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Surface Plasmon Resonance Induced Photothermal Lysis of the Cell

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Abstract — Cell Lysis is the imperative first step towards obtaining the intracellular contents, which hold valuable genetic and pathogenic information. The process must be carried out with extreme care to avoid damaging or altering the cell contents or indeed test conditions. As the resulting clinical information is so important, it is an intensively researched topic. Here we examine the resulting photothermal effects when a human cell in aqueous solution is brought in contact with the noble metal film of a Kretschmann-configuration Surface Plasmon Resonance setup. This specifically targets cells of refractive index in a known desired range, activating only when the target species comes in contact with the metal film and only while possessing the correct refractive index. Depending on the desired application, this can then denature the thin cell membrane, while also generating isotropically scattered transmission light from the radiatively-decaying plasmon, which is useful for signalling. Furthermore, with simple laser intensity, selective cellular necrosis may be induced. We apply the technique specifically towards the *Plasmodium falciparum*-infected red blood cells.

I. INTRODUCTION

This work aims to demonstrate the feasibility of selectively picking out cells of interest which are required to undergo cell lysis or disruption. The desired target cells may be included in a large batch of similar cells suspended in aqueous biological solution, which can be made to pass over the sensor through the advent of microfluidics. The benefit of this work, if successfully realised, would see a highly selective form of Cell Lysis, as opposed to methods which essentially achieve “all or nothing”. Cell selectivity is important as killing non-target or nearby healthy cells is obviously to be avoided. We focus in particular on correctly identifying cells exhibiting a known variation of their refractive indices and tune the plasmonic setup to disrupt these cells upon contact. This requires a careful balance of statistical parameters. The key components of the Surface Plasmon Resonance (SPR), Cell refractive index and Cell Lysis are now briefly described, followed by a description of the experimental setup and initial results.

II. SURFACE PLASMON RESONANCE AND THE REFRACTIVE INDEX OF THE CELL

By far, the most popular setup for SPR applications is the Kretschmann-configuration [1], in which a thin metal film (almost always gold or silver), approximately 50 nm thick, is coated onto the back of an optical prism. The thickness is specifically chosen such that the evanescent field of the illuminating light is able to penetrate the film and excite the resonance, which is exquisitely sensitive to the local wavelength-dependent complex refractive index, $\tilde{n} = n + ik$ of the biological environment. Under “angular-interrogation” mode, the incident angle, θ , of the illuminating laser light is swept, and the reflectivity curve obtained.

The refractive index of the cell is a key biophysical marker, conveying rich information in a seemingly straightforward parameter. It is directly correlated with intrinsic properties such as the mechanical, electrical and optical response of the cell, and also signifies the intracellular masses and concentrations inside the cell. Measurement techniques have, however, traditionally only measured the effective refractive index of a cell or a cell suspension, encompassing the effective medium response of multiple cell components of slightly differing refractive index. This shortcoming obscures the real component level refractive index and hence hinders true analysis and correlation. Techniques to circumvent this typically require a submicron level of mapping, and are developing rapidly but inherently impose small Fields of View, which slows down throughput. It is desirable therefore, to have a high-throughput, label-free, cell lysis device which can respond near-instantaneously. This indeed happens here as the cell approaches the plasmonic metal, specifically, within the decay-length of the surface plasmon in the aqueous dielectric solution (approximately 200 nm). “Tuning” the setup then entails maintaining a tightly collimated laser beam at the specific angle required to maximise SPR excitation at the desired target cell refractive index.

Consider the *Plasmodium falciparum*-infected red blood cell for example. Normal, healthy red blood cells exhibit a refractive index around 1.353 [2], while *Plasmodium falciparum*-infected red blood cells can exhibit refractive indices as high as 1.44 in the schizont stage (advanced stage of cell infection). Earlier stages of the cell infection (ring stage) can show changes in the opposite direction – with refractive indices in spots as low as 1.34 [3].

Such drastic changes are ordinarily easily identifiable; however high n dielectrics demands expensive high refractive index prisms such as sapphire in order to enable the plasmonic excitation. An additional unfortunate problem in utilising SPR sensors is the development of non-specific cell lysate build-up or “fouling”, however steps can be taken to prevent this [4].

III. CELL LYSIS

Various techniques exist to induce cell lysis, including viral, enzymatic or osmotic mechanisms which compromise the cell wall integrity. Further disruption techniques involve electrically induced dielectric breakdown, grinding, ultrasonication, bead milling, microwaving and cryogenic use of liquid nitrogen. As a first step in cell treatment, it is crucial that it is carried out correctly as subsequent analysis is dependant on its quality. Machines to carry out cell lysis tend to be large and expensive, particularly if high volume is required [5]. The cell wall is a complex biological material, approximately 10 nm thick, (a considerable thickness in terms of SPR) mainly composed of lipids (~ 50%), proteins (~ 40%) saccharides and carbohydrates [6]. The cell wall is reported to denature on application of temperature, transitioning from a “gel” to a liquid [7]. The proposed working principle of cell lysis here is photothermal – at all times the cell is “safe” from laser exposure, unless it has the refractive index of interest. Part of the fabrication challenge here is to deliberately induce non-pinholed surface roughness in the metal film, in order to generate sufficient radiative leakage into the cell. Nobel metal films undergoing SPR typically only raise the local metal temperature by a single kelvin, as such, the highly-localised laser light transmission into the target cell is essentially the lysis achieving mechanism.

IV. EXPERIMENTAL SETUP AND RESULTS

Fig 1. depicts the experimental apparatus, with the prism itself situated face-down on an inverted Zeiss Axiovert 200 microscope, with has several modifications including: a PID-controlled temperature stabilised environment, a mounted laser (Raman grade) on a goniometric cradle (Newport) and nanopositioning stage (PI). The typical objective lens used is long focal length, observing through the microfluidic channel, with a PCO-edge 4.2 CCD capturing cell-SPR interaction. Thus far, human endothelial cells have been examined and cell lysis on silver observed. Initial early results indicate cell lysis does indeed readily occur, however several refinements must be made. Non- specific cell disruption must be ruled out (silver is inherently destructive to soft cells) and the degree of control over the refractive index range of target cells requires considerable examination.

Fig. 1. Experimental apparatus. Inset: A temperature controlled microfluidic channel delivers cells over the surface plasmon resonance.

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