Dear all,

The Annual Projects Conference in Biomedical Engineering is hosted by the department of Biomedical Engineering at the Technion – Israel Institute of Technology. As the dean of the Biomedical Engineering department and as the project course staff, we are pleased and honored to welcome you here.

The conference is hosting 4th year students who are eager to present their year-long projects and to receive feedback from academic researchers, industrial experts, and their peers. These projects implement the medical, engineering, and scientific tools that the students have acquired and developed during their BSc journey in Biomedical Engineering.

The students aim to provide solutions that meet research and development needs in the Biomedical industries and research departments. Through working on their projects, students gained invaluable, hands-on experience. They had to work through technical challenges and adhere to strict standards comparable to those in a real-world setting. We believe that this hands-on experience engages graduates with the Biomedical industry and/or the wide variety of Biomedical research in a very strong way encouraging multidisciplinary work that is vital to the students' futures.

Additionally, we encourage the students to think out of the box to initiate new solutions and help foster their entrepreneurship skills. Above all, these projects are a key element of the faculty vision which strives to strengthen the long-term cooperation between academia and industry leaders.

In this booklet we are introducing the abstracts of all presented projects. We wish all students rewarding careers and bright futures. We hope that one day they will take an active part in similar projects as professional mentors from both the industry and academia.

Kindest Regards,
Prof. Shulamit Levenberg, Faculty Dean
Dr. Alex Vilensky, Course Instructor

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(1)

Modeling and Simulation of Mechanobiological Interactions of Cells with Gels

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Introduction: Metastasis is the main cause of death (90%) among cancer patients thus, it is critical to determine their likelihood of occurrence. Current diagnostic tools e.g. biopsy, genetic and laboratory tests are either costly, inaccurate or take weeks to yield results. During metastasis, cancer cells from the primary tumor migrate and invade to a distant site by changing morphology and applying forces. Previous works at the Weihs lab have revealed that metastatic cells seeded on a physiological-stiffness non-degradable and impenetrable gel will apply forces and indent the gel, likely in an attempt to penetrate it; benign cells do not indent the gels. In addition, the percent of indenting cells and the attained indentation depths correlated with the metastatic potential of the cells. Consequently, the ongoing effort is to further define these interactions, towards developing a prognostic tool. Here, we have developed a finite element mechanobiological model to evaluate the forceful effects of the cells on the gels, as a way to optimize gel design.

Methods: We have developed a finite element model, using the FE Bio software (University of Utah), to simulate a series of mechanostructural conditions. The isotropic elastic gel, 2.4kPa Young's modulus (stiffness range of soft tissue), is fixed to a rigid substrate. Cells are distributed across a $1mm^2$ region on the gel, connected by an adhesive interaction. The cells, 25kPa Young's modulus (range of cancer cells), are modeled by cylinders with the radii and the indentation depths taken from the experimental results, those induce calculable strains, forces and pressure gradients throughout the 3-dimensional gel.

Results: The model simulations provided the following optimal characteristics for the gel: (a) A zero displacement boundary conditions in XY axes on the borders of the gel, i.e. the gel edges should be fixed. (b) The gel thickness can be 100µm, less than the currently used 300µm. This reduction maximizes the formation of stresses whilst maintaining the gel as an infinite body for the cells.
We simulated two cancer cell types with low/high metastatic potential, respectively exhibiting smaller and larger indentations. Comparative results of the gel response: force 0.05/0.1mN, pressure 100/430Pa, displacements 3/12µm.

Conclusions: The simulations facilitated adjustment of the system design, to amplify the stresses formed within the gel. This allowed us to distinguish between sub-populations with different invasiveness, which will provide support to experiments in testing this approach as a diagnostic tool for the likelihood of metastasis.

Keywords: mechanobiology, metastasis, finite element modeling

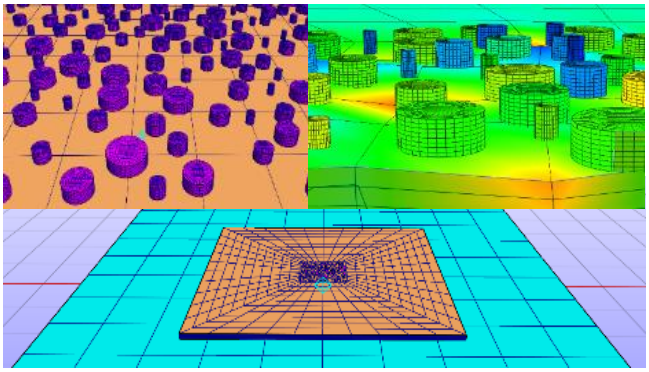

Figure 1: Finite element model of gel on glass. Cells (cylinders) indent the gels inducing a strain field.

(2)
Generalized Semi-Perforated Stent Graft for the Aortic Arch: A Solution for Aortic Arch Aneurysms and Dissections

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Introduction: Due to the complex curved anatomy and multiple bifurcations of the aortic arch (AA), it is difficult to treat aortic arch diseases whilst maintaining proper blood flow to arising vessels. Current treatments for AA aneurysms and dissections include open chest surgery and rerouting natural flow. These treatments carry either heavy risk during implementation or increased wall shear stress due to the unnatural flow created. We propose a new solution for treating AA aneurysms and dissection: using a generalized semi-perforated stent graft. The stent graft proposed is based on the analysis of AAs from a sample of the population and will fit 70% of patients. This method will preserve natural flow, be easier to implement, and provide a safer means to treat AA aneurysms and dissections.

Methods: 3D models of the AA were extracted from CT scans of numerous (20+) patients and analyzed. The dimensions attained were used to create a model of a generic AA on which the stent graft was based, with perforations at the entrance to each bifurcation.

Results: Different numbers of separate bifurcations were found in our population sample (mainly two or three bifurcations). Due to the variety of anatomy, two semi-perforated stent graft models were created in order to fit 70% of the population.

Conclusions: The proposed solution of generalized stent grafts to treat AA aneurysms and dissections will provide a safer, easier, and healthier means than the treatments currently available. Prospective investigation should include a larger database and CFD tests to explore the integration of the stent within the aortic arch.

Keywords: Aortic Arch Aneurysm; Aortic Arch Dissection; Stent Graft;

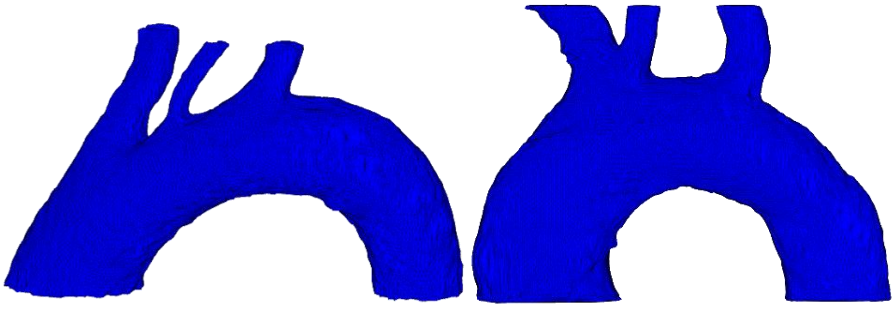

Figure 1: Two sample Aortic Arch STLs extracted from CT scans, exhibiting the anatomic variety between patients. The various diameters and bifurcation locations were extracted through extensive analysis of the geometry. The data was then averaged to create two general models, fitting two and three bifurcations each.

(3)

Spectroscopy based Reflectance Pulse Oximeter

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Introduction: Our project's goal is to develop a method which allows to measure the oxygen saturation in the blood system and could be used in a noninvasive wearable continues oxygen saturation device (hereinafter: "The Device"). The oxygen saturation in blood (hereinafter: "SpO2") is the ratio of oxy-hemoglobin to the total concentration of hemoglobin present in the blood. A noninvasive clinical measurement of SpO2 is today being performed by an attachable Pulse Oximeter Device. This devise gives outputs in a clinical standards thus does not gives a continues measurement needed in order to monitor the SpO2 level during long periods of time (a continuous measurement could improve the diagnosis care for chronical diseases, newborns etc.). Pulse Oximeter reads the SpO2 using optical data analysis. The standard devices analyzes the light that passes through the tissue and therefore being attached on a finger or the ear (hereafter: "*Transmissive Method"*). In order to perform a continues measurement during daytime the device should be wearable and comfortable (such a patch) and therefore has to analysis the light that reflected from the tissue (hereinafter: "*reflective method*").There are several problems in the Reflective Method: the outcome output is a very noisy data that caused by ambient light, and reflectance from the skin. All of the above result a very poor signal to process. Today there are several devices that uses the reflective method, thus these devices do not give outputs in clinical standards. Our goal is to develop a method that could coup with the challenge.

Methods: Research shows hemoglobin's light absorption characteristics depend on the light's wave length. A different results come back whether hemoglobin is oxygenated or not. Pulse oximetry method uses that fact to find the oxidized hemoglobin fraction and so – the SpO2 from the analysis of light transmitted through the tissue. The signal processing algorithm determines the SpO2 using the ratio between the signal from 2 leds that have different wave lengths.

Our project method is based on this theory, but uses white led and spectrometer instead of 2 leds and photodiode as in the traditional method. Therefore we use multiple wavelength for comparison. Our expectation is that the use of multiple wavelength will improve the output of the measurement.

We built an experiment system that uses: white led, spectrometer and a focus lens. We have made various measurements using our method, and built compatible algorithm in "Matlab" that calculates SpO2.

Results: We had developed an algorithm that is compatible with our method, which uses multiple wavelengths. Unfortunately the output signal was too noisy to proses. We have tried many approaches in order to improve the outcome signal, but none of them succeeded to get a signal that can be used.

Conclusions: We have examined several methods in order to deal with the problems of the reflective method, and chose a method that uses a white led and spectrometer. we have expected that by using more wave lengths we will be able to subtract more information and minimize the noise.

We wrote an algorithm that implements the method. The process of building the experiment system was complex and after several modulations we had not yet received a signal that we are able to process, that is why the algorithm had not been validated.

We believe the by using more sensitive components and more advanced signal processing, usable results can be achieved, and a commercial product can be lunched to market.

Keywords: Pulse Oximeter, SpO2, spectroscopy, Hemoglobin.

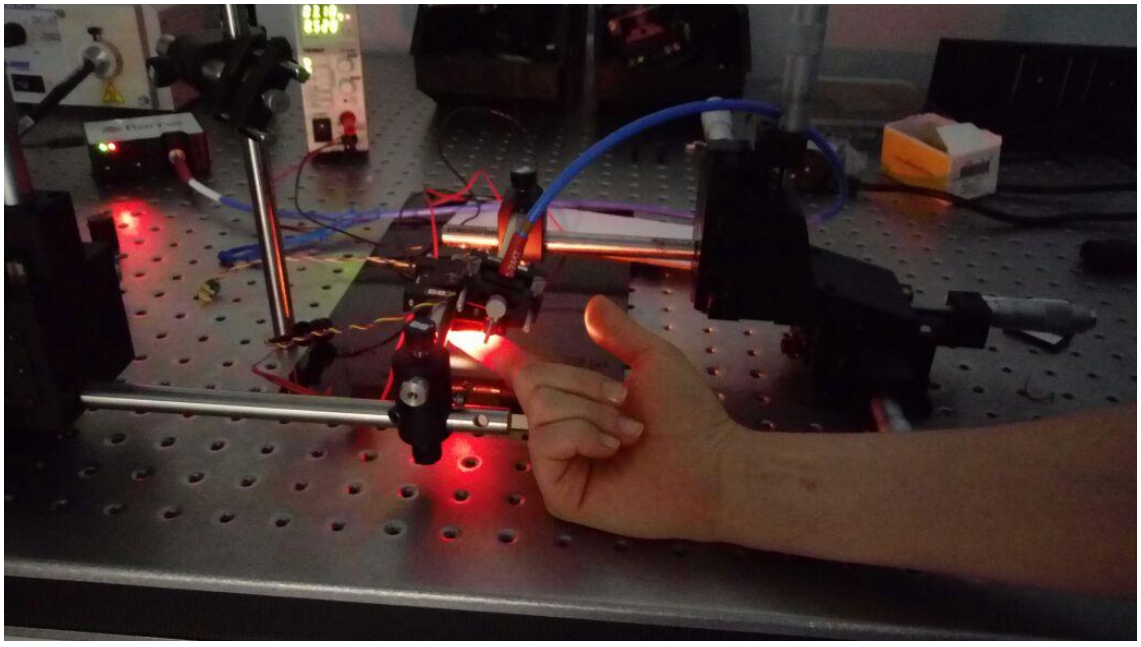

Figure 1: The experimental system assembled.

(4)

A Novel Design of Metering Valve for The Inhalers of The Future

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Introduction: In recent years we are witnessing a gradual discussion on personalization of medicine. In cases of pulmonary diseases, in which the pharmaceutical are delivered through inhalers, the amount of medicine delivered is quantized heavily, and personal dosimetry is not possible with current devices. A non-quantized method of delivery is essential for the progress of personalization of the field . The most commonly used type of inhaler is the Metered Dose Inhaler (MDI), on which we work.

Methods: 3D modelling and simulation with SolidWorks, 3D printing using Form2 printer. We are working to develop such a device, hopefully to be used instead of the current inhalers. To our best understanding, there are 2 main constraints have to be applied in order to assist the implementation of the new device and method we are working at: first, it must be simple to manufacturing and thus cost effective, and secondly it should be easy to use and thus easier to implement and prevent human-factor errors. After considering several possibilities, we figured that the option most probable to apply those constraints is to change the design of the metering valve to a one with sizable metering chamber.

Results: we developed and manufactured a metering chamber which could be implemented in future inhalers. The way to use our mechanism is as similar as can be, to previous MDI's vastly used by patients today. The way to manufacture our mechanism is quite similar to the manufacturing of the previous metering valves, in means of complexity and symmetry.

Conclusions: In this paper we have further investigation in the design and function of the metering valves, with examples from prior work in the field. In these examples one may obtain the importance of a simple mechanism. Overall, the mechanism we developed answers the constraints of simplicity, both to use and to manufacture, compared to prior work. In this paper we also have initial experimental results of the dosimetry of the mechanism. Further investigation is needed, regarding the quality and consistency of the dose delivered by our mechanism.

Keywords: MDI, Metering chamber, Personal medicine

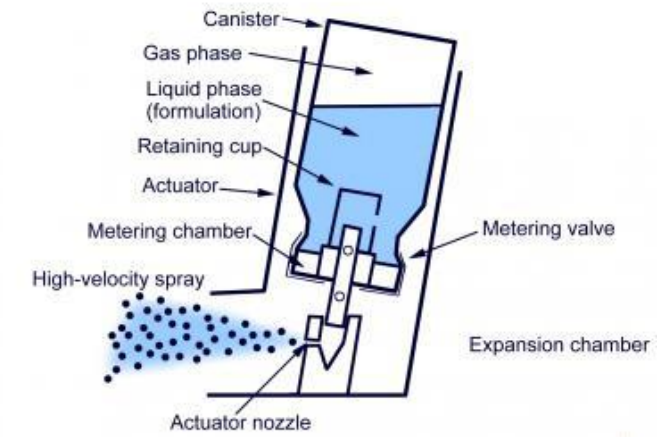

Figure 2: The general anatomy of a MDI.

(5)

Microbubble Producing Catheter for Ultrasound Imaging

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Introduction: In medical imaging, the fallopian tubes are difficult to image due to their complicated structure. Therefore, the use of contrast agents based on imaging technology (x-ray, ultrasound or MR) is common.
The fallopian tubes are evaluated traditionally by Hysterosalpingography (HSG) using ionizing radiation (X ray) and iodine based contrast agent. A possible ultrasound alternative is the Hystero-Contrast-Sonography (HyCoSy). It is conducted by forcing an aqueous fluid possibly containing air bubbles up the fallopian tubes as a contrast medium. However, the short half-life of the bubble serves as a disadvantage.

This work focuses on the production of physical micro air bubbles for future use in HyCoSy procedures.

The feasibility of creating micro air bubble, by using saline flowing over a porous membrane mitigating pressurised air, was evaluated.

Methods: The experimental system included three sub-units.

- The first was the Water-Air Interface Complex which contained a filter used to deliver the pressurised air to the surface of the membrane. On the opposite side was a 3D printed part containing a tubal passage for the water.
- The second was the Measurement Chamber which contained the first subunit's output mixture flowing through a transparent Tygon tube.
- The third was the Ultrasound machine including a linear probe placed above the tube and inside the water filled chamber. The machine provided 2D ultrasound recordings, later analyzed.

The following experiments were conducted: Initial feasibility test of the membrane; influence of gas pressure; and flow rate change on the image brightness.

Results:The experiments showed that bubbles could be created from the membrane and that the water-gas interface in the 3D part was adequate for the main concept. Secondly, as the gas pressure increases for a constant flow rate, the mean intensity of the ROI increases as well. In addition, as the distance from the entrance of the pipe increases, the intensity decreases. Similarly, as the flow rate increases, for a constant air pressure, the intensity of the ROI increases as well.

Conclusions: Based on the results, the membrane tested proved feasible and should be considered in future catheter designs. Also, the optimal parameters of the system were 15 psi for the air pressure. The optimal flow rate has yet to be determined.

Keywords: Fallopian tubes, Ultrasound, Micro air bubble, HyCoSy.

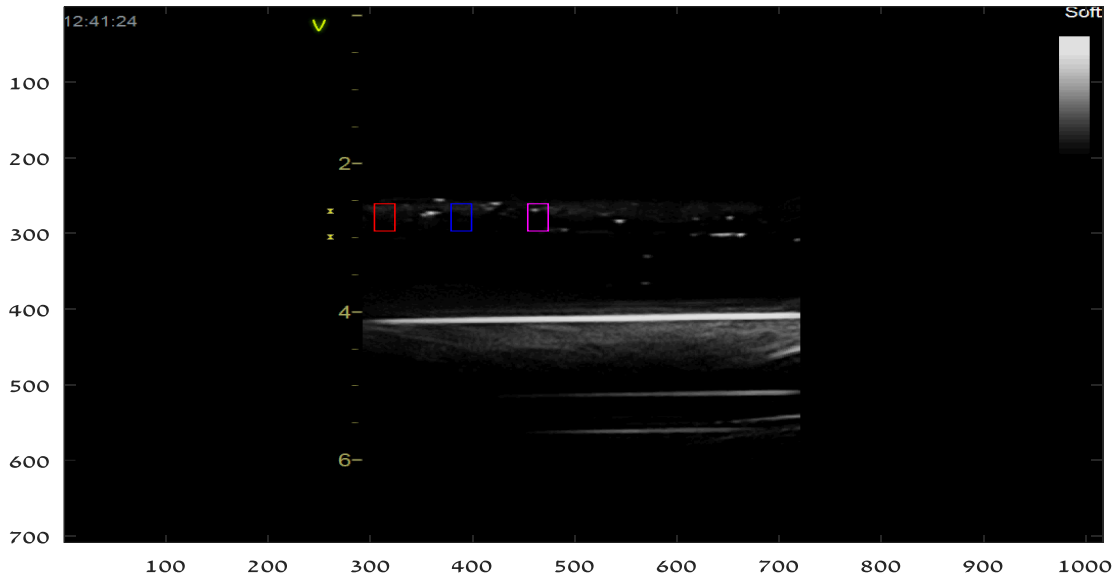

Figure 1: The three different ROIs used to measure the image intensity, placed on the tube under Ultrasound visualization during the air and water solution passage.

(6)

Automated Identification of Invasive Cancer Cells

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Introduction: Cancer is a diverse and versatile worldwide disease, often referred to as the "Emperor of all maladies". The main cause for mortality among patients is metastasis, spreading of cancer cells to distant organs. Metastatic solid tumors display predominantly collective migration and invasion, which initiate when cells penetrate their surroundings. Therefore, evaluating the mechanobiological interactions of groups of metastatic cancer cells with their environment is of great importance, as it can reveal characteristics that would impact research and healthcare. At the Weihs lab, a specific phenomenon has been observed where metastatic cells indent impenetrable gels while benign cells do not, and is evaluated as a potential prognostic tool. The analysis of those experiments is currently mostly manual, requiring user experience and potentially introducing bias. Thus, here we have designed a set of automated image-analysis based processing approaches and modules to accelerate the data analysis.

Methods: The program modules were designed in MATLAB™, using the 'Image Processing Toolbox' and producing a graphical user interface. The tool combined automated and user controlled steps, respectively, to identify cell locations and their viability and to mark indenting cells. We developed a custom segmentation method to automatically detect fluorescently stained cells in microscope images. The algorithm scans varying threshold values derived from the images' grayscale-histogram, identifying the optimal segmentation threshold. Following the image processing, the user may provide input to identify indenting cells and their depths. Finally, the results are compiled into a spreadsheet containing the raw measurements, auto-built histograms, custom averages and statistics.

Results: The automated user interface and algorithms reduced the work time per experiment to a sixth (from 5-6 hours to only 1 hour), where over 85% of the images are correctly segmented. Overlay of different stains applied to the cells provides an automated measure of cell viability. The detected cell locations are also overlaid onto images acquired at different focal depths of the gel, to simplify user marking of indenting cells and identification of their depths (Figure 1).

Conclusions: Our custom built algorithm and user interface, have significantly accelerated the data analysis and have reduced user bias. This approach is flexible and robust, and can be easily modified to different processes and for addition of further modules to expand the post-processing procedures.

Keywords: Automation, Cancer, Indentation, Image Processing.

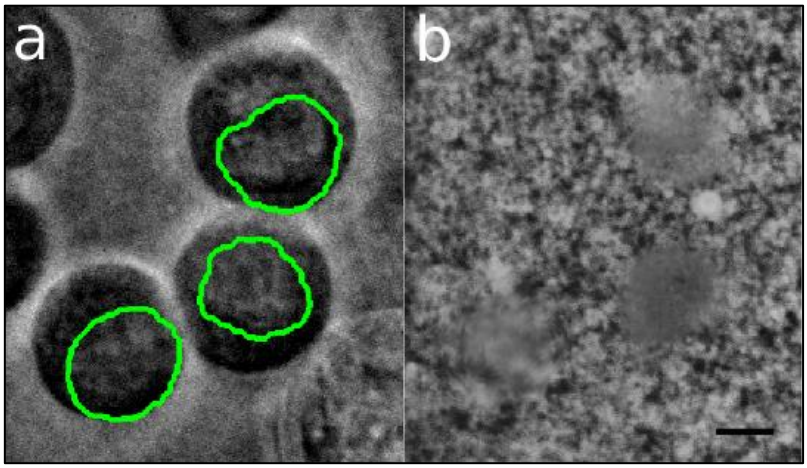

Figure 1: (a) Differential Interference Contrast image overlaid with detected cell nuclei. (b) Gel plane image of the same location, depicting out-of-focus areas indicating cell indentation. Scale bar, 5 µm.

(7)

Co-Registration of CT Images of the Brain

Maria Gerber[1], Anat Lyubin[1], Omri Ziv[1], Ariel Wiegler[1], Eyal Bercovich[1,2]

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Introduction: In the past years, great advances have been made in the way we understand, diagnose and treat various maladies, especially ones that occur internally and usually are not seen, unless an invasive measure is taken. The ability to make a correct diagnosis of the changes in the patient's disease, especially when it occurs in organs like the brain, remains somewhat limited, due to the structure's complexity. Developing the ability to easily and accurately identify the differences in structure characteristics during the treatment course, will hopefully allow progress in the field. The development of an easily applicable, real-time co-registration algorithm that utilizes vastly used DICOM (Digital Imaging and Communications In Medicine) databases is needed. Most methods available to this day, focus on the co-registration of different sequences of the same scanning point, utilizing linear and non-linear registration methods, in healthy subjects as well as in patients with brain tumors.

Methods: The study included usage of an algorithm that organizes DICOM images into easily analyzed three-dimensional matrices. It was done in order to compare between images taken at different time-points and different angles. The background of the images was removed using the Otsu thresholding method. The comparison between axial images, that do not contain the same data because of the patient's movements in correlation the CT scanner bed position was done. Axial images taken and transformed into coronal images were analyzed and the error rate was computed on that plane. The hypothesis used is that the patient's head tilt may occur only on the coronal plane and its rate will not be greater than 5° degrees. Under this hypothesis is the assumption that the coronal images acquired contain similar data.

Results: The Images had gone through a correlation on the z-plane, as well as on the xy-plane. The rate of correlation achieved between two different sets of images has risen from 57.14% before analysis to 67.83% after analysis on the x, y and z planes. The rotation algorithm created in order to compare between coronal images at different angles has an average error rate of 0.74%. This error is acquired while calculating the rotation angle between the static series of images and the same series of images that was rotated.

Conclusions: Usage of image processing and computational techniques allows to create a ground for comparison between two series of images, taken at different time points, with distinctive differences. Based on the results achieved thus far and with further improvements, this algorithm may be of future clinical use.

Keywords: DICOM, Imaging, Co-Registration, Algorithm

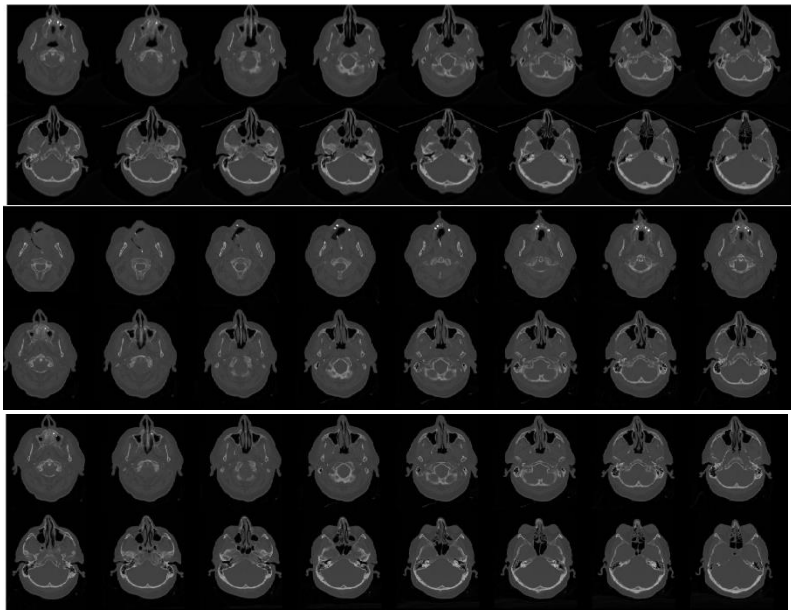

Figure 1: Comparison between main, secondary and secondary images after correlation analysis

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Super Resolution using incoherent holography

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Introduction: Super resolution microscopy techniques such as PALM or STED paved the way for overcoming Abbe's diffraction limit by an order of magnitude. However, methods such as PALM suffer from low temporal resolution, and so, super-resolution techniques using compressed sensing (CS) have emerged, to alleviate that limitation. CS techniques are known to produce better results when data acquisition is performed in the Fourier domain. In this project, our goal was to create a computer simulation for sparsity based super resolution by using incoherent Fourier holograms, which encode in the 3D structure of fluorescing point emitters in a Fourier hologram.

Methods: Using Matlab, we developed an algorithm which receives a 3D scene, projects it in different angels and by using mathematical manipulations creates the 2D Fourier transform i.e. Fourier hologram of the scene. Then, by implementing an inverse Fourier transform, it reconstructs the original scene.

In order to check our code, we encoded 3D scenes with known Fourier transforms e.g. delta function in different positions or DC (ones in the whole scene) into 2D Fourier holograms. Then, a reverse transform was applied to the hologram to produce the scene reconstruction, and compared to the original scene.

Results: In the next step we applied our algorithm on varying 3D scenes, such as 3 spheres in different locations or a “bell” figure, which we created. In the reconstructed images, one can clearly see the original image outlines but in smaller size. Using an appropriate scaling we succeeded to obtain the figure in its original sizes.

Conclusions: We have managed to create simulator which encodes 3D, incoherent scenes into 2D Fourier holograms and successfully recover the object. Furthermore, in order to reconstruct the image in its original size, a scaling action is needed due to the size reduction that the algorithm causes.

Keywords: Fourier transform, projection, reconstruction.

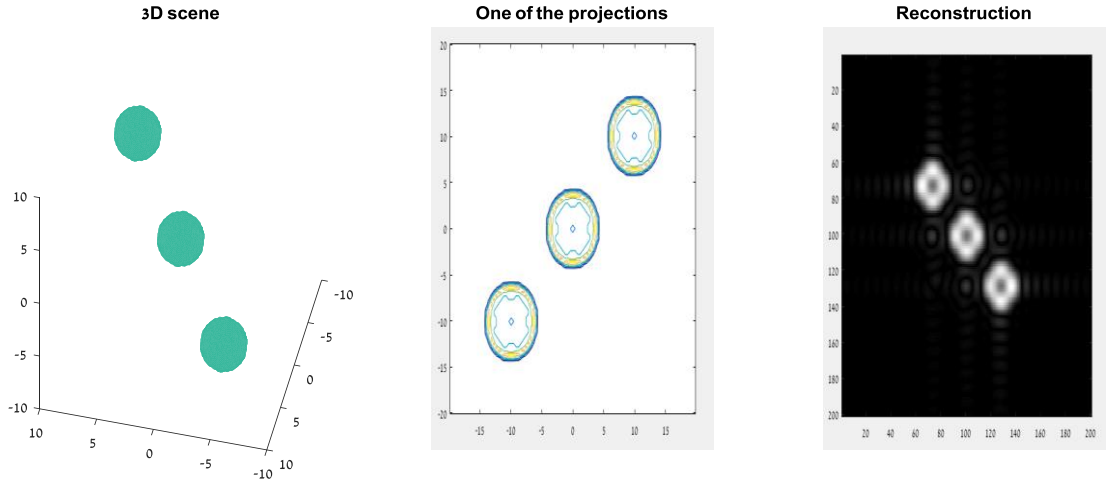

Figure 1: Example of a 3D scene, its projection and reconstruction.

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Applying Machine Learning methods to ruling out Acute Coronary Syndrome in patients

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Introduction: In the United States, above 2.5 million patients are hospitalized annually due to chest pain. A main risk of chest pain is Acute Coronary Syndrome (ACS). Currently, in order to diagnose ACS, doctors rely on ECG, patient's history and results of blood test, especially troponin which takes 6 to 48 hours to manifest. Joint research of Kaplan hospital with GE healthcare collected data on 494 patients with chest pain, out of which 59 were diagnosed positively with ACS (statistically close to the Positive ACS diagnosis percent in the USA). The goal of the study, is to rule out "on arrival" as many patients as possible while maintaining high sensitivity, by using machine learning methods on patient's data which includes ultrasound measurements, physiological metrics and medical history.

Methods: Statistical methods were used to determine correlation between different explanatory variables and the target variable. Afterwards, we used a state-of-the-art machine learning method, Support Vector Machine and optimized iteratively its parameters (Kernel parameters, box constraint and cost matrix) to fit our criterions. Kernel methods were added to deal with the nonlinearity of the data. Additionally, we used oversampling methods (Random and Adaptive Synthetic Data generation) to obtain a more balanced group for learning and reduce a model skew. To reduce the number of variables we tried Principal Component Analysis [PCA], non-linear PCA, SK-PCA and sequential feature selection methods.

Results: The results of the learning algorithm were estimated with cross-validation and testing group, presented in figure 1.

To evaluate the effectiveness of our results, we compared it to learning with troponin results and with "global strain" (an accepted parameter derived from the ultrasound measurement). Feature selection showed that "global strain" doesn't contribute to the model and thus was removed. The result of almost 0% False Positive opens the opportunity to a second stage of learning on the remaining data after initial release. The correlations between the results and variables diminish after the initial data release, and our optimization algorithm couldn't find a good solution for the remaining data which holds the low False Positive.

Conclusions:

- Due to our results, ruling out ACS "on arrival" to the ER is plausible using Machine learning methods, but further studies with a larger and more balanced Data is needed to obtain a better algorithm.
- Based on the current dataset, global strain, an accepted feature for the analysis of cardiac activity, doesn't provide contributing information
- High cross-validation accuracy (0.98) and a 39.5% of Positive release "on arrival" shows the opportunity which this work presents, to the patients and to the healthcare system by saving millions of hospitalization days annually.

Keywords: SVM-Support Vector Machine, ACS- Acute Coronary Syndrome, Kernel methods, Optimization methods, Random Oversampling, Adaptive Synthetic Sampling

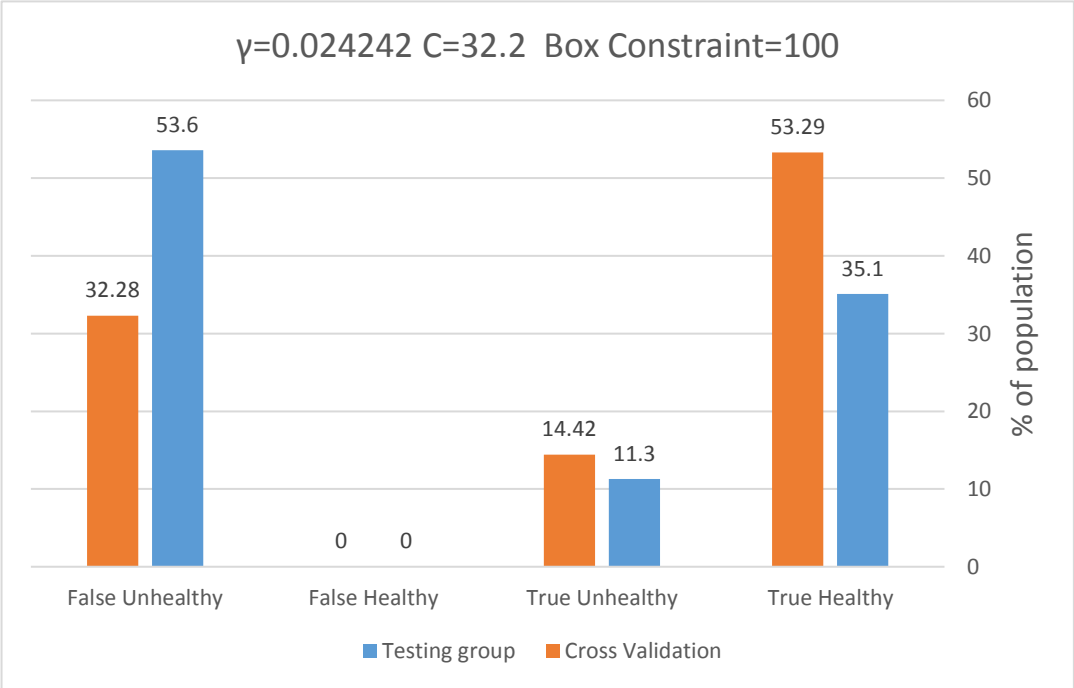

Figure 1: The results of the learning algorithm

(10)

Left Ventricle Diastolic Function - Optimizing Diagnosis of Cardiac Dyspnea

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Introduction: Causes for dyspnea (breathlessness) vary from lung to heart related pathologies, psychological conditions and more. Dyspnea results in poor tissue perfusion throughout the body and therefore can cause immediate and often irreversible damage. Approximately 1.5 million dyspnea cases occur each year, many of which are caused by heart related pathologies. In these cases, the accepted diagnosis process is considered medically questionable, as to ascertain the root cause requires a time consuming and invasive procedure. In this article, we propose a new, non-invasive approach by the means of Ultrasound and Machine Learning techniques in order to discern whether the source of dyspnea is cardiac. Through the understanding of left ventricular pressure levels and a growing database of patient Ultrasound parameters, the dyspnea's derivation can be classified.

Methods: Statistical analysis and Machine Learning tools including: correlation analysis, ROC, dimensionality reduction (PCA), regression models, clustering (K-Means), and classification (SVM and KNN), were used to analyze an input of 45 parameters that were acquired by Ultrasound scans from 183 patients who complained of dyspnea. In all cases, the left ventricular pressure was determined by a licensed physician.

Results: Applying PCA reduced our Interval variables from 17 to 6 components. This reduction led to a more efficient basis set, however it did not present significant results when clustering methods were used. Applying a linear regression model between the major principal components and the LVEDP demonstrated no linear relation. The results were reassured when a similar method was applied upon the raw data-set. A polynomial regression model was applied between the major principal components of the variables that presented high AUC values and the EDP was attempted as well, combined with an iterative optimizing algorithm. The model presented improved results, yet was unsatisfactory in terms of prediction for clinical use. Therefore, the data was divided into 2 classes by thresholding EDP and then classified using SVM and KNN algorithms. The results achieved by a Fine Gaussian Kernel SVM model presented promising accuracy rates in cross-validation, yet performed poorly when

tested on a new data set. The assumption that the phenomena was a result of the bias caused by the inequality between the classes led us to a different approach. A significantly improved accuracy rate of 75% was achieved taking into consideration the Categorical variables and applying a Medium Gaussian Kernel SVM only upon the variables which presented high AUC values along with a method of resampling patient cases to even out the class sizes, as shown in the following figure:

Conclusions:

- The data is most likely not connected linearly; patients cannot be classified using a linear model.
- The classification results of 75% accuracy rate can be improved using larger, more balanced datasets.

Keywords: classification, regression, dyspnea, machine learning, small data, EDP.

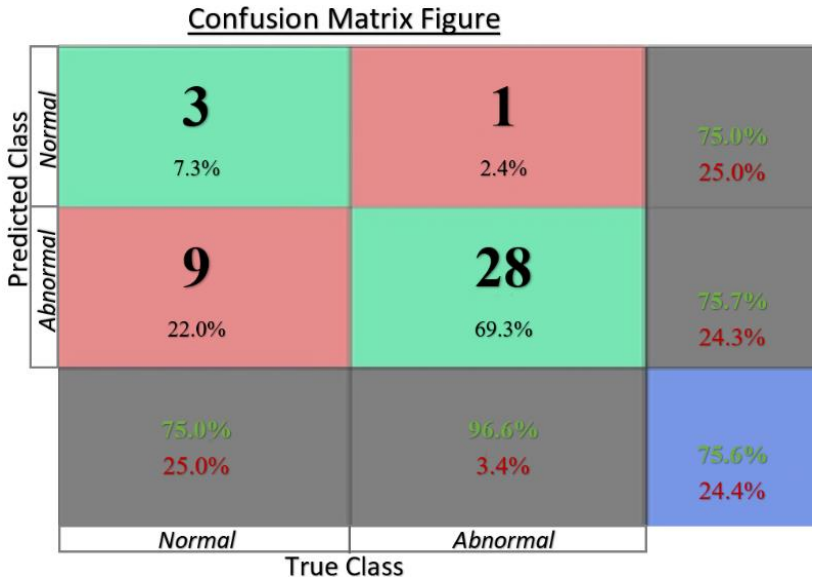

Figure 1: Confusion matrix showing prediction results of a Medium Gaussian SVM model trained with a resampled training set using only variables presenting significant AUC values.

(11)

Evaluation of Targeting Accuracy in Neuro-Functional MRgFUS Treatments

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Introduction: Essential Tremor (ET) is a movement disorder, characterized by uncontrollable shaking, in different parts and sides of the body. About 10 million Americans and millions more worldwide suffer from ET disorder. Until the year 2012, all procedures to treat this condition were invasive, including incision of the skull and insertion of electrodes into the brain. Insightec developed a new method for a noninvasive ET treatment, using high intensity focused ultrasound guided by MRI thermometry, in order to ablate the VIM nucleus of the thalamus. In 2012, the treatment was approved commercially in Europe by the European Conformity (CE). In 2016, the Food and Drug Administration (FDA) approved Insightec's system to treat ET, and ever since over than 500 treatments were performed. Yet, so far no evaluation of targeting accuracy of these treatments was made. The goal of this study is to determine the accuracy of treatment by thermal heat measurements of the targeted area obtained in thermometry images.

Methods: Intra-operative MRI scans of about 60 patients were analyzed using an algorithm we built, which provides a region with a maximal change in temperature. The algorithm extracted the deviation vector between the weighted heating area and the area aimed for ablation using the focused ultrasound beam. In addition, statistical methods to analyze qualitatively the deviation were used, considering some parameters such as temperature and reliable axes of the MRI.

Results: We successfully located the heated area from images of the different planes of every sonication during each treatment. Other important parameters were extracted as well, such as the maximal and weighted temperature, and the distance of the heated area from the target in each coordinate.

Conclusions: We found that there is a deviation between the target and the heated area, and it is variable between different treatments as well between different sonications of the same treatment.. This study provides Insightec a method to estimate this deviation, and to find the maximal and weighted heating points. Hopefully, this study will help improving the quality of future treatments.

Keyword: ET – Essential Tremor, MRgFUS – Magnetic Resonance-guided Focused Ultrasound.

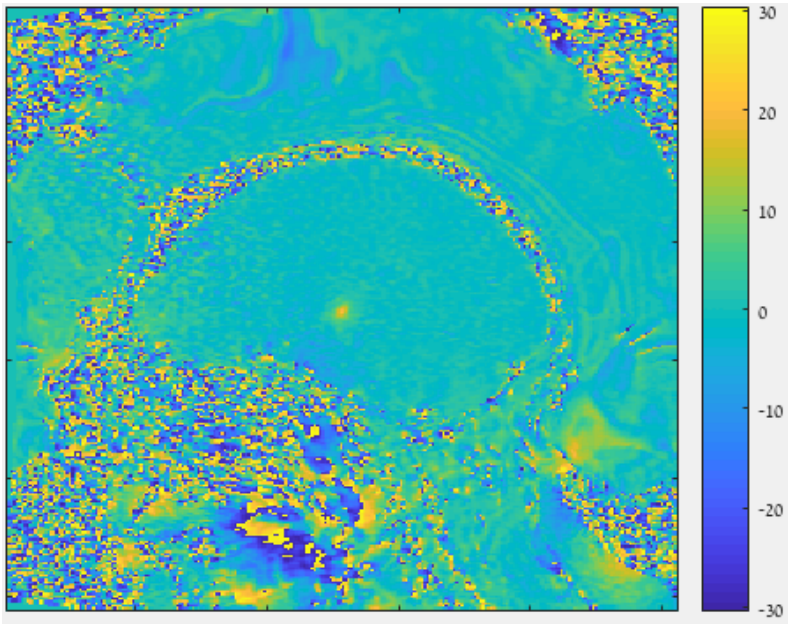

Figure 1: A thermometry image of a sagittal plane, represent the changes in temperature. The target is located in the middle of the image. The yellow round heating area is focused and limited around the target, as expected.

(12)

Early Detection of Partial Peripheral Artery Occlusion

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Introduction: Peripheral arterial disease is a major problem that affects about 200 million people globally, and more than 12% of the population over 60 years old. It is characterized by a stenosis or an obstruction in peripheral blood vessels. It is associated with severe pain, intermittent- claudication and might lead to amputations and even mortality. Current clinical diagnosis employs ultrasound examination and assessment of the blood pressure ratio between the lower and upper extremities. These measurements are performed sporadically (every couple of months), require medical personnel and are insensitive to minor deteriorations. Hence, there is a need for a simple, continuous and accurate home monitoring device, for early detection of progressive deterioration.

Methods: The study included theoretical analysis, development of a unique setup, experiment on humans, signal processing and data analysis. The human experimental study was approved by the Helsinki committee of the Technion. We have utilized a set of non-invasive sensors that measure the dynamic parameters of the cardiovascular system and the lower extremity perfusion. The quantification of the severity of peripheral artery disease is based on the analysis of the changes in the dynamics of the distal extremity perfusion. To emulate stenosis in a group of healthy young volunteers, a blood pressure measurement cuff was placed around the subject's leg. We inflated the cuff to 30, 60 or 90 mmHg. Simultaneously, for each applied pressure, the following signals were acquired: ECG, impedance plethysmography on both legs, photo-plethysmography, pulse oximeter, respiratory signal and the pressure wave under the cuff.

Results: Conspicuous changes were obtained in the impedance signals when the cuff was inflated, in comparison with the contralateral (reference) leg. Proximal vascular obstruction decreased the magnitude of the signals and modulated the shape of signals. Obstruction prolonged the time to peak (crest time) and modified the power spectrum of the signals. The changes intensified as the degree of obstruction increased. Novel indices were derived in the time and frequency domains. These indices were found to be more sensitive to vascular occlusion then other commonly used indices, as the oxygen saturation, which remained constant even at severe occlusion (cuff inflation to 90 mmHg).

Conclusions: Progressive partial occlusion of large artery yields pathognomonic changes in the perfusion dynamics, and can be measured and quantify in the time a

frequency domain. These novel indices can be continuously monitored by a simple to use and non-invasive method and system. Based on the promising results of the current study, Helsinki approval was submitted in Sourasky Medical Center, to validate the clinical utility in improving the precise diagnosis and the ability to detect partial obstruction before it becomes symptomatic and causes irreversible damage.

Keywords: Peripheral artery disease (PAD), Early detection, Impedance Plethysmography, Wave Propagation.

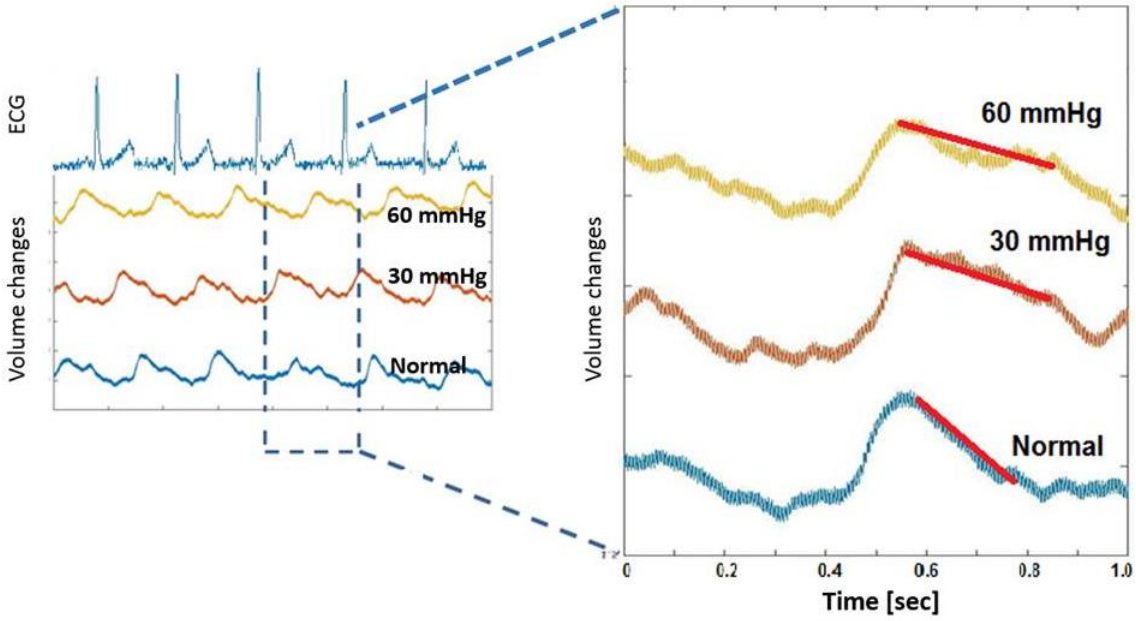

Figure 1: The impedance wave signal acquired at different applied pressures. The figure demonstrates that partial occlusion leads to significant changes in the crest time and in the shape of the signal.

(13)

Remotely Piloted Colonoscopy

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Introduction: Conventional colonoscopy utilizes a colonoscope, which is a semi-flexible endoscope equipped with a steerable tip. Steering the colonoscope through the colon to the caecum may cause pain and discomfort to the patient and for this reason, the procedure is carried out under sedation. Advancing the colonoscope through the colon is technically challenging and increase the risk of colonic perforation. Colonoscopy is associated with about 1% of complications, and the failure rate of reaching the cecum is greater than 3%. Perforation of the colon may lead to death of a heathy person without any colon lesion. Hence, a less painful, safer and more accurate examination is needed, in order to increase the compliance rate and to provide a more cost-effective mass screening method.

Methods: Comprehensive investigations of the colon physiology and structure and of the available technologies for screening the colon were conducted, to tailor the novel approach. A system comprising of a jet propelled capsule joined with a flexible tube was designed with parameters that were optimized under physiological constrains. Analytical modeling and numerical simulations were performed to define the optimal floating regime and optimal structure of the capsule. Four different designs of the capsule were printed in a 3D printer. Flows and forces in the experimental setup were measured, to verify the feasibility in the biological surrounding.

Results: The feasibility of floating and stabilizing the capsules, with minimal pressure applied to the system was established. The four different prototypes were different in the most crucial parameter that determined the required flow. The experimental results confirmed the theoretical predictions. Based on the experimental results, the ideal system parameters suitable for operating in the colonic environment were scrutinized. As predicted, employing air as a jet propellant resulted in high flows. Thus, an aerosol with a low water percentage is assumed more suitable for clinical application. Therefore, a system for creating such aerosol was tested.

Conclusions: The project supports the feasibility of the suggested novel colonoscopy approach and encourages further development that will bring it to the market.

Keywords: Colonoscopy, Propulsion, Robotic, Screening

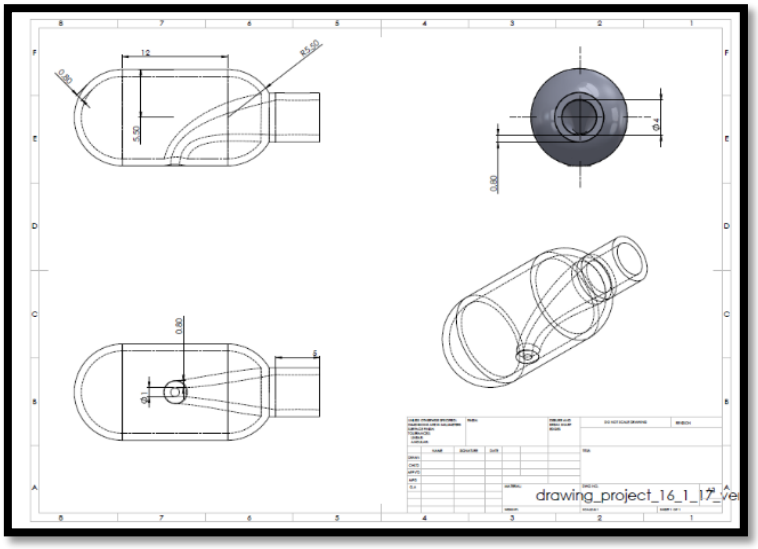

Figure 1: The SolidWorks design of one of the tested capsules

(14)

Development and Implementation of Automated Object Detection Algorithms in Ultrasound Images

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Introduction: The project's objective is to develop a machine learning based algorithm that detects the presence of the aortic arch in ultrasound images and to select the most efficient method to do so. Continuous & non-invasive measurements of blood flow using ultrasound could prove to be a valuable tool in a clinician's arsenal, providing an alternative to invasive and indirect measurements. Hemonitor's patch aspires to do exactly that- measure vital signs such as stroke volume and cardiac output directly and noninvasively. Our algorithm will assist in enabling the acquisition of those vital signs.

Methods: The algorithm is trained on a set of labeled images using a Support Vector Machine (SVM) classifier comparing two methods of feature extraction- gradient based and raw pixel intensity data. Each of the methods used the same data sets for training and testing and was evaluated using statistical parameters. To optimize the algorithm, the false positive images were identified and inspected to detect the origin of the mistake. Subsequently, some of the false positive images were moved to the train set, specifically those that were certainly negative (hard negatives), so that the next training session would have to take them into account when creating a new model.

Results: The models were compared based on performance statistics, where the main evaluation criterion was to achieve as high precision as possible while maintaining a minimum recall rate of 70%. The gradient based model resulted in 89% precision and 85% recall at the first training session while the raw pixel intensity model resulted in 86% precision and 87% recall. After perfecting the model, we were able to achieve 98% precision and 85% recall rates for the gradient based model and 91% precision and 87% recall rates for the raw pixel intensity.

Conclusions: Best results were obtained by using gradient based features and applying hard negative mining.

Keywords: object detection, machine learning, support vector machine, aortic arch.

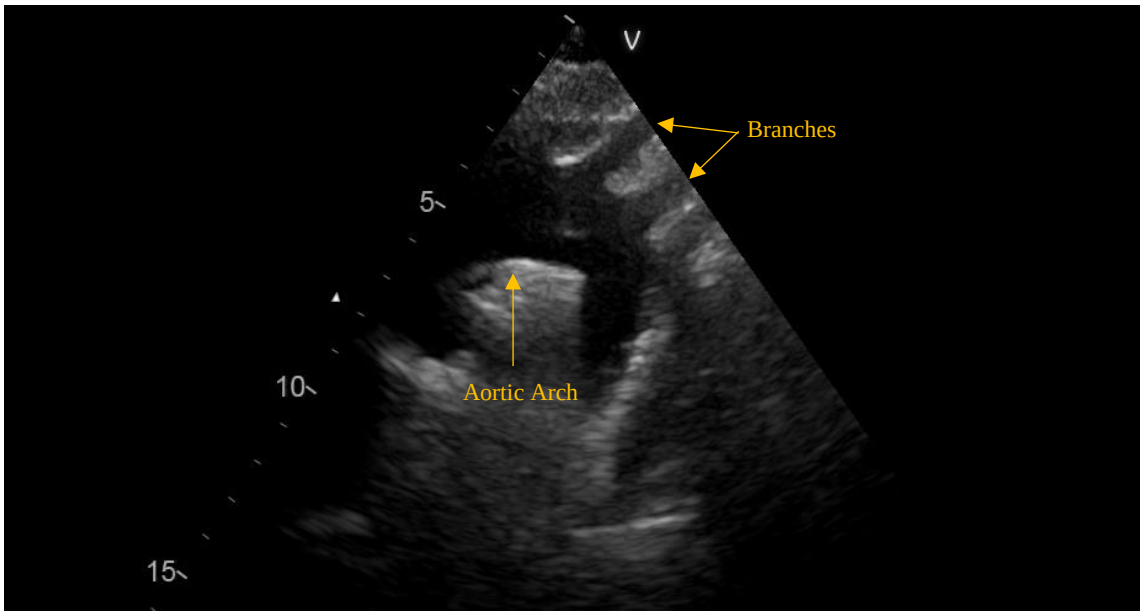

Figure 1: The aortic arch of a volunteer

(15)

Modeling and Implementation of Machine Learning Algorithm in Biological Systems Using Genetic Circuits

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Introduction: One of the main aspects of synthetic biology is the production of artificial biological systems with computational capabilities for biotechnology and biomedical applications. This is achieved by inserting DNA segments with specific regulatory reciprocal relations that can implement any logical function. We aim to create biological systems that can sense environmental changes and respond accordingly. Reaching this target will enable generation of organisms that can continuously adapt their behavior to environmental changes by internal supervised evolution process. Recently, based on biophysics models of gene regulations within the cell, Daniel's lab developed a new algorithm for supervised learning, called Perceptgene, which modifies its input weights based on gradient descent. We compared the performance of the Perceptgene and the Perceptron by simulation and also implemented it in living cells. The construction of micro sized adaptive and evolutionary biological systems will enable developments in personalized medicine, such as drugs that regulate homeostasis of single or multiple elements in the human body.

Methods: We simulated the new Perceptgene algorithm and the Perceptron in different noise environments: None, intrinsic and extrinsic (both Poisson and uniform). To attain the highest reliability in the comparison, we first optimized the parameters for each algorithm by minimization of time of convergence. In addition to the theory, we created the synthetic biological system by implementing AND logic gate in E-coli bacteria. The genetic circuit we used to achieve our target included three plasmids inserted to the bacteria and two co-factors. To link between the theory and the experiments, we repeated the experiment with different parameters (accomplished by mutational gene promoters); these parameters represent the initial weights of the learning algorithm.

Results: In all conditions that we have analyzed, the Perceptgene showed better performance (minimum time of convergence) than the Perceptron (Fig1a – AND gate with extrinsic noise). In addition, AND gate was successfully implemented in living cells, based on the Perceptgene model. As shown in Fig1b, both inputs are necessary for the production of the output protein. Also was found evident that by increasing the concentration of the inputs the production of the output protein increased as well.

Conclusions and Future Work: In all tested conditions the Perceptgene algorithm showed better results than the Perceptron algorithm. After finding the specific initial parameters of the learning system in our experiments, we will update those parameters (weights) according to the Perceptgene learning rule. This will be achieved by creating new genetic circuits with different mutational parameters. The modification of the weights will continue until the system will converge to the desirable output concentration.

Keyword: Synthetic biology, Machine learning, Genetic circuits, Perceptron

a. b.

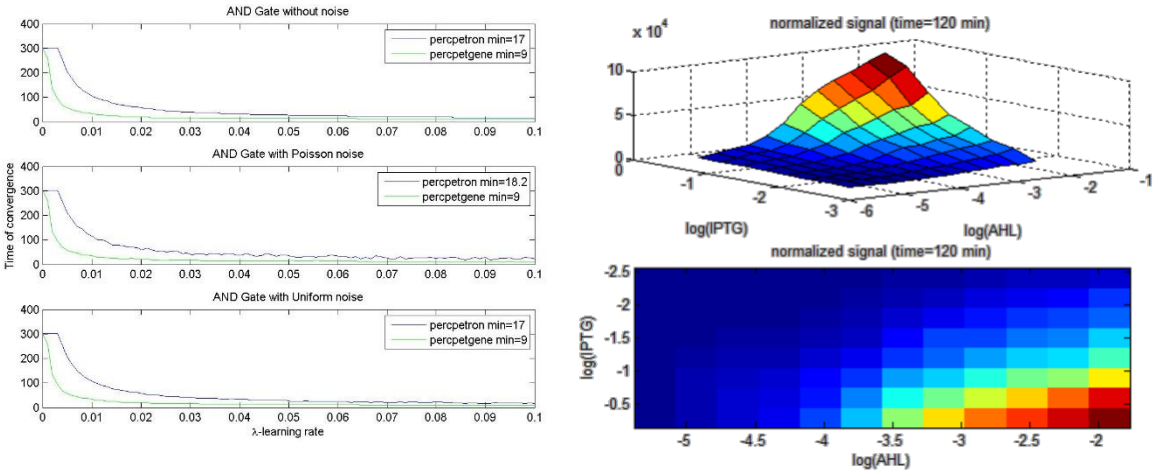

Figure 1: (a) Comparison of AND gate performance between Perceptgene and Perceptron algorithms for different values of learning rate, (b) Implementation of AND gate in E.coli bacteria. The graph represents luminescence values for each set of co-factors (AHL and IPTG).

(16)

Deciphering The Role Of RBM22 In The DNA Damage Response

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Introduction: Eukaryotic genome stability is constantly intimidated by exogenous and endogenous factors that can lead to the formation of DNA damage. In order to maintain genome stability, cells have evolved several DNA repair mechanisms. Defective DNA-repair can lead to the development of cancer and other human diseases. Therefore identifying DNA damage response (DDR) proteins and characterizing their role is crucial.

RBM22 is an RNA binding protein. It belongs to the RRM proteins, that many of them are known to have a role in alternative splicing. RBM22 contains one RNA recognition motif (RRM) and a Zinc-finger motif.

RBM22 protein was found to be recruited to DNA double strand breaks after laser micro-irradiation. These findings, prompted us to characterize the role of RBM22 in the DNA damage response.

Methods: In our research, we used different methodologies in order to decipher the role of RBM22 in the DDR.

For modeling the recruitment mode of RBM22 to DNA damage sites and in order to analyze its crucial domains for recruitment, we used PCR and selected specific primers to generate two RBM22 mutants that lack the RRM and the Zinc-finger domain. Then, we measured their recruitment mode to micro-irradiated sites.

To study the role of RBM22 in DDR, we used CRISPR-Cas9 methodology in order to generate RBM22 knock out cell line. For this purpose, we designed 2 guide RNAs. After gRNA cloning, MCF7 cells were transfected and sorted for single cells with FACS sorter. Western blot was used to screen knock out clones.

We used PCR and Cloning methodology in order to bacterially express RBM22 and to decipher its RNA binding characteristics.

We used shRNA, an artificial RNA molecule with a tight hairpin turn to silence RBM22 expression via RNA interference.

Results:

- MCF7 cells expressing EGFP-RBM22 proteins were subjected to laser micro-irradiation to induce local DNA damage. Results show that EGFP-RBM22 rapidly accumulates at laser micro-irradiated sites (figure (1)).
- RBM22 recruitment to DNA damaged sites highly depends on the Zinc-finger domain. MCF7 cells expressing EGFP-RBM22 mutant that lacks Zinc-finger domain were subjected to laser-microirradiation. Results show that RBM22$^{del(Zinc\text{-}finger)}$ recruitment is highly impaired.
- RBM22 recruitment to DNA damaged sites is independent on its RRM domain. MCF7 cells expressing EGFP-RBM22 mutant that lacks RRM domain were subjected to laser-microirradiation. Results show that RBM22$^{del(RRM)}$ recruits even faster than wild type.
- After using Crispr-Cas9 we screened 50 colonies from each gRNA but all of them expressed the protein. Additional screen is needed in order to find knocked out cells.
- Although we fail to bacterially purify full length RBM22 protein for in-vitro experiments, we succeed to purify a partial protein which contains only the RRM domain. This protein will be used for in-vitro RNA binding assays.

Conclusions:

Full length RBM22 and RBM22$^{del(RRM)}$ are rapidly recruited to sites of laser micro-irradiation. On the other hand, the recruitment of RBM22$^{del(Zinc\text{-}finger)}$ was severely impaired. This result led us to conclude that RBM22 recruitment to DNA damaged sites is highly dependent on its Zinc-finger domain.

Keywords: DNA damage response, RRM proteins.

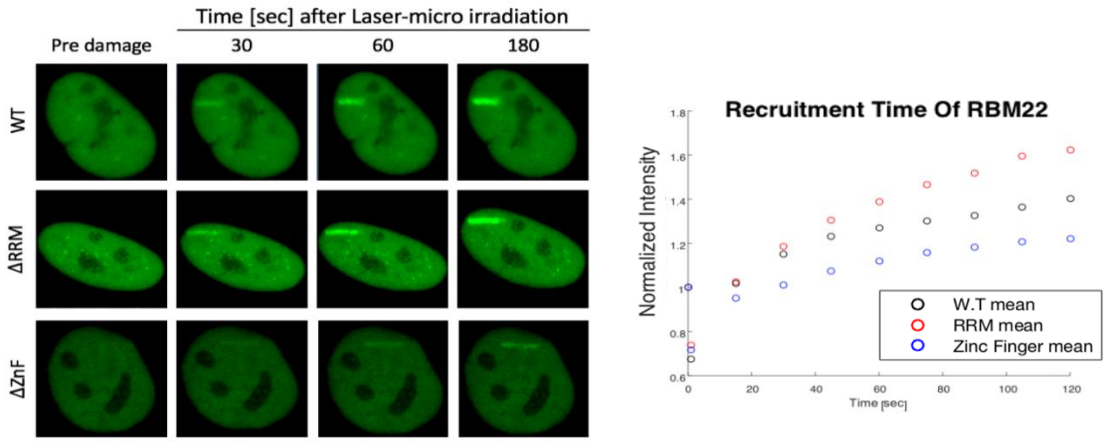

Figure 1: Recruitment of RBM22 to DNA damage sites

(17)

Mechanobiology of Invasive, Metastatic Cancer Cells

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Introduction: Cancer is the third cause of death worldwide, where the main cause of patient mortality is metastasis. The probability and rate of metastasis formation varies for different types of cancer. Previously the Weihs lab showed that metastatic breast cancer cells from lines mechanically indent an impenetrable gel more so when in groups, and correlating with their metastatic potential. The current lab goal is to evaluate this mechanobiological approach as a rapid measure for the likelihood of metastasis. The projects' main goal is to extend the work to pancreatic cancer cell lines and to compare the results with patient-derived samples; the work is part of the PhD project of Ms. Yulia Merkher. In addition, the role of the actin cytoskeleton, typically associated with cell adherence, migration, and force application was evaluated in breast cancer cell lines with varying metastatic potential.

Methods: We used four human, metastatic breast (MDA-MB-231/468) and pancreatic (AsPC-1/BxPC-3) cell lines, respectively with high/low metastatic potential. In addition, we used pancreatic cancer cells that were isolated from resected human tumors, provided by the Rambam Health Care Campus. Cells were seeded on a physiological-stiffness (2.4kPa), synthetic, non-degradable and impenetrable polyacrylamide gel with fluorescent particles embedded at its surface. Images of cells and particles were obtained using an inverted, epifluorescence microscope. When cells indent the gels, the particles at the indentation location (beneath the cells) are pushed to focal depths below the gel surface (see Figure No.1). The difference in focal depths for each cell then provides the indentation depth.

Results: We observed that pancreatic cancer cells exhibit higher percent of indenting cells (77.1±16.7% and 76.1±14.6%, respectively for AsPC-1 and BxPC-3) than breast cancer cells (61±10% and 38.8±8.9%, respectively for MDA-MB-231 and MDA-MB-468). However, the indentation depths are smaller, being 4±1.5μm for both pancreatic cell lines as compared to 10.2±4.3μm and 6.1±3.4μm respectively for MDA-MB-231 and MDA-MB-468. Primary pancreatic cancer cells from tumors exhibited a lower percentage of indenting cells (55±16%) yet with larger indentation depths (7±1.9μm) compared to pancreatic cancer cell lines. Treatment of breast cancer cell lines with Latrunculin A (disrupt actin microfilaments) at concentration of 1mM, reduced the percent of indenting cells, 70±17% and 44±22% for MDA-MB-231 cell line, 37.2±12.6% and 22.4±11.4% for MDA-MB-468 cell line, before and after Latrunculin A treatment (<1.5 hour) respectively.

Conclusions: Multiple-cells with high and low metastatic potential from breast and pancreatic cell lines may be distinguished based on their percent of indenting cells and indentation depths. Using this method on primary cancer cells can shed light on the probability of metastases formation for individual patient in more rapid way than existing methods nowadays. Actin has important role in-indentation process which reveals new target for future treatment and better understanding of metastasis formation.

Keywords: Mechanobiology, Cancer metastasis, Breast cancer, Pancreatic cancer, Metastatic potential.

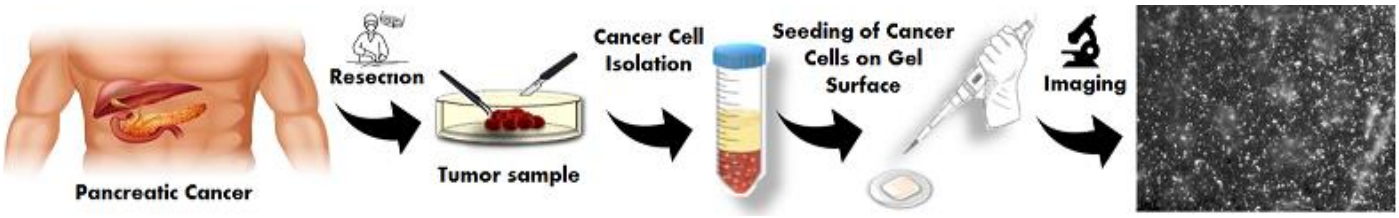

Figure 1: Schematic illustration of the method.

(18)

Forces and Regulation of Vascular Network

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Introduction: Treatment of ischemic tissues is a subject of concern to many researchers, one of the investigated directions in this area is generation of engineered vascular network in-vitro, for later implantation in vivo. The organization and formation of the vessel network is critical for successful implantation as also for optimal function and perfusion in the specific organ. One method for creating an organized blood vessel network is applying mechanical stimuli. According to previous work it was suggested that the final orientation angle of the vessel network depends on the biaxial strain ratio ($\frac{\varepsilon_{yy}}{\varepsilon_{xx}}$). In this project, our main goal was to find and characterize the factors which will lead to the creation of an optimal blood vessel network.

Methods: We co-seeded endothelial and fibroblast cells into a Gelfoam scaffold; this cell combination will spontaneously form vessel network. Physiologically, the endothelial cells line the inner surface of blood vessels and connects the interior of the vessel and its surroundings. Fibroblasts function as pericytes; they are recruited to coat the blood vessels for support and secrete out the building blocks that form the extracellular matrix of the tissue. In previous work it has been shown that fibroblasts stabilize endothelial cell network formation.

In order to create the organized network, we placed the scaffolds in a dedicated bioreactor that operated cyclic strains. Three main parameters and their effect on network organization were examined: 1) The effect of the initial seeding density. We seeded fibroblast cells with varying densities ranging from 2,000 to 200,000 cells and examined the alignment of the cells using confocal microscopy over 21 days. 2) The effect of fibroblasts on network formation. We seeded mono-culture and co-culture on Gelfoam scaffolds and examined the vessel network formation. 3) The effect of the biaxial ratio in different Regions of the scaffold on the alignment direction of the cells. We examined the different ratios through the scaffold using MATLAB and compared it to the organization angle seen with the confocal microscope. Another method we used in order to examine the network's organization was staining with DAPI which allowed us to analyze the alignment of the nucleus.

Results: In the seeding density experiment, we obtained an aligned organization of the cells for density of 200,000, whereas for 2000 we did not receive any alignment. When we compared co-culture seeding to the mono-culture, we obtained an optimal vessel network as well as alignment of the cells only for the co-culture. As a result of the varying biaxial strain ratios, we obtained a 90º angle as the ratio was closer to zero and a 45º angle as the ratio closer to one. Using the nucleus staining, we observed a more elongated form of the nucleus when a network was formed. Moreover, the nuclei were aligned in a uniform direction.

Conclusions: High seeding density as well as the combination of fibroblasts during seeding have a positive effect on the organization of the vascular network. There is an ability to regulate the angle of organization by controlling the biaxial ratio of the strains on the seeded cells.

Keywords: Vascularization, Mechanical Forces, Endothelial cells, engineered tissue.

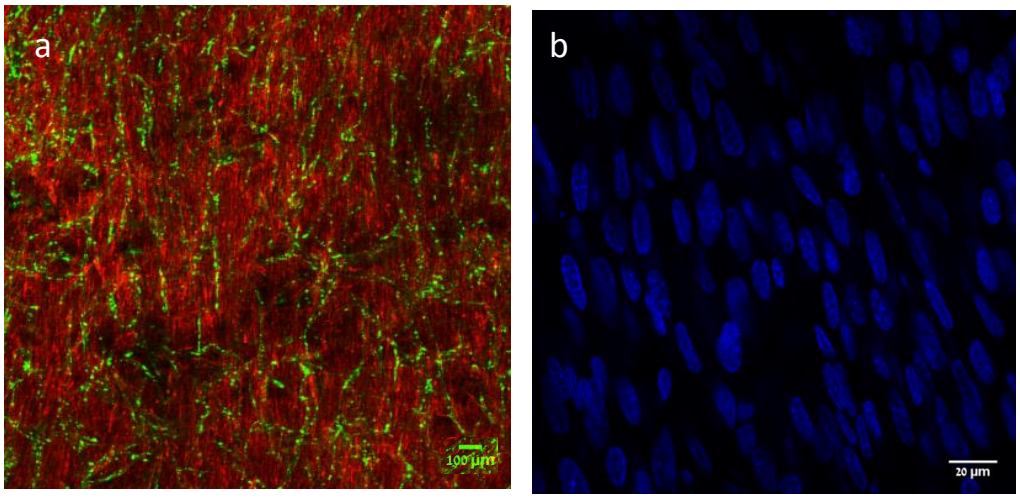

Figure 1: (a) Co-culture - Aligned network, (b) DAPI staining- Aligned and Elongated nuclei.

(19)

Development of PEG Fibrinogen Hydrogel Controlled Release System of Antisense Oligonucleotides for The Treatment of Duchenne Muscular Dystrophy

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Introduction: Duchenne Muscular Dystrophy (DMD) is a lethal genetic recessive disease linked to the X-chromosome. It is caused by a nonsense mutation in the gene that transcribes to the dystrophin protein, leading to muscular dystrophy. One of the ways to treat this disease is to use a RNA molecule which induces the splicing machinery to skip the mutated exons. This treatment molecule is degraded in the cell by RNases, thus it is difficult to maintain an appropriate therapeutic concentration of this molecule without a proper delivery system. Our main objective is to design a suitable system for the delivery of the treatment molecule. In this project, PEG-fibrinogen Hydrogel used to encapsulate the molecule and later on, its ability to release over time was measured.

Methods: PEG-fibrinogen Hydrogel was used to fabricate microspheres (beads) that will be used as a controlled release system. The fabrication is done by cross-linking the hydrogel in an emulsion. That was accomplished by using two phases: aqueous phase which contains solution of the PEG-fibrinogen and a DNA molecule (as a model molecule of the therapeutic RNA molecule) and mineral oil phase. These two phases were vortexed for 4 seconds and exposed to UV light for 30 seconds. . The resulting emulsion was resuspended 3 times with PBS (pH 7.4) and centrifuged to separate the microspheres aqueous phase from the oil phase.
The elastic module of the hydrogel was measured by a rheometer. Characterization of the resulting microspheres was done. The microspheres were microscopically imaged and the size of the microspheres was measured using a laser diffraction method by mastersizer the encapsulation amount of DNA was determined by measuring the fluorescence of the washed PBS.

Results: DNA loaded PEG-fibrinogen microspheres were successfully fabricated. The size of the spheres was measured to be approximately 100µm and this size remains constant with changing the PEG concentration or encapsulating DNA molecule. the elastic module of the PEG-fibrinogen was measured using a rheometer and it was found that G' of the hydrogel was increased with PEG concentration in the aqueous phase solution.
In addition, it was found that microspheres with addition of 3% PEG resulted with

46.5% encapsulation percentage of the DNA as compared to microspheres with addition of 5% PEG which resulted with 64.5%.

Conclusions: PEG-fibrinogen DNA loaded microspheres were successfully fabricated using photo initiator water in oil method. The encapsulation percentage of the DNA was influenced by the concentration of the PEG molecule in the hydrogel. Microspheres with addition of 5% PEG resulted with higher encapsulation due to higher crosslinking in the hydrogel network which prevent the DNA molecule to diffuse out from the gel.

Keywords: gene therapy, splicing machinery, exon skipping, hydrogel, PEG-fibrinogen, emulsion, controlled release, microspheres.

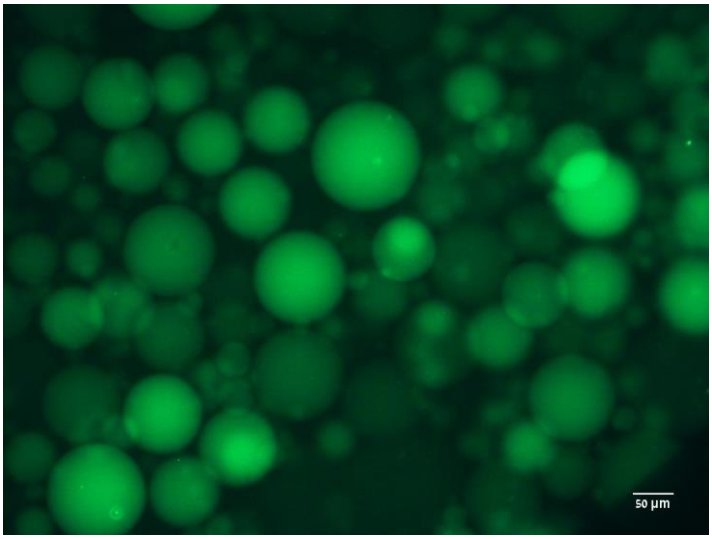

Figure 1: 3% PEG microspheres encapsulating florescence DNA molecules. X10

שלום רב,

אנו שמחים להציג בפניכם את תקצירי הפרויקטים של הסטודנטים המסיימים לימודיהם בשנה זו, שנת תשע"ז.
הפרויקט, המבוצע ע"י סטודנטים בשנת הלימודים האחרונה, מהווה את גולת הכותרת של לימודיהם לתואר בהנדסה ביו-רפואית.
במסגרת הפרויקטים מביאים הסטודנטים לידי ביטוי את הידע והכלים שרכשו במהלך השנים בתחומי ההנדסה, המדע והרפואה.
מטרת הפרויקטים הינה לתת מענה לצרכי הפיתוח והמחקר של חברות העוסקות בתחום ההנדסה הביו-רפואית, תוך עמידה בסטנדרטים המקובלים ובמקביל, לתת ניסיון ואתגר מקצועי לסטודנטים המסיימים ולעודד השתלבותם בתעשייה הביו-רפואית.
לפרויקטים חלק חשוב בעידוד היזמות בקרב הסטודנטים, וחלקם אף מובילים להקמת חברות הזנק ורישום פטנטים.

פרויקטים אלו מהווים נדבך מרכזי בחזון הפקולטה, לחתור לבניית גשר למצוינות ובמה לקשרים ושיתופי פעולה ארוכי טווח בין האקדמיה והחברות המובילות בתעשייה.

הפקולטה מאחלת הצלחה לסטודנטים המסיימים, ומקווה לראותם בעתיד נוטלים חלק פעיל בפרויקטים חשובים אלו כמנחים מהתעשייה.

בברכה,
פרופ' שולמית לבנברג , דיקנית הפקולטה
ד"ר אלכס וילנסקי , אחראי קורס פרויקטים