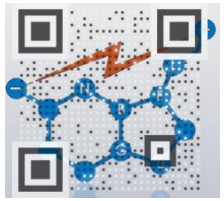

Intelligent Microelectrodes Array for Schizophrenia Treatment Monitoring

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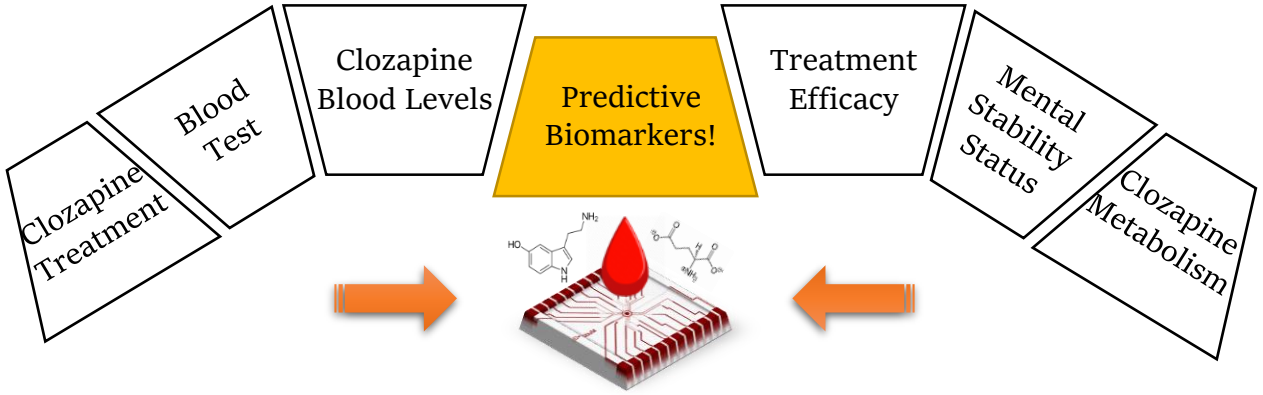
Introduction

Schizophrenia Treatment Monitoring Challenges:

- Schizophrenia (SCZ) is a mental disorder that affects more than 23 million people worldwide [1].
- **PANSS and BPRS** are mental **subjective examinations** performed by a psychiatrist with final scores that reflect the patient's mental condition.
- **Clozapine (CLZ)** is considered the most effective antipsychotic medication for schizophrenia [1]. **Despite the superior efficacy of CLZ,** it is significantly underutilized due to the unavailable objective tests to measure CLZ efficacy, **resulting sub-optimal therapy.**

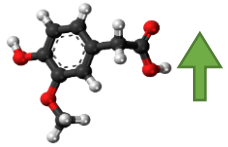
Can you suggest a new treatment efficacy test?



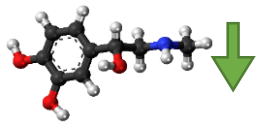
Electrochemical information **Medically information**

Novel Clozapine efficacy monitoring approach:

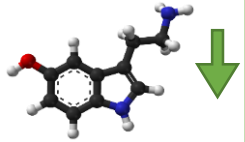
Several blood metabolites with electrochemical activity have shown to be related to CLZ treatment efficacy [2];



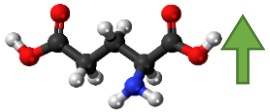
Homovanilic Acid
[1],[2],[3]
Higher concentration
Mw: 182.172
Physio. charge: -1
Redox Potential:~0.2[V]



Adrenaline
[2],[4]
Lower concentration
Mw: 183.204
Physio. charge: +1
Redox Potential:~0.7[V]



Serotonin
[5]
Lower concentration
Mw: 176.215
Physio. charge: +1
Redox Potential:~0.4[V]



Glutamate
[6]
Higher concentration
Mw: 147.129
Physio. charge: -1
Redox Potential:~0.5[V]

** All the standard reduction potentials are vs an Ag/AgCl reference electrode*

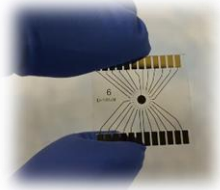
Difference in the redox-active biomarkers concentrations can lead to clozapine treatment efficacy assessment

Intelligent Microelectrodes Array for Schizophrenia Treatment Monitoring

Working Hypothesis

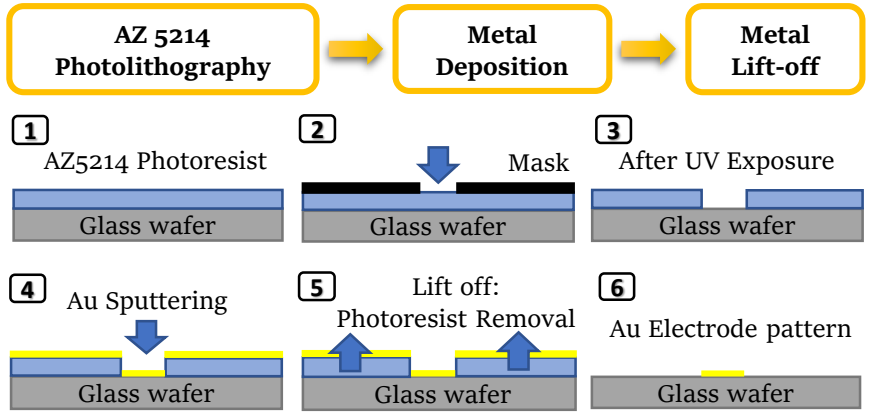
Overall Goal:

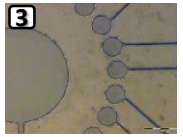
- Investigate electrochemical fingerprints of predictive biomarkers by using an "intelligent" multi-microelectrode array.
- Quantify SCZ patient's treatment efficacy by recording electrochemical signals from capillary blood samples.



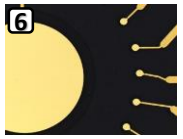
Microfabrication and Validation of the Microelectrodes Array:

Microfabrication of Gold Microelectrodes





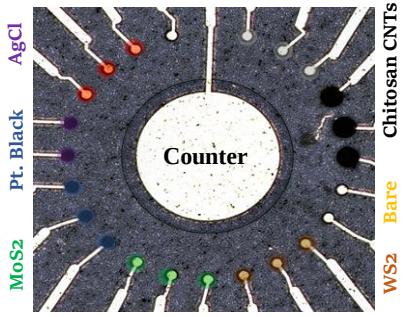
10x Magnification



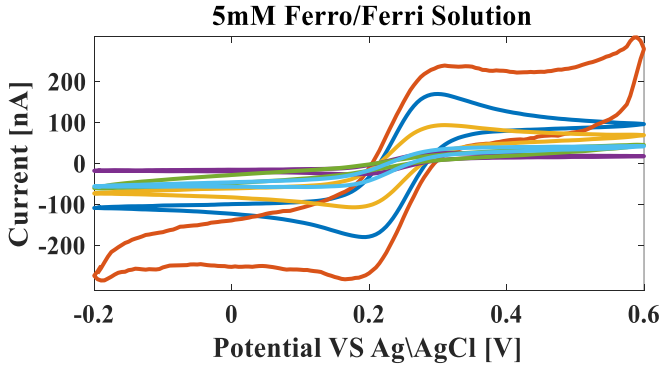
5x Magnification

Nanomaterial Electrodeposition

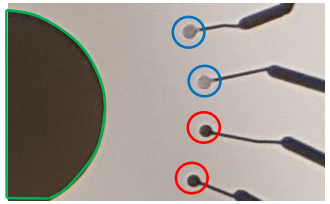
- A multi-microelectrode array was modified with 6 different electrocatalytic materials [3].



5x Magnification.



Electrochemical Validation



Theoretical values:

$E_{OCP} = -0.059 log_{10}(C[M]) + 0.028$

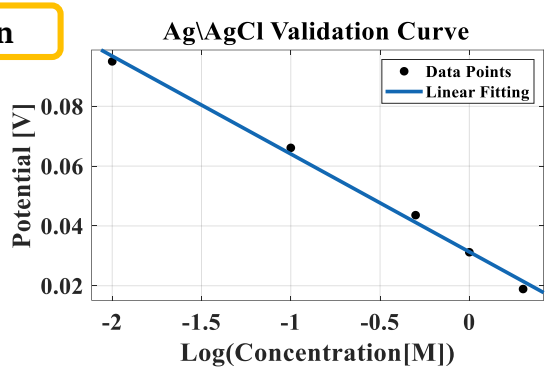
Ag\AgCl Deposition

- Working Electrode
- Reference Electrode
- Counter Electrode

Experimental values:

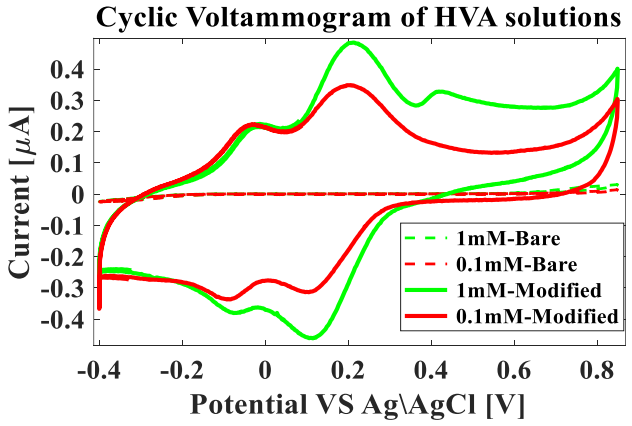
$E_{OCP} = -0.038 log_{10}(C[M]) + 0.028$

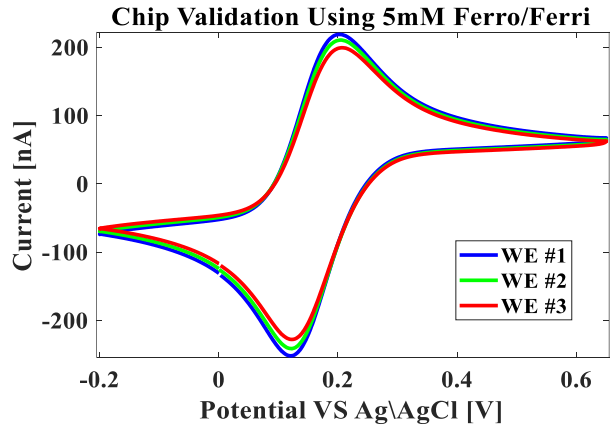
$R^2 = 0.981\,, RMSE = 2.86 \times 10^{-3}$



Homovanilic Acid Detection

- Using Bare microelectrode and Chitosan-CNT modified microelectrode to detect homovanilic acid.





Stable and reproducible electrochemical signal using microelectrode modified with Ag\AgCl as reference electrode

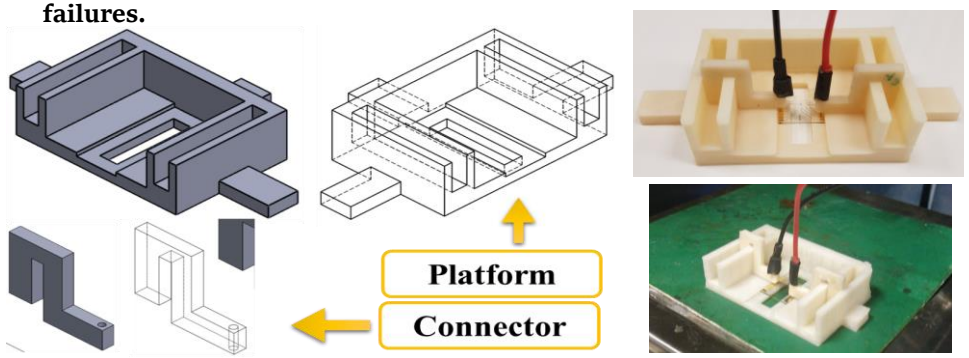
Intelligent Microelectrodes Array for Schizophrenia Treatment Monitoring

Experimental Setup and Results

Chitosan Modification Density Effect on Charged Electroactive Molecules

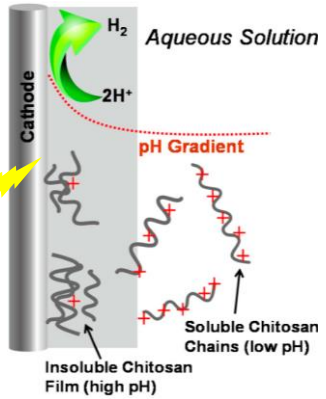
3D printed Experimental Setup

- Easy multiple measurements, and less electrical and mechanical cell failures.

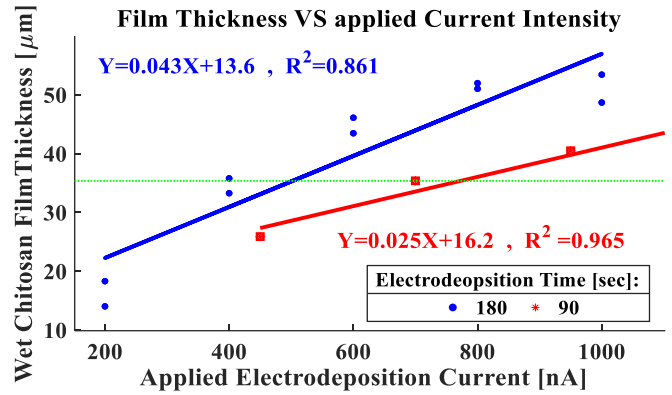


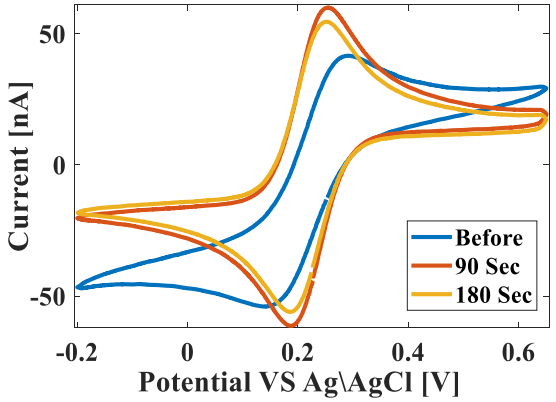
Chitosan Electrodeposition [4]

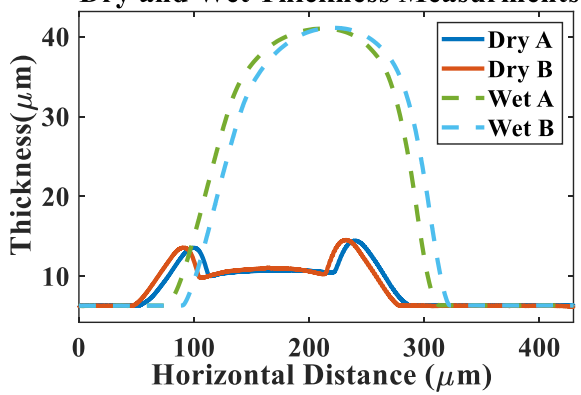
- Applying voltage triggers water hydrolysis
- Electrode's interface pH increases
- Chitosan polymers change solubility into a hydrogel
- Chitosan film is electrodeposited

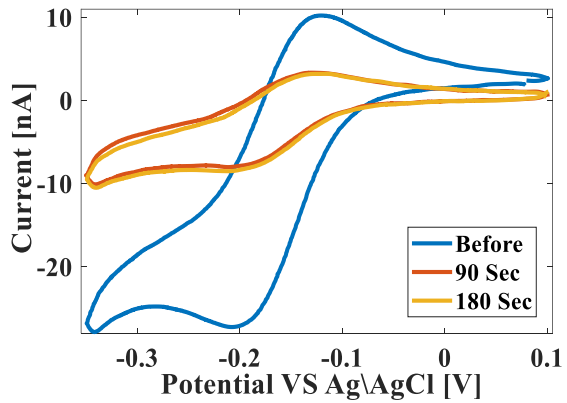


Film Thickness Calibration









Molecular properties		Ferrocyanide	Hexaammineruthenium
Molecular weight / Physiological charge		211.95 / -4	197.2 / +2

Applied current	Electrodeposition duration	Mean modified electrode permeability for each molecule		Dry Thickness (μm)	Porosity
510 nA	90s	1.26 ± 0.02	0.429 ± 0.020	10.7±0.1 μm	5.38±0.09
950 nA	180s	0.972 ± 0.041	0.379 ± 0.025	13.2±0.6 μm	4.36±0.20
T-test Significance (P value)		0.85%	4.57%		

similar wet chitosan thickness (57.6±0.8) was successfully achieved.

Chitosan Different Densities:

- **Same thickness of chitosan yet with different deposition parameters** can result in **different film's porosity architecture**.
- Chitosan is cationic polysaccharide and can affect the mass transfer of positive (**Hexaammineruthenium**) and negative (**Ferricyanide**) redox-active molecules.

Positively charged chitosan affects differently charged redox-active molecules

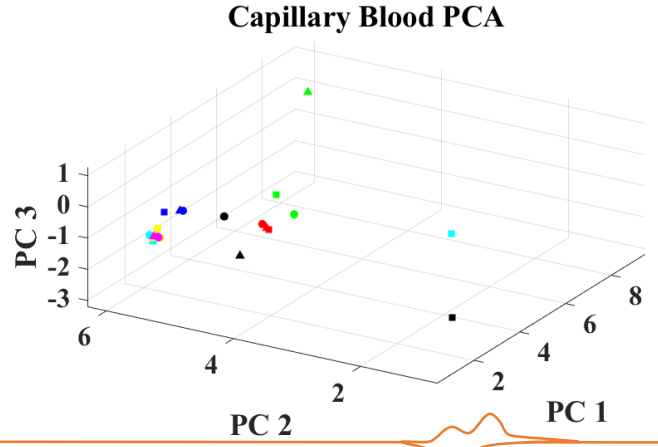
Results and Conclusions

Electrochemical signal variability validation on Schizophrenia blood samples

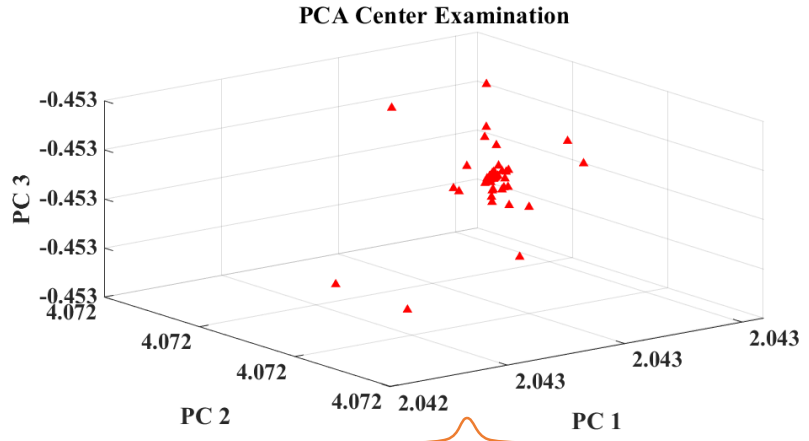
Experimental Information and Signal Processing:

- electro-active biomarkers in the blood is influencing the blood's electrochemical fingerprint.
- We using the records of DPV signals from blood samples of 10 different SCZ patients.
- Our mission is to understand the electrochemical signal variability from the different modified microelectrode in the array.
- In order to do so, we will use principal component analysis (PCA) algorithm to cluster the data based on modification type.

PCA :
Orthogonal linear transformation to new coordinates system based on the data covariance matrix eigenvectors and eigenvalues. The transformation is reducing the problem dimension while preserving the data variability!



- **Each color represents a different modification**. We also discover the reason for each center- The **different position in the array!** Each modification has repeats in the array (The points shape).
- **Each Center is 99 points in a very dense data cluster!**



Conclusions

- Microelectrodes were microfabricated and were modified with several modifications.
- HVA was successfully detected with the modified microelectrodes.
- Chitosan's different thicknesses affected the electrochemical signal recorded from differently charged molecules.
- Principal component analysis showed variable electrochemical signals.

Acknowledgement

- The authors thank the Nano-Fabrication Center at the Ben-Gurion University of the Negev for their help microfabricating the microelectrodes arrays.

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