Article

Sensitivity Enhanced Plasmonic Biosensor Using Bi$_2$Se$_3$-Graphene Heterostructures: A Theoretical Analysis

Fusheng Du$^{1,2}$, Kai Zheng$^{3,4}$, Shuwen Zeng$^5$ and Yufeng Yuan$^{1,3,\ast}$

$^1$ School of Electronic Engineering and Intelligentization, Dongguan University of Technology, Dongguan 523808, China
$^2$ School of Information and Optoelectronic Science and Engineering, South China Normal University, Guangzhou 510631, China
$^3$ Shenzhen Key Laboratory of Photonics and Biophotonics, Key Laboratory of Optoelectronic Devices and Systems of Ministry of Education and Guangdong Province, College of Physics and Optoelectronic Engineering, Shenzhen University, Shenzhen 518080, China
$^4$ School of Civil Aviation, Northwestern Polytechnical University, Xi'an 710072, China
$^5$ Light, Nanomaterials & Nanotechnologies (L2n), CNRS-ERL 7004, Université de Technologie de Troyes, 10000 Troyes, France

* Correspondence: yufengyuan@dgut.edu.cn

Abstract: This study provided a theoretical insight for designing novel plasmonic biosensors using bismuth selenide (Bi$_2$Se$_3$)-Graphene heterostructures. It was a van der Waals (vdWs) stacked configuration composed of gold (Au) film, few quintuple layer (QL) Bi$_2$Se$_3$ and few-layered graphene. In particular, the proposed biosensor was created by Goos-Hänchen (GH) shift rather than phase, resulting in a more sensitive biosensing response. Under the excitation of 632.8 nm, significant sensitivity enhancement performance was obtained via varying the thickness of Bi$_2$Se$_3$-Graphene heterostructures. The best configuration was 32 nm Au film $-$2-QL Bi$_2$Se$_3$-3-layer graphene, generating the largest GH shift, as high as $-1.0202 \times 10^4 \mu$m. Moreover, the highest detection sensitivity was determined to be $8.5017 \times 10^6 \mu$m/RIU, responding to a tiny refractive index (RI) change of 0.0012 RIU (RIU, refractive index unit). More importantly, our proposed biosensor has shown a theoretical feasibility of monitoring virus samples. For example, there was an efficient linear detection range for severe acute respiratory syndrome coronavirus 2 (SARS-CoV$-2$, 0$-$13.44 nanomole (nM)) and its Spike (S) glycoprotein (0$-$59.74 nM), respectively. It is expected that our proposed plasmonic biosensor has a potential application in performing sensitive detection of SARS-CoV$-2$.

Keywords: plasmonic biosensor; Bi$_2$Se$_3$-Graphene heterostructures; differential GH shift; ultrasensitive biosensing

1. Introduction

Surface plasmon resonance (SPR) biosensors are a class of important optoelectronic devices widely employed in the biomedicine science field. To date, significant breakthroughs in plasmonic biosensing are focused on the following two studies: (i) novel plasmonic materials and (ii) optimization of biosensing process [1]. For plasmonic materials, the common plasmonic substrates are metallic conductor films, such as gold, silver and aluminum. To obtain biosensing performance, four signal-modulation methods, including angle-, amplitude-, wavelength- and phase-modulation, are widely employed [2]. However, it is unfeasible to achieve noteworthy development using standard biosensing procedure. Conversely, adopting novel plasmonic materials could provide extraordinary exploration. For example, graphene, a well-known member of two-dimensional (2D) materials family, firstly paved a way to design novel SPR biosensing devices using 2D vdWs material [3]. Afterwards, other 2D layered semiconductor materials, such as transitional metal dichalcogenides (TMDCs), [4,5] phosphorene [6,7], antimonene [8] and tellurene [9], have been...
considered as promising plasmonic materials for creating novel plasmonic biosensors. It is generally accepted that common solid plasmonic materials can be categorized into three classes: conductor, semiconductor and insulator. In the 2D material family, graphene is an excellent conductor at room temperature. Both TMDCs and phosphorene are classical representatives of semiconductor materials. Hexagonal boron nitride (h-BN), known as white graphene, belongs to insulators. However, topological insulators (TIs) do not belong to any of the above classes. Recently, TIs are a new class of promising electronic materials, which have fascinating helical metal surface states and bulk-insulating bandgaps [10]. Interestingly, the metallic surface states cause electrons to accumulate and transfer at the surface. Under the illumination of incident photons, regular electron transfer can form surface plasmon polaritons (SPPs) wave, and SPR effect can be efficiently excited by optimal wave vector matching condition. Owing to their exotic electronic features, TIs have shown great potential for next-generation photonic biosensors. It is worth noting that, due to strong spin-orbit coupling, the surface electrons in TIs can obey a massless Dirac equation, forming a Dirac cone system, which was observed in only graphene atomic monolayer [11]. Then, Dirac charge carriers could form a current and freely move parallel to the topological surface [12]. In early 2013, Dirac plasmons was successfully observed [13]. Unlike noble metal and semiconductor thin films, Bi$_2$Se$_3$ film has unusual Dirac plasmons. Thus, Bi$_2$Se$_3$ film shows an enhanced sensitivity for RI variation [14]. In addition, TIs films usually have a broad photon absorption [15]. It is possible that the broad plasmon modes are able to interact with other phonon modes, producing typical Fano-resonance narrow lines. Therefore, TIs are promising candidates to explore exotic plasmonic biosensors.

It is well-known that TIs family has several prototypical members, which can be described as M$_2$X$_3$. Here, M stands for the element Bi or Sb, and X denotes the element Te or Se. Bi$_2$Se$_3$ is the most common 2D topological insulator material, whose crystal lattice consists of quintuple layers (QL) orderly arranged by a Se–Bi–Se–Bi–Se unit [16,17]. In addition, the QLs can be stacked on each other through weak vdWs interaction. Moreover, Bi$_2$Se$_3$ has shown many unique features, such as a large bandgap of ~0.3 eV [18], well-defined Dirac plasmons [10], high photothermal-conversion ability [19,20] and electrochemical catalytic capacity [21]. It is possible that, stacking novel vdWs heterostructures using various 2D materials can produce unprecedented physical and electric features. More recently, topological insulator/graphene heterostructures are proposed to be an efficient solution to significantly enhance the photon response and carrier mobility. For example, Chae et al. reported that by introducing 10-layer graphene, 10 QL Bi$_2$Se$_3$ films exhibited the maximum photon response [22]. At room temperature, the carrier mobility of Bi$_2$Se$_3$ films with a thickness less than 22 nm is 50–200 cm$^2$V$^{-1}$s$^{-1}$ [23]. However, the carrier mobility could be significantly increased by integrating with graphene. At a low temperature, the carrier mobility of 400 nm Bi$_2$Se$_3$/Graphene heterostructures was observed as high as 5000–6000 cm$^2$V$^{-1}$s$^{-1}$ [24,25]. Moreover, the carrier mobility in Bi$_2$Se$_3$/graphene heterostructures at room temperature can be optimized to be 3400 cm$^2$V$^{-1}$s$^{-1}$ [23]. To the best of our knowledge, there were few observations on creating plasmonic biosensors using topological insulator materials.

Inspired by these observations, we theoretically proposed a novel plasmonic biosensor using vdWs Bi$_2$Se$_3$-Graphene heterostructures to linearly detect SARS-CoV–2 and its S glycoprotein. Rather than phase-modulation, our proposed SPR biosensor was designed by GH shift, showing a higher biosensing performance. Both photon absorption and energy dissipation were optimized to be a balance state by varying thickness of Bi$_2$Se$_3$/Graphene heterostructures. The optimal configuration: 32 nm Au film—2-QL Bi$_2$Se$_3$–3-layer graphene could provide the largest GH shift up to $-1.0202 \times 10^4$ μm. For a tiny RI variation of 0.0012 RIU, the highest detection sensitivity of $8.5017 \times 10^6$ μm/RIU can be achieved. Moreover, the proposed biosensor could be employed to simulate the adsorption behavior of SARS-CoV–2 and its S glycoprotein. A good linear response interval for monitoring SARS-CoV–2 was from 0 to 13.44 nM. For S glycoprotein, a theoretical linear detection interval was
from 0 to 59.74 nM. In all, the optimal biosensor is a potential candidate in quantitatively monitoring SARS-CoV−2 and other infectious viruses in practical clinical applications.

2. Methodology

The theoretically proposed SPR biosensor consists of an SF11 prism, an Au thin film, few layered Bi$_2$Se$_3$ interlayer and graphene overlayer, as shown in Figure 1. Firstly, the plasmonic gold film was efficiently integrated with a SF11 prism. It is worth noting that plasmonic metal materials usually suffer from strong energy dissipation because of inter-band electronic transitions [26]. To further enhance detection sensitivity, it is necessary to supplement low-loss plasmonic materials onto gold film. Considering the vdWs stacked Bi$_2$Se$_3$/Graphene heterostructures having high carrier mobility, it was introduced to work as an important plasmonic layer, significantly developing the energy dissipation. Then, Bi$_2$Se$_3$ interlayer was vdWs stacked onto the top of plasmonic gold film. After this, few layered graphene overlayer was further stacked onto Bi$_2$Se$_3$ interlayer to form Bi$_2$Se$_3$/Graphene heterostructures. The topmost layer was a sealed cell containing work solutions. It is worth noting that the work solutions consisting of 10 mM HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid) and 120 mM NaCl (sodium chloride) was utilized to contain SARS-CoV−2 and its S glycoprotein in this simulation. To really calculate the binding interaction between SARS-CoV−2 and sensing interface of Bi$_2$Se$_3$/Graphene heterostructures, the work buffer consisting of 10 mM HEPES and 120 mM NaCl solutions was injected from left entrance. Once the target analytes in running buffer were bound to the sensing interface, the change in local RI would be different. Generally, the tiny variation in RI could be readout by measuring the change in intensity of reflected light, SPR angle and differential phase. In this work, p-polarized incident light having a wavelength at 632.8 nm was applied to resonate with SPPs wave in Au film/Bi$_2$Se$_3$/Graphene heterostructures. Unlike previous SPR biosensors created by phase modulation, our proposed biosensor was designed by measuring GH shift. It is well-known that GH shift is an interesting displacement behavior of reflected light relative to geometric reflection theory, because practical incident lights generated by lasers are not ideal monochromatic electromagnetic plane waves [27]. Moreover, GH shift can be explained by stationary phase theory [28], indicating that GH shift was highly related with phase transition of reflected light. Specifically, the GH shift can be obtained by calculating the first derivative of reflected light versus incident angle (Equation (12)). However, the actual GH shifts generated by low RI dielectric interface were only 5~10 µm [29,30], which was difficult for experimental measurement. Fortunately, GH shifts could be hugely enhanced using SPR technology [31,32]. Under the strongest SPR excitation, phase of reflected light usually experiences a steep jump and GH shift is the first-order derivative of phase. Then, GH shift was supposed to be more sensitive than phase transition under the strongest SPR effects. Therefore, GH shift could work as an important indicator for evaluating biosensing performance for our proposed biosensor. However, compared with other measurement models, including angle-, amplitude-, wavelength- and phase-modulation, large GH shifts usually suffer from a narrow interval for tuning incident angle.

Both photon absorption and energy dissipation in our proposed configuration highly depend on optical dielectric constant of each layer. Prior to biosensing simulation, the dielectric constant of each layer needs to be determined. Under the excitation light of 632.8 nm, the refractive indices of SF11 prism layer, Au film layer, Bi$_2$Se$_3$ nanosheets and graphene overlayer is 1.7786 [33], 0.1838 + 3.4313i [7], 4.2923 + 1.7922i [34] and 3.000 + 1.1487i [7], respectively. In addition, the thickness of 1-QL Bi$_2$Se$_3$ and monolayer graphene is 0.9725 nm [34] and 0.34 nm [35], respectively. Finally, the refractive index of running buffer containing 10 mM HEPES and 120 mM NaCl solution can be calculated by Equation (1):

\[
y = 0.00004x + 1.3341
\]

where y stands for the calculated RI of running buffer and x is the concentration of HEPES solution (mM). In this simulation, 10 mM HEPES solution was added into 120 mM NaCl
solution and the refractive index of the running buffer \(n_C\) can be determined to be 1.3345 [9]. When S glycoproteins based on SARS-CoV-2 was captured antibody sites on graphene layer, the refractive index of sensing interface based on Bi\(_2\)Se\(_3\)/Graphene configuration was assumed to be proportional to the concentration of S glycoprotein, which can be calculated by Equation (2):

\[
n_A - n_C = (dn/dc)c_A
\]

where \(n_A\) is the RI due to the adsorption interaction of S glycoprotein and \(n_C\) is the RI of running buffer. \(c_A\) is the concentration of S glycoprotein solution. In addition, the parameter \((dn/dc)\) denotes the increment of refractive index and the value of \(dn/dc\) is usually ~0.186 cm\(^3\) g\(^{-1}\) for studying protein-protein binding interactions [36]. For a fixed RI variation in sensing interface, the concentration \((c_A)\) of S glycoproteins can be calculated according to the binding parameter \((dn/dc)\).

![Figure 1. Schematic diagram of TI-enhanced plasmonic biosensor.](image)

In addition to SPR reflectivity, change in incident angle and differential phase, change in GH shift generated by plasmonic enhancement in our proposed SPR configuration was systematically simulated using transfer matrix method (TMM) and Fresnel equations in a N-layer stacked model. Theoretically, each layer was supposed to parallel in Z-direction and each layer was considered to be isotropic and non-magnetic. It was assumed that the number of antibody sites on graphene layers was much more than that of S protein. The adsorption sites on graphene overlayer were S protein antibody, which can be employed for specifically capture SARS-CoV-2 using antibody-antigen interactions. Generally, the electromagnetic fields at the first boundary along the tangential direction was supposed to be \(Z_1 = 0\), and the relationship between the last boundary \(ZN - 1\) and first boundary \(Z1\) could be given as:

\[
\begin{bmatrix}
U_1 \\
V_1
\end{bmatrix}
= M
\begin{bmatrix}
U_{N-1} \\
V_{N-1}
\end{bmatrix}
\]

where \(U\) and \(V\) denote the tangential components of electric fields and magnetic field at the boundary, respectively.

Here, \(M\) is a transfer matrix, which can be obtained by the following equation for p-polarized light:

\[
M = \prod_{k=2}^{N-1} M_k = \begin{bmatrix}
M_{11} & M_{12} \\
M_{21} & M_{22}
\end{bmatrix}
\]
where $M_k$ could be described as:

$$M_k = \begin{bmatrix} \cos \beta_k & ( -i \sin \beta_k)/q_k \\ -i q_k \sin \beta_k & \cos \beta_k \end{bmatrix}$$  \hspace{1cm} (5)$$

where $\beta_k$ and $q_k$ can be determined using the following two Equations (6) and (7):

$$\beta_k = \frac{2\pi d_k}{\lambda} \left( \epsilon_k - n_1^2 \sin^2 \theta_1 \right)^{1/2}$$  \hspace{1cm} (6)$$

$$q_k = \frac{\left( \epsilon_k - n_1^2 \sin^2 \theta_1 \right)^{1/2} \epsilon_k}{\epsilon_k}$$  \hspace{1cm} (7)$$

where $k$ is the $k$-th stacking layer and $d_k$ stands for the thickness of the $k$-th layer. Additionally, $\epsilon_k$ represents the dielectric constant of the $k$-th layer. In Equation (7), $\theta_1$ and $n_1$ are the incident angle and RI of the first stacking layer, respectively.

For s-polarized light, these relationships described above are still practicable. However, $q_k$ was described by Equation (8):

$$q_k = \left( \epsilon_k - n_1^2 \sin^2 \theta_1 \right)^{1/2}$$  \hspace{1cm} (8)$$

Prior to calculating GH shift, the reflectivity ($R_p$) in our proposed configuration can be obtained using Equation (9):

$$R_p = r_p^2 = \left| \frac{(M_{11} + M_{12}q_N)q_1 - (M_{21} + M_{22}q_N)q_1}{(M_{11} + M_{12}q_N)q_1 + (M_{21} + M_{22}q_N)q_1} \right|^2$$  \hspace{1cm} (9)$$

Next, the p-polarized of reflected light phase $\varphi_p$ can be calculated by the following equation:

$$\varphi_p = \arg(r_p)$$  \hspace{1cm} (10)$$

Therefore, the differential phase $\Delta \varphi_d$ can be calculated by Equation (11):

$$\Delta \varphi_d = |\varphi_p - \varphi_s|$$  \hspace{1cm} (11)$$

where $\varphi_s$ stands for the phase of s-polarized light.

According to the stationary phase theory, the GH shift ($GHS$) can be calculated by Equation (12):

$$GHS = -\frac{\lambda}{2\pi} \frac{d \varphi}{d \theta}$$  \hspace{1cm} (12)$$

For p-polarized light, the GH shifts produced by metal films are negative. However, the GH shift excited by s-polarized light in metal films are usually positive [37]. Moreover, the value of GH shift from p-polarized light is much larger than s-polarized light. Similar to the differential phase, the differential GH shift ($\Delta GHS_d$) between p- and s-polarized light can be calculated as follows:

$$\Delta GHS_d = |GHS_p - GHS_s|$$  \hspace{1cm} (13)$$

To evaluate the biosensing performance of our proposed configuration, two parameters, such as phase sensitivity ($S_\varphi$) and GH shift sensitivity ($S_{GHS}$), were introduced. Both of them can be determined as follows:

$$S_\varphi = \frac{\Delta \varphi_d}{\Delta n_{bio}}$$  \hspace{1cm} (14)$$

$$S_{GHS} = \frac{\Delta GHS_d}{\Delta n_{bio}}$$  \hspace{1cm} (15)$$
where \( \Delta n_{\text{bio}} \) denotes a tiny variation of RI in sensing interface of Bi\(_2\)Se\(_3\)/graphene heterostructures due to strong adsorption binding interaction.

### 3. Results and Discussion

Under the illumination of 632.8 nm, the optimal reflectivity, phase and GH shift was obtained, as shown in Figure 2. It can be found that when the incident angle is located at 58.0864°, the stacked configuration: 32 nm Au film – 2-QL Bi\(_2\)Se\(_3\)–3-layer graphene can produce an ultralow reflectivity (purple curve, Figure 2) of \( 5.4402 \times 10^{-9} \), approaching zero. It indicates that almost 100% of photons were absorbed and converted into SPR energy. Meanwhile, the phase produces a sharp transition at the same incident angle (blue curve, Figure 2), perfectly corresponding to the minimum SPR reflectivity. More importantly, the GH shift showed a sharper transition strength than phase at the point of SPR angle. There was a significant enhanced negative GH shift (orange curve, Figure 2) in Au film/Bi\(_2\)Se\(_3\)/graphene heterostructures as high as \(-1.0202 \times 10^{4} \) µm. These observations suggest that a large GH shift is a useful indicator for evaluating biosensing performance.

To further verify sensitivity enhancement ability of our proposed configuration, the GH shift as well as reflectivity, incident angle and phase, were systematically examined by tuning the stacking thickness of Bi\(_2\)Se\(_3\)/Graphene heterostructures (Bi\(_2\)Se\(_3\), 0–5 layers; graphene, 0–5 layers), as shown in Figure 3. In the absence of Bi\(_2\)Se\(_3\)/graphene heterostructures, the plasmonic Au film (32 nm) has a reflectivity of 0.2786 under the illumination of 632.8 nm (black dotted curve, Figure 3a). It means that, single Au film suffers from large energy dissipation. However, the dilemma can be significantly improved by introducing low-loss Bi\(_2\)Se\(_3\)/Graphene heterostructures. When 2-QLs Bi\(_2\)Se\(_3\) film was stacked onto 32 nm Au film, the reflectivity of Au film-Bi\(_2\)Se\(_3\) heterostructures could be decreased to 0.0065 (blue curve, Figure 3a). Moreover, as 3-layer graphene was stacked, the SPR reflectivity (blue curve, Figure 3d) of gold film/Bi\(_2\)Se\(_3\)/graphene heterostructures could be lowered to \( 5.4402 \times 10^{-9} \). In addition, there were obvious red-shifts in incident angle, due to the addition of Bi\(_2\)Se\(_3\)/Graphene heterostructures. Interestingly, the obtained reflectivity of \( 5.4402 \times 10^{-9} \) corresponds to the optimal incident angle at 58.0864°. Meanwhile, phase from reflected light also experienced a Heaviside step-like transition, as shown in Figure 3b–e. Moreover, it showed the steepest phase singularity as the plasmonic configuration biosensor was stacked as 32 nm Au film – 2-QL Bi\(_2\)Se\(_3\)-3-layer graphene. At the phase

![Figure 2](image-url)
singularity, the GH shift can be obtained by calculating the derivative of phase with respect to incident angle. It can be found that the largest GH shift of $-1.0202 \times 10^4$ μm is generated by 32 nm Au film-2-QL Bi$_2$Se$_3$-3-layer graphene, as shown in Figure 3f. Interestingly, with increasing graphene layers, the value of GH shift changes from positive to negative, which is synchronized with phase transition. Figure 3f showed that as the number of Bi$_2$Se$_3$ QLs is from 0 to 5, the obtained GH shift is 5.4312, 7.3689, $-1.0202 \times 10^4$, $-3.9267$, $-1.5591$ and $-0.8831$ μm, respectively. However, Figure 3f also showed that a tunable interval of incident angle for obtaining multiple large differential GH shift is narrow. The reason is that, at the dip of minimum SPR reflectivity, both phase and GH shift of reflected light usually experience significant transition behavior. Moreover, GH shift was obtained by derivating phase with respect to incident angle (Equation (12)). Thus, the GH shift shows a sharper transition strength than phase. The narrow interval of incident angle seems that it will be difficult for performing practical measurement. According to phase-modulation theory, once an optimal incident angle is fixed, both largest differential phase and GH shift will be determined. To perform practical GH measurements, it needs to fix at an optimal incident angle rather than vary incident angle.

Figure 3. Variation in reflectivity (a), phase (b) and GH shift (c) with respect to angle of incidence by varying the number of Bi$_2$Se$_3$ QLs (0–5 layers). The graphene is fixed to be 2 QLs. The Au thin film thickness is 32 nm and the wavelength of incident light is 632.8 nm. Variation in reflectivity (d), phase (e) and GH shift (f) with respect to angle of incidence by varying the number of graphene overlayer (0–5 layers). The number of Bi$_2$Se$_3$ QLs is fixed to be 2. Au thin film thickness is 32 nm and the wavelength of incident light is 632.8 nm. Abbreviation: BS in inset stands for Bi$_2$Se$_3$.

To study the biosensing ability of our proposed biosensor, both differential phase ($\Delta\phi_d$) and GH shift ($\Delta GHS_d$) response for a defined RIU variation ($\Delta n_{bio} = 0.0012$) were plotted, as shown in Figure 4a,b. The largest differential phase (green curve, Figure 4a) is 84.3891°, generated from the configuration of 32 nm Au film/2QL-Bi$_2$Se$_3$/3-layer graphene. Figure 4b showed the change in differential GH shift ($\Delta GHS_d$) by changing the number of Bi$_2$Se$_3$ and graphene layers. The configuration of 32 nm Au film-Bi$_2$Se$_3$ (2 QL)-graphene (3 layer) provides the highest differential GH shift of $1.0202 \times 10^4$ μm (green curve), which is almost 324 times larger than the second highest differential GH shift of 31.466 μm (blue curve) generated by the configuration of 32 nm Au film/2-QL Bi$_2$Se$_3$/2-layer graphene. When the number of BiSe3 QLs is 2, the phase detection sensitivity obtained by varying the number of graphene overlayer are almost on the same order of magnitude of $10^{10}$°/RIU, as
shown in Figure 4c. However, the difference in differential phase can be hugely amplified by further calculating derivative of phase. Thus, the obtained GH shift detection sensitivity shows a larger difference than phase detection sensitivity, as shown in Figure 4d. Thus, the change in GH shift was more significant compared to phase modulation.

![Graphs](image)

**Figure 4.** Change in differential phase (a) and GH shift (b) obtained by tuning the number of Bi$_2$Se$_3$ QLs (0–5) and graphene layers (0–5) for a defined RI variation of 0.0012 RIU. Obtained phase (c) and GH shift (d) detection sensitivity obtained by changing the number of Bi$_2$Se$_3$ QLs (0–5) and graphene layers (0–5).

In addition, we also studied the changes in incident angle (Δθ$_{SPR}$) for a defined RIU variation (Δn$_{bio}$ = 0.0012), as shown in Figure S1. There was only a response of 0.0126° for red-shift in SPR angle. However, such tiny red-shifts in SPR angle cannot be distinguished by an optical detector. Conversely, both differential phase and GH shift can be employed to monitor the RI variation of sensing interface. Afterwards, the obtained largest phase sensitivity was 7.0324 × 10^4 degree/RIU, as shown in Figure 4c. In contrast, Figure 4d showed the largest GH shift sensitivity could reach the value of 8.5017 × 10^4 μm/RIU. It is generally agreed that such a large GH shift can be easily detected by common optical devices. Compared with other reported GH shift-based plasmonic configurations (Table 1), our proposed biosensor exhibited higher detection sensitivity. In addition, considering that few-layered Bi$_2$Se$_3$ nanosheets have the advantages of simple fabrication and low cost [38], our proposed biosensor will be inexpensive and easily fabricated.
Table 1. Comparison of GH shift-based SPR sensors under the excitation of 632.8 nm.

| 2D Material Configuration | Sensitivity (µm/RIU) | Change in RI | Ref.       |
|---------------------------|----------------------|--------------|------------|
| Au/ITO/MoSe$_2$/graphene  | 5.075 × 10$^5$       | 0.002        | [32]       |
| Au/MoSe$_2$/graphene      | 3.509 × 10$^5$       | 0.002        | [31]       |
| Au/graphene/PtSe$_2$       | 1.37 × 10$^5$        | 0.005        | [39]       |
| Au/Bi$_2$Se$_3$/graphene  | 8.5017 × 10$^6$      | 0.0012       | Current work |

Next, the detailed changes in differential GH shift for the RI from 1.3345 to 1.3357 RIU by tuning the number of Bi$_2$Se$_3$ QLs (0–5) and graphene overlayers (0–5) were studied, as shown in Figure 5. When the number of Bi$_2$Se$_3$ layers was less than 2, there was a good linear response for change in differential GH shift by changing the RI of sensing interface. Obviously, the obtained GH shift was relative weak, indicating that there was no significant SPR enhancement effects, as shown in Figure 5a,b. However, when the number of Bi$_2$Se$_3$ layers is 2, the addition of 3-layer graphene can precipitously produce an ultrasensitive response, as shown in Figure 5c. When the number of Bi$_2$Se$_3$ layers was larger than 2, the addition of graphene overlayer could not provide a positive response because of excessive energy loss. It can be concluded that the configuration of 32 nm Au film coated with two-QL Bi$_2$Se$_3$ and three-layer graphene has the strongest GH shift response, showing great promise for performing ultrasensitive biosensing for a tiny RI variation.

To quantitatively monitor the concentrations of target analytes, it is necessary to determine a linear response interval for our optimal plasmonic configuration: 32 nm Au film–2-QL Bi$_2$Se$_3$-3-layer graphene. Figure S2 showed a linear response of GH shift for a tiny RI variation as small as 10$^{-6}$ RIU. In contrast to 32 nm Au thin film, 3-layer graphene coated on 32 nm Au film, the optimal configuration: 32 nm Au film–2-QL Bi$_2$Se$_3$-3-layer graphene can provide an enhancement factor (EF) of 2 × 10$^5$. It was assumed that significantly local field intensity enhancement should contribute to obtain such a high EF. It is well-known that typical nanoscale heterogeneous configurations, such as C-shaped [40], Φ-shaped [41], bowtie-shaped [42] and ring-shaped [43] nanostructures, have shown significant field enhancement. To verify the proposal for producing such a high EF, the electric field distribution of 32 nm Au film–2-QL Bi$_2$Se$_3$-3-layer graphene was further simulated via finite element analysis method, as shown in Figure 6a,b. It clearly showed that, under the illumination of 632.8 nm, there was a significantly enhanced electric field close to the Bi$_2$Se$_3$/graphene sensing interface. Moreover, the electric field intensity decayed exponentially into a running buffer, resulting in a penetration depth of 150 nm. In addition, the charge-transfer mechanism generated by difference in work function (Fermi level) was proposed to contribute to giant electric field enhancement. It has been reported that the work function of Au film is ~5.54 eV and the work function of 2-QL Bi$_2$Se$_3$-3-layer graphene has an excellent response interval (0–13.44 nm) for quantitatively monitoring SARS-CoV concentration of S protein solution. More importantly, our proposed biosensor also exhibited an excellent response interval (0–13.44 nm) for quantitatively monitoring SARS-CoV–2. The linear response can be expressed by such an equation $\Delta GHS_d = 30.1047 * c_{protein}$. Here, $c_{protein}$ denotes the concentration of S protein solution. More importantly, our proposed biosensor also exhibited an excellent response interval (0–13.44 nm) for quantitatively monitoring SARS-CoV–2. The linear response can be expressed by such an equation $\Delta GHS_d = 30.1047 * c_{protein}$.
proposed plasmonic biosensor has shown great feasibility in quantitatively monitoring SARS-CoV-2 and its S protein.

Figure 5. Change in differential GH shift with respect to change in RI of sensing interface by varying the number of graphene (0–5) and Bi$_2$Se$_3$ QLs: (a) 0 layer, (b) 1 layer, (c) 2 layers, (d) 3 layers, (e) 4 layers and (f) 5 layers. Abbreviation: BS in inset stands for Bi$_2$Se$_3$. 

To quantitatively monitor the concentrations of target analytes, it is necessary to determine a linear response interval for our optimal plasmonic configuration: 32 nm Au film−2-QL Bi$_2$Se$_3$-3-layer graphene. Figure S2 showed a linear response of GH shift for a tiny RI variation as small as 10$^{-6}$ RIU. In contrast to 32 nm Au thin film, 3-layer graphene coated on 32 nm Au film, the optimal configuration: 32 nm Au film−2-QL Bi$_2$Se$_3$-3-layer graphene can provide an enhancement factor (EF) of 2 × 10$^5$. It was assumed that significantly local field intensity enhancement should contribute to obtain such a high EF. It is well-known that typical nanoscale heterogeneous configurations, such as C-shaped [40], Φ-shaped [41], bowtie-shaped [42] and ring-shaped [43] nanostructures, have shown significant field enhancement. To verify the proposal for producing such a high EF, the electric field distribution of 32 nm Au film−2-QL Bi$_2$Se$_3$-3-layer graphene was further simulated via finite element analysis method, as shown in Figure 6a,b. It clearly showed that, under the illumination of 632.8 nm, there was a significantly enhanced electric field close to the Bi$_2$Se$_3$/graphene sensing interface. Moreover, the electric field intensity decayed...
Y.Y. conceived this project and designed this study. F.D. performed the
biosensing performance of our proposed configuration was designed by GH shift,
potential application in biosensing, our proposed biosensor was employed to theoreti-
cal model, the change in differential GH shift obtained by optimal configuration: 32 nm Au thin
film/2-QL Bi2Se3/3-layer graphene. Solid curve stands for extracted linear response interval, and dot-
curves demonstrate a linear fitting. Abbreviation: Au (42 nm)_Bi2Se3 (2 QL)_graphene (3L) in Figure 6a
denotes the optimal plasmonic configuration: 32 nm Au film–2-QL Bi2Se3-3-layer graphene.

4. Conclusions

In this work, we theoretically proposed a sensitivity enhanced SPR biosensor by
incorporating Bi2Se3/graphene heterostructures with conventional plasmonic Au film. The biosensing performance of our proposed configuration was designed by GH shift, superior to phase modulation. The energy loss could approach zero by introducing the Bi2Se3/graphene heterostructures. The best configuration employed to achieve the highest photon absorption is 32 nm Au film/2-QL Bi2Se3/3-layer graphene, producing an ultralow (approaching zero) reflectivity of 5.4402 × 10⁻⁹ and a highest GH shift of −1.0202 × 10⁴ μm. Responding to a small RI variation in 0.0012 RIU, the proposed biosensor was able to provide an ultra-high sensitivity of 8.5017 × 10⁶ μm/RIU. To extend the potential application in biosensing, our proposed biosensor was employed to theoretically predict the adsorption response of SARS-CoV−2 in a tiny RI variation as low as 0.000002 RIU. For SARS-CoV−2, a linear relationship (0–13.44 nM) was determined by an equation \( \Delta GHS_d = 133.7987 \times c_{S\text{protein}} \). Here, \( c_{S\text{protein}} \) for its S protein, another linear relationship was described by an equation \( \Delta GHS_d = 30.1047 \times c_{S\text{protein}} \) and there was a linear detection interval (0–59.74 nM). In view of these observations, we concluded that, our optimal plasmonic biosensor shows great promise in quantitatively monitoring SARS-CoV−2 and other infectious viruses for practical applications.

Supplementary Materials: The supplementary materials are available online at https://www.mdpi.com/article/10.3390/nano1224078/s1. Supplementary figures: Figure S1: Change in resonance angle (a) and obtained angle sensitivity (b) by varying the number of Bi2Se3 QLs (0–5) and graphene (0–5) for a defined RI variation of 0.0012 RIU. Figure S2: Comparison of SPR sensing performances generated by 32 nm Au thin film, 3-layer graphene coated on 32 nm Au thin film and 32 nm Au film deposited with 2-QLs Bi2Se3 and 3-layer graphene for a tiny RI variation (as low as 10⁻⁶ RIU).

Author Contributions: Y.Y. conceived this project and designed this study. F.D. performed the simulation and drew the figures. K.Z., S.Z. and Y.Y. discussed the results. Y.Y. wrote and revised the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This work was partially supported by the National Natural Science Foundation of China (62075137/62005172), the Guangdong Basic and Applied Basic Research Foundation (2020A1515010377).
References

1. Zeng, S.; Baillargeat, D.; Ho, H.-P.; Yong, K.-T. Nanomaterials enhanced surface plasmon resonance for biological and chemical sensing applications. Chem. Soc. Rev. 2014, 43, 3426–3452. [CrossRef] [PubMed]

2. Zeng, Y.; Hu, R.; Wang, L.; Gu, D.; He, J.; Wu, S.-Y.; Ho, H.-P.; Li, X.; Qu, J.; Gao, B.Z.; et al. Recent advances in surface plasmon resonance imaging: Detection speed, sensitivity, and portability. Nanophotonics 2017, 6, 1017–1030. [CrossRef]

3. Wu, L.; Chu, H.S.; Koh, W.S.; Li, E.P. Highly sensitive graphene biosensors based on surface plasmon resonance. Opt. Express 2018, 18, 14395–14400. [CrossRef] [PubMed]

4. Ouyang, Q.; Zeng, S.; Jiang, L.; Qu, J.; Dinh, X.-Q.; Qian, J.; He, S.; Coquet, P.; Yong, K.-T. Two-Dimensional Transition Metal Dichalcogenide Enhanced Phase-Sensitive Plasmonic Biosensors: Theoretical Insight. J. Phys. Chem. C 2017, 121, 6282–6289. [CrossRef]

5. Zeng, S.; Hu, S.; Xia, J.; Anderson, T.; Dinh, X.-Q.; Meng, X.-M.; Coquet, P.; Yong, K.-T. Graphene–MoS2 hybrid nanostructures enhanced surface plasmon resonance biosensors. Sens. Actuators B Chem. 2015, 207, 801–810. [CrossRef]

6. Yuan, Y.; Yu, X.; Ouyang, Q.; Shao, Y.; Song, J.; Qu, J.; Yong, K.-T. Highly anisotropic black phosphorous-graphene hybrid architecture for ultrasensitive plasmonic biosensing: Theoretical insight. 2d Mater. 2018, 5, 025015. [CrossRef]

7. Li, K.; Li, L.; Xu, N.; Peng, X.; Zhou, Y.; Yuan, Y.; Song, J.; Qu, J. Ultrasensitive Surface Plasmon Resonance Biosensor Using Blue Phosphorus–Graphene Architecture. Sensors 2020, 20, 3326. [CrossRef]

8. Xue, T.; Liang, W.; Li, Y.; Sun, Y.; Xiang, Y.; Zhang, Y.; Dai, Z.; Duo, Y.; Wu, L.; Qi, K.; et al. Ultrasensitive detection of miRNA with an antimonene-based surface plasmon resonance biosensor. Nat. Commun. 2019, 10, 28. [CrossRef]

9. Peng, X.; Zhou, Y.; Nie, K.; Zhou, F.; Yuan, Y.; Song, J.; Qu, J. Promising near-infrared plasmonic biosensor employed for specific detection of SARS-CoV-2 and its spike glycoprotein. New J. Phys. 2020, 22, 103046. [CrossRef]

10. Zhang, H.; Liu, C.-X.; Qi, X.-L.; Dai, X.; Fang, Z.; Zhang, S.-C. Topological insulators in Bi2Se3, Bi2Te3 and Sb2Te3 with a single Dirac cone on the surface. Nat. Phys. 2009, 5, 438–442. [CrossRef]

11. Stauber, T. Plasmonics in Dirac systems: From graphene to topological insulators. J. Phys. Condens. Matter. 2014, 26, 123201. [CrossRef] [PubMed]

12. Yildiz, D.; Kisiel, M.; Gysin, U.; Gürli, O.; Meyer, E. Mechanical dissipation via image potential states on a topological insulator surface. Nat. Mater. 2019, 18, 1201–1206. [CrossRef] [PubMed]

13. Hasan, M.Z.; Kane, C.L. Colloquium: Topological insulators. Rev. Mod. Phys. 2010, 82, 3045–3067. [CrossRef]

14. Xie, H.; Li, Z.; Sun, Z.; Shao, J.; Yu, X.-F.; Guo, Z.; Wang, J.; Xiao, Q.; Wang, H.; Wang, Q.-Q.; et al. Photothermal Therapy: Metabolizable Ultrathin Bi2Se3 Nanosheets in Imaging-Guided Photothermal Therapy (Small 30/2016). Small 2016, 12, 4158. [CrossRef]

15. Liu, X.-D.; Chen, B.; Wang, G.-G.; Ma, S.; Cheng, L.; Liu, W.; Zhou, L.; Wang, Q.-Q. Controlled Growth of Hierarchical Bi2Se3/CdSe–Au Nanorods with Optimized Photothermal Conversion and Demonstrations in Photothermal Therapy. Adv. Funct. Mater. 2021, 31, 2104424. [CrossRef]

16. Yang, J.; Wang, C.; Ju, H.; Sun, Y.; Xing, S.; Zhu, J.; Yang, Q. Integrated Quasiplane Heteronostructures of MoSe2/Bi2Se3 Hexagonal Nanosheets: Synergetic Electrocatalytic Water Splitting and Enhanced Supercapacitor Performance. Adv. Funct. Mater. 2017, 27, 1703864. [CrossRef]

17. Chae, J.; Hong, S.-B.; Kim, D.; Kim, D.-K.; Kim, J.; Jeong, K.; Park, S.H.; Cho, M.-H. Enhancement of photoresponse in Bi2Se3/graphene heterostructures by effective electron–hole separation through internal band bending. Appl. Surf. Sci. 2021, 554, 149623. [CrossRef]

18. Antonova, I.V.; Nebogatikova, N.A.; Stepina, N.P.; Volodin, V.A.; Kirienko, V.V.; Rybin, M.G.; Obrazstova, E.D.; Golyashov, V.A.; Kokh, K.A.; Tereshchenko, O.E. Growth of Bi2Se3/graphene heterostructures with the room temperature high carrier mobility. J. Mater. Sci. 2021, 56, 9330–9343. [CrossRef]
24. Kim, N.; Lee, P.; Kim, Y.; Kim, J.S.; Kim, Y.; Noh, D.Y.; Yu, S.U.; Chung, J.; Kim, K.S. Persistent Topological Surface State at the Interface of Bi2Se3 Film Grown on Patterned Graphene. *ACS Nano* 2014, 8, 1154–1160. [CrossRef]

25. Bianchi, M.; Guan, D.; Bao, S.; Mi, J.; Iversen, B.B.; King, P.D.C.; Hofmann, P. Coexistence of the topological state and a two-dimensional electron gas on the surface of Bi2Se3. *Nat. Commun.* 2010, 1, 128. [CrossRef]

26. West, P.R.; Ishii, S.; Naik, G.V.; Emani, N.K.; Shalaev, V.M.; Boltasseva, A. Searching for better plasmonic materials. *Laser Photonics Rev.* 2010, 4, 795–808. [CrossRef]

27. Goos, F.; Hänchen, H. Ein neuer und fundamentaler Versuch zur Totalreflexion. *Ann. Phys.* 1947, 436, 333–346. [CrossRef]

28. Artmann, K. Berechnung der Seitenversetzung des totalreflektierten Strahles. *Ann. Phys.* 1948, 437, 87–102. [CrossRef]

29. Snyder, A.W.; Love, J.D. Goos-Hänchen shift. *Appl. Opt.* 1976, 15, 236–238. [CrossRef]

30. Renard, R.H. Total Reflection: A New Evaluation of the Goos–Hänchen Shift. *J. Opt. Soc. Am.* 1964, 54, 1190–1197. [CrossRef]

31. You, Q.; Shan, Y.; Gan, S.; Zhao, Y.; Dai, X.; Xiang, Y. Giant and controllable Goos-Hänchen shifts based on surface plasmon resonance with graphene-MoS2 heterostructure. *Opt. Mater. Express* 2018, 8, 3036–3048. [CrossRef]

32. Han, L.; Pan, J.; Wu, C.; Li, K.; Ding, H.; Ji, Q.; Yang, M.; Wang, J.; Zhang, H.; Huang, T. Giant Goos-Hänchen Shifts in Au-ITO-TMDCs-Graphene Heterostructure and Its Potential for High Performance Sensor. *Sensors* 2020, 20, 1028. [CrossRef] [PubMed]

33. Li, Y.; Yuan, Y.; Peng, X.; Song, J.; Liu, J.; Qu, J. An ultrasensitive Fano resonance biosensor using two dimensional hexagonal boron nitride nanosheets: Theoretical analysis. *RSC Adv.* 2019, 9, 29805–29812. [CrossRef]

34. Fang, M.; Wang, Z.; Gu, H.; Tong, M.; Song, B.; Xie, X.; Zhou, T.; Chen, X.; Jiang, H.; Jiang, T.; et al. Layer-dependent dielectric permittivity of topological insulator Bi2Se3 thin films. *Appl. Surf. Sci.* 2020, 509, 144822. [CrossRef]

35. Zeng, S.; Yu, X.; Law, W.-C.; Zhang, Y.; Hu, R.; Dinh, X.-Q.; Ho, H.-P.; Yong, K.-T. Size dependence of Au NP-enhanced surface plasmon resonance based on differential phase measurement. *Sens. Actuators B Chem.* 2013, 176, 1128–1133. [CrossRef]

36. Ball, V.; Ramsden, J.J. Buffer dependence of refractive index increments of protein solutions. *Biopolymers* 1998, 46, 489–492. [CrossRef]

37. Merano, M.; Aiello, A.; ’t Hooft, G.W.; van Exter, M.P.; Eliel, E.R.; Woerdman, J.P. Observation of Goos-Hänchen shifts in metallic reflection. *Opt. Express* 2007, 15, 15928–15934. [CrossRef] [PubMed]

38. Zhu, J.; Ke, Y.; Dai, J.; You, Q.; Wu, L.; Li, J.; Guo, J.; Xiang, Y.; Dai, X. Topological insulator overlayer to enhance the sensitivity and detection limit of surface plasmon resonance sensor. *Nanophotonics* 2020, 9, 1941–1951. [CrossRef]

39. Guo, Y.; Singh, N.M.; Das, C.M.; Ouyang, Q.; Kang, L.; Li, K.; Coquet, P.; Yong, K.-T. Two-dimensional PtSe2 Theoretically Enhanced Goos-Hänchen Shift Sensitive Plasmonic Biosensors. *Plasmonics* 2020, 15, 1815–1826. [CrossRef]

40. Zaman, M.A.; Padhy, P.; Hesselink, L. Near-field optical trapping in a non-conservative force field. *Sci. Rep.* 2019, 9, 649. [CrossRef]

41. Padhy, P.; Zaman, M.A.; Hansen, P.; Hesselink, L. On the substrate contribution to the back action trapping of plasmonic nanoparticles on resonant near-field traps in plasmonic films. *Opt. Express* 2017, 25, 26198–26214. [CrossRef] [PubMed]

42. Cui, W.; Li, L.; He, Z.; He, H.; He, X.; Xia, B.; Zhong, Z.; Song, C.; Li, L.; Xue, W.; et al. Enhanced plasmonic field and focusing for ring-shaped nanostructures via radial vector beam. *Results Phys.* 2021, 26, 104412. [CrossRef]

43. Tahir ul Qamar, M.; Alqahtani, S.M.; Alamri, M.A.; Chen, L.-L. Structural basis of SARS-CoV-2 3CLpro and anti-COVID-19 drug discovery from medicinal plants. *J. Pharm. Anal.* 2020, 10, 313–319. [CrossRef] [PubMed]

44. Ou, X.; Liu, Y.; Lei, X.; Li, P.; Mi, D.; Ren, L.; Guo, L.; Guo, R.; Chen, T.; Hu, J.; et al. Characterization of spike glycoprotein of SARS-CoV-2 on virus entry and its immune cross-reactivity with SARS-CoV. *Nat. Commun.* 2020, 11, 1620. [CrossRef] [PubMed]