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Symmetries and Biology: a new approach to Biosensing
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ABSTRACT

We propose a novel detection method based on the symmetry breaking induced by the bio-molecule to be detected. Briefly, by choosing a sensor presenting a particular symmetry, the revolution symmetry, the adsorption of an analyte will break this symmetry. By detecting this change in the symmetries of the system, the presence of bio-molecules can be detected. This optical method provides substantial advantages over current approaches for the conception of biosensors. In particular, this approach relies on geometrical considerations, providing important properties such as the possibility to multiplex spatially or in wavelength. In addition, it relaxes strongly the constrains on the sensor as no specific plasmon resonances are necessary. We believe this work opens promising alternatives for the development of biosensors.

Keywords: biosensing, symmetry, multiplexing

1. INTRODUCTION

An important challenge in molecular biology and in biomedical sciences is the ability to detect small quantities of biological molecules (e.g. proteins). Referred to as biosensing (for the ability to detect specific specimens of biological origin or interest), this field has important applications. For example, recent efforts have been underway to detect small amounts of biomolecules specific to cancer cells. This particular work opens the way toward the development of commercially available devices allowing for the early detection of cancer. Such technology will significantly increase our ability to detect cancers during the first stages, simplifying their treatment and greatly improving the outcome of the disease. Research into the different methods involved in biosensing has aimed at achieving high sensitivity, selectivity and throughput, most noticeably with plasmonic [1] and nonmechanical [2] biosensors. Briefly, plasmonic sensors rely on localized surface plasmon, a collective oscillation of conduction electrons in noble metals. The resonance frequency of such oscillations present a very high sensitivity to the nanoparticle composition, size, shape, orientation and local dielectric environment [3,4]. Consequently, molecular binding or even changes in molecular conformation can be detected through modifications of the resonance. Similarly, in the case of nanomechanical biosensors the detection is related to the modification of mechanical resonances or surface-stress due to the binding of molecules [2]. Yet these advanced methods have important limitations and the capabilities of available devices fail to answer to the demand for the efficient and early detection of bio-molecules. In particular the fabrication quality of these sensors has a direct impact on the sensitivity of the device. Also, due to their nanometric dimensions the fabrication still remains challenging. Such technological difficulty hinders their development and commercial transfer. In addition, this type of sensors is sensitive to the presence of any molecules. Their selectivity is only obtained chemically: they are in general fabricated to detect a given molecule.

2. CONCEPT

The use of symmetry for biosensing, though an entirely unexplored concept, would offer unique advantages over the usual approach which typically measure the presence of a biomolecule in terms of mass change [2] (nanomechanical resonators), or optical resonance changes [1] (plasmon resonators). The sensing is thus achieved via the modifications of the properties of the sensor in a continuous manner: the different observables (mass or optical response) can take any value. The sensitivity is then directly related to how small a change can be measured. Remarkably, in the case of symmetry considerations, the impact of the analyte on the sensor is discrete: the symmetry is, or is not, broken. This fundamental aspect has the important potential to increase the sensitivity of biosensor far beyond its current limits. In addition, it also allows for properties such as multiplexing.

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This work exploits a particular symmetry: the cylindrical symmetry. Also known as revolution symmetry, it imposes that the device can be rotated around a particular axis and still remains the same. In its simplest form, such device can be realized using a colloidal metal nanoparticle [5,6] as the sensor. These chemically obtained particles present a high sphericity and are widely available. By probing such spherical particle with a circularly polarized Gaussian laser beam, the whole system presents a cylindrical symmetry along the axis of incidence of the laser (schematized figure 1).

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This important symmetry in the absence of analyte is obtained experimentally by using a piezo-nanopositioning stage to control the exact position of the sensor. As mentioned previously when the symmetry is fulfilled, the pattern of the laser beam as detected by the camera is invariant by rotation. The adding of a defect on the colloidal particle will consequently break the symmetry. As this symmetry is broken, so is the rotational invariance of the detected field pattern. Physically, this modification is due to additional angular momentum components otherwise not allowed. Such breaking of the revolution symmetry induced by the binding of an analyte to the colloidal particle is illustrated in figure 2. Noticeably, the fundamental physics involved in this approach show a very important difference with typical biosensing approaches: the presence of the analyte does not simply modify a property of the sensor but allows for the additional angular momentum components. Such effect, yet unexplored in biosensing, considerably increases the expected signal-to-noise ratio. Indeed, the presence of the analyte will strongly distort the pattern of the laser beam making the detection of its presence easier.

2.1 Theoretical considerations

Because of this revolution symmetry, an important quantity is conserved [7]: the angular momentum projected along the symmetry axis $z$, $J_z$. As long as this symmetry is not broken, this conservation law constrains the angular momentum content of the scattered light by the nanoparticle. Intuitively, as the system is invariant by rotation, the scattered light pattern is also invariant by the same rotation. Breaking the symmetry consequently allows for additional components of the angular momentum, in turn distorting the scattered light pattern. In this context, Bessel beams constitute a convenient choice of vectorial basis function of electromagnetic fields modes [8]. Using this basis, it is easy to calculate the expected scattered field when the system presents the revolution symmetry. In particular, we use the following definition:

$$C_{mp_z}(\rho, \theta, z) = \sqrt{\frac{\rho \rho}{2\pi}} i^m \exp(i(p_z + m\theta)) \left[ \frac{i}{\sqrt{2}} \left( (1 + \frac{p_z}{k}) J_{m+1}(p \rho \rho) \exp(i\theta) \hat{r} + (1 - \frac{p_z}{k}) J_{m-1}(p \rho \rho) \exp(-i\theta) \hat{1} \right) - \frac{\rho \rho}{k} J_m(p \rho \rho) \hat{z} \right],$$

$$D_{mp_z}(\rho, \theta, z) = \sqrt{\frac{\rho \rho}{2\pi}} i^m \exp(i(p_z + m\theta)) \left[ \frac{i}{\sqrt{2}} \left( (1 - \frac{p_z}{k}) J_{m+1}(p \rho \rho) \exp(i\theta) \hat{r} + (1 + \frac{p_z}{k}) J_{m-1}(p \rho \rho) \exp(-i\theta) \hat{1} \right) + \frac{\rho \rho}{k} J_m(p \rho \rho) \hat{z} \right],$$
where an \( \exp(-i\omega t) \) time-dependence is assumed. \( \rho, \theta, z \) denote the cylindrical coordinates, and \( \hat{\mathbf{r}} = \frac{\hat{x} + i\hat{y}}{\sqrt{2}} \), \( \hat{\mathbf{r}} = \frac{\hat{x} - i\hat{y}}{\sqrt{2}} \) the unit vectors for circular polarization. Furthermore, \( m \) is the value of the z-component of the angular momentum \( J_z \), \( k \) is the wave number, \( p_\rho = \sqrt{k^2 - p_z^2} = \sqrt{p_x^2 + p_y^2} \) the transverse wave number, and \( J_m(.) \) are the Bessel functions of the first kind. The above Bessel beams are eigenfunctions of the energy, the z-component of both linear and angular momentum, and of helicity \( (C_{mpz} \text{ has } A = -1, \text{ while } D_{mpz} \text{ has } A = +1) \). Helicity is defined as the projection of the angular momentum onto the linear momentum. Also in the paraxial limit, helicity can be assimilated to the circular polarization of light. Since in the case of our experiment the light is collimated when the projective measurement is performed, it is useful to simplify the Bessel beams in the collimated limit, where \( \frac{p_\rho}{k} \to 0 (p_z \approx k) \).

Then the two types of modes can be written as:

\[
C_{mpz}(\rho, \theta, z) \approx \sqrt{\frac{p_\rho}{2\pi} i^{m+1} \exp(i(p_z z))} J_{m+1}(p_\rho \rho) \exp(i\theta(m + 1)) \hat{\mathbf{r}},
\]

\[
D_{mpz}(\rho, \theta, z) \approx \sqrt{\frac{p_\rho}{2\pi} i^{m+1} \exp(i(p_z z))} J_{m-1}(p_\rho \rho) \exp(i\theta(m - 1)) \hat{\mathbf{I}},
\]

As previously mentioned, for the experiment to present the revolution symmetry, we use a Gaussian beam circularly polarized. In particular, for a left circularly polarized beam (i.e. helicity \( A = +1 \) in the paraxial limit), the incident beam is described by:

\[
D_{1p_\rho}(\rho, \theta, z) \approx -\sqrt{\frac{p_\rho}{\pi}} i \exp(i(p_z z)) J_0(p_\rho \rho) \hat{\mathbf{I}}
\]

Since the whole system is not dual the scattered light presents in general both components of helicity \( (A = \pm 1) \) [9]:

\[
D_{1p_\rho}(\rho, \theta, z) \text{ and } C_{1p_\rho}(\rho, \theta, z) \approx -\sqrt{\frac{p_\rho}{\pi}} i \exp(i(p_z z)) J_2(p_\rho \rho) \exp(2i\theta) \hat{\mathbf{r}}
\]

In the context of this work, we used the component of changed helicity \( (A = -1) \) which presents a optical vortex of charge 2 (factor \( \exp(2i\theta) \)) to monitor the revolution symmetry of the system with a Charged-Couple Device (CCD) camera. By using a projective measurement on the helicity basis, it is indeed possible to select the \( C_{mpz} \) components. When the system presents the revolution symmetry, we just shown that the only components are the \( C_{1p_\rho} \). The beam intensity pattern is consequently rotationally invariant (dependence on \( \theta \) only through a phase term). Conversely, when this symmetry is broken, additional \( C_{mpz} \) components are allowed consequently breaking the rotational invariance of the beam pattern. The presence of an analyte on the surface of the colloidal particle induces a symmetry breaking in turn detected through its impact on the beam pattern.

### 2.2 Monitoring method

In order to monitor the change of symmetry in the scattered beam profile after the projection on the changed helicity \( (A = -1) \), we extracted two particular quantities from the image. To provide a clear illustration of the method, figure 3a shows an image obtained from a large off-centre scatterer instead of the nanoparticles used for sensing. The two quantities are: the midpoint between the two minima and the position of the centroid weighted with respect to the intensity value (intensity-weighted centroid). Using these two points, we define their distance \( d \) and the angle \( \alpha \) between the edge connecting the two vertices and the horizontal (parallel to the x-axis defined by the CCD camera frame). It is important to note here that we observe two charge 1 optical vortices instead of a single charge 2 vortex. Indeed, we used a polarizer and a waveplate to select the changed helicity term \( (A = -1) \), yet this selection is not perfect and a portion of the unchanged helicity term leaks. In particular, the polarizer extinction was experimentally measured to be \( -5 \times 10^{-5} \), allowing a small portion of the \( D_{mpz} \) components \( (A = +1) \) through. Since this components of the beam present a Gaussian profile, this small contribution leads to the splitting of the charge 2 vortex present in the changed helicity beam \( (A = -1) \) into two charge 1 vortices [10]. To compensate for the splitting, we consequently used the midpoint between those two minima. Conversely, the ring-shaped high-intensity region shows an important asymmetry, clearly underlined by the position of the intensity-weighted centroid (yellow square in fig. 3a). For comparison, fig. 3b shows...
the scattered beam pattern obtained for a slightly off-center 110 nm gold colloidal particle, the typical particle used for sensing.

To demonstrate the sensitivity of this monitoring method to symmetry breaking, we raster-scanned the same large scatterer over 200x200nm$^2$ (including the position fulfilling the revolution symmetry). The scan was done by steps of 10 nm and a picture of the scattered beam pattern was retrieved for each positions. Using the method previously explained, the distance (d) and angle ($\alpha$) were calculated for each image (i.e. position). Figure 4 shows the values of this distance (fig 4a) and angle (fig 4b) over the 200x200 nm$^2$ scan. In this figure there clearly exists a position at which the distance decreases to zero and the angle exhibits a singularity, as expected. This reference position is obtained when the high-intensity region is rotationally invariant. Also, this position is directly related to the physical position of the scatterer that fulfills the revolution symmetry. Such scan clearly shows the sensitivity of the method to the symmetry breaking induced when the scatterer is off-centered with respect to the optical setup revolution axis. Also this method is the subject of a patent [11] for accurate position sensing based on symmetry breaking.

Figure 4. (color online) Experimental monitoring of the symmetry breaking. a distance d between midpoint of intensity minima and the intensity-weighted centroid (arbitrary units). b angle between the horizontal and the edge connecting the midpoint and the intensity-weighted centroid.

2.3 Properties
While typical biosensing approaches remain difficult to multiplex, this approach offers remarkable potential for an advanced multiplexing technique. In particular, two different types of multiplexing are envisaged: wavelength multiplexing and spatial multiplexing.

The wavelength multiplexing will allow identification of different biomolecules or chemical pollutant based on the ability to optically distinguish them. To illustrate this property, let us consider two different analytes A1 and A2 with a distinct optical response. For some specific wavelengths, A1 will have an optical response stronger than A2; conversely for other wavelengths A2 will present the strongest optical response. By carefully choosing two wavelengths, the sensor will be sensitive to one analyte or the other depending on the wavelengths used. By monitoring both at the same time, it is then possible to follow the binding of two different analytes on the same sensor using different wavelengths. This method, while it allows for the distinction between two optically distinct analytes, becomes much more complex for a large number of analytes. For this reason, the possibility to not only multiplex in wavelength but also in space allows for an efficient multiplexing scheme without the need for a complex experimental setup (use of only two wavelengths).

The potential spatial multiplexing relies on the particular impact an analyte will have on the laser beam pattern depending on the spatial position of its binding site on the sensor. Following geometrical considerations, the position of an analyte on the sensor can be inferred from the pattern modification. This effect can also be seen in the scan figure 4 where the values of the distance (d) the angle (α) provide insights about both the distance and the direction to the reference position. As schematised in Figure 5, an analyte binding on the top or bottom position produces two distinguishable patterns. By chemically preparing the sensors “by sectors”, it is then possible to detect the different analytes as they bind on their relative sectors. Such method could be first implemented on large particle for only two sector by doing a multi-step functionalization. In addition with the wavelength multiplexing, the detection of a very large number of analytes could be achieved with only one sensor.

![Functionalization sectors](image_url)

**Figure 5.** (color online) Spatial multiplexing. By functionalizing the nano-particle by sectors, the different analyte can be distinguished through the different impact they have on the scattered beam pattern. For example, using two sectors (top and bottom), the adsorption of analyte 1 (on top sector) will lead to a pattern particular pattern distortion. The distortion of the pattern is underlined by the red contours.

### 3. Conclusion

This novel approach to biosensing relying on symmetry considerations constitutes an interesting alternative to current technologies (e.g. plasmon resonators or nano-mechanical resonators). In particular, colloidal metallic nano-particles can be used as sensors. Such sensors can be easily fabricated chemically, and since the method does not rely on a specific resonance from the sensor, the constrains on the sensors size are also relaxed. In addition, it is possible to implement wavelength and spatial multiplexing in order to increase the throughput of such sensors without major fabrication
difficulties. It also possible to envisage coupling this symmetry breaking method to plasmonic biosensing approaches since both technologies are fully compatible.

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