A novel proprietary device utilizing magneto-optical technology to provide accurate, early-stage malaria diagnoses

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Abstract

The objective is to develop a novel malaria diagnostic device with automated data analysis. The device utilizes magneto-optical spectroscopy which detects change in levels of hemozoin, a disposal byproduct of malaria, in infected blood. Hemozoin is a magnetic nanoparticle, and the device utilizes this property to read change in optical signal from transmitted light through a sample while a magnetic field is applied. I conducted experiments with varying concentrations of magnetic iron oxide nanoparticles in solvents of varying viscosities, looking at how the response changes with nanoparticle concentration and viscosity. I also wrote MATLAB code that parses through the output data, export relevant information, and plot subsequent graphs. In each dilution of the nanoparticles tested, there was a noticeable change in transmission of signal, though there was smaller change with greater dilution. These results fundamentally prove the device's concept, even in low concentrations, meaning that the device may be capable of detecting the presence of hemozoin in early stages of malaria. Ongoing proof-of-concept experiments are being conducted with beta-hematin (a hemozoin mimic) as well as with malaria-infected blood samples.

Introduction

3.3 billion people live in malaria-endemic regions. Early diagnosis is the leading factor of decreased morbidity because treatment is nearly 100% effective when quickly prescribed. However, half of the 500 million annual infections go undiagnosed, and half of those diagnoses are incorrect. Meanwhile, current diagnostics are expensive, inaccurate, slow, and either require some form of refrigeration or medical training to make the diagnosis or prescribe treatment, severely limiting their impact. Since treatment costs approximately 4x that of a current diagnostic test, any false positive diagnoses have a multiplier effect.

Every disease is unique, and this uniqueness can be leveraged to intelligently design a diagnostic which is inherently specific and selective. For malaria, as the parasite digests red blood cells, a magnetic disposal product known as hemozoin is created. Magnetic by-products are not normally present in the blood. Therefore, the presence of hemozoin can be directly correlated with the disease state.

Because hemozoin is a magnetic nanoparticle, it can be moved by magnetic fields. Based on this interaction, we have created a malaria diagnostic. It combines an active magnetic field with single-wavelength transmission loss measurements. The change in the optical signal indicates the concentration of the hemozoin in the sample, which is directly related to malaria stage.

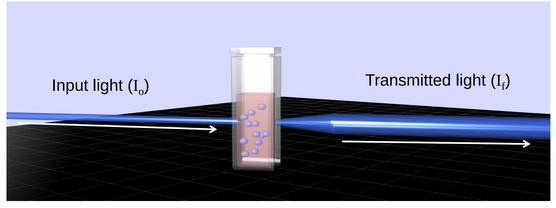


Figure 1: Schematic explaining optical spectroscopy. When light is shone on a given sample, a certain amount of light is transmitted. More light is transmitted when fewer particles are present to block the passage of light. Similarly, less light is transmitted when more particles are present.

Objectives

- To develop an automated data analysis program
- To conduct proof-of-concept experiments using hemozoin mimics

To accelerate time-to-decision, I will automate the signal analysis.
To verify the new program, I will perform a series of measurements using magnetic nanoparticles and beta-hematin, a hemozoin mimic. The results from these experiments will allow the limit of detection and working range to be determined.

Results

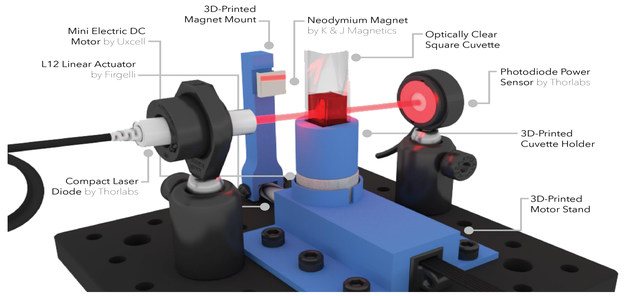
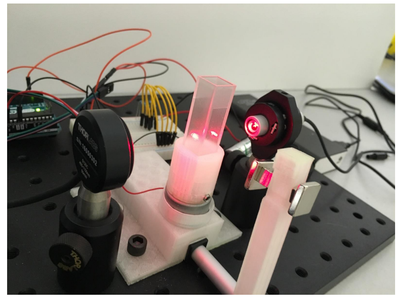
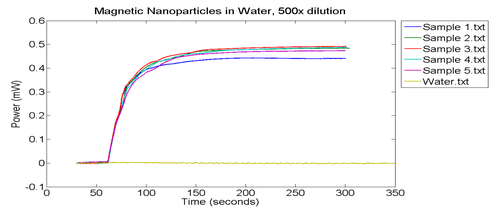
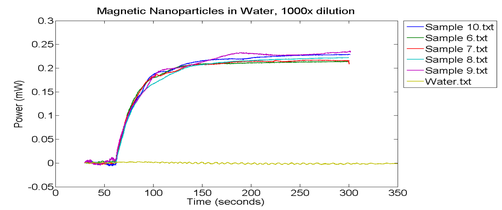
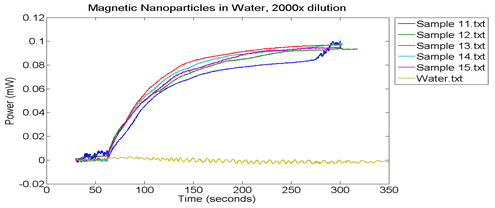


Figure 2: Rendering of our malaria diagnostic.









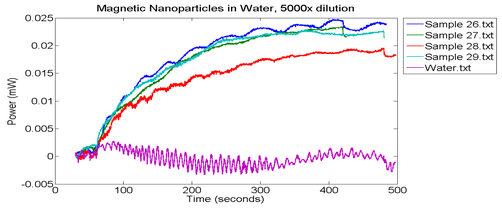
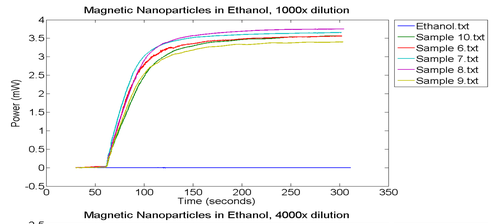
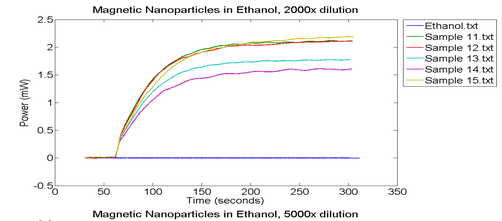
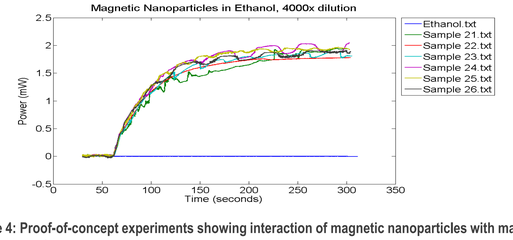


Figure 3: Proof-of-concept experiments showing interaction of magnetic nanoparticles with magnetic field at varying MNP concentrations, in water. I tested each dilution five times, obtaining consistent reproducible results. As the dilution increases, the change in signal decreases (as is noticed by looking at the y-axis). However, the change in signal remains reasonably constant between cycles for each dilution.







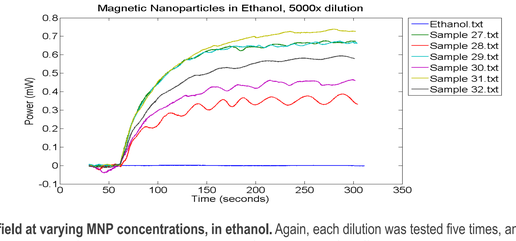
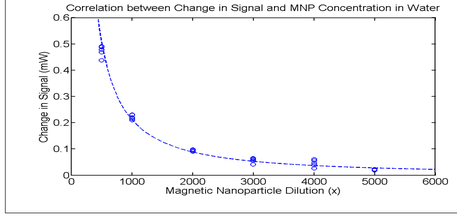


Figure 4: Proof-of-concept experiments showing interaction of magnetic nanoparticles with magnetic field at varying MNP concentrations, in ethanol. Again, each dilution was tested five times, and results proved to be fairly consistent between cycles. As the dilution increases, the change in signal decreases because there are fewer nanoparticles in the path of light, so less of a difference between when particles are blocking the light and when they are aligned to the magnetic field.



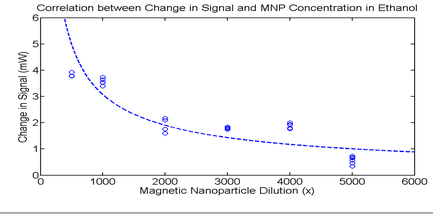


Figure 5: Correlation between change in signal and MNP concentration in various solvents. There is a clear correlation between an increased dilution (or decrease concentration) and a decrease change in signal between when the magnetic field is applied and when it is removed.

Methods

AUTOMATION OF DATA ANALYSIS: I wrote a MATLAB code that parses through the output text file and extracts the important information – namely, the timestamp and transmission signal. The MATLAB code outputs this data into an Excel file and generates relevant plots.

PROOF-OF-CONCEPT EXPERIMENTS: I conducted experiments with varying concentrations of magnetic iron oxide nanoparticles in solvents of varying viscosities, looking at how the response changes with nanoparticle concentration (from 0 to 5000x dilution) and viscosity. All measurements are performed multiple (N>5) times to ensure reproducibility, and blank solutions are used as controls to determine the baseline noise. The samples are mixed using a vortexer in between measurements. To account for slight changes in the optical path length that can appear with changes in signal intensity, a differential signal change is reported.

Discussion

As we can see in Figures 3 and 4, we observe a smaller change in signal as the concentration of nanoparticles increases. However, even at 5000x dilution, we are still seeing a noticeable increase in transmission upon application of the magnetic field. This bodes well for determining the limit of detection of our device – it has proven to maintain high sensitivity at low nanoparticle concentrations, meaning that at early stages of malaria, it may still be capable of detecting the presence of hemozoin, despite there being an exceedingly low concentration of hemozoin present in any given blood sample.

Figure 5 plots the absolute change in signal – the difference between the baseline signal and the plateau, once all the nanoparticles are aligned to the magnetic field – versus nanoparticle concentration. We expected to, and do, see a downward trend – again, a decrease in the change in signal as the dilution increases. This data was fit to an exponential curve, allowing us to predict signal change as the dilution continues to increase.

Overall, these results bode well for the future of our diagnostic. It is proven that the fundamental concept of our device works. We also show that, even as the dilution increases to 5000x, there is still a considerable change in transmission, allowing us to continue detecting a change when a magnetic field is applied.

Future Work

My future work involves three main steps:

- Conduct further proof-of-concept experiments with solvents of increasing viscosity
- Confirm validity of device with beta-hematin, a hemozoin mimic
- Test with malaria-infected blood samples

I plan to make solutions of varying polyethylene glycol (PEG) concentrations to study how viscosity affects the response time of the magnetic nanoparticles. I predict that, as viscosity increases, the response will get slower (or increase) due to the inability of the magnetic nanoparticles to move through the solution.

Upon synthesizing beta-hematin, I will test our device similarly to tests conducted here, with varying concentrations of beta-hematin. This will allow us to, once again, confirm our device's functionality and calculate the limit of detection in something more akin to blood samples we plan to use in the field.

Lastly, we will take our device to UCSD to continue testing malaria-infected blood samples. This will allow for further proof of concept, in addition to providing insight as to how we can change the device itself to improve general functionality.

Acknowledgements

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