLC chromatograms for the experimental groups are presented in Figure 6-6. The results illustrate a peak of 31703 mAU absorbance at around 7.5 min in group A, while a much higher peak of 100566 mAU appeared at the same time in group B. We estimated the corresponding

Figure 6-6. HPLC chromatograms for tissue fluids: the porcine skin samples are treated by the proposed drug delivery system used in different modes: i) 10 min of TENG operation; ii) 18 min. of discontinuous TENG operation; iii) absence of TENG operation. The area value of the peak as shown in the graphs can be used to quantify the amount of the DEX according to the calibration curve in Figure 6-

amount of DEX⁻ according to its absorbance calibration as shown in Figure 6-7. The results illustrated that 30.7 ng/cm² of DEX⁻ was detected in the porcine skin with the TENG operated for 10 min, while no released DEX⁻ was found in the control group when TENG was not operated. It demonstrated that the drug could be successfully released from the drug reservoir and delivered into the skin by simply operating TENG. As the TENG charging time increased to 18 min, the DEX⁻ penetration into the skin

Figure 6-7. The estimated amount of released DEX⁻ penetration into the porcine skin. In group A, TENG was operated manually for 10 min to power the SPE (the generated electricity was used to power the electric-stimulated DEX⁻ release process for ~15 min and the iontophoresis treatment for ~30 min). In group B, the TENG was operated for 18 min to power the SPE (the generated electricity was used to power the DEX⁻ release process for ~15 min and the iontophoresis treatment for ~60 min). For the control groups, TENG was not operated during the entire treatment. The unit of ng/cm² refers to the amount of the penetrated DEX⁻ in per square centimeter of the tested porcine skin.

increased as well and reached up to 69.1 ng/cm². Also, negligible DEX⁻ penetration was observed in the porcine skin without the aid of TENG during the entire treatment. These results demonstrate that the on-demand drug release could be explicitly governed by TENG operation.

6.2.4 Release of FLU

In order to visualize the drug delivery process into the skin, we loaded 6-carboxyfluorescein (FLU) in place of DEX⁻ into the PPy film carrier. Similar to DEX⁻, the negatively-charged FLU also served as the counterion within the PPy backbones.

When the reduction reaction of PPy is triggered by the applied voltage, FLU molecules get released into the local environment. The 6-Carboxyfluorescein is a fluorescent dye with an emission wavelength around 518 nm. We measured the fluorescence intensity of a series of FLU solutions with different concentrations, as shown in Figure 6-8 a. As the concentration increased, the emission wavelength redshifted due to the fluorescence quenching effect. The calibration curve was plotted in Figure 6-8 b, indicating a linear relationship between the FLU concentration and the fluorescence intensity (<10 µg/mL). We measured the fluorescence intensity of the PBS solution in the sponge with/without the TENG operation (Figure 6-8 c). The amount of FLU in the PBS sample solutions was then estimated according to the calibration curve, as shown in Figure 6-8 d. These results illustrate clearly that TENG can precisely control the FLU release profiles and that the released dosage increased proportionally with the TENG operation duration, while no FLU was released without TENG stimulation. Figure 6-9 a-b present the corresponding images of the FLU-loaded SPE before and after the TENG operation. It is obvious that negligible FLU was released from the PPy film without the stimulation of TENG, while visible FLU can be observed

in the sponge after the TENG triggering both in bright field and UV field. Next, we performed the drug delivery experiment on the porcine skin with the FLU-loaded drug delivery system. From the fluorescence intensity of the FLU molecules, we can deduce the drug penetration profiles in the skin under the fluorescence microscope. The experiment was divided into three groups. Group A was the control group, which was not triggered by TENG during the entire treatment. Group B was triggered by TENG for 2 min. (the generated electricity powered the stimulated drug release for 15 min.).

Figure 6-8 The calibration of fluorescence intensity: (a) the measurement of fluorescence with excitation wavelength at 450 nm and the emission wavelength between at 500 nm and 600 nm; (b) the calibration curve for 6-carboxyfluorescein (FLU) emission at 518 nm as a function of the Ca-FLU concentrations. (c) The fluorescence emission at 518 nm of the drug released solutions triggered by TENG for 8, 12 and 20 min., respectively. (d) The corresponding amounts of the released FLU deduced using the calibration curve.

Group C was triggered by TENG for 7.5 min. (the generated electricity was used to power the stimulated drug release for 15 min., followed by an iontophoresis treatment for 20 min). We treated the tested porcine skin samples by the freezing sectioning method and observed the obtained slides with the fluorescence microscope (Figure 6-9c-e). The fluorescent images of the porcine skin cross-sections subjected to the three different treatments were presented in Figure 6-10. The thickness of the observed porcine skin is ~ 1 mm. Generally, the thickness of stratum corneum and epidermis of porcine skin is within 100-150 μm [353, 354]. In Figure 6-10, the dash line is set at

Figure 6-9 The 6-carboxyfluorescein (FLU) was loaded by PPy to demonstrate the drug release process controlled by TENG visually. The screen-printed electrode (SPE) with deposited FLU-loaded PPy and the PBS soaked sponge before (a) and after (b) the electric-stimuli from TENG. (c) The thickness of the experimental porcine skin is 1 mm. (d) The distance between the iontophoresis patch electrode and the SPE is around 4.5 cm. (e) The target porcine skin was cut into 20 μm thick tissue sections for fluorescence imaging.

around 100 μm away from the skin surface in the control group A, for which the TENG was not operated during the entire process. We did not detect any traces of fluorescein in the stratum corneum, epidermis, or dermis layer, indicating that there was no passive penetration of the drug in the absence of TENG operation. The group B was sampled 20 min. after the 15 min. electrically stimulated release treatment. In this case, a high

Figure 6-10 The three fluorescent images show the drug delivery profiles on porcine skin *ex vivo* for the proposed system. The total thickness of the porcine skin is around 1 mm, consisting of the epidermis and dermis. FLU was doped into the PPy films to visualize the drug delivery procedure. (a) TENG is not triggered during the whole process. (b) The TENGs were rotated for 2 min to power the stimulated drug release for 15 min. The skin was sampled 20 min later. (c) The TENG was operated for 7.5 min to power the stimulated drug release for 15 min., followed by iontophoresis treatment for 20 min.

concentration of FLU in the epidermis and slight penetration of the FLU to the dermis of the porcine skin can be observed clearly in Fig. 6-10 b. As for the group C, it was treated with a 15 min electrically stimulated release and a 20 min iontophoresis treatment. Compared with group B, we observed significant enhancement in the penetration depth of the FLU in the dermis, as it can be seen in Fig. 6-10 c. The FLU molecules distributed evenly in the dermis rather than mainly accumulated in the epidermis. Specifically, the fluorescence intensity of group C at a depth of around 800 μm (from the epidermis) equaled that of group B but at a depth of only around 400 μm , indicating that the depth of the drug's delivery efficiency improved by $\sim 100\%$ with the help of TENG-triggered iontophoresis treatment. These results convincingly support the ability of the TENG-based transdermal drug delivery system to address the issues of on-demand drug release and drug delivery efficiency enhancement. Therefore, these achievements showed the feasibility of the proposed drug delivery system for realizing the zero-order transdermal delivery: First, the drug release amount and rate can be controlled customized according to the specific therapeutic requirements, such as slow release or prolonged release. Second, the concentration delivered into the dermis can be controlled by the drug delivery efficiency. In order to achieve the zero-order drug release in clinical applications, more engineering work for the proposed system needs to be carried out. For example, we can balance the drug release rate and the drug delivery efficiency by optimizing the resistance in the power management circuit to realize constant concentration in the dermis.

6.2.5 *In vitro* experiments on RAW 264.7 cells

Finally, in order to further investigate the bioactivity of the drug after release from the novel system (PPy films), we conducted *in vitro* experiments on RAW 264.7

cells. It is known that the bacterial lipopolysaccharide (LPS) can stimulate the generation of interleukin 1 β (IL-1 β) in RAW 264.7, but the presence of DEX can inhibit this process [355]. Therefore, to determine whether DEX still retains the bioactivity or not after release from the PPy film, we investigated the concentration changes of IL-1 β protein in LPS-stimulated RAW cells in the presence and absence of released DEX. In this *in vivo* experiment, we prepared one control group and seven experimental groups, as shown in Figure 6-11a. The control group cells were cultured with standard medium, while the seven experimental groups were cultured with the medium as well as 1 μ g/ml of LPS that was used to stimulate the production of IL-1 β protein. Among the seven experimental groups, three of them were cultured with DEX released from the PPy films at different concentrations, namely, 0.005, 0.01, 0.1, 1 and 2 μ M; other three groups were cultured with unproduced DEX at the same gradient concentrations in order to compare and evaluate the bioactivity of the released DEX. After culturing cells for 48 hrs, the cells supernatants of the eight groups were harvested to determine their IL-1 β concentration. An ELISA kit was used to quantify the IL-1 β amount in the cells supernatant (as detailed in the Section 6.3.1 of Materials and methods). The standard calibration curve for IL-1 β was plotted by measuring the difference in absorbance of the standard solutions at 450 nm and 550 nm, as shown in Figure 6-11b. The measured absorbances for the experimental groups of cells supernatant at 450 nm and 550 nm were then recorded and their difference was obtained, as shown in Table 6-3 to Table

6-1. Next, the amount of IL-1 β protein concentration in the RAW 264.7 cells was

Figure 6-11 (a) The RAW 264.7 cells were plated in 24-well culture plate at the concentration of 5×10^5 cells/mL in Dulbecco's modified Eagles medium (DMEM). The medium volume for each well was 1 mL. **(b)** The calibration curve of the mouse IL-1 β of known standard concentrations namely, 0, 31.25, 62.5, 125, 250, 500, 1000, and 2000 pg/mL, respectively. The absorbance was measured on an ELISA plate reader set at 450 nm and 550 nm. The detailed measurement results of the absorbance are shown in Table 6-3 to Table 6-1.

deduced using the standard calibration curve, as shown in Figure 6-12. It is obvious that the concentration of IL-1 β protein decreased in the six groups treated with DEX as compared with that of the “LPS” group. Also, as the concentration of DEX increased, the concentration of IL-1 β protein decreased gradually. Most importantly, we compared the effects between the DEX that released from the PPy film of our proposed system (red column) and the unprocessed DEX (blue column) on the IL-1 β protein. From the results in Figure 6-12, we can find that the DEX released from PPy demonstrate effective inhibition to the IL-1 β . In addition, as the concentration of DEX increase, the inhibition to the IL-1 β increase as well. This inhibition profile is similar to that of the

Figure 6-12 DEX inhibits IL-1 β gene expression in LPS-stimulated RAW 264.7 cells. Except for the control cell, all the remaining groups of cells are cultured with 1 μ g/mL LPS initially. The DEX released from the TENG-assisted PPy and directly administered DEX were used to culture the cells for 48 hrs in the last three groups; DEX LPS + 0.01 μ M DEX, LPS + 0.1 μ M DEX, and LPS + 1 μ M DEX. The results show similar therapeutic effects of DEX in both the cases.

reference DEX. Therefore, we concluded that the DEX still remains the bioactivity after released from the PPy.

Table 6-3 The absorbance measurement of the control and experimental groups at 450 nm.

450 nm	Control	LPS (1ug/mL)	1 μ M DEX+LPS	0.01 μ M DEX+LPS	0.001 μ M DEX+LPS	1 μ M DEX-T+LPS	0.1 μ M DEX-T+LPS	0.001 μ M DEX-T+LPS
1	0.0566	0.2568	0.1251	0.1723	0.1617	0.0969	0.1753	0.1694
2	0.0686	0.1994	0.1244	0.1277	0.1844	0.0996	0.0956	0.2239
3	0.0609	0.2217	0.086	0.1283	0.165	0.0856	0.0899	0.1731

Table 6-2 The absorbance measurement of the control and experimental groups at 550 nm.

550 nm	Control	LPS (1ug/mL)	1 μ M DEX+LPS	0.01 μ M DEX+LPS	0.001 μ M DEX+LPS	1 μ M DEX-T+LPS	0.1 μ M DEX-T+LPS	0.001 μ M DEX-T+LPS
1	0.0389	0.0436	0.0443	0.0456	0.0436	0.0434	0.0435	0.0430
2	0.0406	0.0431	0.0429	0.0429	0.0378	0.0440	0.0445	0.0442
3	0.0419	0.0428	0.0428	0.0443	0.0371	0.0425	0.0437	0.0435

Table 6-1 The final absorbance values that subtract 550 nm values from 450 nm values; the corresponding average and standard deviation of each group.

A ₄₅₀ -A ₅₅₀	Control	LPS (1ug/mL)	1 μ M DEX+LPS	0.01 μ M DEX+LPS	0.001 μ M DEX+LPS	1 μ M DEX-T+LPS	0.1 μ M DEX-T+LPS	0.001 μ M DEX-T+LPS
1	0.0177	0.2132	0.0808	0.1267	0.1181	0.0535	0.1318	0.1264
2	0.0280	0.1563	0.0815	0.0848	0.1466	0.0556	0.0511	0.1797
3	0.0190	0.1789	0.0432	0.0840	0.1279	0.0431	0.0462	0.1296
AVG	0.0216	0.1828	0.0685	0.0985	0.1309	0.0507	0.0764	0.1452
STD	0.0046	0.0234	0.0179	0.0199	0.0118	0.0055	0.0392	0.0244

6.3 Materials and methods

6.3.1 The RAW 264.7 cells culture

The RAW 264.7 cells were cultured in an incubator using Dulbecco's modified Eagles medium (DMEM) supplemented with 100 µg/mL penicillin, 100 µg/mL streptomycin, and 10% fetal bovine serum (FBS) at 37°C in an atmosphere with 5% CO₂. The RAW 264.7 cells were plated in the 24-well culture plates at 5×10^5 cells/ml and stimulated with LPS (1 µg/ml) in the presence or absence of DEX (0.01 µM, 0.1 µM, and 1 µM) for 48 hrs.

6.3.2 The mouse IL-1β ELISA assay

The mouse IL-1β ELISA kit (Cat. No.: EM2IL1B, ThermoFisher) was used to quantify the IL-1β amount in the cells supernatant. All the operation was in accordance with the standard manual:

- 1) Add 100 µL of standards/ samples to each well in duplicate;
- 2) Cover the plate and incubate at room temperature (20-25°C) for 2 hours;
- 3) Wash plate deionized water three times;
- 4) Add 100 µL of biotinylated antibody reagent to each well; then cover the plate and incubate at room temperature for 1 hour;
- 5) Wash plate three times;
- 6) Add 100 µL of prepared streptavidin-HRP solution to each well;
- 7) Cover the plate and incubate at room temperature for 30 minutes;
- 8) Wash plate three times;

- 9) Add 100 μL of TMB substrate to each well;
- 10) Develop plate in the dark at room temperature for 30 minutes;
- 11) Add 50 μL of stop solution to each well;
- 12) Measure the absorbance on a plate reader at 450 nm minus 550 nm and finally, calculate the results using curve-fitting statistical software.

6.3.3 The high-performance liquid chromatography assay

The target porcine skin was cut into pieces of $0.5 \times 0.5 \text{ cm}^2$ and then soaked in PBS for 12 hours. The supernatant was collected and centrifuged with the centrifuge tube filters (Costar, Spin-X®, CLS8161) at 6000 rpm for 10 min. High-performance liquid chromatography (Shimadzu, UFLC, 20A) was employed to assay the concentrations of DEX that penetrated into the porcine skin under isocratic conditions. The mobile phase of 30%-60% acetonitrile (0.5 mL/min) was pumped through a $4.6 \times 150 \text{ mm}$ column packed with $3.6 \mu\text{m}$ C18 end-capped silica reversed-phase particles (Aeris PEPTIDE 00B-4507-AN). The column temperature was maintained at 40°C . The injection volume was 100 μL . The UV absorbance at 242 nm was used for detection.

6.3.4 Porcine skin preparation

The porcine skins were obtained in the local market. The fat of the skin was first removed. Afterward, the skins were rinsed with deionized water several times to clean the surface impurities and excess grease. The skins were cut into the pieces of $4 \times 8 \text{ cm}^2$ and stored at -20°C for the experiment.

6.3.5 The quantitative determination of released FLU

The amount of released 6-carboxyfluorescein (FLU) was quantified using the Infinite® 200 PRO plate reader (Tecan). The samples were placed in the Costar® 96-Well Black Polystyrene Plate. The 6-Carboxyfluorescein is a fluorescent dye with an emission wavelength around 518 nm.

6.3.6 Freezing sectioning method

The target skin was cut into pieces of $0.5 \times 0.5 \text{ cm}^2$ and stored at -20°C . The temperature of the main cryostat chamber and the quick freeze compartment was set at -20°C and -18°C respectively (LEICA, CM 1950). The angle of the blade was adjusted to 15° . Some embedding compound were put on the stage first and the sample tissue were then placed on the stage. The sample was frozen with the cryospray. Next, the stage with sample was placed on the stage clamp and the angle was adjusted until the cross-section of the sample was parallel to the blade. The sample was cut to a thickness of $20 \text{ }\mu\text{m}$ and then was attached onto the prepared slide immediately. The slides were stored at -20°C until use.

6.3.7 Fabrication of the transdermal drug delivery system

The proposed system contains rotary triboelectric nanogenerator (TENG), transdermal patches (drug patch and iontophoresis electrode patch), and power management circuit. The TENG was fabricated with a thin film of nanostructured polymer polytetrafluoroethylene (PTFE) and two radial arrayed copper sheets. The drug patch consisted of nanoporous polypyrrole (PPy) coated screen-printed electrode (SPE) and a sponge. The SPE was purchased from Metrohm DropSens Inc. (DRP-220AT, dimensions $3.4 \times 1.0 \times 0.05 \text{ cm}^3$). The sponge ($9 \times 9 \times 2 \text{ mm}^3$) was injected with

100 μ l phosphate-buffered saline (10 mM PO_4^{3-} , 137 mM NaCl, and 2.7 mM KCl). The iontophoresis electrode patch was purchased from IOMED® and cut into pieces of $1.5 \times 1.5 \text{ cm}^2$. (The detailed fabrication process of the TENG and the drug-loaded PPy drug carrier were described in Chapter 5)

6.3.8 Circuit design

The main components of the circuit included a rectifier, a capacitor, two Zener diode, a resistor and a bidirectional switch. The rectifier was used to convert AC to DC; the capacitor (470 μ F, 50 V) was used to stored and converted the discontinuous electric pulse to continuous output voltage. The Zener diode (1.7 V) was used to maintain the DC voltage within the range 0.8-1.2 V that was suitable for the operation of the screen-printed electrode, while another diode (6.8 V) was used for iontophoresis patches to limit the voltage and limit the electrical current at the output below 0.5 mA/cm^2 for safety. The bidirectional switch was used to control the entire drug delivery process: when the switch connected with terminal (b), the TENG started to power electrically-controlled drug release process; while the switch connected with terminal (c), the TENG powered the iontophoresis treatment. The electrodes A, B, C (Figure 6-1) connect with terminals (a), (b), (c) respectively (Figure 6-4b).

6.4 Conclusion

In conclusion, the first controllable transdermal drug delivery system based on a triboelectric nanogenerator was presented, aiming to provide a self-powered and easily-operated transdermal drug delivery technology for personalized healthcare. Two approaches have been developed for tuning the drug release rate, namely changing the TENG charging time and changing the circuit resistance. Both methods can precisely

control the drug delivery rate from $\sim 0.05 \mu\text{g}/\text{cm}^2$ to $\sim 0.25 \mu\text{g}/\text{cm}^2$ per min. The drug delivery procedure of the proposed system was performed *ex vivo* on porcine skin. The system exhibited good controllability of drug dosage by operating the triboelectric nanogenerator; $30.7 \text{ ng}/\text{cm}^2$ of the drug was delivered into the skin in less than 10 min of TENG operation. In addition, the electricity generated from TENG has been further utilized to power the iontophoresis treatment, leading to a $\sim 100\%$ enhancement in drug delivery efficiency compared with conventional transdermal patches. Finally, the *in vitro* experiment on RAW 264.7 cells demonstrated the drug DEX still remains the bioactivity after released from the PPy. These results confirm that the triboelectric nanogenerator-based drug delivery system is able to realize effective and highly controllable drug dosing with a small footprint, providing a convenient solution to satisfy customized needs of personalized therapeutic healthcare.

Chapter 7 Conclusions

7.1 Conclusions

In this Thesis, two-dimensional materials and nanostructured polymers were successfully employed to overcome technological limitations faced in current healthcare diagnostics and therapeutics fields, particularly the low detection sensitivity of optical biosensors and the large footprint of external stimuli-controlled drug delivery systems. The content of this Thesis work was divided into two parts.

Part I: In disease diagnostics, biosensors are powerful analytical tools used to detect the types and concentrations of chemical or biological species. Among them, optical biosensors, specifically the surface plasmon resonance (SPR)-based biosensors, have been widely used to due to their unique advantages of high sensitivity real-time and label-free detection. Currently, SPR biosensors have been extensively applied to monitor molecular interactions and to detect various biomolecules, such as DNA, protein, and glucose. However, the sensitivity of conventional SPR biosensors is insufficient to detect small molecules such as hormones, ssDNA and metabolites, significantly reducing the precision of disease diagnostics.

In order to improve the sensitivity, two-dimensional (2D) transition metal dichalcogenides (TMDCs) have been used as the sensing platform of SPR biosensors to enhance their detection sensitivity for small molecules. Generally, the SPR sensitivity can be significantly affected by light coupling condition between the incident light and the SPW: under the same configuration, the closer the light coupling condition to the optimum coupling, the better the sensitivity will be. Owing high

absorption rate, while still maintaining a similar atomic thickness of less than 1 nm, the 2D TMDCs are excellent candidates as the lossy materials coating on the gold surface to improve the light coupling, thus enhance the sensitivity of the SPR biosensor. In addition, due to the 2D structure, the thickness of TMDCs atomic films can be easily and controlled by tuning the number of layers, which can be used to adjust the light coupling condition. Lastly, the TMDCs have hexagonal structures analogous to aromatic rings of analytes, thereby significantly increasing the adsorption of the molecules onto the sensing platform.

Before engineering the proposed biosensors, we first conducted a systematic theoretical study of four respective types of TMDC-based SPR biosensors, namely WS₂, WSe₂, MoS₂, and MoSe₂. The models were studied under both angular and phase modulation schemes, as a result, we obtained the optimized geometries of TMDC-enhanced biosensors, as well as the optimized detection sensitivity, accuracy, and the detected concentration range for the four respective TMDCs. The simulated results demonstrated all four 2D TMDCs can enhance the sensitivity, but the enhancement ratio is greatly affected by the wavelength of incident light, thickness of TMDC and gold, and the mode of sensing modulation. For visible wavelength, the best performance was monolayer WS₂ with a sensitivity reaching 155.68 deg/RIU, which is three times that of conventional SPR biosensors (under angular modulation). On the other hand, for near-infrared wavelength, the highest sensitivity was achieved by 5 layers of MoSe₂, an ultrahigh 1.1×10^7 deg/RIU, which is three orders of magnitude higher than those with bare gold sensing platform (under phase modulation).

According to the optimized design resulted from of the theoretical studies, a monolayer WS₂-based SPR sensing chip was fabricated by using chemical vapor deposition (CVD) and the poly (methyl methacrylate)(PMMA) wet transfer technique.

In order to measure the sensitivity, optical setups for both angular and phase modulation schemes were built. Glycerin solutions with different concentrations were detected. The sensitivity of the WS₂-based sensing platform is generally higher than that of the conventional bare gold sensing platform, but the enhancement ratio was different for different concentrations of analytes. The highest sensitivity reached 15,000 deg/RIU for 1% glycerin, which was ~2.5 times that of bare gold sensing substrates used in conventional SPR biosensors. All the results above demonstrated that coating 2D TMDCs onto the gold substrate was an effective solution to enhance the sensitivity of the standard SPR biosensor and achieve more precise detection for small molecules, and, therefore, improving diagnostic precision.

Part II: In disease therapy, the mode of drug delivery significantly affects the therapeutic efficacy of drug administration. When drugs enter the body, their pharmacological activity can be damaged by the environmental changes (e.g., pH, moisture), or by the metabolism. Therefore, the commonly used drug delivery modes (e.g., oral, injectable) require repeated and frequent doses to maintain the therapeutic efficacy, which generally results in toxic side effects and a waste of drugs. In order to improve the efficacy as well as minimize side effects, controlled release technology has been extensively developed. The zero-order release is one of the desired controllable drug release profile, which refers to releasing drug at a constant rate independent of time. Generally, functional and biocompatible materials are employed as drug carriers for controlled release, aiming to protect drugs from breakdown *in vivo* while also maintaining their concentration within the safe therapeutic window. Currently, stimuli-responsive polymers are the most widely developed carriers for controlled drug delivery systems. Depending on the different material used for this purpose, the drug carriers can respond to both exogenous stimuli (e.g., electric field, temperature, light) and

endogenous stimuli (e.g., enzymes, glucose, pH) to release the drug. The diversity of such stimuli-responsive polymers allows great flexibility in the design of controlled drug delivery systems for meeting various therapeutic requirements. However, it is difficult to precisely control the release for materials responsive to the endogenous stimuli, since stimuli such as pH and enzymes are greatly affected by patient-to-patient variability. Although the exogenous stimuli-responsive materials can overcome this problem, their limitation lies in the need for bulky auxiliary equipment to generate the stimuli, such as lasers and power supplies. This necessitates a larger footprint for the controlled drug delivery system, which directly limits the therapeutic environment and increases patient inconvenience, in opposition to the ideals of individual treatment tools for personalized healthcare.

In order to create systems with high controllability of drug release as well as small footprint, we proposed a novel self-powered, electric-stimulated drug delivery platform: A miniaturized triboelectric nanogenerator (TENG) (diameter =15 cm) was developed to generate exogenous stimuli (i.e., electric voltage), and an electric-stimuli responsive polymer, polypyrrole (PPy), was engineered as the drug carrier for controllable drug release. The TENG is a self-powered nanodevice used to harvest and convert small-scale mechanical energy into electrical energy. It mainly consists of a copper film, and a nanowire arrayed polytetrafluoroethylene (PTFE) film. When the two films rub against each other under external force, an electric potential difference can be established between them due to contact electrification and electrostatic induction. The mechanical energy, therefore, can be converted and transferred into electricity. The nanowire structure can significantly improve the contacted area and the surface charge density, thus enhancing the energy conversion efficiency. As for the drug carrier, it was fabricated by electrochemically depositing the nanoporous PPy on

a planar screen-printed electrode (SPE), where the nanoporous structure can increase the drug release volume of PPy. The SPE was connected to the TENG via a power management circuit used to transfer the TENG's original AC output to the desired DC value. The results demonstrated that the controllable drug release platform can achieve efficient and precise drug release by operating the TENG. Lightly rotating the TENG manually for 1.5 min can release 3 $\mu\text{g}/\text{cm}^2$ of the drug from the PPy. More importantly, the drug release profile was nearly zero-order release. Next, based on the release platform, a self-powered transdermal drug delivery system was built. In this system, the electricity from TENG was utilized in two actions:

- 1) Generate the electric-stimuli to actuate release from the PPy drug nanocarrier;
- 2) Activate the iontophoresis treatment over the skin to enhance the drug delivery efficiency.

The results showed that the system can achieve tunable zero-order release with the release rate ranging from 0.05 to 0.25 $\mu\text{g}/\text{cm}^2$, tunable by changing either the TENG operation time or the resistance of the management circuit. The device performance was further demonstrated on porcine skin *ex vivo*. Manually rotating the TENG for 10 min, a drug dose of 30.7 ng/cm^2 was determined in the dermis. In addition, the measured drug delivery efficiency represents an enhancement by ~100% over conventional transdermal patches.

All results above demonstrate that the TENG can successfully link with stimuli-responsive drug nanocarriers to realize highly controllable drug release. Also, owing to the simple structure and wide range of materials that can be used as drug carrier, the TENG size can be minimized for various drug administration routes, allowing for a small footprint for stimuli-responsive drug delivery systems. Therefore, the utilization

of the TENG enables us to overcome the limitations in current exogenous stimuli-responsive drug release, thus achieving unlimited therapeutic environment and improved patient compliance, making the TENG an ideal candidate for individual drug delivery tools for personalized healthcare.

In summary, this Thesis has provided efficient solutions by engineering 2D materials and nanostructured polymers to improve medical diagnostics precision and to develop individual therapeutic tools, jointly pushing the development of personalized healthcare forward.

7.2 Recommendations for future work

In this Thesis, the application of two-dimensional materials been demonstrated to successfully enhance detection sensitivity of SPR biosensors, thus enhancing the precision of disease diagnostics. The nanostructured polymers, at the same time, have been designed to build an efficient and miniaturized electric-stimuli drug delivery system, improving the therapeutic level of individual treatment tools. However, there are still some studies which need to be performed before these proposed strategies and systems are ready for practical personalized healthcare.

For 2D TMDC layers, more studies can be conducted to show their sensitivity enhancement in other types of optical biosensors, such as optical waveguide-based biosensors, fiber-based biosensors, and ring resonator-based biosensors. The significant reasons for the sensitivity-enhancing effects of the 2D TMDCs in SPR biosensors are the high light absorption and the high biomolecular adsorption, which are likely to be effective for other optical biosensors and improve their sensitivity as well. Therefore, detailed studies on how to design and fabricate 2D TMDCs as sensing platforms for these optical biosensors are necessary. This would give a systematic demonstration of

the 2D TMDCs as a universally applicable method to improve the diagnostic precision of optical biosensors. In addition, in order to push the biosensors forward to individual diagnostic tools for personalized healthcare, the TMDC-based biosensors are required to be miniaturized into portable devices. The TMDCs can be designed as reusable sensing chips, which can be easily washed and cleaned after each use. Therefore, an investigation of TMDC surface functionalization for enhancing their stability and durability is also warranted.

For the triboelectric nanogenerator- (TENG-) based controlled drug delivery platform, it has been demonstrated in this Thesis that it can be successfully incorporated with the transdermal delivery route to achieve efficient control of drug dosing. However, applications of the TENG in other drug delivery routes such as injection, active implantation, and oral administrations to build various other controlled drug delivery systems remain to be studied. For example, the platform is promising for its potential use in controlling the drug carriers injected or implanted subcutaneously for localized and prolonged drug delivery. In such a study, the *in vivo* investigation is further necessary to evaluate the therapeutic efficacy and the biocompatibility of the TENG-based system. In addition, studies on the ability of the platform to deliver other therapeutic agents, such as antibodies, enzymes, peptides, DNA, and si-RNA, are also needed, as they can contribute to a systematic understanding of the universal applicability of TENG-based platforms for controlled delivery. Lastly, for the TENG itself, more studies can be performed to apply it in wearable and foldable devices. In this case, the TENG can be incorporated into the clothes or shoes, or directly attached to the limbs to harvest small-scale mechanical energy from daily human motion.[356-360]

Author's Publication

Journal paper

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Appendix

Table A1. The optimized values of gold thin film, silicon nanosheet thickness and the number of WS₂ layers with corresponding change in resonance angle and FWHM in SPR curve for 600 nm excitation wavelength.

Au thickn ess (nm)	Si thickn ess (nm)	Numbe r of WS ₂ layers (L)	Minimum Reflectivity	θ_{SPR} w/o biomole cules (Deg)	θ_{SPR} with biomolecu les (Deg)	$\Delta\theta_{\text{SPR}}$ ($\Delta n_{\text{bio}}=0.005$) (Deg)	Sensiti vity (Deg/RIU)	FWHM (Deg)
30	0	9	1.0306×10^{-3}	68.6670	69.1079	0.4409	88.18	22.3953
35	0	6	4.5593×10^{-4}	63.4245	63.8173	0.3928	78.56	15.3217
40	0	4	9.6791×10^{-4}	60.6633	61.0124	0.3491	69.82	9.0687
50	0	0	6.0974×10^{-5}	56.7966	57.0636	0.2670	53.40	2.3134
30	5	5	4.4617×10^{-4}	79.2675	79.7532	0.4857	97.14	21.3792
35	5	3	7.4642×10^{-3}	74.8978	75.5304	0.6326	126.52	19.5973
40	5	2	2.3410×10^{-4}	72.6477	73.2982	0.6505	130.10	16.7183
50	5	0	2.6443×10^{-3}	67.5897	68.1553	0.5656	113.12	8.0491
30	7	3	7.7163×10^{-3}	83.6202	83.8693	0.2491	49.82	18.0984
35	7	1	2.5592×10^{-2}	80.5633	81.3417	0.7784	155.68	17.4644

Table A2. The optimized values of gold thin film, silicon nanosheet thickness and the number of WS₂ layers with corresponding change in resonance angle and FWHM in SPR curve for 633 nm excitation wavelength.

Au thickness (nm)	Si thickness (nm)	Number of WS ₂ layers (L)	Minimum Reflectivity	θ_{SPR} w/o biomolecules (Deg)	θ_{SPR} with biomolecules (Deg)	$\Delta\theta_{\text{SPR}}$ ($\Delta n_{\text{bio}}=0.005$) (Deg)	Sensitivity (Deg/RIU)	FWHM (Deg)
30	0	9	2.3193×10^{-3}	81.5711	81.8895	0.3184	63.68	20.9457
35	0	7	4.4970×10^{-3}	73.2828	73.8314	0.5486	109.72	20.9152
40	0	5	8.3104×10^{-4}	65.3435	65.7847	0.4412	88.24	14.0670
50	0	0	1.4822×10^{-5}	56.1871	56.4280	0.2409	48.18	2.1004
30	5	5	2.5504×10^{-2}	84.4157	84.5338	0.1181	23.62	17.4124
35	5	4	1.3915×10^{-2}	82.1903	82.5787	0.3884	77.68	18.1349
40	5	3	2.6591×10^{-3}	77.5365	78.2352	0.6987	139.74	17.9590
50	5	0	5.0702×10^{-4}	63.7243	64.1544	0.4301	86.02	5.9887
30	7	3	1.0791×10^{-3}	84.8480	85.1460	0.2980	59.60	16.3374
35	7	2	1.1042×10^{-2}	81.6272	82.2923	0.6651	133.02	17.3960
40	7	1	2.4099×10^{-2}	75.8606	76.6000	0.7394	147.88	16.2417
50	7	0	5.5667×10^{-3}	70.7232	71.3733	0.6501	130.02	10.1617

Table A3. The optimized values of gold thin film, silicon nanosheet thickness and the number of WS₂ layers with corresponding change in resonance angle and FWHM in SPR curve for 660 nm excitation wavelength.

Au thickness (nm)	Si thickness (nm)	Number of WS ₂ layers (L)	Minimum Reflectivity	θ_{SPR} w/o biomolecules (Deg)	θ_{SPR} with biomolecules (Deg)	$\Delta\theta_{\text{SPR}}$ ($\Delta n_{\text{bio}}=0.005$) (Deg)	Sensitivity (Deg/RIU)	FWHM (Deg)
30	0	12	6.9049×10^{-3}	83.6359	83.8531	0.2172	43.44	18.5826
35	0	10	3.2174×10^{-3}	77.4934	78.0683	0.5749	114.98	20.2094
40	0	8	6.0830×10^{-4}	69.6006	70.1215	0.5209	104.18	16.8688
50	0	0	2.9483×10^{-4}	55.7750	55.9976	0.2226	44.52	1.9505
30	5	7	2.9289×10^{-3}	84.9508	85.1453	0.1945	38.90	16.4019
35	5	6	1.0379×10^{-2}	83.0225	83.3793	0.3568	71.36	17.2624
40	5	5	7.9432×10^{-3}	79.5416	80.1900	0.6484	129.68	17.5843
50	5	0	4.7825×10^{-4}	61.7097	62.0757	0.3660	73.20	4.9425
30	7	5	1.9914×10^{-4}	85.5051	85.7139	0.2088	41.76	15.3163
35	7	4	1.7959×10^{-3}	83.6110	84.0177	0.4067	81.34	16.3604
40	7	3	3.3778×10^{-5}	79.7827	80.5109	0.7282	145.64	16.8245
50	7	0	1.4158×10^{-3}	66.5248	67.0197	0.4949	98.98	7.8452

Table A4. The optimized values of gold thin film, silicon nanosheet thickness and the number of WS₂ layers with corresponding change in resonance angle and FWHM in SPR curve for 785 nm excitation wavelength.

Au thickness (nm)	Si thickness (nm)	Number of WS ₂ layers (L)	Minimum Reflectivity	θ_{SPR} w/o biomolecules (Deg)	θ_{SPR} with biomolecules (Deg)	$\Delta\theta_{\text{SPR}}$ ($\Delta n_{\text{bio}}=0.005$) (Deg)	Sensitivity (Deg/RIU)	FWHM (Deg)
35	0	20	8.2664×10^{-4}	85.1560	85.5004	0.3444	68.88	14.3217
40	0	19	3.5797×10^{-3}	83.0847	83.5818	0.4971	99.42	15.2830
50	0	0	1.0244×10^{-2}	54.4952	54.6566	0.1614	32.28	1.4493
30	5	16	4.6561×10^{-4}	87.3434	87.4381	0.0947	18.94	11.0503
35	5	14	2.4740×10^{-2}	84.3228	84.8311	0.5083	101.66	14.7978
40	5	13	2.5767×10^{-3}	81.9147	82.5542	0.6395	127.90	15.5232
50	5	0	8.3559×10^{-3}	57.1765	57.3998	0.2233	44.66	2.6852
30	7	14	2.2110×10^{-2}	87.5234	87.5085	0.0149	2.98	10.4471
35	7	12	9.2000×10^{-3}	85.1560	85.5773	0.4213	84.26	13.9815
40	7	11	6.7116×10^{-5}	82.9231	83.5107	0.5876	117.52	14.9616
50	7	0	7.3315×10^{-3}	58.8242	59.0838	0.2596	51.92	3.5672

Table A5. The optimized values of gold thin film, silicon nanosheet thickness and the number of WS₂ layers with corresponding change in resonance angle and FWHM in SPR curve for 1024 nm excitation wavelength.

Au thickness (nm)	Si thickness (nm)	Number of WS ₂ layers (L)	Minimum Reflectivity	θ_{SPR} w/o biomolecules (Deg)	θ_{SPR} with biomolecules (Deg)	$\Delta\theta_{\text{SPR}}$ ($\Delta n_{\text{bio}}=0.005$) (Deg)	Sensitivity (Deg/RIU)	FWHM (Deg)
30	0	26	2.9561×10^{-3}	84.5610	84.7037	0.1427	28.54	17.6854
35	0	23	8.4630×10^{-5}	79.3182	79.6444	0.3262	65.24	20.7662
40	0	4	2.3986×10^{-5}	54.5510	54.6765	0.1255	25.10	2.5545
30	5	21	1.7205×10^{-3}	84.0361	84.2409	0.2048	40.96	17.8724
35	5	19	1.3643×10^{-5}	80.3472	80.6762	0.3290	65.80	19.7136
40	5	4	3.2235×10^{-5}	56.2789	56.4394	0.1605	32.10	4.1127
30	7	20	3.9117×10^{-3}	85.0778	85.2133	0.1355	27.10	16.4240
35	7	17	1.0331×10^{-3}	79.5564	79.9109	0.3545	70.90	19.7501
40	7	4	1.3462×10^{-5}	57.2099	57.3881	0.1782	35.64	5.0626

Table A6. The optimized values of gold thin film, silicon nanosheet thickness and the number of MoSe₂ layers with corresponding change in resonance angle and FWHM in SPR curve for 600 nm excitation wavelength.

Au thickness (nm)	Si thickness (nm)	Number of MoSe ₂ layers (L)	Minimum Reflectivity	θ_{SPR} w/o biomolecules (Deg)	θ_{SPR} with biomolecules (Deg)	$\Delta\theta_{\text{SPR}}$ ($\Delta n_{\text{bio}}=0.005$) (Deg)	Sensitivity (Deg/RIU)	FWHM (Deg)
30	0	5	5.5708×10^{-4}	64.6016	64.9844	0.3828	76.56	21.8215
35	0	3	1.1107×10^{-3}	60.7113	61.0508	0.3395	67.90	13.1344
40	0	2	7.7992×10^{-4}	59.1615	59.4776	0.3161	63.22	7.9253
50	0	0	6.0974×10^{-5}	56.7966	57.0636	0.2670	53.40	2.3134
30	5	3	2.5544×10^{-4}	76.6972	77.1832	0.4860	97.20	22.8996
35	5	2	2.8247×10^{-5}	74.1700	74.7548	0.5848	116.96	20.6998
40	5	1	7.6602×10^{-4}	70.8050	71.4040	0.5990	119.80	16.1867
50	5	0	2.6443×10^{-3}	67.5897	68.1553	0.5656	113.12	8.0491
30	7	2	1.4748×10^{-2}	82.3111	82.5772	0.2661	53.22	19.8431
35	7	1	4.7627×10^{-3}	81.4620	81.9848	0.5228	104.56	18.2235

Table A7. The optimized values of gold thin film, silicon nanosheet thickness and the number of MoSe₂ layers with corresponding change in resonance angle and FWHM in SPR curve for 633 nm excitation wavelength.

Au thickness (nm)	Si thickness (nm)	Number of MoSe ₂ layers (L)	Minimum Reflectivity	θ_{SPR} w/o biomolecules (Deg)	θ_{SPR} with biomolecules (Deg)	$\Delta\theta_{\text{SPR}}$ ($\Delta n_{\text{bio}}=0.005$) (Deg)	Sensitivity (Deg/RIU)	FWHM (Deg)
30	0	7	1.6289×10^{-4}	66.2496	66.6354	0.3858	77.16	23.3425
35	0	4	5.0453×10^{-4}	60.6540	60.9799	0.3259	65.18	13.5831
40	0	2	1.7684×10^{-3}	58.0731	58.3531	0.2800	56.00	6.3803
50	0	0	1.4822×10^{-5}	56.1871	56.4280	0.2409	48.18	2.1004
30	5	5	5.5646×10^{-3}	77.1007	77.5029	0.4022	80.44	23.4522
35	5	3	1.9344×10^{-5}	71.7805	72.3006	0.5201	104.02	20.7472
40	5	2	2.2213×10^{-3}	68.9529	69.4724	0.5195	103.90	16.6804
50	5	0	5.0702×10^{-4}	63.7243	64.1544	0.4301	86.02	5.9887
30	7	3	2.5112×10^{-3}	79.2825	79.7482	0.4657	93.14	21.5461
35	7	2	3.8936×10^{-4}	77.2114	77.8079	0.5965	119.30	20.0590
40	7	1	2.0438×10^{-3}	74.0203	74.6787	0.6584	131.68	17.0915
50	7	0	5.5667×10^{-3}	70.7232	71.3733	0.6501	130.02	10.1617

Table A8. The optimized values of gold thin film, silicon nanosheet thickness and the number of MoSe₂ layers with corresponding change in resonance angle and FWHM in SPR curve for 660 nm excitation wavelength.

Au thickness (nm)	Si thickness (nm)	Number of MoSe ₂ layers (L)	Minimum Reflectivity	θ_{SPR} w/o biomolecules (Deg)	θ_{SPR} with biomolecules (Deg)	$\Delta\theta_{\text{SPR}}$ ($\Delta n_{\text{bio}}=0.005$) (Deg)	Sensitivity (Deg/RIU)	FWHM (Deg)
30	0	8	2.0024×10^{-5}	65.765	66.1360	0.3705	74.10	23.010
				5				4
35	0	5	4.1023×10^{-9}	60.685	61.0023	0.3171	63.42	14.163
				2				2
40	0	3	7.0439×10^{-4}	58.260	58.5362	0.2755	55.10	7.1902
				7				
50	0	0	2.9483×10^{-4}	55.775	55.9976	0.2226	44.52	1.9505
				0				
30	5	6	4.9718×10^{-4}	75.525	75.9472	0.4217	84.34	23.680
				5				9
35	5	4	1.6159×10^{-4}	70.587	71.0686	0.4808	96.16	20.866
				8				2
40	5	2	5.4002×10^{-4}	65.602	66.0354	0.4330	86.60	13.832
				4				0
50	5	0	4.7825×10^{-4}	61.709	62.0757	0.3660	73.20	4.9425
				7				
30	7	4	7.5071×10^{-3}	77.191	77.6631	0.4715	94.30	22.297
				6				1
35	7	3	9.8331×10^{-5}	75.107	75.6525	0.5446	108.92	20.702
				9				3
40	7	2	1.4928×10^{-3}	72.352	72.9287	0.5760	115.20	17.908
				7				0
50	7	0	1.4158×10^{-3}	66.524	67.0197	0.4949	98.98	7.8452
				8				

Table A9. The optimized values of gold thin film, silicon nanosheet thickness and the number of MoSe₂ layers with corresponding change in resonance angle and FWHM in SPR curve for 785 nm excitation wavelength.

Au thickness (nm)	Si thickness (nm)	Number of MoSe ₂ layers (L)	Minimum Reflectivity	θ_{SPR} w/o biomolecules (Deg)	θ_{SPR} with biomolecules (Deg)	$\Delta\theta_{\text{SPR}}$ ($\Delta n_{\text{bio}}=0.005$) (Deg)	Sensitivity (Deg/RIU)	FWHM (Deg)
30	0	12	6.9696×10^{-5}	63.8125	64.1238	0.3113	62.26	22.2247
35	0	7	1.2317×10^{-5}	58.4074	58.6481	0.2407	48.14	11.1258
40	0	4	8.6083×10^{-4}	56.3328	56.5346	0.2018	40.36	4.9499
50	0	0	1.0244×10^{-2}	54.4952	54.6566	0.1614	32.28	1.4493
30	5	11	3.2961×10^{-5}	71.7805	72.1464	0.3659	73.18	24.0905
35	5	6	4.0347×10^{-4}	63.2847	63.6101	0.3254	65.08	16.9494
40	5	3	6.4830×10^{-5}	59.7064	59.9776	0.2712	54.24	8.4272
50	5	0	8.3559×10^{-3}	57.1765	57.3998	0.2233	44.66	2.6852
30	7	10	6.6560×10^{-6}	74.5006	74.8712	0.3706	74.12	23.7053
35	7	6	1.3075×10^{-4}	66.8284	67.2055	0.3771	75.42	19.4897
40	7	3	1.2280×10^{-5}	62.1570	62.4760	0.3190	63.80	11.2734
50	7	0	7.3315×10^{-3}	58.8242	59.0838	0.2596	51.92	3.5672

Table A10. The optimized values of gold thin film, silicon nanosheet thickness and the number of MoSe₂ layers with corresponding change in resonance angle and FWHM in SPR curve for 1024 nm excitation wavelength.

Au thickness (nm)	Si thickness (nm)	Number of MoSe ₂ layers (L)	Minimum Reflectivity	θ_{SPR} w/o biomolecules (Deg)	θ_{SPR} with biomolecules (Deg)	$\Delta\theta_{\text{SPR}}$ ($\Delta n_{\text{bio}}=0.005$) (Deg)	Sensitivity (Deg/RIU)	FWHM (Deg)
30	0	37	2.9735×10^{-7}	77.3629	77.6634	0.3005	60.10	22.2105
35	0	15	2.6734×10^{-6}	57.3488	57.5279	0.1791	35.82	8.0993
40	0	3	2.8889×10^{-5}	53.9991	54.1124	0.1133	22.66	1.9736
30	5	32	1.3502×10^{-5}	79.3635	79.6543	0.2908	58.16	21.1464
35	5	15	3.4001×10^{-6}	60.5473	60.7810	0.2337	46.74	13.5613
40	5	3	3.8306×10^{-5}	55.3581	55.5002	0.1421	28.42	3.0126
30	7	30	6.6588×10^{-6}	80.1581	80.4423	0.2842	56.84	20.6365
35	7	15	5.9800×10^{-6}	62.3205	62.5821	0.2616	52.32	15.8192
40	7	3	6.5065×10^{-5}	56.0704	56.2266	0.1562	31.24	3.6162

Table A11. The optimized values of gold thin film, silicon nanosheet thickness and the number of MoS₂ layers with corresponding change in resonance angle and FWHM in SPR curve for 600 nm excitation wavelength.

Au thickness (nm)	Si thickness (nm)	Number of MoS ₂ layers (L)	Minimum Reflectivity	θ_{SPR} w/o biomolecules (Deg)	θ_{SPR} with biomolecules (Deg)	$\Delta\theta_{\text{SPR}}$ ($\Delta n_{\text{bio}}=0.005$) (Deg)	Sensitivity (Deg/RIU)	FWHM (Deg)
30	0	6	3.8765×10^{-4}	64.3065	64.6843	0.3778	75.56	21.9370
35	0	4	1.9345×10^{-3}	61.1528	61.5006	0.3478	69.56	14.5927
40	0	2	1.5126×10^{-5}	58.6783	58.9833	0.3050	61.00	7.1320
50	0	0	6.0974×10^{-5}	56.7966	57.0636	0.2670	53.40	2.3134
30	5	4	6.1501×10^{-3}	76.8775	77.3078	0.4303	86.06	23.3656
35	5	2	2.6005×10^{-3}	72.4389	73.0104	0.5715	114.30	20.0467
40	5	1	3.1793×10^{-3}	69.9714	70.5499	0.5785	115.70	15.4579
50	5	0	2.6443×10^{-3}	67.5897	68.1553	0.5656	113.12	8.0491
30	7	2	9.6041×10^{-5}	81.2746	81.7083	0.4337	86.74	20.2786
35	7	1	1.7734×10^{-4}	80.5325	81.1722	0.6397	127.94	18.4122

Table A12. The optimized values of gold thin film, silicon nanosheet thickness and the number of MoS₂ layers with corresponding change in resonance angle and FWHM in SPR curve for 633nm excitation wavelength.

Au thickness (nm)	Si thickness (nm)	Number of MoS ₂ layers (L)	Minimum Reflectivity	θ_{SPR} w/o biomolecules (Deg)	θ_{SPR} with biomolecules (Deg)	$\Delta\theta_{\text{SPR}}$ ($\Delta n_{\text{bio}}=0.005$) (Deg)	Sensitivity (Deg/RIU)	FWHM (Deg)
30	0	6	1.1588×10^{-5}	65.0423	65.4132	0.3709	74.18	22.9767
35	0	4	9.8118×10^{-4}	61.0689	61.4022	0.3333	66.66	15.2011
40	0	2	3.3624×10^{-6}	58.2075	58.4904	0.2829	56.58	6.8984
50	0	0	1.4822×10^{-5}	56.1871	56.4280	0.2409	48.18	2.1004
30	5	4	3.7343×10^{-6}	75.1781	75.6259	0.4478	89.56	23.6669
35	5	3	3.8228×10^{-3}	72.6068	73.1200	0.5132	102.64	21.5806
40	5	2	9.6549×10^{-3}	69.5062	70.0324	0.5262	105.24	17.6990
50	5	0	5.0702×10^{-4}	63.7243	64.1544	0.4301	86.02	5.9887
30	7	3	1.5195×10^{-3}	79.7645	80.1558	0.3913	78.26	21.8300
35	7	2	2.5629×10^{-3}	77.7725	78.3248	0.5523	110.46	20.4299
40	7	1	1.1513×10^{-5}	74.4025	75.0610	0.6586	131.72	17.5728
50	7	0	5.5667×10^{-3}	70.7232	71.3733	0.6501	130.02	10.1617

Table A13. The optimized values of gold thin film, silicon nanosheet thickness and the number of MoS₂ layers with corresponding change in resonance angle and FWHM in SPR curve for 660nm excitation wavelength.

Au thickness (nm)	Si thickness (nm)	Number of MoS ₂ layers (L)	Minimum Reflectivity	θ_{SPR} w/o biomolecules (Deg)	θ_{SPR} with biomolecules (Deg)	$\Delta\theta_{\text{SPR}}$ ($\Delta n_{\text{bio}}=0.005$) (Deg)	Sensitivity (Deg/RIU)	FWHM (Deg)
30	0	6	1.8860×10^{-4}	63.0347	63.3709	0.3362	67.24	21.6314
35	0	4	4.3030×10^{-4}	59.7976	60.0976	0.3000	60.00	13.5477
40	0	2	2.7099×10^{-5}	57.4727	57.7309	0.2582	51.64	6.1343
50	0	0	2.9483×10^{-4}	55.7750	55.9976	0.2226	44.52	1.9505
30	5	5	1.5371×10^{-3}	73.8012	74.2142	0.4130	82.60	24.3312
35	5	3	3.3096×10^{-6}	68.5553	69.0066	0.4513	90.26	20.2592
40	5	2	3.5910×10^{-3}	66.0163	66.4559	0.4396	87.92	15.3721
50	5	0	4.7825×10^{-4}	61.7097	62.0757	0.3660	73.20	4.9425
30	7	4	2.4965×10^{-3}	77.6969	78.0907	0.3938	78.76	23.1151
35	7	2	6.6891×10^{-3}	72.3108	72.8323	0.5215	104.30	20.1227
40	7	1	6.5220×10^{-3}	69.3471	69.8655	0.5184	103.68	15.4924
50	7	0	1.4158×10^{-3}	66.5248	67.0197	0.4949	98.98	7.8452

Table A14. The optimized values of gold thin film, silicon nanosheet thickness and the number of MoS₂ layers with corresponding change in resonance angle and FWHM in SPR curve for 785 nm excitation wavelength.

Au thickness (nm)	Si thickness (nm)	Number of MoS ₂ layers (L)	Minimum Reflectivity	θ_{SPR} w/o biomolecules (Deg)	θ_{SPR} with biomolecules (Deg)	$\Delta\theta_{\text{SPR}}$ ($\Delta n_{\text{bio}}=0.005$) (Deg)	Sensitivity (Deg/RIU)	FWHM (Deg)
30	0	21	4.1054×10^{-3}	85.4520	85.6781	0.2261	45.22	15.6719
35	0	19	8.0650×10^{-3}	81.8865	82.3516	0.4651	93.02	18.1127
40	0	18	1.6636×10^{-3}	79.4828	80.0256	0.5428	108.56	18.2150
50	0	0	1.0244×10^{-2}	54.4952	54.6566	0.1614	32.28	1.4493
30	5	15	1.9347×10^{-2}	85.4900	85.7774	0.2874	57.48	15.1351
35	5	14	1.7224×10^{-3}	84.3663	84.6635	0.2972	59.44	15.8351
40	5	12	1.5890×10^{-3}	78.7526	79.3507	0.5981	119.62	17.5634
50	5	0	8.3559×10^{-3}	57.1765	57.3998	0.2233	44.66	2.6852
30	7	13	6.0457×10^{-3}	86.1192	86.3435	0.2243	44.86	14.0449
35	7	12	1.1254×10^{-2}	85.0190	85.2241	0.2051	41.02	14.9529
40	7	10	1.4479×10^{-3}	79.7251	80.3357	0.6106	122.12	17.0554
50	7	0	7.3315×10^{-3}	58.8242	59.0838	0.2596	51.92	3.5672

Table A15. The optimized values of gold thin film, silicon nanosheet thickness and the number of MoS₂ layers with corresponding change in resonance angle and FWHM in SPR curve for 1024 nm excitation wavelength.

Au thickness (nm)	Si thickness (nm)	Number of MoS ₂ layers (L)	Minimum Reflectivity	θ_{SPR} w/o biomolecules (Deg)	θ_{SPR} with biomolecules (Deg)	$\Delta\theta_{\text{SPR}}$ ($\Delta n_{\text{bio}}=0.005$) (Deg)	Sensitivity (Deg/RIU)	FWHM (Deg)
30	0	37	3.7590×10^{-4}	86.6058	86.7180	0.1122	22.44	13.1950
35	0	34	3.9641×10^{-3}	83.4687	83.7908	0.3221	64.42	16.6822
40	0	24	6.6910×10^{-7}	64.8861	65.2007	0.3146	62.92	15.7915
30	5	31	3.5648×10^{-4}	86.7583	86.8695	0.1112	22.24	12.6806
35	5	29	2.9629×10^{-3}	85.0857	85.2971	0.2114	42.28	14.8210
40	5	26	1.6573×10^{-6}	79.6388	80.0887	0.4499	89.98	17.5445
30	7	29	9.2532×10^{-3}	86.9999	87.0640	0.0641	12.82	12.0259
35	7	26	3.2804×10^{-3}	84.1379	84.4549	0.3170	63.40	15.6223
40	7	24	2.6466×10^{-5}	80.4023	80.8507	0.4484	89.68	17.0995

Table A16. The optimized values of gold thin film, silicon nanosheet thickness and the number of WSe₂ layers with corresponding change in resonance angle and FWHM in SPR curve for 600nm excitation wavelength.

Au thickness (nm)	Si thickness (nm)	Number of WSe ₂ layers (L)	Minimum Reflectivity	θ_{SPR} w/o biomolecules (Deg)	θ_{SPR} with biomolecules (Deg)	$\Delta\theta_{\text{SPR}}$ ($\Delta n_{\text{bio}}=0.005$) (Deg)	Sensitivity (Deg/RIU)	FWHM (Deg)
30	0	6	1.3325×10^{-3}	65.9641	66.3667	0.4026	80.52	22.2635
35	0	4	9.8589×10^{-5}	61.9820	62.3467	0.3647	72.94	14.8483
40	0	2	1.4661×10^{-3}	58.9733	59.2852	0.3119	62.38	7.1293
50	0	0	6.0974×10^{-5}	56.7966	57.0636	0.2670	53.40	2.3134
30	5	4	8.8668×10^{-3}	79.1252	79.5096	0.3844	76.88	22.3640
35	5	2	6.5971×10^{-3}	73.6359	74.2378	0.6019	120.38	19.8777
40	5	1	7.0381×10^{-3}	70.5039	71.0993	0.5954	119.08	15.4087
50	5	0	2.6443×10^{-3}	67.5897	68.1553	0.5656	113.12	8.0491
30	7	2	5.6634×10^{-4}	82.6512	83.0077	0.3565	71.30	19.1634
35	7	1	1.1040×10^{-5}	81.4876	82.0996	0.6120	122.40	17.8356

Table A17. The optimized values of gold thin film, silicon nanosheet thickness and the number of WSe₂ layers with corresponding change in resonance angle and FWHM in SPR curve for 633nm excitation wavelength.

Au thickness (nm)	Si thickness (nm)	Number of WSe ₂ layers (L)	Minimum Reflectivity	θ_{SPR} w/o biomolecules (Deg)	θ_{SPR} with biomolecules (Deg)	$\Delta\theta_{\text{SPR}}$ ($\Delta n_{\text{bio}}=0.005$) (Deg)	Sensitivity (Deg/RIU)	FWHM (Deg)
30	0	11	2.2768×10^{-3}	78.5367	78.9284	0.3917	78.34	22.8451
35	0	8	5.8035×10^{-4}	69.4428	69.9257	0.4829	96.58	20.4245
40	0	5	6.9205×10^{-5}	62.2455	62.6176	0.3721	74.42	11.1533
50	0	0	1.4822×10^{-5}	56.1871	56.4280	0.2409	48.18	2.1004
30	5	6	2.2033×10^{-3}	82.4372	82.7518	0.3146	62.92	19.6486
35	5	4	9.6397×10^{-3}	76.3932	77.0125	0.6193	123.86	19.7620
40	5	3	3.3950×10^{-4}	72.9343	73.5571	0.6228	124.56	17.3262
50	5	0	5.0702×10^{-4}	63.7243	64.1544	0.4301	86.02	5.9887
30	7	4	3.3021×10^{-3}	84.1284	84.3689	0.2405	48.10	17.5654
35	7	3	1.1646×10^{-2}	82.5553	82.9505	0.3952	79.04	17.5903
40	7	2	5.3807×10^{-3}	79.5347	80.2417	0.7070	141.40	17.2340
50	7	0	5.5667×10^{-3}	70.7232	71.3733	0.6501	130.02	10.7091

Table A18. The optimized values of gold thin film, silicon nanosheet thickness and the number of WSe₂ layers with corresponding change in resonance angle and FWHM in SPR curve for 660nm excitation wavelength.

Au thickness (nm)	Si thickness (nm)	Number of WSe ₂ layers (L)	Minimum Reflectivity	θ_{SPR} w/o biomolecules (Deg)	θ_{SPR} with biomolecules (Deg)	$\Delta\theta_{\text{SPR}}$ ($\Delta n_{\text{bio}}=0.005$) (Deg)	Sensitivity (Deg/RIU)	FWHM (Deg)
30	0	14	9.9083×10^{-4}	82.0877	82.4070	0.3193	63.86	20.0880
35	0	12	4.3537×10^{-5}	77.0606	77.6036	0.5430	108.60	20.6870
40	0	9	2.4735×10^{-5}	67.8256	68.3062	0.4806	96.12	16.1546
50	0	0	2.9483×10^{-4}	55.7750	55.9976	0.2226	44.52	1.9505
30	5	8	2.8380×10^{-3}	83.5346	83.8918	0.3572	71.44	18.0605
35	5	7	4.3860×10^{-3}	81.8189	82.2685	0.4496	89.92	18.2067
40	5	5	1.0418×10^{-3}	74.7498	75.3946	0.6448	128.96	17.5697
50	5	0	4.7825×10^{-4}	61.7097	62.0757	0.3660	73.20	4.9425
30	7	6	6.2526×10^{-4}	84.9979	85.2229	0.2250	45.00	16.1847
35	7	5	1.8639×10^{-2}	83.5895	83.8794	0.2899	57.98	16.6250
40	7	3	6.8553×10^{-3}	76.5740	77.2831	0.7091	141.82	16.9720
50	7	0	1.4158×10^{-3}	66.5248	67.0197	0.4949	98.98	7.8452

Table A19. The optimized values of gold thin film, silicon nanosheet thickness and the number of WSe₂ layers with corresponding change in resonance angle and FWHM in SPR curve for 785nm excitation wavelength.

Au thickness (nm)	Si thickness (nm)	Number of WSe ₂ layers (L)	Minimum Reflectivity	θ_{SPR} w/o biomolecules (Deg)	θ_{SPR} with biomolecules (Deg)	$\Delta\theta_{\text{SPR}}$ ($\Delta n_{\text{bio}}=0.005$) (Deg)	Sensitivity (Deg/RIU)	FWHM (Deg)
30	0	22	8.4871×10^{-3}	87.4001	87.4328	0.0327	6.54	11.0742
35	0	20	6.7847×10^{-3}	85.0150	85.3998	0.3848	76.96	14.6494
40	0	19	3.7420×10^{-4}	82.9005	83.4261	0.5256	105.12	15.6095
50	0	0	1.0244×10^{-2}	54.4952	54.6566	0.1614	32.28	1.4493
30	5	16	3.0767×10^{-4}	87.4542	87.5420	0.0878	17.56	10.8336
35	5	14	2.5920×10^{-2}	84.5495	85.0380	0.4885	97.70	14.7270
40	5	13	3.0089×10^{-3}	82.1762	82.8034	0.6272	125.44	15.5520
50	5	0	8.3559×10^{-3}	57.1765	57.3998	0.2233	44.66	2.6852
30	7	14	2.9648×10^{-2}	87.6125	87.5761	0.0364	7.28	10.2158
35	7	12	6.9144×10^{-3}	85.4400	85.8225	0.3825	76.50	13.7719
40	7	11	1.5685×10^{-7}	83.2732	83.8288	0.5556	111.12	14.8756
50	7	0	7.3315×10^{-3}	58.8242	59.0838	0.2596	51.92	3.5672

Table S20. The optimized values of gold thin film, silicon nanosheet thickness and the number of WSe₂ layers with corresponding change in resonance angle and FWHM in SPR curve for 1024nm excitation wavelength.

Au thickness (nm)	Si thickness (nm)	Number of WSe ₂ layers (L)	Minimum Reflectivity	θ_{SPR} w/o biomolecules (Deg)	θ_{SPR} with biomolecules (Deg)	$\Delta\theta_{\text{SPR}}$ ($\Delta n_{\text{bio}}=0.005$) (Deg)	Sensitivity (Deg/RIU)	FWHM (Deg)
30	0	30	1.9402×10^{-3}	83.6259	83.8350	0.2091	41.82	18.6024
35	0	27	7.0563×10^{-5}	78.6477	78.9901	0.3424	68.48	20.8099
40	0	4	3.6825×10^{-5}	54.3710	54.4926	0.1216	24.32	2.3459
30	5	25	1.8613×10^{-3}	84.0992	84.3069	0.2077	41.54	17.6802
35	5	23	6.5693×10^{-4}	81.1789	81.4915	0.3126	62.52	19.1731
40	5	4	4.6665×10^{-5}	55.9801	56.1347	0.1546	30.92	3.7128
30	7	23	2.6872×10^{-3}	84.2168	84.4294	0.2126	42.52	17.3711
35	7	21	1.2616×10^{-4}	81.2364	81.5596	0.3232	64.64	18.9030
40	7	5	2.2124×10^{-5}	57.3452	57.5259	0.1807	36.14	5.2062

Table A21. The change in differential phase of various refractive index change of the biomolecular sample with optimized thickness of 44 nm gold and 5 nm silicon at 633 nm excitation wavelength in silicon-WSe₂ model.

Number of WSe ₂ layers (L)	Change in differential phase (Deg) $\Delta n=1 \times 10^{-5}$	Change in differential phase (Deg) $\Delta n=3 \times 10^{-5}$	Change in differential phase (Deg) $\Delta n=5 \times 10^{-5}$	Change in differential phase (Deg) $\Delta n=7 \times 10^{-5}$	Change in differential phase (Deg) $\Delta n=9 \times 10^{-5}$
0	0.0982	0.2949	0.4916	0.6883	0.8851
1	12.2576	34.2615	49.9405	60.2348	67.1041
2	0.0502	0.1507	0.2511	0.3514	0.4517
3	0.0135	0.0404	0.0674	0.0943	0.1212
4	0.0017	0.0052	0.0087	0.0122	0.0157
5	0.0007	0.0023	0.0038	0.0054	0.0070
6	0.0008	0.0026	0.0044	0.0061	0.0079

Table A22. The phase sensitivity of various refractive index change of the biomolecular sample with optimized thickness of 44 nm gold and 5 nm silicon at 633 nm excitation wavelength in silicon-WSe₂ model.

Number of WSe ₂ layers (L)	Phase sensitivity (Deg/RIU) $\Delta n=1 \times 10^{-5}$	Phase sensitivity (Deg/RIU) $\Delta n=3 \times 10^{-5}$	Phase sensitivity (Deg/RIU) $\Delta n=5 \times 10^{-5}$	Phase sensitivity (Deg/RIU) $\Delta n=7 \times 10^{-5}$	Phase sensitivity (Deg/RIU) $\Delta n=9 \times 10^{-5}$
0	9.8295×10^3	9.8311×10^3	9.8325×10^3	9.8340×10^3	9.8353×10^3
1	1.2258×10^6	1.1421×10^6	9.9881×10^5	8.6050×10^5	7.4560×10^5
2	5.0264×10^3	5.0246×10^3	5.0228×10^3	5.0209×10^3	5.0191×10^3
3	1.3500×10^3	1.3494×10^3	1.3488×10^3	1.3482×10^3	1.3476×10^3
4	1.7554×10^2	1.7537×10^2	1.7521×10^2	1.7505×10^2	1.7489×10^2
5	7.7862×10^1	7.7883×10^1	7.7904×10^1	7.7925×10^1	7.7946×10^1
6	8.8553×10^1	8.8553×10^1	8.8553×10^1	8.8553×10^1	8.8553×10^1

Table A23. The change in differential phase of various refractive index change of the biomolecular sample with optimized thickness of 28 nm gold, 7 nm silicon at 660 nm excitation wavelength in silicon-MoSe₂ model.

Number of MoSe ₂ layers (L)	Change in differential phase (Deg) $\Delta n=1 \times 10^{-5}$	Change in differential phase (Deg) $\Delta n=3 \times 10^{-5}$	Change in differential phase (Deg) $\Delta n=5 \times 10^{-5}$	Change in differential phase (Deg) $\Delta n=7 \times 10^{-5}$	Change in differential phase (Deg) $\Delta n=9 \times 10^{-5}$
0	0.0105	0.0317	0.0528	0.0739	0.0951
1	0.0107	0.0321	0.0535	0.0749	0.0964
2	0.0113	0.0339	0.0566	0.0793	0.1019
3	0.0132	0.0397	0.0662	0.0927	0.1192
4	0.0199	0.0598	0.0997	0.1397	0.1796
5	11.1660	38.5214	63.7063	80.4979	90.8135
6	0.0072	0.0216	0.0360	0.0504	0.0648

Table A24. The phase sensitivity of various refractive index change of the biomolecular sample with optimized thickness of 28 nm gold and 7 nm silicon at 660 nm excitation wavelength in silicon-MoSe₂ model.

Number of MoSe ₂ layers (L)	Phase sensitivity (Deg/RIU) $\Delta n=1 \times 10^{-5}$	Phase sensitivity (Deg/RIU) $\Delta n=3 \times 10^{-5}$	Phase sensitivity (Deg/RIU) $\Delta n=5 \times 10^{-5}$	Phase sensitivity (Deg/RIU) $\Delta n=7 \times 10^{-5}$	Phase sensitivity (Deg/RIU) $\Delta n=9 \times 10^{-5}$
0	1.0567×10^3	1.0567×10^3	1.0568×10^3	1.0568×10^3	1.0569×10^3
1	1.0710×10^3	1.0711×10^3	1.0711×10^3	1.0712×10^3	1.0712×10^3
2	1.1328×10^3	1.1329×10^3	1.1330×10^3	1.1330×10^3	1.1331×10^3
3	1.3247×10^3	1.3248×10^3	1.3249×10^3	1.3250×10^3	1.3252×10^3
4	1.9947×10^3	1.9952×10^3	1.9957×10^3	1.9961×10^3	1.9966×10^3
5	1.1166×10^6	1.2840×10^6	1.2741×10^6	1.1500×10^6	1.0090×10^6
6	7.2197×10^2	7.2154×10^2	7.2111×10^2	7.2068×10^2	7.2025×10^2

Table A25. The change in differential phase of various refractive index change of the biomolecular sample with optimized thickness of 31 nm gold and 4 nm silicon at 1540 nm excitation wavelength in silicon-WS₂ model.

Number of WS ₂ layers (L)	Change in differential phase (Deg) $\Delta n=1 \times 10^{-5}$	Change in differential phase (Deg) $\Delta n=3 \times 10^{-5}$	Change in differential phase (Deg) $\Delta n=5 \times 10^{-5}$	Change in differential phase (Deg) $\Delta n=7 \times 10^{-5}$	Change in differential phase (Deg) $\Delta n=9 \times 10^{-5}$
0	1.5913	4.7404	7.8307	10.8474	13.7776
1	2.4114	7.3091	12.2496	17.1620	21.9780
2	5.7761	16.6771	26.2493	34.3003	40.9254
3	12.3201	34.8428	51.0375	61.6276	68.6356
4	2.7394	8.0375	13.0367	17.6907	21.9772
5	1.5417	4.6442	7.7562	10.8589	13.9335
6	1.0446	3.1367	5.2279	7.3121	9.3837

Table A26. The phase sensitivity of various refractive index change of the biomolecular sample with optimized thickness of 31 nm gold and 4 nm silicon at 1540 nm excitation wavelength in silicon-WS₂ model.

Number of WS ₂ layers (L)	Phase sensitivity (Deg/RIU) $\Delta n=1 \times 10^{-5}$	Phase sensitivity (Deg/RIU) $\Delta n=3 \times 10^{-5}$	Phase sensitivity (Deg/RIU) $\Delta n=5 \times 10^{-5}$	Phase sensitivity (Deg/RIU) $\Delta n=7 \times 10^{-5}$	Phase sensitivity (Deg/RIU) $\Delta n=9 \times 10^{-5}$
0	1.5914×10^5	1.5802×10^5	1.5662×10^5	1.5496×10^5	1.5308×10^5
1	2.4115×10^5	2.4364×10^5	2.4499×10^5	2.4517×10^5	2.4420×10^5
2	5.7762×10^5	5.5590×10^5	5.2499×10^5	4.9001×10^5	4.5473×10^5
3	1.2320×10^6	1.1614×10^6	1.0208×10^6	8.8040×10^5	7.6262×10^5
4	2.7394×10^5	2.6792×10^5	2.6074×10^5	2.5272×10^5	2.4419×10^5
5	1.5418×10^5	1.5481×10^5	1.5513×10^5	1.5513×10^5	1.5482×10^5
6	1.0446×10^5	1.0456×10^5	1.0456×10^5	1.0446×10^5	1.0426×10^5

Table A27. Changes in differential phase, minimum reflectivity and FWTM at the optimum Au/Si thickness with different number of TMDC layers, $\Delta n_{bio} = 1.2 \times 10^{-4}$ RIU and $\lambda_{inc} = 600$ nm.

Type of MX ₂	d_{Si} (nm)	d_{Au} (nm)	MX ₂ (L)	$\Delta\Phi_d$ (Deg) ($\Delta n_{bio}=0.00012$)	R_{min}	FWTM
WS ₂	0	44	0	25.4786	2.16×10^{-5}	2.2138
WS ₂	1	34	5	28.0130	2.07×10^{-6}	8.2923
WS ₂	2	41	1	84.3387	4.92×10^{-8}	4.5984
WS ₂	3	43	0	12.1720	5.41×10^{-5}	4.4829
WS ₂	4	39	1	43.2718	1.07×10^{-6}	7.2312
WS ₂	5	24	6	31.4174	2.78×10^{-8}	8.9625
WS ₂	6	37	0	9.1372	4.11×10^{-5}	8.1865
WS ₂	7	27	2	1.8333	2.10×10^{-4}	7.2983
MoSe ₂	0	44	0	25.4786	2.16×10^{-5}	2.2138
MoSe ₂	1	36	2	47.1928	9.67×10^{-7}	6.3217
MoSe ₂	2	32	3	34.8934	1.21×10^{-6}	9.6521
MoSe ₂	3	38	1	30.7865	3.81×10^{-6}	6.8639
MoSe ₂	4	42	0	15.1347	2.68×10^{-5}	5.7752
MoSe ₂	5	40	0	17.4421	1.99×10^{-5}	7.1907
MoSe ₂	6	24	3	121.9218	5.07×10^{-8}	9.3155
MoSe ₂	7	28	1	2.4393	1.40×10^{-4}	7.9146
MoS ₂	0	44	0	25.4786	2.16×10^{-5}	2.2138
MoS ₂	1	40	1	10.3849	5.99×10^{-5}	4.0957
MoS ₂	2	33	3	31.3808	1.78×10^{-6}	8.7790
MoS ₂	3	35	2	13.9273	1.10×10^{-5}	8.3841
MoS ₂	4	42	0	15.1347	2.68×10^{-5}	5.7752
MoS ₂	5	23	5	17.5948	1.99×10^{-6}	10.7847
MoS ₂	6	32	1	66.5637	8.10×10^{-7}	9.1242
MoS ₂	7	23	3	1.6243	1.84×10^{-4}	8.5796
WSe ₂	0	44	0	25.4786	2.16×10^{-5}	2.2138
WSe ₂	1	30	5	77.7661	9.16×10^{-10}	10.6304
WSe ₂	2	31	4	12.9384	8.45×10^{-6}	10.3329
WSe ₂	3	39	1	18.2029	1.17×10^{-5}	6.4929
WSe ₂	4	42	0	15.1347	2.68×10^{-5}	5.7752
WSe ₂	5	40	0	17.4421	1.99×10^{-5}	7.1907
WSe ₂	6	37	0	9.1372	4.11×10^{-5}	8.1865
WSe ₂	7	25	2	1.5108	3.19×10^{-4}	7.6906

Table A28. Changes in differential phase, minimum reflectivity and FWTM at the optimum Au/Si thickness with different number of TMDC layers, $\Delta n_{\text{bio}} = 1.2 \times 10^{-4}$ RIU and $\lambda_{\text{inc}} = 633$ nm.

Type of MX ₂	d_{Si} (nm)	d_{Au} (nm)	MX ₂ (L)	$\Delta\Phi_d$ (Deg) ($\Delta n_{\text{bio}}=0.00012$)	R_{min}	FWTM
WS ₂	0	46	1	79.4344	3.64×10^{-7}	1.5998
WS ₂	1	44	2	27.0561	1.65×10^{-5}	2.8565
WS ₂	2	48	0	11.8867	2.10×10^{-4}	1.6494
WS ₂	3	33	5	21.4171	2.08×10^{-6}	8.8177
WS ₂	4	34	4	30.6098	4.50×10^{-6}	8.5708
WS ₂	5	44	1	41.9326	3.07×10^{-6}	5.1822
WS ₂	6	46	0	50.5494	3.37×10^{-6}	4.4271
WS ₂	7	44	0	7.6502	2.03×10^{-4}	5.7758
MoSe ₂	0	48	0	22.7254	7.71×10^{-5}	1.1215
MoSe ₂	1	40	2	82.4562	5.37×10^{-8}	3.3558
MoSe ₂	2	43	1	22.5774	2.38×10^{-5}	2.7675
MoSe ₂	3	36	3	32.9377	2.42×10^{-6}	7.1903
MoSe ₂	4	35	3	19.1008	6.95×10^{-6}	8.4974
MoSe ₂	5	47	0	19.6202	3.90×10^{-5}	3.3646
MoSe ₂	6	46	0	50.5494	3.37×10^{-6}	4.4271
MoSe ₂	7	44	0	7.6502	2.03×10^{-4}	5.7758
MoS ₂	0	43	1	69.7853	7.50×10^{-7}	1.9154
MoS ₂	1	39	2	56.1445	1.02×10^{-6}	3.7147
MoS ₂	2	48	0	11.8867	2.10×10^{-4}	1.6494
MoS ₂	3	42	1	19.3913	2.38×10^{-5}	3.7032
MoS ₂	4	47	0	15.2238	8.58×10^{-5}	2.6407
MoS ₂	5	23	6	31.4098	6.94×10^{-7}	10.6824
MoS ₂	6	46	0	50.5494	3.37×10^{-6}	4.4271
MoS ₂	7	37	1	17.2734	9.47×10^{-6}	8.2734
WSe ₂	0	44	2	55.5541	2.76×10^{-6}	2.0832
WSe ₂	1	42	3	36.1885	5.72×10^{-6}	3.5162
WSe ₂	2	48	0	11.8867	2.10×10^{-4}	1.6494
WSe ₂	3	43	2	39.9789	4.44×10^{-6}	4.1412
WSe ₂	4	47	0	15.2238	8.58×10^{-5}	2.6407
WSe ₂	5	44	1	72.7657	4.66×10^{-7}	4.8841
WSe ₂	6	46	0	50.5494	3.37×10^{-6}	4.4271
WSe ₂	7	27	4	56.1200	1.65×10^{-6}	6.4279

Table A29. Changes in differential phase, minimum reflectivity and FWTM at the optimum Au/Si thickness with different number of TMDC layers, $\Delta n_{\text{bio}} = 1.2 \times 10^{-4}$ RIU and $\lambda_{\text{inc}} = 660$ nm.

Type of MX ₂	d_{Si} (nm)	d_{Au} (nm)	MX ₂ (L)	$\Delta\Phi_d$ (Deg) ($\Delta n_{\text{bio}}=0.00012$)	R_{min}	FWTM
WS ₂	0	51	0	54.1463	1.68×10^{-5}	0.6642
WS ₂	1	51	0	56.3993	1.23×10^{-5}	0.7842
WS ₂	2	51	0	61.3262	6.57×10^{-6}	0.9349
WS ₂	3	51	0	78.5233	1.06×10^{-6}	1.1274
WS ₂	4	51	0	68.4871	2.39×10^{-6}	1.3777
WS ₂	5	49	1	41.2683	1.10×10^{-5}	2.4711
WS ₂	6	43	3	16.4468	2.95×10^{-5}	6.4366
WS ₂	7	44	2	62.2411	2.73×10^{-7}	6.0890
MoSe ₂	0	43	2	56.0190	3.07×10^{-6}	1.6423
MoSe ₂	1	51	0	56.3993	1.23×10^{-5}	0.7842
MoSe ₂	2	37	4	75.8760	6.45×10^{-8}	5.0264
MoSe ₂	3	51	0	78.5233	1.06×10^{-6}	1.1274
MoSe ₂	4	51	0	68.4871	2.39×10^{-6}	1.3777
MoSe ₂	5	38	3	32.7873	2.69×10^{-6}	6.7355
MoSe ₂	6	45	1	30.1733	1.11×10^{-5}	3.9178
MoSe ₂	7	28	5	104.4463	7.17×10^{-8}	9.6017
MoS ₂	0	51	0	54.1463	1.68×10^{-5}	0.6642
MoS ₂	1	45	1	88.9629	5.67×10^{-8}	1.4677
MoS ₂	2	37	3	78.0628	5.11×10^{-8}	4.5186
MoS ₂	3	51	0	78.5233	1.06×10^{-6}	1.1274
MoS ₂	4	51	0	68.4871	2.39×10^{-6}	1.3777
MoS ₂	5	32	4	33.5449	1.32×10^{-6}	9.9692
MoS ₂	6	51	0	12.5599	2.11×10^{-4}	2.1631
MoS ₂	7	23	6	25.3862	1.05×10^{-6}	10.1407
WSe ₂	0	45	5	74.0878	3.81×10^{-7}	2.2602
WSe ₂	1	51	0	56.3993	1.23×10^{-5}	0.7842
WSe ₂	2	51	0	61.3262	6.57×10^{-6}	0.9349
WSe ₂	3	48	2	81.1361	2.45×10^{-7}	1.9919
WSe ₂	4	51	0	68.4871	2.39×10^{-6}	1.3777
WSe ₂	5	49	1	48.8066	6.69×10^{-6}	2.3717
WSe ₂	6	44	3	33.4627	9.08×10^{-6}	5.7033
WSe ₂	7	41	3	55.9564	1.82×10^{-7}	6.9620

Table A30. Changes in differential phase, minimum reflectivity and FWTM at the optimum Au/Si thickness with different number of TMDC layers, $\Delta n_{bio} = 1.2 \times 10^{-4}$ RIU and $\lambda_{inc} = 785$ nm.

Type of MX ₂	d_{Si} (nm)	d_{Au} (nm)	MX ₂ (L)	$\Delta\Phi_d$ (Deg) ($\Delta n_{bio}=0.00012$)	R_{min}	FWTM
WS ₂	0	49	4	78.3404	5.82×10^{-7}	0.4827
WS ₂	1	49	4	71.9183	3.33×10^{-6}	0.5478
WS ₂	2	49	5	61.5106	7.98×10^{-6}	0.7127
WS ₂	3	49	5	80.0963	1.01×10^{-6}	0.8227
WS ₂	4	49	5	74.4712	1.66×10^{-6}	0.9563
WS ₂	5	49	6	70.6259	1.73×10^{-6}	1.3159
WS ₂	6	50	0	84.0873	2.22×10^{-7}	0.6066
WS ₂	7	50	0	63.9810	7.08×10^{-6}	0.6956
MoSe ₂	0	38	5	65.3912	1.16×10^{-6}	1.3471
MoSe ₂	1	50	0	33.1394	1.34×10^{-4}	0.3299
MoSe ₂	2	36	6	66.7761	5.06×10^{-7}	2.3722
MoSe ₂	3	41	3	56.8907	3.23×10^{-6}	1.2250
MoSe ₂	4	50	0	48.8351	3.25×10^{-5}	0.4691
MoSe ₂	5	50	0	61.3429	1.05×10^{-5}	0.5320
MoSe ₂	6	50	0	84.0873	2.22×10^{-7}	0.6066
MoSe ₂	7	46	1	71.2325	1.39×10^{-6}	1.1044
MoS ₂	0	47	6	78.0034	9.58×10^{-8}	0.7339
MoS ₂	1	47	6	73.3092	1.77×10^{-6}	0.8476
MoS ₂	2	47	6	58.1068	6.03×10^{-6}	0.9848
MoS ₂	3	47	6	50.4105	9.01×10^{-6}	1.1524
MoS ₂	4	47	6	49.3718	8.50×10^{-6}	1.3590
MoS ₂	5	50	0	61.3429	1.05×10^{-5}	0.5320
MoS ₂	6	50	0	84.0873	2.22×10^{-7}	0.6066
MoS ₂	7	47	6	81.5861	1.31×10^{-7}	2.3576
WSe ₂	0	49	5	81.6871	2.78×10^{-7}	0.5418
WSe ₂	1	49	5	72.0227	2.93×10^{-6}	0.6188
WSe ₂	2	49	6	73.1656	1.71×10^{-6}	0.8153
WSe ₂	3	49	6	78.5531	6.80×10^{-7}	0.9496
WSe ₂	4	49	6	49.3341	1.21×10^{-5}	1.1148
WSe ₂	5	50	0	61.3429	1.05×10^{-5}	0.5320
WSe ₂	6	50	0	84.0873	2.22×10^{-7}	0.6066
WSe ₂	7	50	0	63.9810	7.08×10^{-6}	0.6956

Table A31. Changes in differential phase, minimum reflectivity and FWTM at the optimum Au/Si thickness with different number of TMDC layers, $\Delta n_{bio} = 1.2 \times 10^{-4}$ RIU and $\lambda_{inc} = 904$ nm.

Type of MX ₂	d_{Si} (nm)	d_{Au} (nm)	MX ₂ (L)	$\Delta\Phi_d$ (Deg) ($\Delta n_{bio}=0.00012$)	R_{min}	FWTM
WS ₂	0	51	0	54.1463	1.68×10^{-5}	0.6642
WS ₂	1	51	0	56.3993	1.23×10^{-5}	0.7842
WS ₂	2	51	0	61.3262	6.57×10^{-6}	0.9349
WS ₂	3	51	0	78.5233	1.06×10^{-6}	1.1274
WS ₂	4	51	0	68.4871	2.39×10^{-6}	1.3777
WS ₂	5	49	1	41.2683	1.10×10^{-5}	2.4711
WS ₂	6	43	3	16.4468	2.95×10^{-5}	6.4366
WS ₂	7	44	2	62.2411	2.73×10^{-7}	6.0890
MoSe ₂	0	43	2	56.0190	3.07×10^{-6}	1.6423
MoSe ₂	1	51	0	56.3993	1.23×10^{-5}	0.7842
MoSe ₂	2	37	4	75.8760	6.45×10^{-8}	5.0264
MoSe ₂	3	51	0	78.5233	1.06×10^{-6}	1.1274
MoSe ₂	4	51	0	68.4871	2.39×10^{-6}	1.3777
MoSe ₂	5	38	3	32.7873	2.69×10^{-6}	6.7355
MoSe ₂	6	45	1	30.1733	1.11×10^{-5}	3.9178
MoSe ₂	7	28	5	104.4463	7.17×10^{-8}	9.6017
MoS ₂	0	51	0	54.1463	1.68×10^{-5}	0.6642
MoS ₂	1	45	1	88.9629	5.67×10^{-8}	1.4677
MoS ₂	2	37	3	78.0628	5.11×10^{-8}	4.5186
MoS ₂	3	51	0	78.5233	1.06×10^{-6}	1.1274
MoS ₂	4	51	0	68.4871	2.39×10^{-6}	1.3777
MoS ₂	5	32	4	33.5449	1.32×10^{-6}	9.9692
MoS ₂	6	51	0	12.5599	2.11×10^{-4}	2.1631
MoS ₂	7	23	6	25.3862	1.05×10^{-6}	10.1407
WSe ₂	0	45	5	74.0878	3.81×10^{-7}	2.2602
WSe ₂	1	51	0	56.3993	1.23×10^{-5}	0.7842
WSe ₂	2	51	0	61.3262	6.57×10^{-6}	0.9349
WSe ₂	3	48	2	81.1361	2.45×10^{-7}	1.9919
WSe ₂	4	51	0	68.4871	2.39×10^{-6}	1.3777
WSe ₂	5	49	1	48.8066	6.69×10^{-6}	2.3717
WSe ₂	6	44	3	33.4627	9.08×10^{-6}	5.7033
WSe ₂	7	41	3	55.9564	1.82×10^{-7}	6.9620

Table A32. Changes in differential phase, minimum reflectivity and FWTM at the optimum Au/Si thickness with different number of TMDC layers, $\Delta n_{bio} = 1.2 \times 10^{-4}$ RIU and $\lambda_{inc} = 1150$ nm.

Type of MX ₂	d_{Si} (nm)	d_{Au} (nm)	MX ₂ (L)	$\Delta\Phi_d$ (Deg) ($\Delta n_{bio}=0.00012$)	R_{min}	FWTM
WS ₂	0	39	0	70.3182	4.23×10^{-6}	0.1709
WS ₂	1	37	5	73.5659	1.29×10^{-6}	0.3312
WS ₂	2	37	5	75.6991	9.41×10^{-7}	0.3565
WS ₂	3	37	5	54.8073	8.82×10^{-6}	0.3839
WS ₂	4	39	0	42.2959	4.44×10^{-5}	0.2201
WS ₂	5	39	0	36.6173	6.42×10^{-5}	0.2346
WS ₂	6	39	0	31.7666	8.96×10^{-5}	0.2501
WS ₂	7	39	1	28.9342	8.91×10^{-5}	0.2969
MoSe ₂	0	39	0	70.3182	4.23×10^{-6}	0.1709
MoSe ₂	1	39	0	62.6717	9.60×10^{-6}	0.1820
MoSe ₂	2	39	0	56.3707	1.77×10^{-5}	0.1939
MoSe ₂	3	39	0	49.1560	2.91×10^{-5}	0.2065
MoSe ₂	4	39	0	42.2959	4.44×10^{-5}	0.2201
MoSe ₂	5	38	2	40.1997	3.75×10^{-5}	0.2864
MoSe ₂	6	38	2	38.7968	3.96×10^{-5}	0.3061
MoSe ₂	7	37	4	42.0614	2.23×10^{-5}	0.4022
MoS ₂	0	39	1	74.6193	1.50×10^{-6}	0.1811
MoS ₂	1	39	1	70.1876	1.15×10^{-7}	0.1930
MoS ₂	2	39	1	73.2836	4.30×10^{-7}	0.2057
MoS ₂	3	39	1	78.2750	2.87×10^{-6}	0.2194
MoS ₂	4	39	2	84.1904	1.14×10^{-6}	0.2488
MoS ₂	5	39	1	55.5188	1.63×10^{-5}	0.2495
MoS ₂	6	39	2	77.6588	1.49×10^{-6}	0.2840
MoS ₂	7	39	3	69.5566	2.92×10^{-6}	0.3244
WSe ₂	0	38	4	77.6413	6.97×10^{-8}	0.2440
WSe ₂	1	38	4	72.0875	2.53×10^{-7}	0.2612
WSe ₂	2	38	4	73.2766	1.38×10^{-6}	0.2799
WSe ₂	3	38	4	70.0332	3.15×10^{-6}	0.2999
WSe ₂	4	38	4	62.9035	5.21×10^{-6}	0.3217
WSe ₂	5	38	4	59.7836	7.19×10^{-6}	0.3452
WSe ₂	6	39	1	58.2881	1.14×10^{-5}	0.2716
WSe ₂	7	39	1	67.9075	5.43×10^{-6}	0.2902

Table A33. Changes in differential phase, minimum reflectivity and FWTM at the optimum Au/Si thickness with different number of TMDC layers, $\Delta n_{bio} = 1.2 \times 10^{-4}$ RIU and $\lambda_{inc} = 1319$ nm.

Type of MX ₂	d_{Si} (nm)	d_{Au} (nm)	MX ₂ (L)	$\Delta\Phi_d$ (Deg) ($\Delta n_{bio}=0.00012$)	R_{min}	FWTM
WS ₂	0	35	2	68.4698	5.24×10^{-6}	0.1733
WS ₂	1	35	2	70.0671	4.61×10^{-6}	0.1834
WS ₂	2	35	2	68.1031	3.87×10^{-6}	0.1940
WS ₂	3	35	2	74.0581	3.05×10^{-6}	0.2053
WS ₂	4	35	2	69.9061	2.19×10^{-6}	0.2172
WS ₂	5	35	2	73.9773	1.34×10^{-6}	0.2298
WS ₂	6	34	6	88.2542	3.06×10^{-7}	0.3541
WS ₂	7	34	6	117.6180	8.53×10^{-9}	0.3769
MoSe ₂	0	34	5	75.2997	9.25×10^{-7}	0.2076
MoSe ₂	1	34	5	99.5785	8.06×10^{-8}	0.2197
MoSe ₂	2	34	5	68.8610	1.54×10^{-7}	0.2325
MoSe ₂	3	34	5	78.3040	9.85×10^{-7}	0.2460
MoSe ₂	4	34	5	73.1671	2.46×10^{-6}	0.2603
MoSe ₂	5	34	5	64.0636	4.38×10^{-6}	0.2755
MoSe ₂	6	34	5	59.8401	6.58×10^{-6}	0.2917
MoSe ₂	7	34	5	54.8111	8.84×10^{-6}	0.3090
MoS ₂	0	35	6	45.9460	2.41×10^{-5}	0.2005
MoS ₂	1	35	6	42.6396	3.02×10^{-5}	0.2123
MoS ₂	2	35	6	39.1526	3.77×10^{-5}	0.2247
MoS ₂	3	35	6	36.1432	4.68×10^{-5}	0.2378
MoS ₂	4	35	6	32.3795	5.79×10^{-5}	0.2519
MoS ₂	5	35	6	29.3824	7.13×10^{-5}	0.2667
MoS ₂	6	35	6	26.4072	8.76×10^{-5}	0.2826
MoS ₂	7	35	6	23.6715	1.07×10^{-4}	0.2995
WSe ₂	0	35	2	81.7198	1.78×10^{-6}	0.1697
WSe ₂	1	35	2	80.0662	1.26×10^{-6}	0.1795
WSe ₂	2	35	2	72.1552	7.89×10^{-7}	0.1899
WSe ₂	3	35	2	92.4998	3.61×10^{-7}	0.2008
WSe ₂	4	35	2	106.7738	7.69×10^{-8}	0.2125
WSe ₂	5	35	2	46.5774	2.72×10^{-8}	0.2247
WSe ₂	6	35	2	83.6190	3.15×10^{-7}	0.2377
WSe ₂	7	35	2	76.2414	1.13×10^{-6}	0.2515

Table A34. Changes in differential phase, minimum reflectivity and FWTM at the optimum Au/Si thickness with different number of TMDC layers, $\Delta n_{bio} = 1.2 \times 10^{-4}$ RIU and $\lambda_{inc} = 1540$ nm.

Type of MX ₂	d_{Si} (nm)	d_{Au} (nm)	MX ₂ (L)	$\Delta\Phi_d$ (Deg) ($\Delta n_{bio}=0.00012$)	R_{min}	FWTM
WS ₂	0	31	3	65.0793	4.10×10^{-6}	0.1551
WS ₂	1	31	3	68.7883	3.93×10^{-6}	0.1629
WS ₂	2	31	3	70.4834	3.70×10^{-6}	0.1710
WS ₂	3	31	3	67.3035	3.37×10^{-6}	0.1795
WS ₂	4	31	3	65.1504	2.99×10^{-6}	0.1884
WS ₂	5	31	3	69.5642	2.51×10^{-6}	0.1977
WS ₂	6	31	3	75.1198	2.01×10^{-6}	0.2073
WS ₂	7	31	3	73.3835	1.47×10^{-6}	0.2176
MoSe ₂	0	31	1	40.9327	3.51×10^{-5}	0.1373
MoSe ₂	1	31	2	69.7317	1.02×10^{-7}	0.1500
MoSe ₂	2	31	2	86.2928	4.01×10^{-7}	0.1574
MoSe ₂	3	31	2	71.4586	9.82×10^{-7}	0.1650
MoSe ₂	4	31	2	79.3834	1.88×10^{-6}	0.1730
MoSe ₂	5	31	2	67.6098	3.14×10^{-6}	0.1813
MoSe ₂	6	31	2	62.5667	4.91×10^{-6}	0.1900
MoSe ₂	7	31	2	57.5821	7.24×10^{-6}	0.1992
MoS ₂	0	31	6	27.9027	7.97×10^{-5}	0.1663
MoS ₂	1	31	6	26.3277	8.96×10^{-5}	0.1746
MoS ₂	2	31	6	24.5728	1.01×10^{-4}	0.1832
MoS ₂	3	31	6	23.1975	1.13×10^{-4}	0.1922
MoS ₂	4	31	6	21.6919	1.27×10^{-4}	0.2016
MoS ₂	5	31	6	20.2169	1.43×10^{-4}	0.2114
MoS ₂	6	31	6	18.8294	1.61×10^{-4}	0.2218
MoS ₂	7	31	6	17.6506	1.82×10^{-4}	0.2326
WSe ₂	0	31	3	66.8542	4.34×10^{-6}	0.1510
WSe ₂	1	31	3	63.4480	3.99×10^{-6}	0.1585
WSe ₂	2	31	3	68.2731	3.54×10^{-6}	0.1664
WSe ₂	3	31	3	68.5191	3.06×10^{-6}	0.1745
WSe ₂	4	31	3	71.4741	2.52×10^{-6}	0.1831
WSe ₂	5	31	3	72.6041	1.96×10^{-6}	0.1920
WSe ₂	6	31	3	78.6172	1.41×10^{-6}	0.2014
WSe ₂	7	31	3	81.6451	8.76×10^{-7}	0.2112

Table A35. The phase sensitivity S of the four types of TMDC structured plasmonic models with optimum number of layers for refractive index change (Δn_{bio}) from 2×10^{-5} RIU to 1×10^{-4} RIU.

Wavelength (nm)	Enhanced model	S (Deg/ RIU) $\Delta n_{bio}=2 \times 10^{-5}$	S (Deg/ RIU) $\Delta n_{bio}=4 \times 10^{-5}$	S (Deg/ RIU) $\Delta n_{bio}=6 \times 10^{-5}$	S (Deg/ RIU) $\Delta n_{bio}=8 \times 10^{-5}$	S (Deg/ RIU) $\Delta n_{bio}=1 \times 10^{-4}$
600	WS ₂	2.4623×10^6	1.6992×10^6	1.2641×10^6	1.0004×10^6	8.2602×10^5
785	MoS ₂	2.5176×10^6	1.6791×10^6	1.2349×10^6	9.7218×10^5	8.0045×10^5
904	WSe ₂	3.4025×10^6	2.0421×10^6	1.4428×10^6	1.1133×10^6	9.0586×10^5
1024	MoSe ₂	4.7036×10^6	2.5459×10^6	1.7395×10^6	1.3205×10^6	1.0641×10^6

Table A36. Comparison of the plasmonic sensing performances with or without the optimum WS₂ layers structured on the Au substrate ($\Delta n_{bio} = 2 \times 10^{-6}$ and $\lambda_{inc} = 600$ nm). High phase sensitivities always correspond to low minimum reflectivities, showing the TMDC layers have induced a strong phase singularity.

Enhanced models	Resonance angle (deg)	Minimum reflectivity	FWTM (deg)	$\Delta\phi_d$ (deg)
Au(41nm)/ Si(2nm)/WS ₂ (1L)	64.1231	4.9248×10^{-8}	6.2818	3.140923×10^6
Au(41nm)/Si(2nm)	62.5265	0.0077	0.0199	9.928260×10^3
Au (50nm)	58.8499	0.0458	0.0091	4.543305×10^3