High Throughput Droplet Scanning for Limited Resource Bacterial Infection Monitoring

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Background:

Bloodstream infection(BSI) causes high mortality rate due to the inability to rapidly detect and identify bacteria in the early stages of infection. It annually effects over 18 million people worldwide and 700,000 people in the United States, with a mortality rate of 30-40% [1].

Motivation:

Effective detection and monitoring of patients to diagnose a BSI at an early stage have a profound effect on survival rate.

Project Goal:

Develop and test peak detection algorithms for counting the number of bacteria-infected droplets in a high throughput infection scanning system which can help doctors to easily find out the concentration of bacteria on patient's blood sample.

IC 3D Technology

(Integrated Comprehensive Droplet Digital Detection)

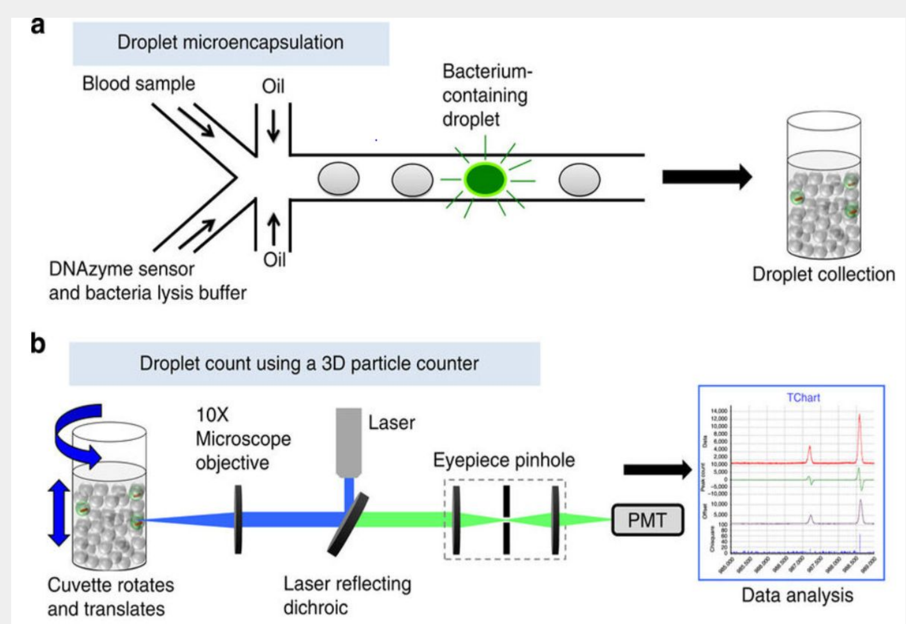

Figure 1: Schematic description of the IC 3D technology [1]

- DNAzyme sensors produce an instantaneous signal in the droplets that contain the bacterium
- Droplets are collected and analysed using high throughput 3D particle counter that permits accurate detection of single-fluorescent droplets
- **Small peak**: far from the cuvette surface, small droplet size
- **Large peak**: close to the cuvette surface, large droplet size

Technical Approaches

Method 1

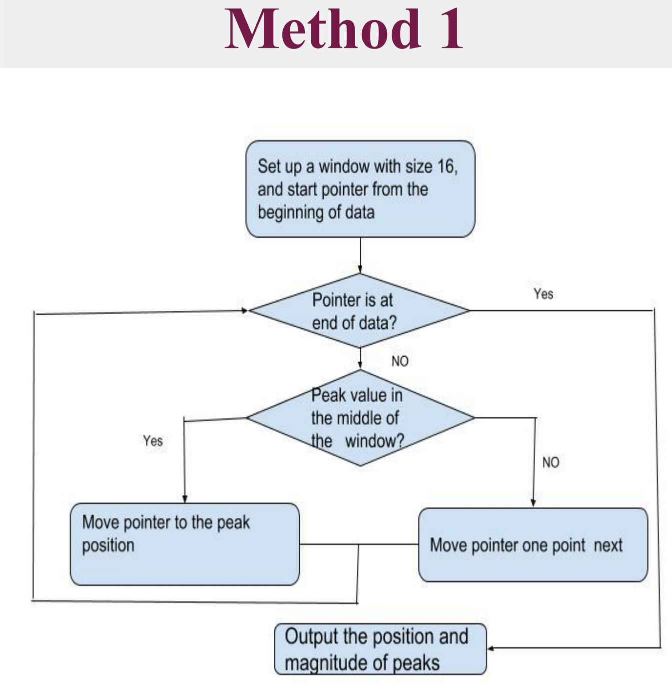

Figure 2: Flowchart of Algorithm One

Method 2

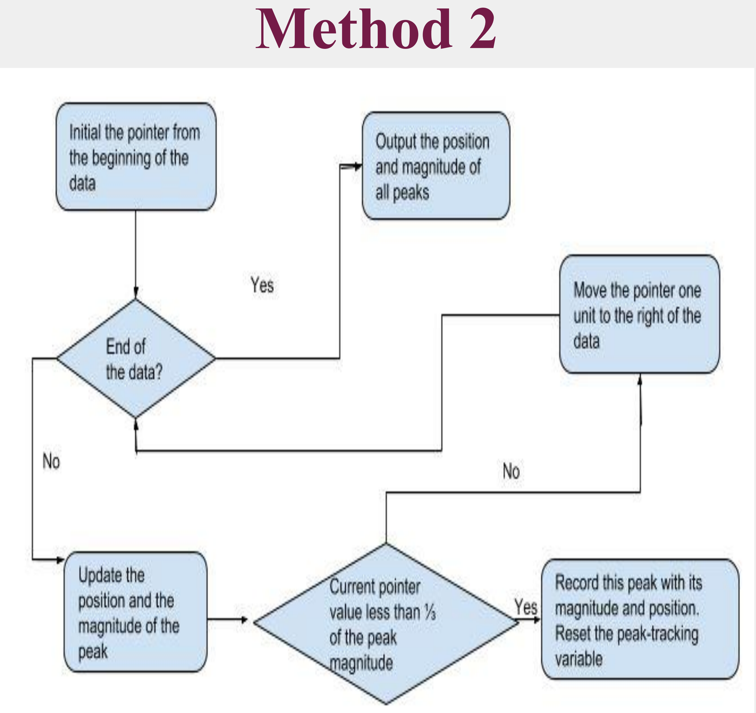

Figure 3: Flowchart of Algorithm Two

Challenges	Solutions
Original data has background noises	Apply moving average filter (MAF) to attenuate background noises
Moving average filter also attenuates peaks in high concentration (above 0.1%)	Use variance to decide whether use MAF or not for different level of concentration

Known Data Test Result

(Concentration Level: 0%, 0.001%, 0.01%, 0.1%, 1%)

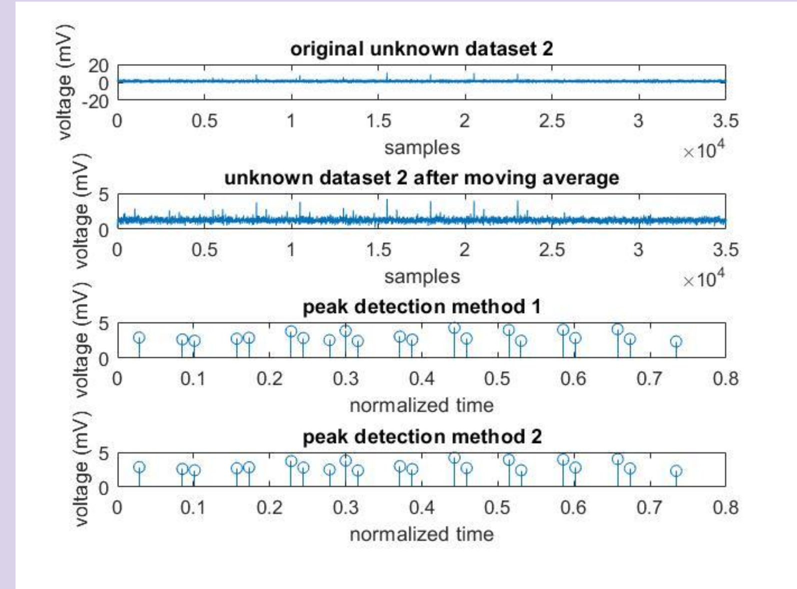

Figure 4: Test Result of 0.01% Concentration Data

- Average 2.1 peaks/set, expected average: 2 peaks/set

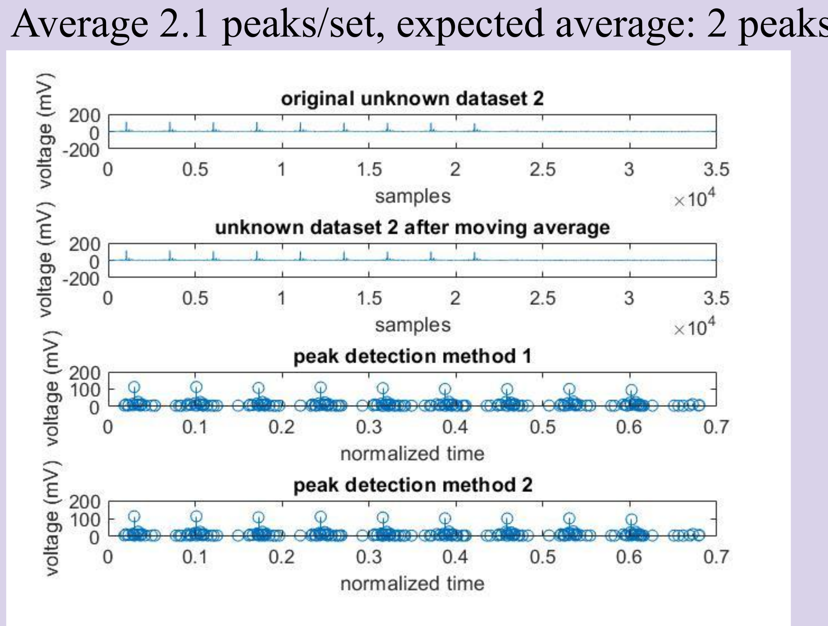

Figure 5: Test Result of 0.1% Concentration Data

- Average 20.6 peaks/set, expected average: 20 peaks/set

Standard Curve of Known Data

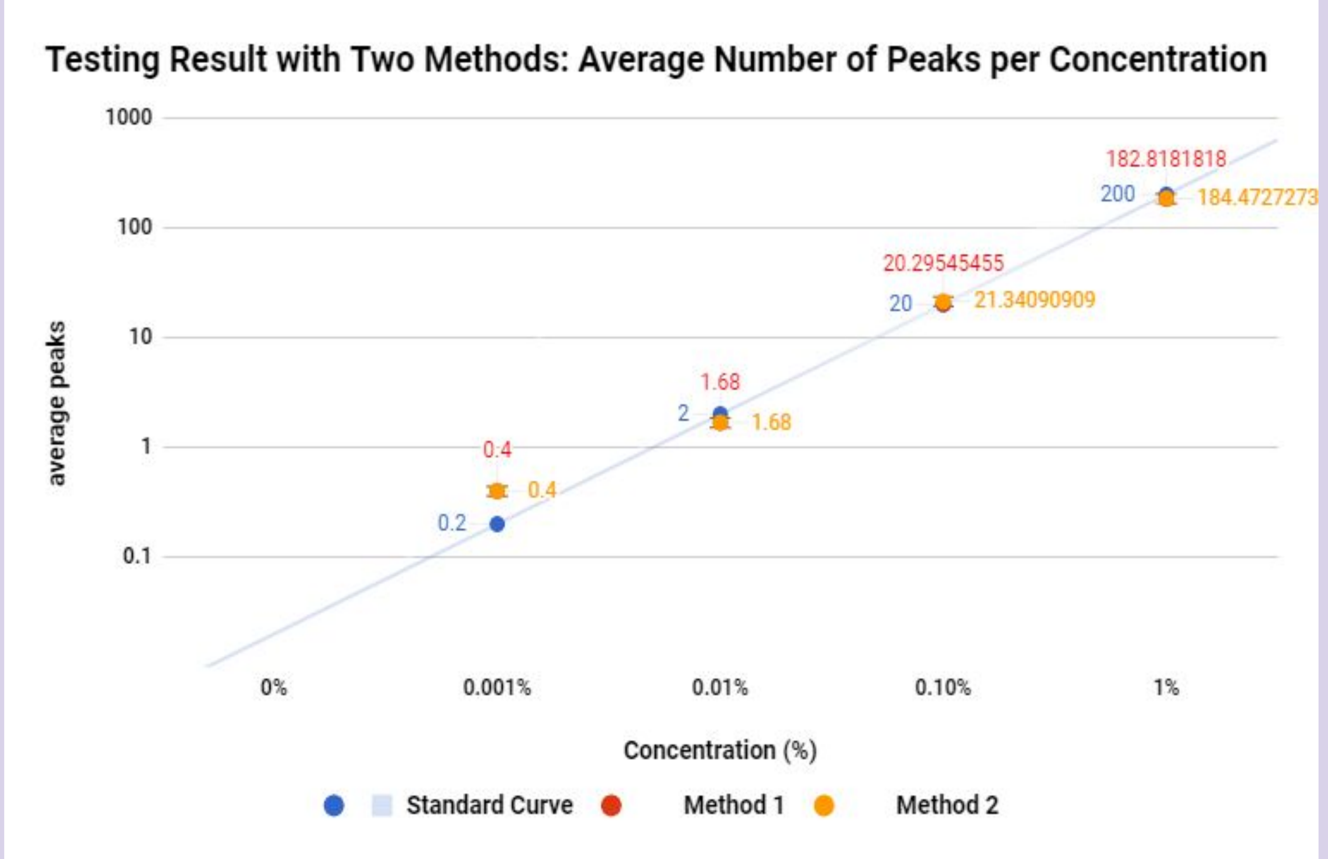

Figure 6: Standard curve of expected average number of peaks and the test result of average number of peaks of method 1 and method 2

- Standard curve shows expected average # of peaks
- Method 1 and Method 2 detect peaks within 90% accuracy above 0.1% concentration

Unknown Data Test Result

We tested unknown concentration data A - F and compared our test result with correct average # of peaks & concentration

Average Number of peaks	A	B	C	D	E	F
Method 1	1.9	108.8	0.1	5.3	1.4	105.9
Method 2	1.9	106.2	0.1	5.3	1.4	107
Correct number & concentration	2 peaks, 0.01%	100 peaks, 0.5%	0 peaks, 0%	6 peaks, 0.03%	2 peaks, 0.01%	86 peaks, 0.43%
% difference	± 0.05	± 0.062	± 0.1	± 0.011	± 0.3	± 0.23

Overall, our two methods work better in lower concentration compared to higher concentration

Spin Rate Test Result at 0.01%

sampling rate: 10k/second

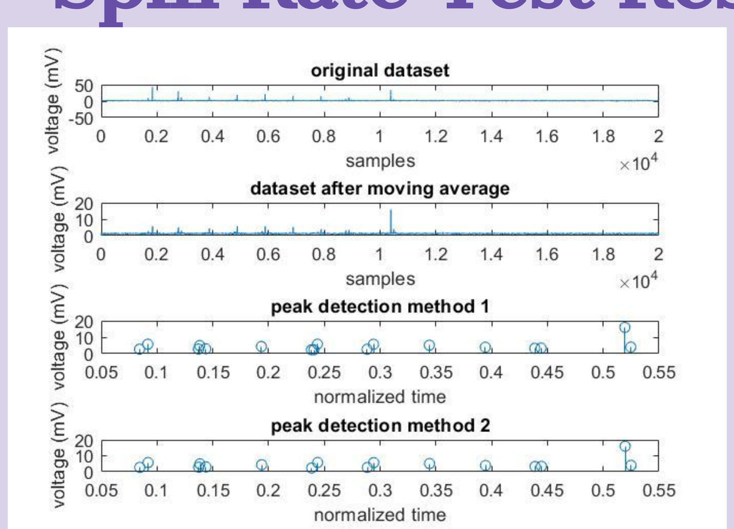

Figure 7:. Test Result of Spin Rate at 0.1 s/ revolution

- Average 1.78 peaks/set

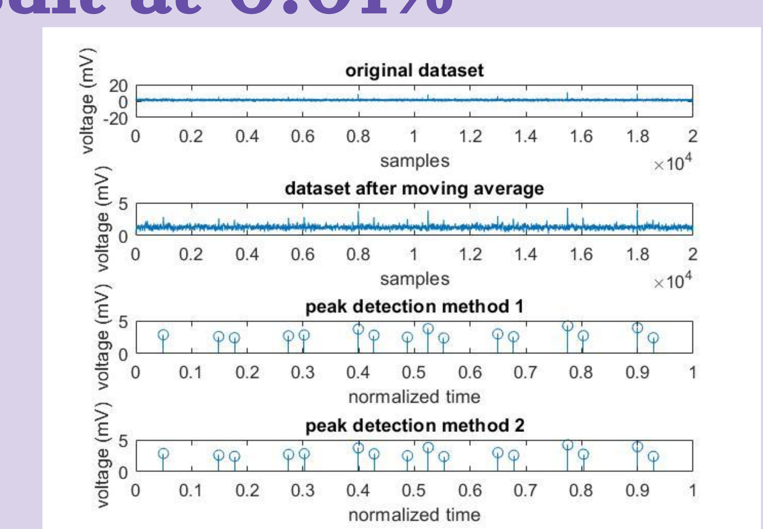

Figure 8: Test Result of Spin Rate at 0.25 s/ revolution

- Average 2 peaks/set

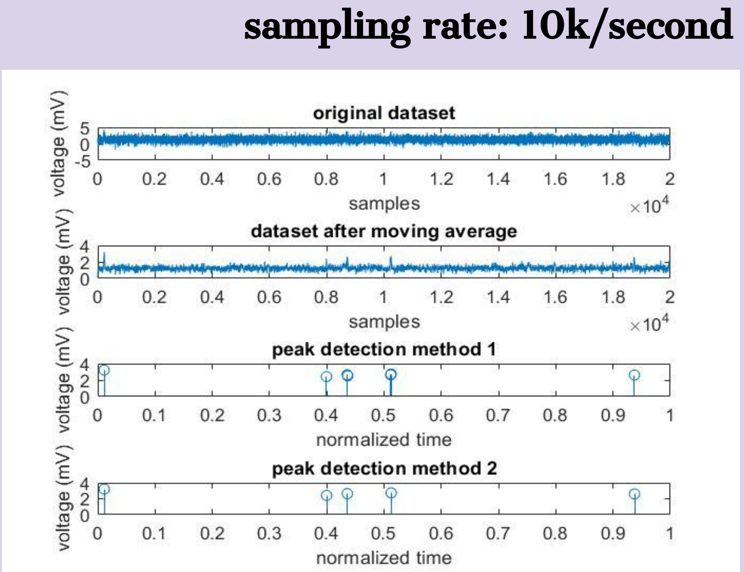

Figure 9: Test Result of Spin Rate at 1 s/ revolution

- Average 0.56 peaks/set

-For 0.01% concentration sample, the expected average number of peaks is 2. The result of 1 spin rate ends up having noisy data. In this case, moving average filter is not functional enough to attenuate noise.

Research Applications

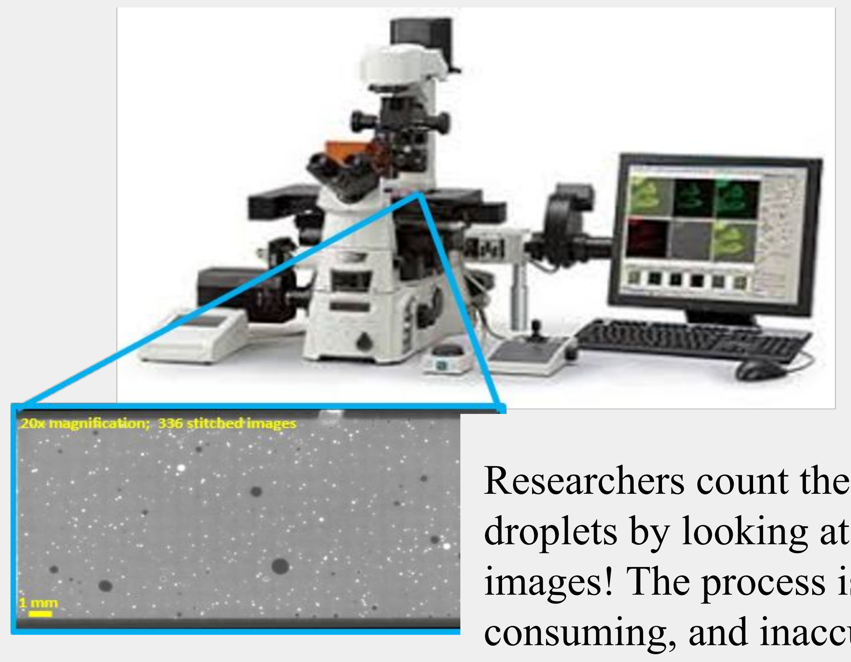

Figure 10: Image of Droplets Under Microscope

Researchers count the number of droplets by looking at microscopic images! The process is laborious, time consuming, and inaccurate.

By using Our Droplet Counting Methods:

- **Researchers will save huge amount time**
- **Researchers will get more accurate results** (they don't have to worry about counting the same droplet twice or missing small droplets)

Further Discussion

Through developing and testing our methods, we found that there does not exist a perfect algorithm that works well in every condition. In our case, some methods work well in lower concentration, but not in higher concentration and vise versa for other methods. The most promising way to improve peak detection algorithm is to test a large amount of experiments by using various data with different testing conditions. Also, during testing, generating plots of algorithms and comparing with the standard curve is a useful way to evaluate how accurate the algorithm is.

Conclusion

BSI patients have high death rate, because most patients cannot receive timely treatment. This project can significantly improve the efficiency of detecting and diagnosing BSI. Specifically, our peak detection algorithms simplify the process of analyzing the number of infected droplets in the testing sample.

Overall, our peak detection algorithms meet the sponsor's expectations to this project. However, they could be further improved by continuous testing and training with a larger and more diverse data set.

Reference

[1] Rapid detection of single bacteria in unprocessed blood using Integrated Comprehensive Droplet Digital Detection. (2014). [ebook] Dong-Ku Kang, M. Monsur Ali, Kaixiang Zhang. Available at: http://dx.doi.org/10.1038/ncomms6427 [Accessed 1 Mar. 2018].