7.4.2019

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BI-ANNUAL
INTERNATIONAL
CONFERENCE

In the presence of
DR. DIMITRY ZIMIN

ZIMIN INSTITUTE

for Engineering Solutions
Advancing Better Lives

SUN • 9:30 AM

George S. Wise Senate Building,
Raya and Josef Jaglom Auditorium,
Tel Aviv University

TEL AVIV UNIVERSITY
Pursuing the Unknown

Greetings

Yearly Reports

#1

BI-ANNUAL INTERNATIONAL CONFERENCE 2019

DR. DMITRY ZIMIN

Founder of Vimpelcom & Dynasty Foundation

Dear friends,

The dream behind my creation of the Zimin Institute for Engineering Solutions Advancing Better Lives at Tel Aviv University was for the Zimin Foundation to enable talented Israeli researchers to translate their academic work into real-life technologies that will make our world a better place for future generations.

The first Zimin Institute Conference is a remarkable milestone for us. It has gathered and connected hundreds of researchers from various fields, Nobel Prize laureates, University management leaders, businessmen and investors. The conference is taking place in a successful year both for Israeli science and research-driven businesses, some of which have just made headlines.

We are announcing the second group of Zimin institute grantees at the Conference. The family of wonderful projects is growing and each of these projects has great potential for impact.

I wish all the participants a productive conference, learning from other brilliant minds and exchanging ideas for the mutual benefit of humanity.

Best Regards,

DR. DMITRY ZIMIN

PROF. JOSEPH KLAFTER

President of Tel Aviv University

Dear Zimin family,

I take this opportunity to express my sincere appreciation to the Zimin family for their generosity and friendship in establishing the Zimin Institute for Engineering Solutions Advancing Better Lives. There is no doubt that it will create a platform for Tel Aviv University's engineering ingenuity in tackling and generating solutions to global challenges, thereby improving the quality of life for many.

I am delighted to enclose reports of the five recipients of the first Call for Proposal for the Zimin Institute for Engineering Solutions Advancing Better Lives.

These excellent researchers well represent the success of the Zimin Institute for Engineering Solutions Advancing Better Lives through their research focused on addressing some of the world's most pressing challenges. At the same time, the Zimin Institute greatly enhances the University's ability to offer promising researchers the opportunity to advance further into their chosen field, which is of vital importance both to the University and to the country — particularly in the areas of Artificial Intelligence and Advanced Sensors in Engineering Solutions.

We look forward to the continued resultant achievements of the research projects with real-world impact in 2019.

PROF. JOSEPH KLAFTER

PROF. DAVID MENDLOVIC

Head of Zimin Institute

Esteemed Colleagues,

I am honored and delighted to welcome you to the Bi-annual International Workshop of Zimin Institute for Engineering Solutions Advancing Better Lives, and hope for fruitful and exciting event.

This Institute was established by the Zimin Foundation, a unique organization that plays a role in making our world better. Tel Aviv University was selected to host the first Zimin Institute following the vision of Dr. Zimin, the Founder of Zimin Foundation that significant technologies for better world should come from academic institute.

I'm sure that this brave and significant dream of Dr. Zimin will push extraordinary deep technologies from basic science stage to commercial implementation. This transformation will be done by kind financial support of Zimin Institute as well as an active business development efforts by Zimin Foundation experts.

This is the first bi-annual Zimin Institute workshop, and we are proud to have the highly respected speakers.

It is a great opportunity to exchange visions and technical aspects among the researchers. We believe that this significant step towards a better world is only the first and hope to enjoy the great results come from the research activities.

We would like to deeply thank Zimin Foundation for the king support and the great vision, and wish you all a fruitful workshop.

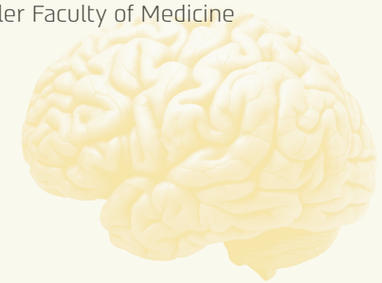
Yours,

PROF. DAVID MENDLOVIC

Yearly Reports **2018**

Development of a multimodal Brain-Computer Interface based on artificial intelligence for rehabilitation of people with motor disorders

DR. JASON FRIEDMN
DR. KONSTANAIN SOKNIN
Sackler Faculty of Medicine



Research and Development Progress

The project aims to develop a multimodal brain-computer interface (BCI) for control of devices, which is based on a combination of brain signals and residual movement recordings. The system performs decoding of brain and body signals, measured by EEG, accelerometers and gyroscopes, by means of advanced artificial intelligence techniques. The technology aims to improve quality of life of millions of people with severe movement disorders by satisfying their needs to be independent and able to participate in modern life by means of a software-hardware system for touchless control of devices and neuro-rehabilitation.

The developed AI-based classification system performs a real time cycle of 1) multimodal parallel acquisition of EEG and IMU signals; 2) signal processing; 3) advanced feature extraction (including principal component analysis, kinematic landmarks analysis, spectrum analysis, wavelet transform and feature selection); 4) decoding of motor commands by means of classifiers based on machine learning; and 5) control of devices. A detailed block diagram of the developed system is shown in Appendix Fig. 1. Results of the preliminary study demonstrated required performance of the system for control of devices in real time based on decoding voluntary movements from

a combination of residual movement recordings and motor imagery (registered in EEG).

Currently the following *results* have been achieved:

- prototype of multimodal BCI system based on a combination of EEG and movement data decoding in real time has been developed;
- invention Disclosure Form was submitted to Technology Transfer Office TAU (Ramot) and United States Provisional Patent Application No. 62/756,156 "Multi-modal brain-computer interface based system and method" has been filed in November 2018;
- the study design in healthy subjects was developed and application has been filed to the human ethics committee of Tel Aviv University in December 2018;
- a letter of intent to conduct pilot clinical trials has been received from the Division of Neurological Rehabilitation of the Chaim Sheba Medical Center, Tel Hashomer

Thus, all the planned tasks for the first year of the grant were implemented, which allowed us to reach the 1st year milestone – "Multimodal classification system based on AI for motor command decoding is developed and ready for testing on healthy subjects".

Initial testing of the system

A prototype of multimodal real-time BCI prototype combining brain and body signal analysis has been developed. Decoded motor commands in real time are applied to control assistive devices and specialized applications. The basic principle of the multimodal system is to use mutual validation of motor command decoding obtained from both IMU and EEG pattern recognition. If one classifier recognizes the pattern corresponding to a motor command, the other classifier has to validate it, with minimal time delays. Within the scope of the project special neurofeedback applications in game form were developed and paired with the prototype (see Appendix Fig. 2).

EEG – recording, feature extraction, selection and classification.
Using EEG, the initiation of any voluntary muscle movement is seen in unique electric patterns on the scalp. Similar patterns may also appear when a muscle contraction does not occur (e.g., imagined movements, including in the case of paralysis or amputation). Hence, we focused on developing a comprehensive system to record and quickly analyze EEG →

data from subjects. This online (real-time) analysis allows us to create a prediction of the intended movement, based solely on EEG data. EEG is recorded during the training protocol, where subjects move (or imagine movement) at cue. Raw EEG data is transformed into the power-frequency domain. Then, frequency features are selected using statistical methods and are used to train an SVM classifier. Once a classifier is trained, new EEG segments can be classified by it in real-time. By experimenting with many parameters, at this point, we were able to increase accuracy of classification to more than 80% in some cases. For example, by selecting features individually, based on a subject's EEG recordings - the achieved classification accuracy was higher compared with using a set of features that are selected for a different subject or a general set of features.

Movement data - recording, analysis and classification.
For signal acquisition two wireless Inertial Measurement Units (IMU) were placed on two shoulders inside special bracelets. 4 types of shoulder movements and rest were recorded. Filtering, time-series analysis and principal component analysis were performed on the 14-dimensional data to decrease its dimensionality to two dimensions. Descriptive features, such as kinematic landmarks, velocity peaks, were extracted from the first principal component for each IMU. A classifier based on machine learning was trained and tested for each subject (5-fold cross-validation was performed). 10 subjects participated in two types of experiments: in "Lab Conditions" experiment the patient trained the system and immediately tested it. In "Day to Day Usage" experiment a previously trained classification model was tested. In the "Lab Conditions" experiment the mean classification accuracy was on average 98±2%, whereas in "Day to Day Usage" the mean accuracy was on average 89±13%. Preliminary results indicate that the system learns to decode a subject specific movement profile accurately in real time. The position of the sensors affects the accuracy significantly, however usability of the system will be secured even without retraining of the classifier in day to day usage.

Continuation of R&D towards technology commercialization

The next stage of the project aims at bringing the technology to the market of rehabilitation devices. Market research has been done in order to specify and verify the need and future positioning. The postdoc in charge of the project in the lab was invited to join the Global MBA program of Tel Aviv University

in order to elaborate go-to-market strategy and business models using MBA interns under the supervision of faculty professors. During the 2nd year of the project, a full business plan will be built.

Further development will include:

- minimal viable product development,
- testing of the system in real time conditions on campus,
- modification to target rehabilitation purposes,
- obtaining Helsinki committee approval and pilot testing on patients with motor disorders.

These steps will allow to develop a valuable Intellectual Property (IP) with high applicative potential in 2 main segments:

1. **B2C:** Touchless control of devices such as laptops and smartphones in special accessibility mode for communication and independent control of applications using imaginary and actual residual movements available for a user. Automatic adaptation is provided for users with different motor capabilities - from light impairment of fine motor skills (caused by stroke, traumatic brain injury (TBI), etc.) to severe disabilities and even paralysis (e.g. caused by spinal cord injury (SCI)).
2. **B2B:** Rehabilitation of impaired motor function, based on feedback from the combination of relevant brain signals and residual movements. By relying on brain plasticity, multimodal BCI helps train persisting cortical connections to execute motor output of the motor-impaired limb (e.g., hand). In general, BCI has implications for the potential of recovery while it can be considered as an assistive solution to traditional physiotherapeutic approaches. Several clinical studies showed evidence for the feasibility and positive effect of BCI-based neurofeedback systems for motor post-stroke recovery (Arvaneh et al., 2016; Lazarou et al., 2018).

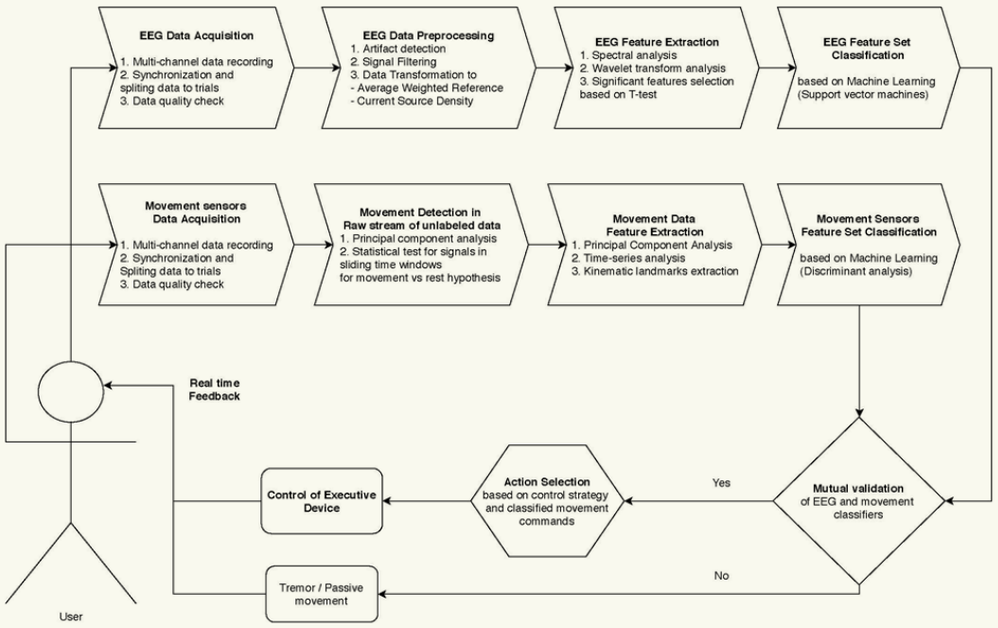
In addition to the R&D process and clinical trial, a special analysis should be done in the field of regulation and reimbursement policy in the US and the EU markets, which together allocate more than 70% of the global neuro-rehabilitation market. This study aims to define a value proposition and market fit for optimal market penetration.

Thus, the second year of the project will develop a minimal viable product based on the developed technology, will →

test the technology in a target population of users, and will elaborate a market penetration strategy in order to improve the efficiency of rehabilitation for patients with motor disorders. We have started discussions with the Life Sciences business development manager at Ramot in order to determine the best way to commercialize our technology, and we look forward to discussing these options with representatives from the Zimin Institute.

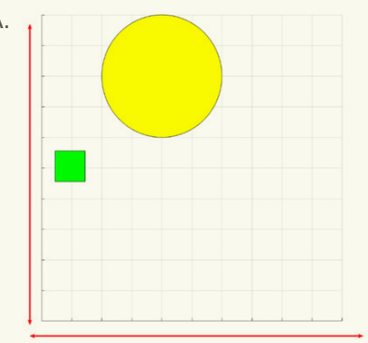
Appendix

Fig. 1. A detailed block diagram of the developed system



describing main steps in parallel signal processing and classification based on machine learning.

A.



B.

Fig. 2. Feedback interface for experiment phase (a) and for user application (b)

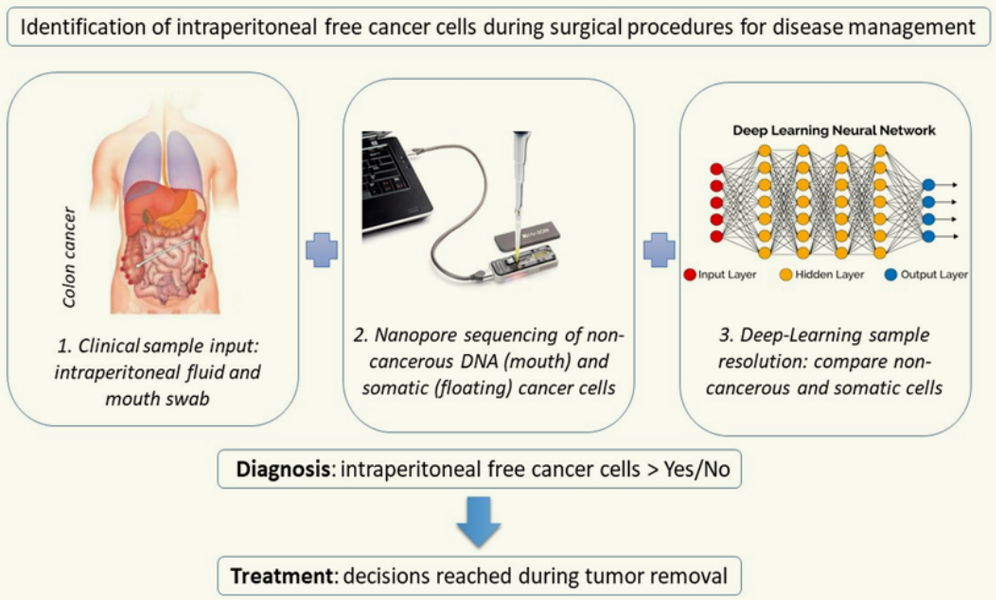
Notes: (a) In the experimental phase, a simple game will facilitate as interactive feedback platform. The task is to move the square towards the yellow circle. Classification of both types of data is done in parallel. By means of neurofeedback, this should encourage users to change their brain electrical patterns to be synched with actual movement. The difficulty level will be continually adjusted according to the patient's improvement (b) Later, the system would operate a range of applications that would benefit patients with severe motor deficit. This is an example of an application – a special environment, where user can navigate and select required actions and entertainments, call for help. ■

ZIMIN INSTITUTE ⚽ BI-ANNUAL INTERNATIONAL CONFERENCE 2019

Identification of intraperitoneal free cancer cells during surgical procedures for disease management: a multidisciplinary engineering solution using deep learning and real-time-rapid sequencing technology

PROF. NOAM SHOMRON

SACKLER FACULTY OF MEDICINE



Why we fit the Zimin Institute ideas

We propose a solution for a pertinent medical question.
We employ deep learning algorithms in our solution.
We use a multi-disciplinary approach in our research.

Abstract

Intra-abdominal malignancies often result in intraperitoneal free cancer cells (IPCCs), which increase the chances of cancer spreading to distal organs, and serve as an important prognostic tool in cancers such as ovarian and gastric cancers. Curative treatments based on intraperitoneal chemotherapy often have effective outcomes, however, the time between IPCC sampling and detection is critical, currently taking weeks to reach a conclusion. The MinION (Oxford Nanopore Technologies) – the first handheld genetic sequencer – is capable of reading long stretches of DNA in a real-time, but has not yet reached the level of accuracy of older, slower technologies. Deep learning techniques mimic the learning process of the human brain in order to recognize patterns in digital representations. In our lab, we use deep learning to circumvent the limitations of Nanopore sequencing by learning the 'signal' rather the 'sequence' of the DNA. The aim of our project is to establish a rapid real-time method for the detection of IPCCs during colorectal resection. We propose a solution that takes advantage of our close collaboration with the Surgery Division at Sourasky Medical Center, and is based on three components: (i) access to clinical samples (abdominal fluid and mouth swabs) collected during resection; (ii) rapid real-time DNA sequencing; and, (iii) deep learning algorithms for the discrimination between somatic versus non-cancerous DNA. We believe the time has come to merge DNA sequencing (as a 'digital signature') with deep learning in order to afford surgeons the opportunity to quickly identify IPCCs during surgical procedures, thereby allowing immediate treatment and decreasing the need for future intervention.

Update

We have established protocols for collection and extraction of DNA from several sample scenarios (swab, fluid with high and low number of cells). We have run some of the experimental protocols and the MinION on human (non-patient) positive and negative control samples in our lab. We have performed Deep Learning on MinION sequencing →

data we have collected. We have regular meetings and a submitted IRB with Sourasky Medical Center (with Dr. Guy Lahat and Dr. Shelly Loewenstein) which is pending final signatures at the local (Sourasky) committee. Since the National Ethical Committee was non-functional for more than four months, our approval was delayed and therefore we will receive the samples from patients undergoing operations at Sourasky upon approval. This is expected in the coming couple of weeks as they have only asked our team for a small amendment.

In year two

We expect to complete the scanning of the tissue samples, to identify cancer cells in the abdominal fluid, and to prove that this could be done in a timely fashion, namely during (and not after) the operative procedure.

Challenges and Solutions

Intraperitoneal free cancer cells (IPCCs): Intra-abdominal malignancies often result in IPCCs, which increase the chances of cancer spreading to distal organs, and serve as an important prognostic tool in cancers such as ovarian and gastric cancers. Colorectal cancer is one of the most frequent cancers worldwide, with development of peritoneal carcinomatosis in 10-30% of patients. Curative treatments for peritoneal carcinomatosis, such as cytoreductive surgery and intraperitoneal chemotherapy, have been shown to be effective, especially in malignancies of colorectal origin, thus increasing interest in free malignant cell detection.

Nanopore sequencing: Oxford Nanopore Technologies (ONT) has developed several devices that use newly developed nanopore technology to read DNA sequences. The smallest model, the MinION, is half the size of a mobile phone and can be directly connected to a laptop or even, making it the most portable genetic sequencing device currently on the market.

Deep Learning: In simple terms, deep learning techniques attempt to mimic the learning process of the human brain in order to recognize patterns in digital representations of sounds, images, and other data. We will use deep learning to identify and differentiate digital signatures of non-cancerous DNA (healthy DNA from patient mouth swabs) and DNA from cancer cells (collected from intraperitoneal fluid) that have undergone Nanopore sequencing.

Combining fields

Here we introduce a novel approach for IPCC identification during colorectal cancer surgery. We will use deep learning on signal output from rapid real-time sequencing. Our negative control (baseline measurement) would be non-cancerous DNA derived from patient mouth swabs, which is potentially 'healthy' non-mutated DNA. We will compare this signal to intraperitoneal fluid that might contain cancer cells and will supply mutated cancer DNA. Contrary to the current approach to sequencing, which is only capable of reading DNA sequences, we intend to use this technology to identify multifactorial patterns of DNA characteristics for cancer cell classification. Cancerous and non-cancerous DNA signals will be translated into digital signatures (voltage measurements), which will be processed using deep learning algorithms.

Goals and Milestones

1. Collect clinical samples in the operating room: mouth swabs and intraperitoneal fluid from each colorectal patient. Send to clinical/pathological evalation.

   Todate *we have conducted multiple meetings with the medical team at Sourasky Medical Center, Dr Guy Lahat and Dr Shelly Loewenstein. We have outlined and tested protocols for collection of the samples from the operation room. We are currently waiting for the final IRB committee ethical approvals in order to receive the samples. We have applied severeal DNA extraction protocols on practice samples and evaluated the yeild and purity.*

   In year two we will run our tested protocols on the sample we will receive from the operation theater.

2. Train the deep learning algorithm on non-cancerous and cancerous data in order to evaluate its ability to characterize both types of sampes.

   Todate *we have run simulations to demonstrate that the Nanopore machine is productive in our hands. Valuable data was collected on control samples (see the results presented below).*

   In year two *we will apply these algorithms on the clinical samples.*

3. Run MinION experiments on mixed cancer cell line and →

primary healthy cells at various ratios for testing our deep learning algorithm to seperate the two types of cells.

Todate *we have run simulations to make sure that the Nanopore analysis gives useful and meangful data in our hands on several non patient samples (see the results presented below).*

In year two *we will apply these algorithms on the clinical samples.*

4. Extract DNA from the clinical samples and characterize using rapid real-time DNA sequencing. Initial quality control of sequencing data will include elimination of non-informative data, such as non-human derived signals (Steps 3-4, expected 6 months).

   To be *carried out in year two, commencing April 2019 or before.*

5. Apply deep learning techniques to develop effective tests of discriminiation performance. Then, apply the resulting algorithms to collected DNA data from positive/negative controls (from above) and validate accuracy (Expected 6 months).

   Todate *we have run simulations to make sure that the Nanopore analysis gives useful and meangful data in our hands on several non patient samples.*

   In year two *we will run the analysis on the patient data commencing April 2019 or before.*

6. Apply algorithms to rapid real-time data from samples with
   unidentified cancer cells in order to distinguish between and classify IPCCs for prognostic evaluaiton (Expected 6 months).

   To be *carried out in year two, commencing April 2019 or before.*

Overall, we intend to combine all of the goals listed above for rapid real-time analysis of IPCCs in colorectal cancer resection procedures for better therapeutic outcomes.

Our year two studies are critical for our success as they will transform our simulations to real life data based on the clinical samples. At the end of the second year we expect to be at a position where we will be able to present our findings and to discuss potential applications of our study.

Preliminary results

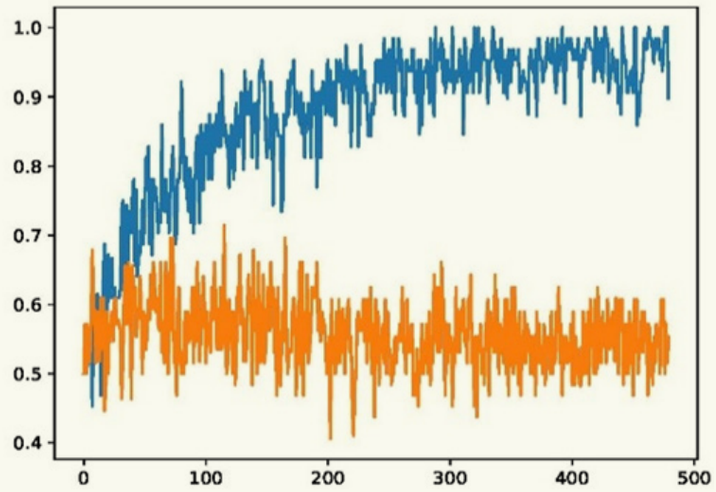


Figure 1: Training process for selective sequencing of a specific gene. Training process of LSTM with recurrent batch normalization model, the figure demonstrates one of the possible problems during deep learning model training. The divergence between accuracy values on the training dataset and test dataset indicate a clear case of overfitting where the model "remembers" the training dataset therefore have a high accuracy of that dataset, but when the model encounters unseen samples from the test dataset the classification accuracy decrease drastically. Accuracy on the training dataset (blue) compared to the accuracy on the validation dataset (orange). The time-span of the X is equivalent to 300 epochs.

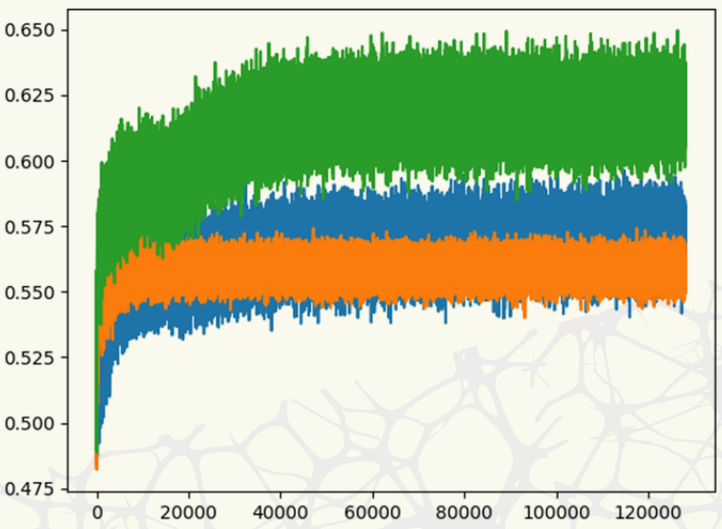


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Figure 2: Training dataset accuracy of three separate models. Training dataset accuracy of the three separate models, which were combined into the final model, during the training process. It can be seen that all three models increased their accuracy during training, meaning all inputs were important for the classification of the reads, therefore combining all models into one final model should utilize all the available data to perform the classification. Blue tracks the accuracy of model based on nucleotide sequence. Green tracks the accuracy of the model based on the aligned sequence length parameters. Orange tracks the accuracy of the model based on the first and last positions of the alignment on the chromosome. The Y axis is the accuracy value; X axis is number of mini-batches from the beginning of training.

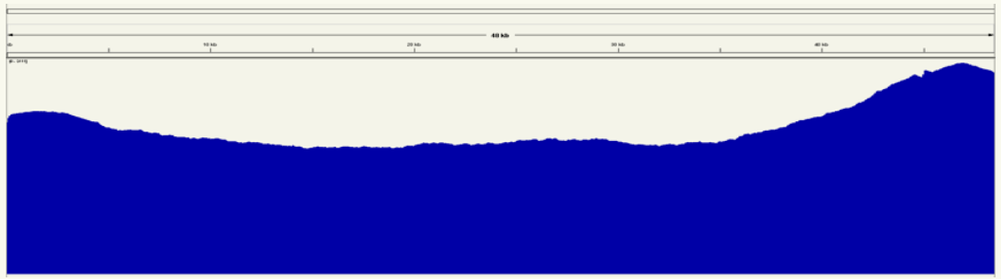

Figure 3: Genome coverage of a virus (Enterobacteria phage λ) as represented by IGV (a visualization software). This genome might represent an anomaly in a genomic sequence from a cancer cell. There is an even coverage on the Labmda phage genome with slight elevation at the last portion of the genome. The increase in coverage is caused by the control DNA added during library preparation steps, the control DNA is identical to this portion of the Lambda phage genome. The x-axis represents the genome of Enterobacteria phage λ in length, the y-axis represents the coverage of each nucleotide of the Enterobacteria phage λ genome.

Figure 4: Coverage of human genome as represented in IGV. The coverage of the human genome (which is the background in our experiments) achieved from sequencing a human cell line sample. Although it may appear the reads cover large portions of the genome, in reality the reads aligned sparsely to the genome with large gaps in between. This was the expected result based on the amount of output data from the sequencing. This would be the basis for our future comparison when looking at cancer genomes compared to non-cancerous ones.

Year two is essential for commercialization

Our project is at the verge of its critical experiments. We expect year two to be our turning point in establishing the proof of concept that cancer cells could be told apart from non-cancer ones using a rapid analysis while the patient is still in the operation room. Our preliminary results of year one prove that as a concept it is possible, yet it is critical for us to show it in a 'real-life' setting. Once this is achieved we can plan how to implement it as a standard of care where physicians require rapid feedback during invasive procedures.

Potential commercialization of our project

We believe that rapid feedback during medical procedures is essential for improving clinical intervention. We reached this project after carrying out extensive discussions with physicians from multiple departments. We are aware that there is missing information that the physicians require to carry out knowledgeable decisions and there are very little solutions that can assist them at the moment. We believe that our project should be integrated into one of the departments at a leading hospital. For example, in the Pathology department where samples are received regularly for analysis, or closer to the decision making physician at the Surgical department in the operation room. Once one of these hospital units adopts our setting, a routine protocol could be followed for sample collection, processing, analysis and reporting. Early adopters could be our test case and should work closely with our team to make sure that valuable data is transferred back to the decision makers. We want to make sure that the decision could lead to better treatment, therapeutics or procedures. Given that we focus on the academic – experimental side, any valuable commercial – business guidance would be welcome. ■

Artificial Intelligence Algorithm for Predicting the Optimal Interventional Time for Transcatheter Aortic Valve Replacement

PROF. RAMI HAJ-ALI

THE IBY AND ALADAR FLEISCHMAN FACULTY OF ENGINEERING

Brief Summary

Calcific aortic valve disease (CAVD) is a formation of tissue similar to bone on the leaflets of the aortic valve (AV), which rapidly leads to aortic stenosis (AS). However, patients usually do not have symptoms until the disease has progressed to an advanced stage. Transcatheter Aortic Valve Replacement (TAVR) is a new technology that provides an alternative to open-heart surgical valve replacement. In this type of minimally invasive intervention, a stent with a mounted bioprosthetic valve is delivered through the arterial tree and deployed through the stenotic native valve. Still, there are some doubts regarding the optimal time for intervention in CAVD patients, and concerns regarding TAVR implantation related to complications such as incomplete anchoring, paravalvular leakage, and annular rupture. Our aim is to expand our methods of retrospectively calcification growth

evaluation techniques to develop an artificial neural network (ANN) algorithm that will allow us to predict the optimal time for TAVR intervention in CAVD patients and the optimal TAVR device needed to be implanted.

CT scans of pre-TAVR TAV patients were collected from our existing database of CAVD scans. Our Reverse Calcification Technique (RCT) was employed for selected patients in a similar manner to our previously suggested RCT method, to generate various stages of the CAVD disease. This technique is based on using CT scans of calcified AVs to study the calcification progression that leads to the current state. In addition, from each CT scan we extracted additional input parameters: volume & pattern of the calcification deposits for each leaflet and the orifice area of the calcified AV.

The output of the algorithm will result in scoring of the CAVD severity, which will be evaluated according to calculation of the input parameters. The RCT results for each scan will be compared with old CT scans of selected patients in order to relate the CAVD stage with time. This type of information and data will allow us to predict the development of calcification in time, and eventually, the optimal time for TAVR intervention (Figure 1).

Simulations of TAVR deployment inside calcified AV has been performed by our group, towards trained ANN from the simulated biomechanics models. Finite Element (FE) simulations of the deployment of the TAVR devices: Sapien 3, Evolut R and PRO, were modeled inside calcified bicuspid aortic valve (BAV) anatomy (Figure 2). The stents were initially crimped with a cylindrical crimper. The Evolut R deployment is a result of the residual stresses present in the stent after the crimping while gradually pulling the sleeve toward the aorta. The FE solver is SIMULIA Abaqus (Dassault Systèmes, Providence, RI). Computed tomography scan of severely stenotic BAV patient with heavily calcified raphe region was acquired. For this purpose, our existing parametric geometry and mesh generation method was modified for asymmetric BAV, with non-fused cusp angle of 140° and symmetrical fused leaflet. The native leaflets and root were meshed with 3D elements, and have native hyperelastic tissue properties. The calcium deposits were embedded inside the leaflets and have calcium material properties. The paravalvular leakage (PVL) was also compared using computational fluid dynamics (CFD) models of the diastole in the resulted deployed configurations. →

FlowVision HPC 3.09 (Capvidia, Leuven, Belgium) was used for the CFD simulations. Similar deployment models will be solved for previous stages of the disease to estimate the desired occasion for intervention.

The RCT subtraction algorithm was commenced and used to generate various stages of the CAVD disease in the BAV patient, as seen in Figure 3. An initiation nodule of the calcification growth appears on the raphe region, a location that is subjected to higher stresses in healthy BAV type 1. The non-fused leaflet has similar arc shaped pattern as in TAVs while the arcs are connected in the fused leaflet.

Publications as a result of full or partial Zimin grant

1. Paper submitted: Lavon K, Marom G, Bianchi M, Halevi R, Hamdan A, Morany A, Raanani E, Bluestein D, Haj-Ali R. "Biomechanical Modeling of Transcatheter Aortic Valve Replacement in a Stenotic Bicuspid Aortic Valve: Deployments and Paravalvular Leakage".

Oral presentations at conferences as a result of full or partial Zimin grant

1. Morany A, Lavon K, Haj-Ali R. "Integrated Parametric Aortic Valve Models with the LHHM including Pathology and FSI Co-Simulations". Living Heart Human Model (LHHM) annual users meeting, Paris, France April 2018.
2. Morany A, Lavon K, Haj-Ali R. Webinar: "Numerical Analysis of Healthy, Diseased, and Prosthetic Aortic Valve within the LHHM. Part 1 - Integrated parametric aortic valve model including pathology and FSI simulations". Living Heart Human Model (LHHM) community, August 2018.
3. Lavon K, Marom G, Bianchi M, Halevi R, Hamdan A, Morany A, Raanani E, Bluestein D, Haj-Ali R. "Biomechanical Modeling of Transcatheter Aortic Valve Replacement in a Stenotic Bicuspid Aortic Valve: Deployments and Paravalvular Leakage". The 8th World Congress of Biomechanics (WCB), Dublin, Ireland, July 8-12, 2018.
4. Lavon K, Marom G, Bianchi M, Halevi R, Hamdan A, Morany A, Raanani E, Bluestein D, Haj-Ali R. "Biomechanical Modeling of Transcatheter Aortic Valve Replacement in a Stenotic Bicuspid Aortic Valve: Deployments and Paravalvular Leakage". Biomedical Engineering Society (BMES) Annual Meeting, Atlanta, Georgia USA, October 17-20, 2018.

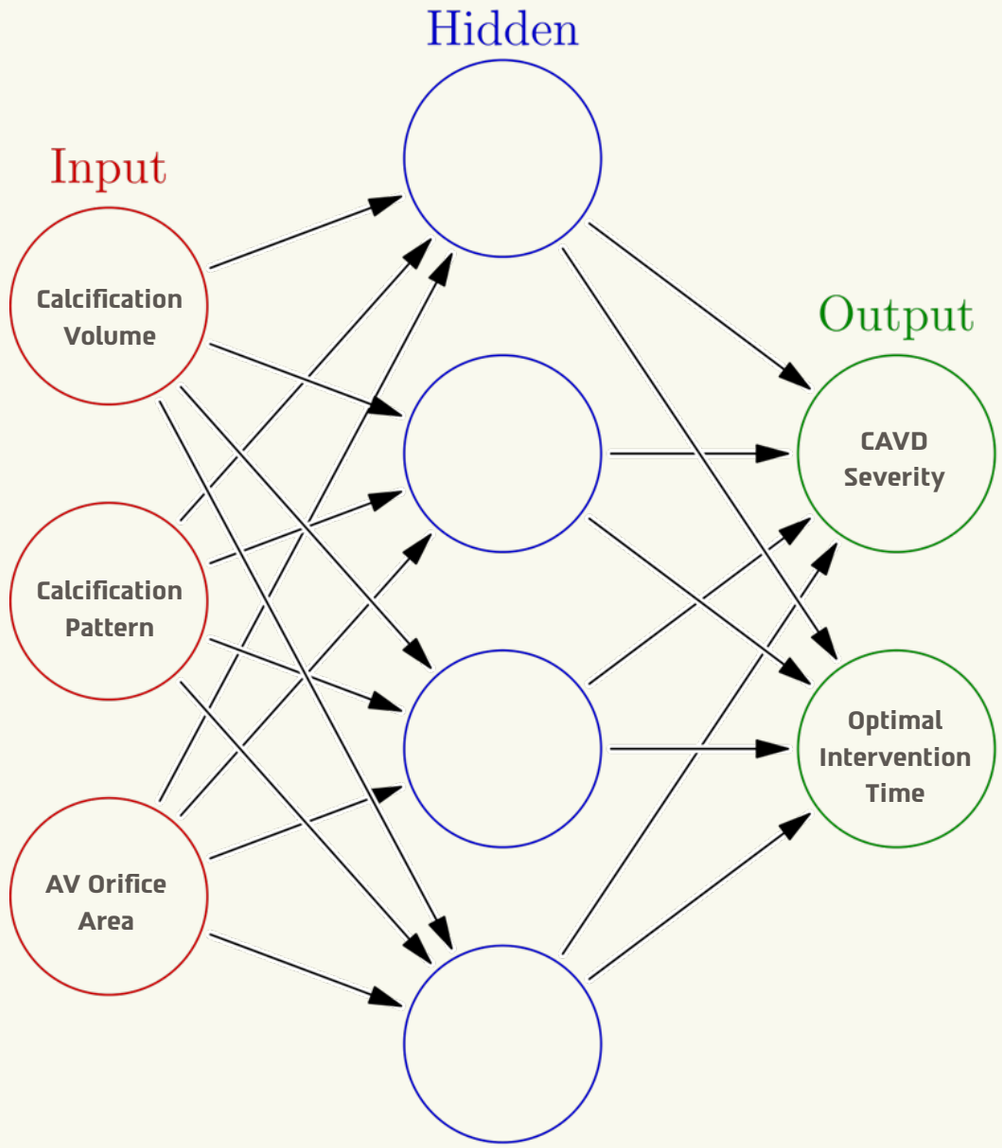

Figure 1: Schematic Artificial Neural Network (ANN) diagram illustrating our AI learning modules and algorithms. The overall CAVD pathology is extracted from CT scans of calcified AV we extract the input parameters: volume & pattern of the calcification deposits in each leaflet and the orifice area of the calcified AV. The output of the algorithm will include scoring of the CAVD severity and recommendation for the optimal TAVR intervention time.

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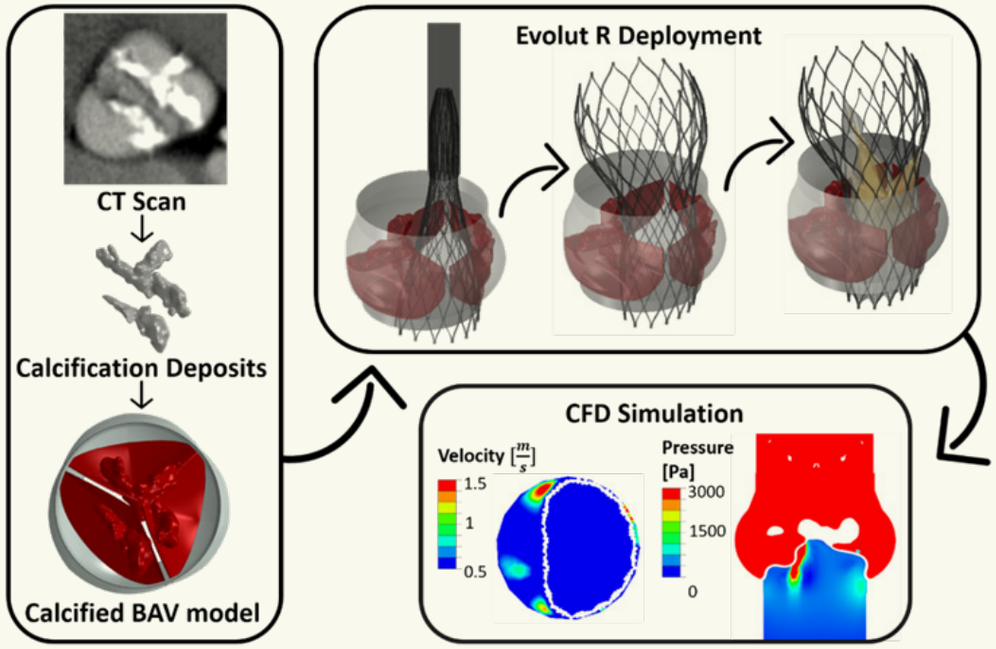


Simulations of TAVR deployment towards trained ANNs

Figure 2: Computed tomography scan of severely stenotic BAV patient was acquired. The 3D calcium deposits were generated and embedded inside a parametric model of the BAV. Deployments of the Evolut R and PRO inside the calcified BAV were simulated. The cuff and closed bio-prosthetic leaflets were added to the deployed stent to obtain the diastolic state. The resulted structural geometry was utilized for computational fluid dynamics simulations to calculate the paravalvular leakage.

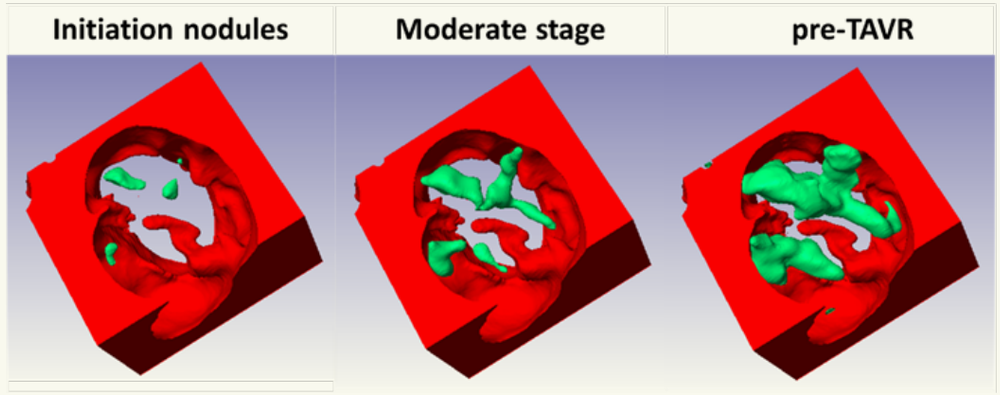


Figure 3: RCT of the calcified BAV patient starting from pre-TAVR CT scan.

Tasks Completed — Year 1

- Collect and built a new CT-scans database of pre-TAVR TAV patients from Rabin medical center. Those scans include cases of patients with scans from previous years, different calcification patterns and varied stages of the disease. A Helsinki protocol was formulated and approved for the proposed research.
- Programmed and conducted the Reverse Calcification Technique (RCT) on selected sample (n=20) calcified patients.
- Generated new FE simulations of TAVR deployment inside calcified BAV. Those simulations include deployments of the Evolut R, Evolut PRO and Sapien 3 current commercial devices available in the market. In addition, subsequent CFD simulations were also performed to calculate the best suited TAVR (among the three) for each case and quantitate the associated paravalvular leakage.
- ANN structures and training strategies were explored using several open-source and commercial training software.

Tasks Planned for — Year 2

- Continue collect and built the CT-scans database of pre-TAVR TAV patients from Rabin medical center.
- Continue conducting RCT on larger number of patients (n=50) calcified patients.
- Continue FE and CFD simulations of TAVR deployment inside calcified AV using the Evolut R, Evolut PRO and Sapien 3 available commercial devices. The additional results will allow us to better assess the optimal intervention time and the resulting consequences.
- Extensive focus will be on: generating new trained ANN capable of predicting the mechanical and pathological metrics (performance) of the AV given CT-Scans. These will ultimately aid in future medical diagnostics and intervention.
- Analyzing the collected database including measurements of the calcification deposits volumes, orifice area of the calcified AV, in order to determine a mathematical connection between the calculated parameters to the disease stage.
- Analyzing and compare the RCT results with old scans to related the disease development with time.
- Generate several computer simulations of the stages of the disease (based on the resulted RCT), for selected patients →

with different calcification patterns. Those models will allow us to calculate accurately the severity of the disease.

Zimin group members and responsibilities

- Karin Lavon, PhD candidate – Performing FE simulations of calcified AV and TAVR deployment.
- Adi Morany, Msc student – Performing FE simulations of calcified AV and TAVR deployment.
- Maya Karnibad, Msc student - Analyzing the CT database and determining mathematical connection between the different measured parameters.
- Nofar Keizman, research assistant – Collecting the CT scan database from Rabin Medical center.
- Shlomo Spitzer, Msc student –ANN algorithm.

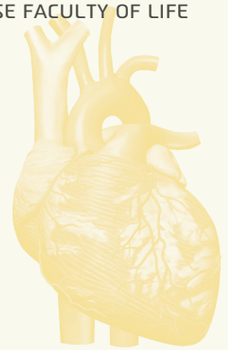
Collaborations

- Mirit Sharabi, PhD, lecturer at Ariel University – joint supervision of Maya Karnibad with Prof. Haj-Ali.
- Dr. Ashraf Hamdan, MD - is the director of Cardiovascular Imaging at Rabin Medical Center, Israel. His specialty is in Cardiology and Internal medicine and expertise in cardiovascular CT, MRI, and Nuclear Cardiology. ■

3D printing of cardiac patches with integrated sensors and actuators to regenerate the infarcted heart

PROF. TAL DVIR

THE GEORGE S. WISE FACULTY OF LIFE SCIENCES



Myocardial infarction (MI; heart attack) is associated with sudden death as well as significant morbidity and mortality. MI results from blockage of one of the coronary arteries that supply the cardiac tissue, leading to ischemia of a segment of the heart. This process eventually leads to the death of contractile cells and the formation of a scar tissue. Since cardiomyocytes cannot proliferate, the cardiac tissue is unable to regenerate, leading to chronic cardiac dysfunction. Cardiac tissue engineering has evolved as an interdisciplinary field of technology combining principles from the material, engineering and life sciences with the goal of developing functional substitutes for the injured myocardium. Rather than simply introducing cells into the diseased area to repopulate the injured heart and restore function, cardiac tissue engineering involves the seeding of contracting cells in or onto 3-dimensional (3D) biomaterials prior to transplantation. Following implantation and full integration in the host, the scaffold degrades, leaving a functional cardiac patch on the defected organ. However, once the 3D cardiac patches have been engineered, in vitro assessment of their →

quality in terms of electrical activity without affecting their performance is limited. This situation might lead to implantation of cardiac patches with limited or no potential to regenerate the infarcted heart. Therefore, engineering an implantable tissue that can provide information on its own function and actively intervene with the tissue function would contribute immensely to the success of this tissue engineering approach. In this research we focused on the development of a method in which recording and stimulating electrodes were simultaneously 3D printed together with extracellular matrix (ECM)-based hydrogel and cardiac cells to generate a microelectronic cardiac patch (microECP). To this end, we developed a unique formulation of autologous, thermoresponsive ECM-based hydrogels, originated from decellularized omental tissue, which can be easily and safely extracted from the patient. These hydrogels, that self-assemble under physiological temperature, have been found to support cultivation and tissue organization of cardiac cells. The printing process is executed using a multi-nozzle 3D printer that extrudes a unique formulation of conducting materials (based on a mixture of graphite flakes in PDMS) for electrode fabrication, alongside cradiomyocyte-containing ECM hydrogel that serves as "bio-ink". The electrodes in the hybrid patch have been found to be elastic, mechanically durable and electrically conductive (Figure 1 and 2). Microscopic analysis and biochemical assays revealed that cardiomyocytes maintained good viability and functionality while growing in close proximity to the printed electrodes. We have demonstrated the capacity of the electrode-containing constructs to implement real-time recordings of cardiac extracellular potentials and actively control and interfere with the patch function by applying acute electrical stimulation at different frequencies. This resulted in activation and synchronization of the contraction of the cells throughout the patch (Figure 3). Future experiments will be conducted to investigate the potential of the printed electronic patch to perform in vivo and to improve heart function following infarction. In conclusion, we have developed and tested precisely-printed electronic cardiac patches that enable monitoring and regulation of the integrated engineered tissue. Such functions would provide control over the in vitro process of cardiac tissue engineering, and guarantee successful (and controlled) regeneration of the diseased heart following implantation. It will provide quality assurance for the

engineered tissue prior to implantation, which is extremely important to attain appropriate structural and electrical integration with the healthy part of the heart. The technology has the potential to significantly decrease mortality and improve the quality of life for millions of patients.

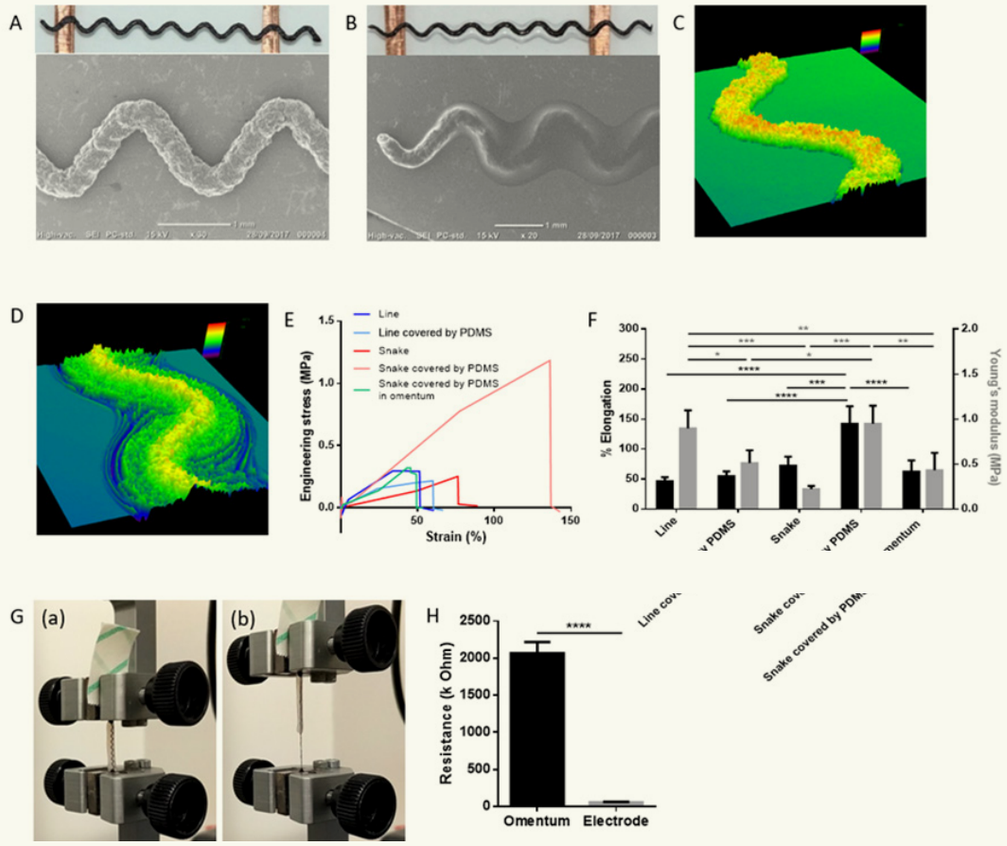


Figure 1. 3D printing of electrodes
Snake-shaped graphite electrode, without (A,C) and with (B,D) PDMS passivation coating in the electrode center. (A-B) Upper panels: photographs of the electrodes, lower panels: SEM images. (C-D) Confocal laser scanning microscope images. (E) Stress vs. strain diagram and (F) the calculated Young's modulus and elongation percentage (n=3(of different electrode variations; graphite straight vs. snake-shaped electrodes and with vs. without passivation coating and ECM hydrogel. (G) Photographs of the tension examination of graphite electrode in omentum hydrogel at the beginning of the exam (a) and before the torn (b). (H) Resistance measurements of the electrode and the surrounding omentum-based hydrogel.

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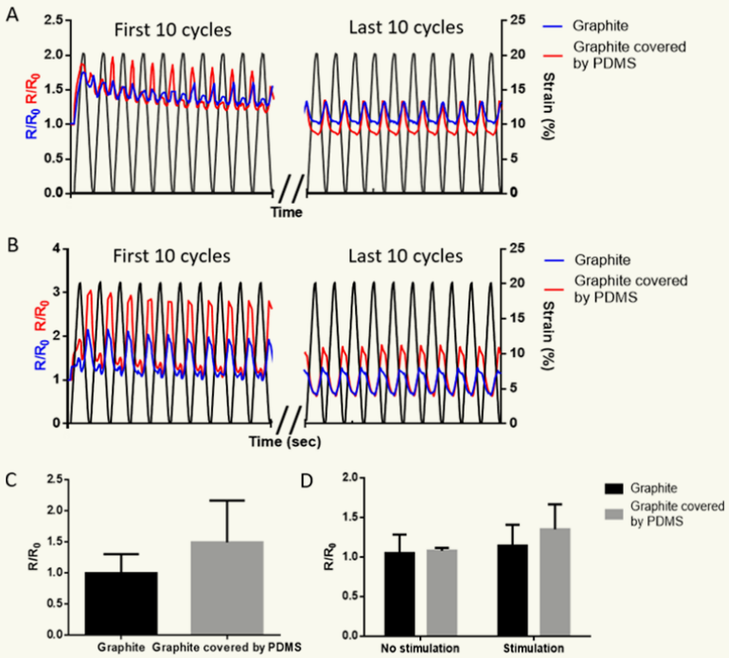

Figure 2. Electrical function of the printed electrodes
Electrical resistance during repetitive bending (A) and tension examinations (B) at the 10 first and last cycles (of 1000 cycles). The test was performed on graphite snake-shaped electrodes w/ and w/o passivation. (C) Resistance after two months at physiological conditions. (D) Resistance after pulsed electrical stimulation of 3V at 1Hz for 30min.

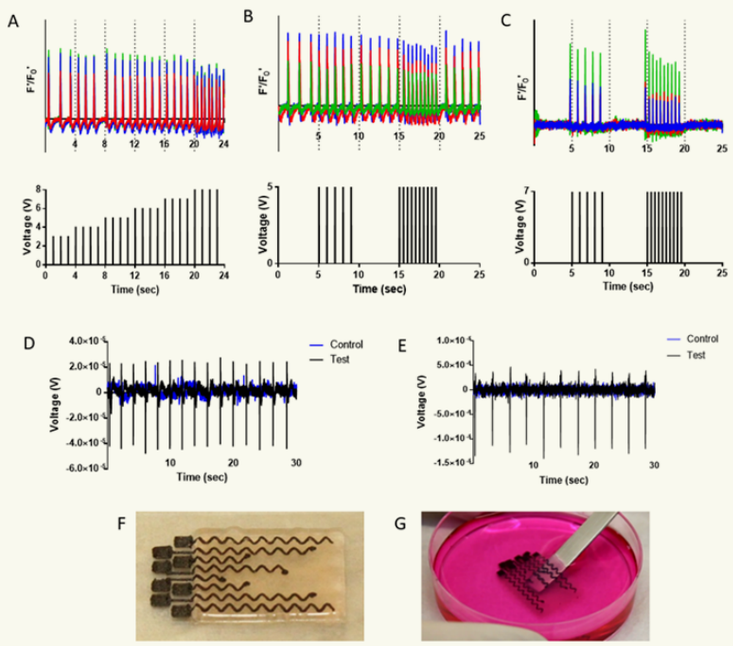

Figure 3. Electrical stimulation and monitoring of neonatal cardiomyocytes using graphite electrodes
(A) Stimulation threshold of 5V at 1 Hz on 2D cardiomyocytes culture and (B) on/off stimulation of 5V at 1 and 2 Hz through printed T-shaped graphite electrodes. (C) On/off stimulation of 7V at 1 and 2 Hz on 3D culture of cardiomyocytes in omentum hydrogel. Upper panel represents first derivative of the normalized Ca^{2+} signal, the lower panel represents the voltage applied. (D) Monitoring of the electrical activity of cardiomyocytes in 2D cultures and (E) in 3D cultures in omentum hydrogel. Test signal is obtained from contracting cardiomyosytes in warm medium; control signal is obtained from the same culture in cold medium (when contraction is inhibited). (F-G) 3D printed graphite electrodes in omentum hydrogel. ■

Individualized closed-loop sensorized virtual reality for behavioral change

PROF. YAEL HANEIN

THE IBY AND ALADAR FLEISCHMAN FACULTY OF ENGINEERING

DR. TOM SCHONBERG

THE GEORGE S. WISE FACULTY OF LIFE SCIENCES

In the first 8 months of the project we were able to establish **a proof-of-concept showing a high resolution, wireless surface electromyography (sEMG) recordings during VR engagement combined with eye-tracking.** To the best of our knowledge, this is the first demonstration of a system capable of recording internal states during a VR task. Figure 1 shows the 16 channel wireless facial EMG with the VR headset on a participant face.

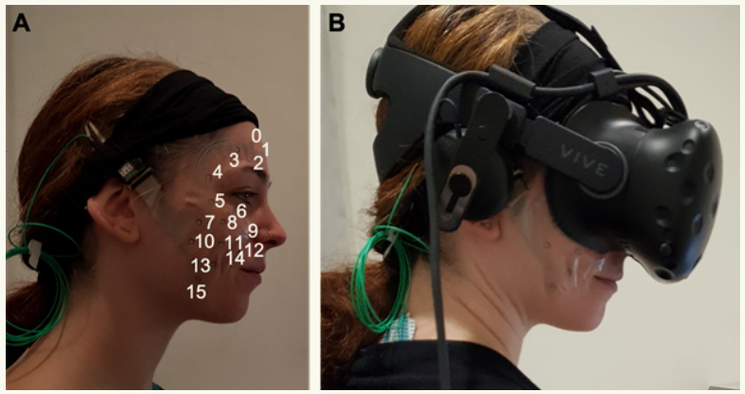

Figure 1: Sensorized VR setup. **A**) sEMG electrode array with 16 channels location and a wireless amplifier. **B**) HTC-Vive VR headset, combined with Tobii's eye-tracker, positioned on top of the sEMG electrodes array.

We show for the first time the ability to identify different expressions with the unique sEMG electrodes while wearing the VR headset. Figure 2 shows differential signals for different facial expressions during a calibration phase: closed smile, open smile, disgust and anger.

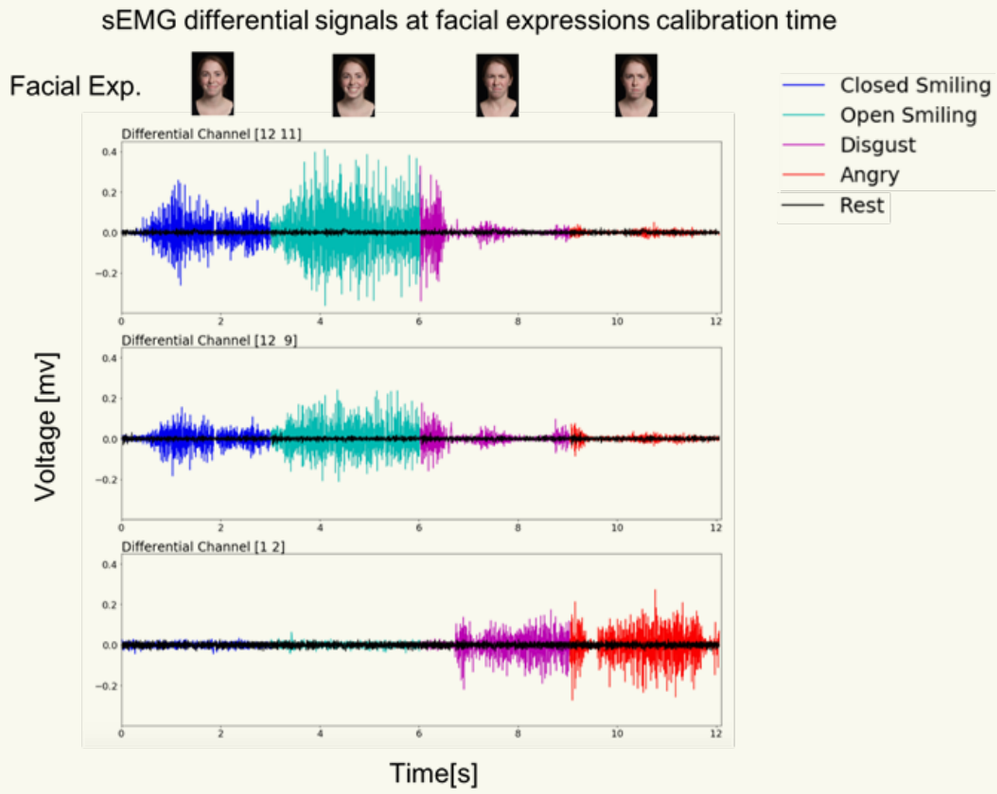

Figure 2: sEMG differential signals during calibration and rest in the VR task. Colors code for different facial expressions. Each panel plots a different combination of channels. For channels location refer to Figure 1.

In the past 8 months we **developed a dynamic VR task** (Figure 3) using the Unity software. The VR task induces positive internal states (For example a cute creature, Figure 3A, 3B top) and allows to compare these responses to the response to neutral (geometric, Figures 3A, 3B bottom) figures in a controlled fashion. While participants explore a house using head movements within the VR task, animals and control objects appear in pre-defined random places. as can be seen in Figure 3.

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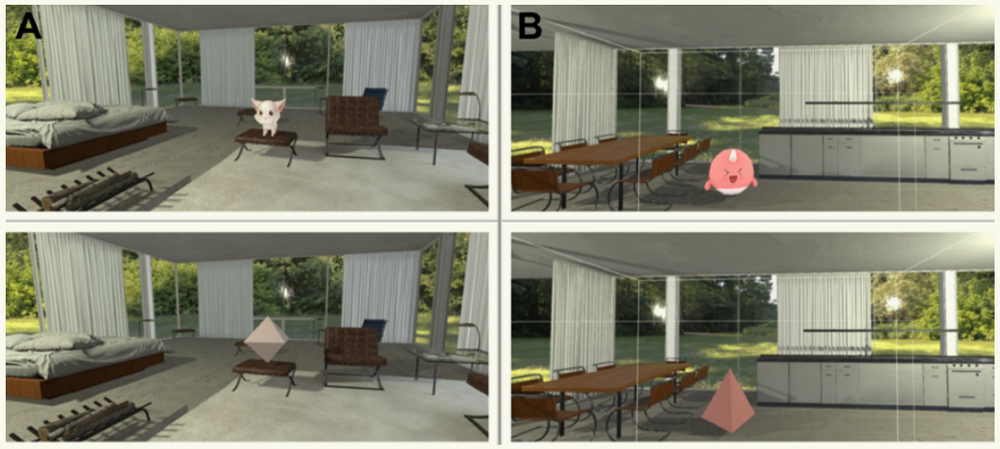


Figure 3: Dynamic VR Task. Participants search and look at appearing stimuli (pet or shape). Pairs of pet (top) and shape (bottom) appear at the same location in the scene on different times A) a cat and a diamond. B) a laughing narwhal and a pyramid.

In our pilot study we found a differential pattern in the sEMG signal during presentation of animals compared to a neutral geometric shapes showing stronger signals for the positive emotion inducing stimuli. Figure 4 shows an example of such differential response.

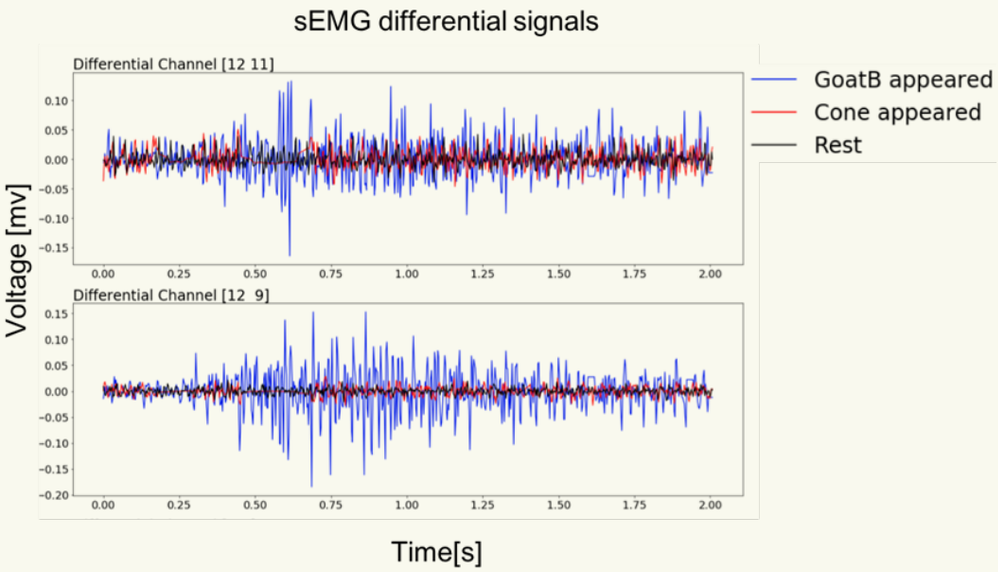
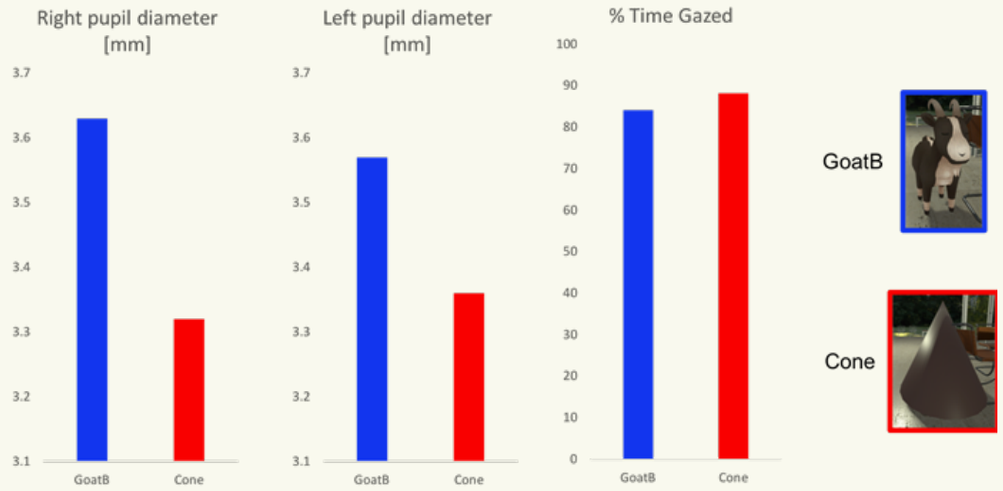


Figure 4: sEMG differential signals while viewing an animal (GoatB – blue line) vs. Cone (red line and the signal during rest (black). Each panel plots a different combination of differential



signals which were sensitive to smiling expressions: channels (12,11), and channels (12,9). For channels location refer to Figure 1.

We also obtained gaze tracking and pupil diameter measures from the Tobii-installed VR HTC Vive system (Figure 5). We have one of the first systems delivered worldwide and have been working with Tobii R&D to develop more precise output measures that will fit our aims to allow for as rich as possible dataset.

Figure 5: Preliminary eye tracking measures obtained from the Tobii-installed VR HTC Vive. We obtained proportion of gaze as well as binocular pupil diameter measures of two stimuli: one that was highly ranked (goat) versus the cone that was ranked low.

Budget of 1st year

We will use the remaining budget to continue the support of the PhD student and lab technician. We will purchase a professional dynamic graphic design to induce stronger emotions including negative ones. We will produce additional electrodes to allow testing of more participants and hire CS engineers to perform integration of all signal sources towards signal analysis.

Plans for Year 2

In the second year of the grant we aim to achieve our full goal of creating an **individualized closed-loop sensorized virtual reality for behavioral change** towards commercialization of the technology. We will develop the final component linking all the data will be the development of **advanced machine** →

learning algorithms that will be applied on the rich data from all sensors (electrodes and eye-tracking) to decode the current internal state and then inform the real-time the task presented to participants to enhance learning and behavior.

We will test a full cohort of n=25 participants that will allow to achieve a large enough sample to train and test the ML algorithms. The PhD student will code ML algorithms that combine all signal sources: sEMG electrodes, head-movements, eye-gaze and pupil diameter. We will then recruit CS engineers to finalize the coding of our environment to change the task based on the identified internal states from all sensor sources.

Commercialization process

A preliminary market analysis we performed established the huge market value of the proposed project: The Global Emotion Detection and Recognition (EDR) Market is a robust and growing market which "is estimated to witness a CAGR of 32.7% over the forecast period (2018-2023), driving the market to reach 24.74 billion by 2020. In general, Tractica forecasts that worldwide revenue from sentiment and emotion analysis software will be worth $3.8 billion by 2025. The most likely early market penetration for the subject technology will be the medical and security industries. Some EDR companies operating in the emotion detection and recognition industry are Affectiva, Beyond Verbal, iMotions, Noldus Information Technology, Sentiance, Sightcorp, Realeyes, CrowdEmotion, Kairos AR, Inc., nViso SA., and SkyBiometry. **None of these companies integrated sensors or algorithms into a VR setting with the ability to be AI adapted.**

Entrance into the Global Emotion Detection and Recognition market and specifically the Global Facial Recognition (GFR) niche of this market will be eased with collaboration.

We aim to first enter the health sector by partnering with a current VR treatment content provider such as VRHealth www.xr.health who have already expressed their interest in our technology.

IPR position and strategy

We plan to file a patent application that will cover the specific utility of virtual reality (VR) and computational methods for detection of individual internal states. We envision that a solution would include a client server system that will assist with protection of our proprietary algorithm. ■

zimin-institute.tau.ac.il · zimin@tauex.tau.ac.il
+972-3-6405532 · +972-3-6407221