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Phase-driven progress in nanophotonic biosensing

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Abstract

In the continuous pursuit of enhancing the sensitivity of nanophotonic biosensors by leveraging phase phenomena, a recent development involved the engineering of an atomically thin $\text{Ge}_2\text{Sb}_2\text{Te}_5$ layer on a silver nanofilm to generate large Goos–Hänchen-shifts associated with phase singularities. The resulting detection limit reached $\sim 7 \times 10^{-7}$ RIU.

Early developments in nanophotonic biosensing focused on exploiting the unique optical properties of nanomaterials, such as plasmonic nanoparticles and photonic crystals¹, to enable label-free and real-time monitoring of biological interactions. Leveraging phenomena like surface plasmon resonances and whispering gallery modes to detect minute changes in refractive index now allows the detection of biomolecular interactions at the single-molecule level with implications for clinical diagnostics. Recent technical advances² include the integration of metamaterials and advancements in fabrication techniques, like nanoimprint lithography, which have enabled the development of low-cost, compact and portable biosensing devices.

Simultaneously, there is an ongoing quest to further enhance the sensitivity of nanophotonic biosensors, especially by exploiting phase phenomena associated with photonic resonances. The goal is to enable label-free sensing technology with a maximized refractive index resolution while reducing the requirements in nanofabrication, setup complexity, and cost.

In recent decades, successful applications of detection schemes utilizing spectral or angular information, along with intensity-based read-out approaches as transducers, have been observed in label-free biomolecular detection using nanophotonic sensors. These advancements have led to the development of various platforms that exhibit competitive or, in some cases, superior, sensitivity compared to the diagnostic standard ELISA. However,

improving the performance typically entailed a relatively high system complexity. Fortunately, new alternative approaches promise to achieve high sensitivity in simpler platforms by exploiting steep phase responses.

Two parallel paths are being explored for phase-driven progress:

1. Direct phase interrogation: This method uses interferometry to directly interrogate photonic resonances. It has shown promise in both plasmonic³ and dielectric⁴ platforms, offering enhanced sensitivity and potential for miniaturization.
2. Phase-enhanced, indirect detection: Another approach leverages phase phenomena, for instance, enhanced intensity-based detection. Recently, there has been significant interest in topologically protected phase singularities^{5,6} and amplified Goos–Hänchen-shifts⁷ for biosensing.

In their recent paper published in *Light Science & Applications* (LSA), Zhu et al.⁸ have achieved significant progress in Goos–Hänchen (G–H)-shift-based sensing. Their method specifically generated singularized phase responses through the integration of an atomically thin layer of $\text{Ge}_2\text{Sb}_2\text{Te}_5$ (GST) on a silver nanofilm. G–H-shifts are small lateral beam displacements associated with total internal reflection and interference of phase-shifted components of the beam, leading to a dependence of the shift on the refractive index at the interface due to evanescent waves. Since the G–H shift is proportional to the phase shift differences acquired upon total internal reflection, the small beam displacements that are acquired with single-layer dielectric interfaces can reach hundreds of microns due to steeper phase responses arising from

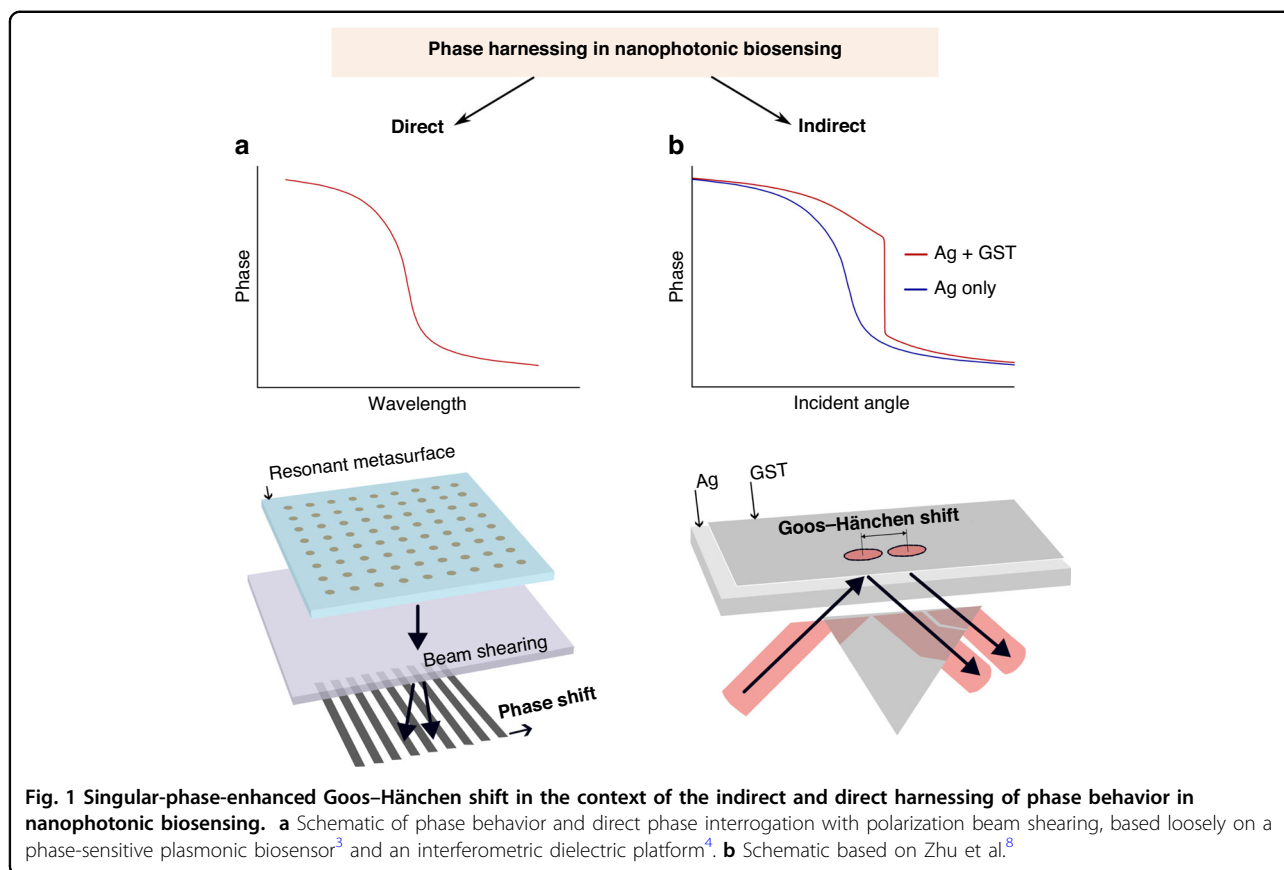
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resonances and enhanced absorption with additional materials.

Zhu et al.⁸ show that the phase singularity associated with the engineered absorption in the GST layer resulted in a steep phase curve (Fig. 1b) and unprecedented position shifts of up to $\sim 440 \mu\text{m}$, which is higher than previously achieved even with similar approaches. Since the authors target their technology at medical diagnostics beyond typical laboratory settings, they characterized the noise of their system in addition to the sensitivity, demonstrating a limit-of-detection ($\text{LOD} = \text{Noise}/\text{Sensitivity}$) of $\sim 7 \times 10^{-7}$ RIU. This result is superior to several simpler direct phase interrogation approaches (LOD down to $\sim 10^{-6}$ RIU) and close to some direct phase-sensitive SPR modalities (resolution $\sim 10^{-8}$ RIU). However, it should be noted that some of these reported findings in phase-sensitive modalities are not based on the above-defined LOD with its proportionality to the system noise, which, in an un-stabilized biosensing system with temperature- and mechanical drift, can greatly surpass the theoretical phase-resolution.

Zhu et al.⁸ further verified the label-free detection of small cytokine biomarkers (e.g., $\text{TNF-}\alpha$, 17.3 kDa) down to a concentration of 0.1 fM, which represents an order of magnitude improvement compared to similar approaches.

For future validation, however, these proof-of-principle detection limits would need to be confirmed in complex matrices, such as serum, with adequate biochemical controls.

A relevant difference between sensors based on, for instance, plasmonic and dielectric nanohole arrays⁹ and on G-H shift detection is the imaging capability. While hyperspectral imaging, intensity-based or direct interferometric approaches^{3,4} with resonant metasurfaces, allows imaging of refractive index distributions on the sensor surface and imaging-based, multichannel detection^{10,11}, G-H-shift-based platforms are currently not imaging-based. Despite the impressive sensitivity, the simultaneous detection of multiple biomarkers for sufficient clinical accuracy with high throughput represents one of the challenges going forward.

Published online: 18 March 2024

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