Quantum Phase-based Plasmonic Biosensing for Enhanced COVID-19 Detection

Kelvin T. Mpofu [1]* and Patience Mthunzi-Kufa [1,2,3]

[1] Council for Scientific and Industrial Research (CSIR) , National Laser Centre , Pretoria , South Africa.
[2] School of Chemistry and Physics , University of KwaZulu-Natal , Durban 4041, South Africa.

[3] Orthopaedic Biomechanics Lab , Division of Biomedical Engineering , Department of Human Biology , Faculty of Health Sciences , University of Cape Town , Anzio Road , Observatory South Africa.

E-mail: `kmpofu@csir.co.za*`

Abstract. The recent COVID-19 pandemic has made clear the need for rapid and sensitive diagnostic tools to allow effective monitoring and control of the disease. In this study, the authors theoretically model an approach to COVID-19 detection by employing quantum phase-based surface plasmon resonance biosensing, with the intent to enhance the limit of detection measurement compared to its classical equivalent. The authors demonstrate a theoretical framework of a quantum plasmonic biosensor, designed to target the SARS-CoV-2 spike protein with high specificity. In this work the authors model and simulate the operation of the biosensor in an ideal noiseless setup as well as in a noisy setup which more realistically resembles the conditions in a lab. The modeled sensor explores the advantages of quantum phase sensitivity and surface plasmon resonance to achieve a precision level below the shot noise limit. The results show that a quantum plasmonic biosensor could potentially outperform its classical counterparts in terms of LOD in the absence of noise but does not perform as well when there is noise in the system, offering rapid and precise identification of viral presence at very low concentrations. The quantum state considered in this work is the NOON state, but this work opens up the potential to work with other quantum states such as squeezed states and Fock states. This work has the potential to lead to more precise optical diagnostic devices and pave the way for more effective public health strategies to combat future pandemics.

1. Introduction

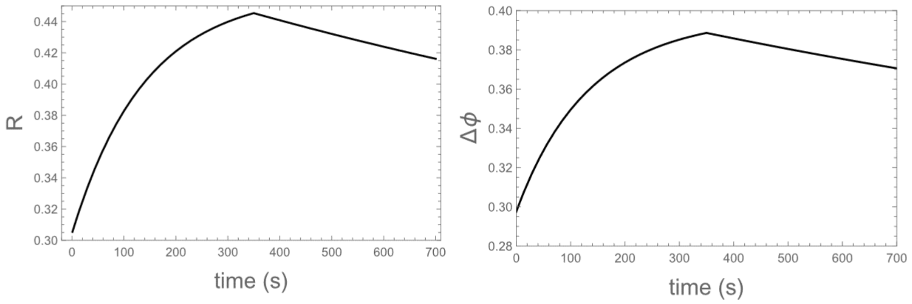
The ongoing and continuous evolution of viruses and bacteria is a global concern, as it results in pandemics and epidemics [1]. Of late the world has been under attack by COVID-19. Infection with the COVID-19 coronavirus causes serious illness. This is mainly due to the response of the immune system of the patient or host, which results in the release of a large number of pro-inflammatory cytokines [2, 3, 4, 5]. This "cytokine storm" leads to intense inflammatory and immune reactions, this occurs mostly in the lungs, which results in acute respiratory failure or distress. Widespread vaccination has been instrumental in reducing the number of infections and hospitalizations, effectively alleviating the burden of COVID-19 [6]. The use of vaccines has played an essential role in mitigating infections, thus preventing disease-related deaths and hospitalizations, and is helping to control its spread. In addition to vaccination and protection strategies, early diagnosis of COVID-19 infected individuals is crucial for pandemic management.

Some examples of methods that are used to detect SARS-CoV-2 infection are molecular methods [7] and lateral flow-based methods [8]. Molecular biology based tests, for example polymerase chain reaction (PCR) tests, typically are very sensitive and specific in detecting viral RNA and are mostly recommended for symptomatic individuals and implementing public health measures [7]. Lateral flow-based antigen rapid detection assays detect viral proteins and, though less sensitive than molecular tests, are advantageous because they are affordable, fast and easily performed by individuals. These tests can be used to screen high-risk individuals, protect vulnerable populations, ensure safe travel and resume activities, and promote economic recovery. In order to enhance and extend regular disease detection and testing it is necessary to focus on the development of fast techniques, which require low-infrastructure tests or allow for self-testing with a sensitivity comparable to that of PCR testing. Diagnostic tests have played and will continue to play a crucial role in the transition from pandemic response to pandemic control. Although the above-mentioned techniques have been truly valuable in the diagnosis of COVID-19, optical biosensors should also be considered in the conversation as well, this is in particular because of their rapid and highly accurate detection capacity and the capacity to enhance these properties by making use of quantum resources. In light of the recent COVID-19 pandemic, the need for highly sensitive biosensors is highlighted. Optical biosensors are a good candidate because they typically offer rapid, highly sensitive, and precise detection. Plasmonic-based optical biosensors typically have high sensitivity and, consequently, low limit of detection (LOD) compared to other optical biosensors [9]. The incorporation of quantum optics can enhance their sensitivity and precision.

The plasmonic setup of interest in this work is known as the Kretschmann configuration [10, 11]. It has been incorporated in commercial products such as Biacore devices; however, these devices operate on an angular mechanism whose detection limit cannot be broken with the use of quantum states, unlike intensity and phase-based mechanisms [12, 13]. Plasmonic biosensors can work in an intensity-sensing approach, a wavelength-sensing approach, an angular-sensing-based approach, and a phase-sensing-based approach [14]. In phase-based plasmonic biosensors [15, 16, 17, 18, 19, 20], a phase shift is used to infer the presence of specific molecules in the sample. This work focuses on the simulation of phase-based plasmonic biosensors. In the phase-based surface plasmon resonance (SPR) biosensor, a Krestchmann configuration-based plasmonic biosensor is integrated into one of the Mach-Zender interferometer arms. Although classical phase-based SPR biosensors are highly sensitive, their limit of detection (LOD) is bound by the shot-noise limit (SNL) imposed on the coherent state of light. When quantum states of light are used as probe input states in the SPR biosensor, the biosensor is generally referred to as a quantum plasmonic biosensor. The LOD of phase-based optical biosensors in the context of the refractive index, n, can be calculated using the equation Eq. 1 below,

$$\Delta n = \Delta\phi|\frac{\partial\phi}{\partial n}|^{-1} \tag{1}$$

where n is the refractive index on the biosensor surface and ϕ is the phase measured in the biosensing setup. The ratio, $|\frac{\partial\phi}{\partial n}|$, measures the sensitivity of the biosensor. Certain quantum states of light such as the Fock state and squeezed states have been shown to enhance detection to below the SNL in an intensity-based SPR sensing setup [21, 22, 23, 24, 25, 26]. In this work, the effect of the NOON state on enhancing the detection precision below the SNL is considered. This work shows how the use of quantum states of light in SPR biosensing has the potential to give an enhancement over using classical states and some limitations that may need to be overcome. Quantum SPR biosensors represent the future of optical biosensing.



(a)

(b)

Figure 1: **This is a picture which shows the sensorgrams of the kinetic binding interaction between the S1 spike protein and a 20-base aptamer “CFA0688T”. (a) shows an intensity-based sensorgram whose kinetic parameters are. (b) Shows the phase change based system which is derived or transformed from the intensity based sensorgram using Eq. 2.**

2. Sensing model

In this work the kinetic binding interaction between the S1 spike protein and a 20-base aptamer “CFA0688T” from BasePairBio together with the surface chemistry architecture is theoretically modelled. The authors start by studying the binding interaction between the S1 spike protein and the 20-base aptamer “CFA0688T”, which is well documented in the work of Szunerits *et al.* [27]. An intensity-based surface plasmon resonance sensorgram with kinetic parameters $k_a = 1.2 \times 10^5 \mathrm{M}^{-1}\mathrm{s}^{-1}$ and $k_d = 7.05 \times 10^{-4}\mathrm{s}^{-1}$ is transformed to a phase-based sensorgram using the relationship shown in Eq. 2,

$$r_p = |r|e^{i\phi} \tag{2}$$

where r_p is the reflectivity with respect to the p polarization which is the polarization which causes plasmon resonance and ϕ is the phase. The transformation allows us to modify and model the intensity based intensity based binding reaction into a phase based one from which analysis can be conducted. Figure 3 (a) shows the intensity based figure binding sensorgram for the binding interaction between, and Figure 3 (b) shows the phase based transformed equivalent which is used to calculate the LOD values. In this work the authors consider a two-mode Mach-Zender intefereometer system that has a Krestchman configuration plasmonic biosensor integrated. By developing such a configuration, the authors can track the biological interactions on the biosensor surface as a function of a phase shift, as opposed to the traditional angle shift and intensity change probes. The setup considered in this work is shown in Figure 2 and it shows how phase based plasmonic biosensing can be setup in the lab.

2.1. Quantum states considered

The typical states used in the Krestchmann configuration setup is the coherent state. As such the authors use it as the benchmark standard for comparison with quantum states. The two mode coherent state (TMC) is expressed mathematically as Eq. 3 below,

$$|\mathrm{TMC}\rangle = |\gamma\rangle_m |\sigma\rangle_n = \hat{D}_m(\gamma)\hat{D}_n(\sigma)\, |0\rangle_m |0\rangle_n \,, \tag{3}$$

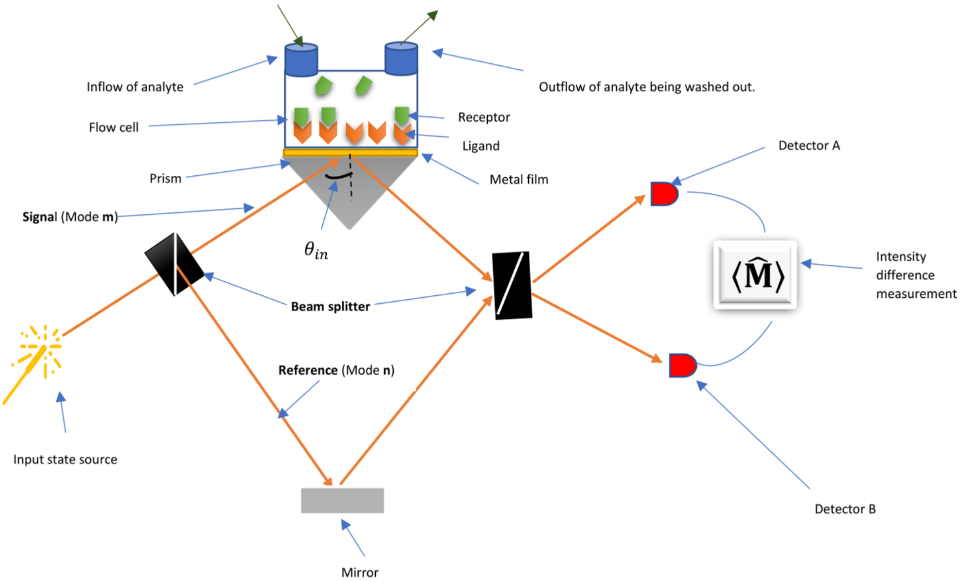


Figure 2: **This is a picture of a surface plasmon resonace setup embbedded in a Mach-Zender interferometer to allow for phase based biosensing.**

where $\hat{D}_m(\gamma) = e^{\gamma\hat{m}^\dagger - \sigma^*\hat{m}}$ is called the displacement operator for the mode m, which has a displacement parameter $\gamma \in \mathbb{C}$. $\hat{m}^\dagger$ and $\hat{m}$ are the creation and annihilation operators, respectively, for the mode m. The measurement operator, $\hat{M}$, used for the coherent state is the intensity difference measure,

$$\langle\hat{M}\rangle = \langle\hat{m}^\dagger\hat{m} - \hat{n}^\dagger\hat{n}\rangle. \tag{4}$$

In this work the authors look at the use of a quantum state of light known as the NOON state for comparison. The NOON state is an N-photon entangled state which can be generated using the Hong Ou Mandel effect [28] or via post processing of single photons generated via spontaneous parametric down conversion [29, 30] and circuit QED [31]. Mathematically, the NOON state can be expressed as shown in Eq. 5,

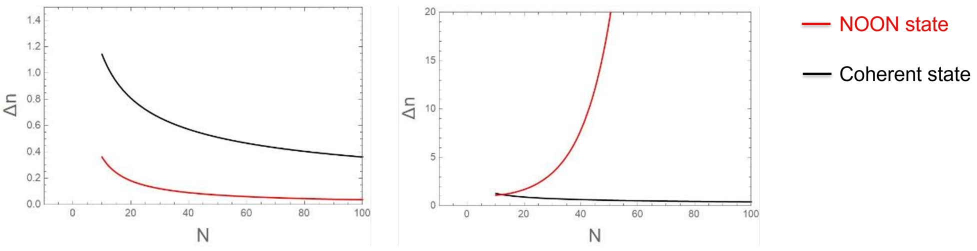
$$|\psi_{\mathrm{NOON}}\rangle = \frac{1}{\sqrt{2}}(|\mathrm{N}\rangle_m |0\rangle_n + |0\rangle_m |\mathrm{N}\rangle_n). \tag{5}$$

Where m and n are the modes of the states. The measurement operator used for the NOON state analysis in this work is written as in Eq. 6,

$$\hat{\mathrm{A}}_{\mathrm{NOON}} = |\mathrm{N}\rangle_m |0\rangle_n \langle 0|_m \langle \mathrm{N}|_n + |0\rangle_m |\mathrm{N}\rangle_n \langle \mathrm{N}|_m \langle 0|_n \,. \tag{6}$$

2.2. Analysis

From Figure 3 (a) it is clear that an ideal case of the simulation, i.e., when losses to the environment are not accounted for and are assumed to be zero then the NOON state outperforms the coherent state in limit of detection measures for varying photon numbers. However, in real lab experiments it is crucial to account for losses to the environment, hence in these simulations the authors account for environmental losses, when the authors add a 20% loss to both arms of the experiment, it is apparent and clear from Figure 3 (b) that the NOON state is not robust to losses to the environment and the limit of detection measure grows exponentially fast.



(a) (b)

Figure 3: **This is a picture which shows the LOD of the plasmonic biosensor in the context of the refractive index on the biosensor surface. Image (a) shows refractive index would change with changing photon number, N, in the ideal case where there are no losses to the environment. Image (b) shows the plasmonic sensing experiment but with the inclusion of a 20% loss in both modes of the eperiment. We see that the NOON state is not robust against any losses to the environment and the LOD quickly becomes unstable with increasing photon number, N.**

3. Conclusion

In this work, it is shown that using the NOON state of light as a probe in the phase-based plasmonic biosensor we can enhance the LOD of the measurement of the refractive index in the diagnosis of COVID-19. The NOON state is unfortunately not robust against losses in the system, and when minor losses are introduced, it quickly fails to surpass the SNL. The knowledge that it is possible in theory to break the SNL is a great positive, though. The answer may lie in considering other quantum states of light such as the squeezed states of light and or Fock basis states which are known to be more robust against losses. This is a possible direction for future research, both theoretical and experimental. This work highlights the potential to use optical biosensors for diesease detection and highlights how they can be enhanced in order to address future pandemics. Future work will look at using squeezed states and Fock states as these may be more robust against environmental losses and could result in a higher LOD and may be easier to produce in a practical setting.

Acknowledgements.— This research was supported by the Council for Scientific and Industrial Research (CSIR) and the Department of Science and Innovation (DSI) in South Africa.

Data Availability: The data sets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

[1] P. Singh, “Surface plasmon resonance: A boon for viral diagnostics,” *Reference Module in Life Sciences*, 2017.

[2] M. P. Da Silveira, K. K. da Silva Fagundes, M. R. Bizuti, É. Starck, R. C. Rossi, and D. T. de Resende E Silva, “Physical exercise as a tool to help the immune system against covid-19: an integrative review of the current literature,” *Clinical and experimental medicine*, vol. 21, no. 1, pp. 15–28, 2021.

[3] S. Felsenstein, J. A. Herbert, P. S. McNamara, and C. M. Hedrich, “Covid-19: Immunology and treatment options,” *Clinical immunology*, vol. 215, p. 108448, 2020.

[4] E. Mortaz, P. Tabarsi, M. Varahram, G. Folkerts, and I. M. Adcock, “The immune response and immunopathology of covid-19,” *Frontiers in immunology*, vol. 11, p. 2037, 2020.

[5] D. Darif, I. Hammi, A. Kihel, I. E. I. Saik, F. Guessous, and K. Akarid, “The pro-inflammatory cytokines in covid-19 pathogenesis: What goes wrong?” *Microbial pathogenesis*, vol. 153, p. 104799, 2021.

[6] J. P. Gómez Vázquez, Y. E. García, A. J. Schmidt, B. Martínez-López, and M. Nuño, “Testing and vaccination to reduce the impact of covid-19 in nursing homes: an agent-based approach,” *BMC Infectious Diseases*, vol. 22, no. 1, p. 477, 2022.

[7] Y. Yan, L. Chang, and L. Wang, "Laboratory testing of sars-cov, mers-cov, and sars-cov-2 (2019-ncov): Current status, challenges, and countermeasures," *Reviews in medical virology*, vol. 30, no. 3, p. e2106, 2020.

[8] S. Agarwal, C. Warmt, J. Henkel, L. Schrick, A. Nitsche, and F. F. Bier, "Lateral flow–based nucleic acid detection of sars-cov-2 using enzymatic incorporation of biotin-labeled dutp for poct use," *Analytical and Bioanalytical Chemistry*, vol. 414, no. 10, pp. 3177–3186, 2022.

[9] P. Damborskỳ, J. Švitel, and J. Katrlík, "Optical biosensors," *Essays in biochemistry*, vol. 60, no. 1, pp. 91–100, 2016.

[10] E. Kretschmann and H. Raether, "Radiative decay of non radiative surface plasmons excited by light," *Zeitschrift für Naturforschung A*, vol. 23, no. 12, pp. 2135–2136, 1968.

[11] M. S. Islam, A. Z. Kouzani, X. J. Dai, and W. P. Michalski, "Parameter sensitivity analysis of surface plasmon resonance biosensor through numerical simulation," in *IEEE/ICME International Conference on Complex Medical Engineering*. IEEE, 2010, pp. 171–176.

[12] L. Jason-Moller, M. Murphy, and J. Bruno, "Overview of biacore systems and their applications," *Current protocols in protein science*, vol. 45, no. 1, pp. 19–13, 2006.

[13] M. Fivash, E. M. Towler, and R. J. Fisher, "Biacore for macromolecular interaction," *Current opinion in biotechnology*, vol. 9, no. 1, pp. 97–101, 1998.

[14] J. Homola and M. Piliarik, *Surface plasmon resonance (SPR) sensors*. Springer, 2006.

[15] Y. Huang, H. Ho, S. Wu, and S. Kong, "Detecting phase shifts in surface plasmon resonance: a review," *Advances in Optical Technologies*, vol. 2012, 2012.

[16] M. Kashif, A. A. A. Bakar, N. Arsad, and S. Shaari, "Development of phase detection schemes based on surface plasmon resonance using interferometry," *Sensors*, vol. 14, no. 9, pp. 15 914–15 938, 2014.

[17] S. Zeng, X. Yu, W.-C. Law, Y. Zhang, R. Hu, X.-Q. Dinh, H.-P. Ho, and K.-T. Yong, "Size dependence of au np-enhanced surface plasmon resonance based on differential phase measurement," *Sensors and Actuators B: Chemical*, vol. 176, pp. 1128–1133, 2013.

[18] Y. Huang, H. P. Ho, S. K. Kong, and A. V. Kabashin, "Phase-sensitive surface plasmon resonance biosensors: methodology, instrumentation and applications," *Annalen der Physik*, vol. 524, no. 11, pp. 637–662, 2012.

[19] S. Mohammadzadeh-Asl, A. Keshtkar, J. E. N. Dolatabadi, and M. de la Guardia, "Nanomaterials and phase sensitive based signal enhancment in surface plasmon resonance," *Biosensors and Bioelectronics*, vol. 110, pp. 118–131, 2018.

[20] X. Guo, "Surface plasmon resonance based biosensor technique: a review," *Journal of biophotonics*, vol. 5, no. 7, pp. 483–501, 2012.

[21] C. Lee, B. Lawrie, R. Pooser, K.-G. Lee, C. Rockstuhl, and M. Tame, "Quantum plasmonic sensors," *Chemical Reviews*, vol. 121, no. 8, pp. 4743–4804, 2021.

[22] K. T. Mpofu, "Quantum plasmonic sensing with application to hiv research." Ph.D. dissertation, 2020.

[23] C. Lee, F. Dieleman, J. Lee, C. Rockstuhl, S. A. Maier, and M. Tame, "Quantum plasmonic sensing: beyond the shot-noise and diffraction limit," *Acs Photonics*, vol. 3, no. 6, pp. 992–999, 2016.

[24] K. Mpofu, C. Lee, G. Maguire, H. Kruger, and M. Tame, "Experimental measurement of kinetic parameters using quantum plasmonic sensing," *Journal of Applied Physics*, vol. 131, no. 8, 2022.

[25] J.-S. Lee, S.-J. Yoon, H. Rah, M. Tame, C. Rockstuhl, S. H. Song, C. Lee, and K.-G. Lee, "Quantum plasmonic sensing using single photons," *Optics express*, vol. 26, no. 22, pp. 29 272–29 282, 2018.

[26] K. Mpofu, C. Lee, G. Maguire, H. Kruger, and M. Tame, "Measuring kinetic parameters using quantum plasmonic sensing," *Physical Review A*, vol. 105, no. 3, p. 032619, 2022.

[27] S. Szunerits, H. Saada, Q. Pagneux, and R. Boukherroub, "Plasmonic approaches for the detection of sars-cov-2 viral particles," *Biosensors*, vol. 12, no. 7, p. 548, 2022.

[28] C.-K. Hong, Z.-Y. Ou, and L. Mandel, "Measurement of subpicosecond time intervals between two photons by interference," *Physical review letters*, vol. 59, no. 18, p. 2044, 1987.

[29] P. Walther, J.-W. Pan, M. Aspelmeyer, R. Ursin, S. Gasparoni, and A. Zeilinger, "De broglie wavelength of a non-local four-photon state," *Nature*, vol. 429, no. 6988, pp. 158–161, 2004.

[30] M. W. Mitchell, J. S. Lundeen, and A. M. Steinberg, "Super-resolving phase measurements with a multiphoton entangled state," *Nature*, vol. 429, no. 6988, pp. 161–164, 2004.

[31] Q.-P. Su, C.-P. Yang, and S.-B. Zheng, "Fast and simple scheme for generating noon states of photons in circuit qed," *Scientific reports*, vol. 4, no. 1, p. 3898, 2014.