Measurement of binding kinetics using quantum plasmonic resonance sensing applied to HIV-1

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The work done in this paper is an extension of the work done by Mpofu et al in [1]. The motivation for this paper is to show the potential of quantum bio-sensing techniques in applications to complex viruses like the human immunodeficiency virus (HIV) and to show its potential in binding reactions where the signal is small and can potentially be buried in noise. In this paper we show theoretically that using quantum states of light such as the Fock state improves the precision in the estimation of kinetic parameters measured from the sensorgrams produced by the Kretschmann configuration. Though the Fock state is not the only quantum state in this study we look only at the Fock state because it has been shown to be the state which offers the best enhancement [1]. We show here that the Fock state allows us to measure the parameters more accurately in comparison to the classical (Coherent) state of light. We consider in this paper a binding reaction involving HIV type 1 (HIV-1). Specifically we look at the binding reaction between a variant of HIV-1 protease and nelfinavir which is an inhibitor. Such a study is also offers value for drug discovery research as it points to the development of new technologies which can be applied to testing the efficacy of new drugs. Quantum technologies can prove to be useful in the fight against the HIV pandemic and assist in the continual research towards the development of treatments and a cure.

I. INTRODUCTION

HIV type 1 (HIV-1) is the causative agent of the acquired immunodeficiency syndrome (AIDS). Early detection, diagnosis and treatment of human immunodeficiency virus (HIV) infection is the key to reducing acquired immunodeficiency syndrome (AIDS) mortality [2]. Popular methods for clinical diagnosis of HIV infection such as enzyme-linked immunosorbent assay (ELISA) and western blot (WB) are limited in their ability to identify the early stage of infection when there are low HIV antibody levels [3, 4] which is problematic when it comes to early detection of HIV. Other methods such as Polymerase chain reaction (PCR)-based techniques have been shown to be more sensitive and reliable. However these techniques require thermal cycling and complicated primer design [5], so simpler techniques would be more ideal. Various biosensing techniques have been developed for HIV-related detection as alternatives, these include electrochemistry [6], colorimetry [7], fluorescence resonance energy transfer (FRET) [8], and surface plasmon resonance (SPR) [9] amongst others. In this paper we are interested in SPR.

SPR is a highly sensitive technique for monitoring changes in the optical properties of a substance in the immediate vicinity of a sensor surface, which makes it very useful in biosensing and surface science research [10]. The focus of this paper will be on a bio-sensing SPR setup known as the Kretschmann configuration in which surface plasmons are excited using a bulk prism and a gold coated microscope slide. The excitation is performed by means of an evanescent field arising from total internal reflection from the backside of the metal surface of the sensor [11]. Surface plasmon resonance biosensors allow for the analysis of real-time and label free interactions of any biomolecule, be it protein, nucleic acid, lipid, carbohydrate or small molecule [12–16]. The use of (SPR)-based optical biosensors has contributed extensively to our understanding of functional aspects of many viruses [17]. Amongst said viruses is the human immunodeficiency virus (HIV). SPR biosensors have been used to provide a unique and detailed view into the inner workings of HIV [18]. SPR plays an important role in helping us understand how different anti-HIV therapies bind and interact with the HIV virus, thus preventing the virus from either entering into our immune cells or replicating once inside our cells [18].

Despite the high throughput of SPR biosensors, they are still bound in their precision by the shot-noise limit, this has led to the development of quantum biosensors [19–24]. High precision in kinetic parameters measured from SPR experiments of great importance. Preliminary results of such experiments which measure more precise kinetic parameters have been shown [25]. However despite the successful performance of plasmonic sensors for measuring kinetics in a wide range of scenarios [26], the precision in the estimation of kinetic parameters is bound by the classical limit, given by the shot noise of the classical light source used in the bio-sensors [27]. In this paper we study theoretically the measurement of the interaction kinetics of the binding reaction between a variant of HIV-1 protease and nelfinavir which is an inhibitor using a plas-
FIG. 1: Measuring interaction kinetics using a quantum plasmonic sensor. (a) Surface plasmon resonance sensor with ligands (nelfinavir) binding to receptors (HIV-1 protease) bound to the metal surface (metal film). The ligand is introduced in an analyte when it is introduced into the setup. The arrow coming from the receptor (top arrow) shows an image of the structural model of the HIV-1 protease structure in a complex with an inhibitor taken from Ref. [32]. The arrow coming from the CDD detector (at the bottom) in the inset point to a diagram which shows how the transmittance, $T$, of the sensor changes as the refractive index $n_{\text{signal}}$ (or permittivity $\varepsilon_{\text{signal}} = n_{\text{signal}}^2$) above the gold surface varies due to the presence of the analyte and a surface plasmon polariton (SPP). The arrow points to a sensor signal, known as a sensorgram, describing the kinetics as the flow cell is filled with the analyte. The first phase is association as the ligands in the analyte bind to the receptors immobilized on the gold surface. Mass transport effects due to diffusion are neglected in the model. The second phase is steady state when the binding and unbinding rates are equal. The final phase is dissociation as a buffer solution is injected into the flow cell to remove the ligands. (b) The surface plasmon resonance sensor can be placed in a two-mode setup in order to exploit quantum sensing techniques. Here, it plays the role of a beamsplitter with time-varying transmittance, $T(t)$. Loss on the mode labelled signal (reference) due to experimental imperfections can be modelled as an additional beamsplitter with transmittance $\eta_{\text{signal}}$ ($\eta_{\text{reference}}$). The signal mode is also referred to as mode (a) and the reference as mode (b) in later sections hence, $\eta_{\text{signal}} = \eta_a$ and $\eta_{\text{reference}} = \eta_b$ in later sections.

monic resonance sensor and quantum states of lights. We only consider the Fock state in this study as opposed to the work done in [1] where other quantum states were considered such as the two-mode squeeze vacuum states and two-mode squeeze displaced states [11]. The reason for not considering the squeezed states is that in this previous work we have already seen that the Fock state well outperforms the other quantum states as far as extracting good precision in kinetic parameters. In the case of a parameter extracted from a static transmittance, the Fock state is known to be the optimal state [24, 25, 29] and therefore we focus on using it for the case here involving parameters estimated from a dynamic transmittance.

The work is organized as follows: In Section II, we introduce the physical model which we consider for plasmonic sensing, we provide general details of the sensor setup and its signal response to a dynamically changing environment. We also introduce the Fock state and the measurements we study. We discuss the general sensorgram fit for interaction kinetics used and show how the kinetic parameters can be measured, for a given interaction, from the plasmonic sensor’s signal. In Section III, we present the results for the molecular interaction processes studied. In Section IV we summarize our findings.

II. SENSING MODEL

In FIG. 1(a) we show the Kretschmann configuration setup which we use to measure the binding kinetics of the binding reaction between the ligand (nelfinavir) and the receptor (HIV-1 protease). Here we send a signal through a prism onto a thin metal surface (nano-metres thin). At an angle $\theta_{\text{in}}$ where the correct coupling conditions are met, the signal excites conduction electrons on the metal surface which creates a surface electromagnetic wave – a surface plasmon polariton (SPP) – that is confined to the upper metal surface. The result of this SPP excitation is represented as a drop in the intensity of the reflected light in the signal mode, which is a phenomenon known as surface plasmon resonance (SPR).

The top arrow going from the sensor setup shows the structural model of the HIV-1 protease structure in a complex with an inhibitor taken from Ref. [32]. This is the complex formed after the binding reaction. The bottom arrow going from the detector shows the sensorgram which we observe as the reaction goes on, we observe a rise in intensity as association (binding) occurs until we reach a steady state where the intensity remains constant.
FIG. 2: Sensorgrams from the experiment by Shuman et al. which investigates the binding reaction between a variant of HIV-1 protease and nelfinavir which is an inhibitor. The T model for the angle model in Ref. [31]. (a) Angular sensorgram, $\Delta \theta(t)$, where the full sensorgram is $\theta(t) = \theta(0) + \Delta \theta(t)$ with $\theta(0) = 67$ degrees. (b) Reconstructed transmittance sensorgram, $T(t)$, with $\theta_m = 67$ degrees set.

Typically in the Kretschmann configuration, as described above, the source of light is a laser. This source of classical light is well represented as a coherent state in the quantum formalism [11]. In this paper we consider only one quantum state which is the two-mode Fock (TMF) state, which is expressed as

$$|\text{TMF}\rangle = |N\rangle_a |N\rangle_b = \frac{(\hat{a}^\dagger)^N (\hat{b}^\dagger)^N \sqrt{N!}}{\sqrt{N!}} |0\rangle_a |0\rangle_b. \quad (1)$$

The TMF state has $N$ photons in each mode, and thus a mean photon number of $\langle N_a \rangle = N$ and $\langle N_b \rangle = N$ in modes $a$ and $b$, respectively.

### III. INTERACTION KINETICS

Interaction kinetics refers to the dynamic binding and unbinding processes of ligands to receptors [12], which are divided into 3 main phases: association, steady state and dissociation. The appendix of [11] provides details of the model we use for the interaction kinetics [12] and how it is linked to the transmittance, $T$, of the sensor. Below is a brief summary of the model.

The changing, $T$, value over time is a response to the changing refractive index, the refractive index can be understood as a change in the dipole moments of the immobilized receptors as they are converted into complexes and then unconverted [12]. For a fixed incidence angle of light, an increase in the complex concentration $[C]$ therefore increases the value of the refractive index, $\epsilon_a$, and thus $T$, as shown in the inset of FIG. 2(a).

The kinetics of the interaction between drug-resistant variants of HIV-1 protease and clinically used inhibitors are of particular interest in HIV studies [31]. An enzyme inhibitor is a molecule that binds to an enzyme and decreases its activity. HIV-1 protease is a retroviral aspartyl protease (retropepsin), an enzyme involved with peptide bond hydrolysis in retroviruses, that is essential for the life-cycle of HIV, the retrovirus that causes AIDS [30]. The HIV-1 protease variant is immobilized on a biosensor chip and the association and dissociation rate constants for interactions with inhibitors are determined. The kinetic parameters are important because they can be used in inhibitor design. Changes in the kinetic parameters reflect a change in the drug resistance capacity of the HIV-1 protease. Due to the importance of research in HIV drug discovery studies we decided to use the kinetics of HIV as a test case for showing the potential benefits of a quantum approach.

In this section we construct a model for the transmission, $T$, for the binding reaction involving HIV protease and the inhibitor nelfinavir. Details of how we construct the T model are given in [1]. We used values from the experiment by Shuman et al. [31], where we chose nelfinavir as the inhibitor and the wild-type enzyme for the reaction. We had to use a low concentration to be consistent with [31]. A low concentration meant that there was a smaller $R$ change. The following parameters were used: $k_a = 3.79 \times 10^5 M^{-1}s^{-1}$, $k_d = 5.65 \times 10^{-4} s^{-1}$ and $L_0 = 80 \times 10^{-9} M$. We will show plots of the results for the parameter vs photon-number and for the case of the parameter vs $\nu$.
can be found from the relation $k\eta_t$ association phase, $T_{et}$, as well as the extracted kinetic parameters stated from the transformation. The knowledge of this parameter

$$T(t) = \begin{cases} T_\infty(1 - e^{-kt}) & 0 \leq t < \tau \\ T_\infty e^{-kd(t-\tau)} & t \geq \tau, \end{cases} \quad (2)$$

where $T_\infty$ is a constant determined by the initial concentration of the ligands and receptors, the thickness of the receptor and ligand layers above the gold surface, and the affinity $k_A = \frac{k_s}{k_d}$. We then have the constant $T_r = T_\infty(1 - e^{-k_s\tau})$. In the above, the kinetic parameter $k_s = k_s[L_0] + k_d$ represents the observable rate for the association phase, $k_a$ is the association constant measured in M$^{-1}$s$^{-1}$ (per molarity per second), $k_d$ is the dissociation constant measured in s$^{-1}$ and $[L_0]$ is the initial ligand concentration. Equation (2) is the theoretical model for the sensor’s response, which is the sensorgram that would be measured in an ideal experiment (no noise). From the measured sensorgram a nonlinear fit is then performed, e.g., using the Gauss-Newton method, with respect to the theoretical model in order to extract the association and dissociation kinetic parameters. From the fit, $k_d$ and $k_a$ are obtained and with a knowledge of the initial ligand concentration $[L_0]$, the parameter $k_a$ can be found from the relation $k_a = (k_s - k_d)/[L_0]$. We need to know what the value of $T_\infty$ (and therefore $T_r$) in Eq. (2) would be in the experiment in order to perform the transformation. The knowledge of this parameter, as well as the extracted kinetic parameters stated above allow us to build the equivalent transmittance sensorgram that we can use in our simulations. To obtain the value of $T_\infty$, we use the angular sensorgram from the experiment, which is shown in FIG. 2(a), to find the time dependence of the refractive index, $n_\alpha(t)$, above the gold surface. We use this and the other physical parameters from the experiment to reconstruct a time dependent model $T(t)$ for the transmittance with the correct $T_\infty$ value. With the full time dependence of $n_\alpha(t)$ known from the angular sensorgram, we use it in Eq. (2) to obtain $T(t) = |r_{app}(t)|^2$, which is shown in FIG. 2(b) as a solid line. Other methods for extracting the kinetic parameters could have had been used but we chose this method as it is one of the most direct [12]. When considering a realistic sensorgram that is measured in an experiment with noise, the extracted kinetic parameters from the fit will have this noise imparted to them and the estimate obtained will have an estimation error (estimation precision).

### A. Standard two-mode case

In this case, i.e., the standard two mode sensing case we consider the general sensing model shown in FIG. 2 where we set the loss in either mode to be the same. We begin with an ideal scenario where we have no loss in either mode, i.e., $\eta_s = \eta_r = 1$. Where $\eta_{signal} = \eta_s$ and $\eta_{reference} = \eta_r$. In FIG. 3(a)-(c) we show the estimation value (mean as a point) and estimation precision (standard deviation as an error bar) for the kinetic parameters $k_a$, $k_s$, and $k_d$ for increasing sample size $\nu$ and fixed photon number $N = 5000$. In FIG. 3(g)-(i) we show the estimation value (mean as a point) and estimation precision (standard deviation as an error bar) for the kinetic parameters $k_a$, $k_s$, and $k_d$ for increasing photon number $N$ and fixed $\nu = 10^6$. The number of sets of sensorgrams simulated is $p = 1500$, which is chosen as it provides a stable distribution of the extracted kinetic parameters from the fits. We use this value of $p$ for all the simulations in this work. It is clear from FIG. 3(a)-(c) that the TMF state provides a better estimation of the kinetic parameters compared to the TMC state for any $\nu$ and one can see from FIG. 3(g)-(i) that the TMF state still outperforms the TMC for all photon numbers $N$. The estimation precision shown for each state physically corresponds to that of a fixed set of $m = 10$ sensorgrams, each of which has $\nu$ states probed at a given instance of time, with a step-size between instances of time of 10s. In the present scenario, the sensorgram is 2500 seconds in duration and so there are 250 points in total, each point having $\nu$ probe states measured. The step-size for the points was chosen so that there was a fine enough mesh for the fit to return the exact values in the ideal case when there is no noise. In FIG. 3(d)-(f) we present an enhancement measure which is a quantification of the improvement in the estimation precision by considering the ratio, $R_k$. $R_k$ is a measure of a quantum state’s measurement precision for parameter $k$, given by $\Delta k_0$, to that of the TMC state with matching mean photon number in each mode, $\Delta k_c$, i.e., $R_k = \Delta k_c/\Delta k_0$. We call this the enhancement ratio in the plot. The enhancement is shown in FIG. 3(d)-(f) for $k_a$, $k_s$ and $k_d$ as $\nu$ increases. The TMC state has no enhancement and the ratio value is 1 naturally. We have a similar measure in FIG. 3(j)-(l), the enhancement here is for increasing photon number $N$. In FIG. 3(d)-(f) and FIG. 3(j)-(l), the dotted lines for each state are a guide to the impact of loss on the signal and reference modes. This is more representative of a practical assessment in a potential experimental setting. In FIG. 4(a)-(c) we show the estimation value and estimation precision for the kinetic parameters $k_a$, $k_s$, and $k_d$ for increasing set size $\nu$, with $\eta_s = \eta_r = 0.8$. For this example, we have used $N = 10$ for the photon number and $m = 10$. One can see that even in the presence of moderate loss the TMF state clearly provides the best estimation in the kinetic parameters for any $\nu$, the enhancement is shown in FIG. 4(a)-(c). In FIG. 4(g)-(i) we see that the TMF is still outperforming the TMC with increasing photon
number, \( N \). The general enhancement is a bit lower (<2) in the lossy case as compared to the ideal case where the enhancement is a value > 2.

### B. Optimized two-mode case

In this second scenario, we set \( \eta_b = \eta_a T_{\text{mid}} \), with \( T_{\text{mid}} = 0.4124 \). In FIG. 5(a)-(c) we show the estimation value and estimation precision for the kinetic parameter \( k_a \) as we vary \( \nu \) from \( 10^2 \) to \( 10^5 \) for the ideal case of \( \eta_a = 1 \) and \( \eta_b = T_{\text{mid}} \). One can see that as \( N \) increases the TMF state provides the best estimation in the kinetic parameters for any \( \nu \). The enhancement plot is shown in FIG. 5(d)-(f). In this optimized two-mode sensing scenario, the TMF state is clearly the state that offers the best estimation precision. In FIG. 5(h)-(i) we show the estimation value and estimation precision for the kinetic parameters for increasing photon number \( N \), with \( \eta_a = 1 \) and \( \eta_b = T_{\text{mid}} \). One can see that the TMF state again provides the best estimation in the kinetic parameters.

#### 1. Lossy optimized two-mode case

In the optimized case we also consider the impact of loss. In FIG. 5(a)-(c) we show the estimation value and estimation precision for the kinetic parameters \( k_a, k_s \) and \( k_d \) for increasing \( \nu \), with \( \eta_a = 0.8 \) and \( \eta_b = 0.8T_{\text{mid}} \). We also show in FIG. 5(g)-(i) the estimation value and estimation precision for the kinetic parameters \( k_a, k_s \) and \( k_d \) for increasing photon number \( N \), with \( \eta_a = 0.8 \) and \( \eta_b = 0.8T_{\text{mid}} \). One can see that even in the presence of moderate loss the TMF state again provides the best estimation in the kinetic parameters.

### C. Single-mode case

In a final scenario, we reduce the two-mode sensing model to a single-mode model by effectively removing the reference mode \( b \) by setting \( \eta_b = 0 \). This means that there will be no transmittance in that mode and the intensity-difference measurement, \( \langle M \rangle \), becomes an intensity measurement of the signal mode. This scenario is more representative of experiments.

In FIG. 7(a)-(c) we show the estimation value and estimation precision for the kinetic parameters \( k_a, k_s \) and \( k_d \) for increasing \( \nu \), with \( N = 10 \) and \( m = 10 \). It is clear that the Fock state (TMF state with \( \eta_b = 0 \)) provides the best estimation in the kinetic parameters for any \( \nu \) when compared to a coherent state in the signal mode with matched mean photon number (TMC state with \( \eta_b = 0 \)). The corresponding enhancement is shown in FIG. 7(d)-(f) for \( k_s, k_d \) as \( \nu \) increases. The enhancements are all similar and roughly in line with that expected from the mid-point value \( R_{\text{M}} \) (dotted line) and independent of \( \nu \). The same can be said for FIG. 7(g)-(i) where it is clear that the TMF state outperforms the TMC for increasing photon number.

#### 1. Lossy single-mode case

In the single mode case we also consider the impact of loss. In FIG. 8(a)-(c) we show the estimation value and estimation precision for the kinetic parameters \( k_a, k_s \) and \( k_d \) for increasing \( \nu \), with \( \eta_a = 0.8 \) and \( \eta_b = 0 \). We also show in FIG. 8(g)-(i) the estimation value and estimation precision for the kinetic parameters \( k_a, k_s \) and \( k_d \) for increasing photon number \( N \), with \( \eta_a = 0.8 \) and \( \eta_b = 0 \). One can see that even in the presence of moderate loss the TMF state again provides the best estimation in the kinetic parameters.
FIG. 4: Standard two-mode sensing using Fock and coherent states (loss, $\eta_a = \eta_b = 0.8$). Panels (a), (b) and (c) show the estimation values and precisions for the kinetic parameters $k_a$, $k_s$ and $k_d$ as $\nu$ increases for $m = 10$. Panels (d), (e) and (f) show the corresponding enhancement ratio for the Fock state for $m = 10$. Panels (g), (h) and (i) show the estimation values and precisions for the kinetic parameters $k_a$, $k_s$ and $k_d$ as $N$ increases for $m = 10$ and $\nu = 10^6$. Panels (j), (k) and (l) show the corresponding enhancement ratio for the Fock state. In panels (d), (e), (f), (j), (k) and (l) the dotted lines are a guide representing the enhancement expected from the ratio $R_M$ at the mid-point of the sensorgram.

FIG. 5: Optimized two-mode sensing using Fock and coherent states (no loss, $\eta_a = 1$ and $\eta_b = \eta_a T_{mid}$). Panels (a), (b) and (c) show the estimation values and precisions for the kinetic parameters $k_a$, $k_s$ and $k_d$ as $\nu$ increases for $m = 10$. Panels (d), (e) and (f) show the corresponding enhancement ratio for the Fock state for $m = 10$. Panels (g), (h) and (i) show the estimation values and precisions for the kinetic parameters $k_a$, $k_s$ and $k_d$ as $N$ increases for $m = 10$ and $\nu = 10^6$. Panels (j), (k) and (l) show the corresponding enhancement ratio for the Fock state. In panels (d), (e), (f), (j), (k) and (l) the dotted lines are a guide representing the enhancement expected from the ratio $R_M$ at the mid-point of the sensorgram.
FIG. 6: Optimized two-mode sensing using Fock and coherent states (loss, $\eta_a = 0.8$ and $\eta_b = \eta_a T_{\text{mid}}$). Panels (a), (b) and (c) show the estimation values and precisions for the kinetic parameters $k_a$, $k_s$ and $k_d$ as $\nu$ increases for $m = 10$. Panels (d), (e) and (f) show the corresponding enhancement ratio for the Fock state for $m = 10$. Panels (g), (h) and (i) show the estimation values and precisions for the kinetic parameters $k_a$, $k_s$ and $k_d$ as $N$ increases for $m = 10$ and $\nu = 10^6$. Panels (j), (k) and (l) show the corresponding enhancement ratio for the Fock state. In panels (d), (e), (f), (j), (k) and (l) the dotted lines are a guide representing the enhancement expected from the ratio $R_M$ at the mid-point of the sensorgram.

FIG. 7: Single-mode sensing using Fock and coherent states (no loss, $\eta_a = 1$ and $\eta_b = 0$). Panels (a), (b) and (c) show the estimation values and precisions for the kinetic parameters $k_a$, $k_s$ and $k_d$ as $\nu$ increases for $m = 10$. Panels (d), (e) and (f) show the corresponding enhancement ratio for the Fock state for $m = 10$. Panels (g), (h) and (i) show the estimation values and precisions for the kinetic parameters $k_a$, $k_s$ and $k_d$ as $N$ increases for $m = 10$ and $\nu = 10^6$. Panels (j), (k) and (l) show the corresponding enhancement ratio for the Fock state. In panels (d), (e), (f), (j), (k) and (l) the dotted lines are a guide representing the enhancement expected from the ratio $R_M$ at the mid-point of the sensorgram.
FIG. 8: Single-mode sensing using Fock and coherent states (loss, $\eta_a = 0.8$ and $\eta_b = 0$). Panels (a), (b) and (c) show the estimation values and precisions for the kinetic parameters $k_a$, $k_s$ and $k_d$ as $\nu$ increases for $m = 10$. Panels (d), (e) and (f) show the corresponding enhancement ratio for the Fock state for $m = 10$. Panels (g), (h) and (i) show the estimation values and precisions for the kinetic parameters $k_a$, $k_s$ and $k_d$ as $N$ increases for $m = 10$ and $\nu = 10^6$. Panels (j), (k) and (l) show the corresponding enhancement ratio for the Fock state. In panels (d), (e), (f), (j), (k) and (l) the dotted lines are a guide representing the enhancement expected from the ratio $R_M$ at the mid-point of the sensorgram.
The work done here is an extension of previous work done in the paper by Mpofu et al. [1]. In the work done here we theoretically modelled the binding reaction between HIV-1 protease and nelfinavir as the inhibitor of the protease. We started off by briefly introducing the physical model for plasmonic sensing applied to HIV-1 based binding reactions and provided details of the sensor setup, its response to a dynamically changing environment, the general model for interaction kinetics, and the various quantum states and measurements. We studied the measurement of the kinetic parameters of the binding reaction between HIV-1 protease and its inhibitor nelfinavir using a plasmonic sensor and quantum states of light. For the interaction processes we considered the classical TMC state and the quantum state TMF. The TMF state gives better precision and enhancement in all the cases, especially in the standard two-mode case. The single mode offers a similar enhancement to the optimized case but it is more practical for experiments as only one mode is required. While the enhancement in the precision found using quantum states is small at around 1-3 times that of the classical case, even such a small improvement in the estimation precision could make a big difference in accurately determining the kinetic parameters when operating close to the intensity and noise limits of a sensor.

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