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2008 ISMBE Annual Meeting

Wednesday, March 12, 2008, Tel Aviv

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Program of 2008 ISMBE Annual Meeting

Wednesday, March 12, 2008, Tel Aviv

Registration	08:40 - 09:20
Prof. David Elad, Tel Aviv University, ISMBE President **– Opening Remarks**	09:20 - 09:30
Bio-engineering Advances, Chairman: **Dr. Zehava Blechman**	09:30 – 10:50
Prof. Eitan Kimmel, Biomedical Engineering, Technion **On therapeutic use of microbubbles generated by laser-heated nanoparticles**	09:30 – 09:50
Dr. Amir Karniel, Biomedical Engineering, Ben-Gurion University **Telemanipulation: How does the brain control delayed environment?**	09:50 – 10:10
Dr. Shy Shoham, Biomedical Engineering, Technion **Optically interfacing with large populations of neurons**	10:10 – 10:30
Ms. Zoya Gordon, Biomedical Engineering, Tel Aviv University **Anthropometry of fetal vasculature in the placenta**	10:30 – 10:50
The BME Industry, Chairman: **Prof. Shmuel Einav**	10:50 – 11:50
Dr. David Freundlich, InSightec, Tirat Hacarmel **MRI guided focused ultrasound treatment of malignant tumors**	10:50 – 11:20
Mr. Meir Porat, STI Lasers, Or Akiva **Manufacturing miniature devices: medical implants and tools for surgery**	11:20 – 11:50
ISMBE Business meeting	11:50 – 12:00
Lunch Break – Exhibition – Poster Session (graduate students)	12:00 – 14:00
Cellular Engineering, Chairman: **Prof. Yoram Lanir**	14:00 – 15:00
Dr. Avishay Bransky, Biomedical Engineering, Technion **Cell manipulation using microfluidic devices**	14:00 – 14:30
Ms. Nurit Even-Tzur, Biomedical Engineering, Tel Aviv University **Exposure of air-liquid interface cultured nasal epithelial cells to airflow stresses**	14:30 – 15:00
Coffee Break	– 15:20 15:00
Clinical Applications of Medical Engineering, Chairman: **Prof. Ofer Barnea**	15:20 – 16:40
Prof. Haim Azhari, Biomedical Engineering, Technion **Application of through transmission ultrasonic waves to breast imaging**	15:20 – 15:40
Dr. Amit Gefen, Biomedical Engineering, Tel Aviv University **Patient specific models for understanding deep tissue injury**	15:40 – 16:00
Dr. Meital Zilberman, Biomedical Engineering, Tel Aviv University **Novel drug-eluting fibers for various biomedical applications**	16:00 – 16:20
Dr. Hayit Greenspan, Biomedical Engineering, Tel Aviv University **MR brain image segmentation and multiple-sclerosis lesion delineation**	16:20 – 16:40

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Abstracts of Lectures

ON THERAPEUTIC USE OF MICROBUBBLES GENERATED BY LASER-HEATED NANOPARTICLES

Eitan Kimmel and Boris Krasovitski

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There is a growing need for microbubbles in the human body. In presence of ultrasound of moderate intensity those microbubbles can be used for therapeutic and diagnostic purposes. Microbubbles can be either generated in the body by high intensity ultrasound or introduced intravenously as encapsulated bubbles known also as ultrasound contrast agents (UCA). The potential use of microbubbles include a wide variety of medical treatments such as ultrasonically induced targeted hyperthermia, inducing programmed death (apoptosis) in cells, increasing membrane permeability of cells for e.g. gene transfection, increasing permeability of blood vessel walls for facilitated transport, and enhancing drug delivery.

In difference from tap water, moderate intensity ultrasound cannot initiate bubbles in-vivo because of absence of pre-existing nucleation sites for bubble generation in most tissues. UCA, for instance, might serve as a way of delivering nucleation sites into the target region yet they are short lived and thus require frequent administering.

An alternative method for generating nucleation sites by exposing light absorbing gold nanoparticles to laser was suggested some 3 years ago. Nanobubbles of diameter of about 150nm were maintained by exposing gold nanoparticles embedded in gel to a 532nm (peak absorption of near-spherical nanoparticles) laser pulse phase-synchronized with ultrasound wave pocket with acoustic pressure of 0.9MPa (20W/cm^2) and frequency of 1.1MHz. Threshold laser energy densities for this case of isolated nanoparticles were about 5mJ/cm^2.

Exposing bacteria-attached clusters of gold nanoparticles to 532nm laser pulse generated nuclei which evolved into microbubbles at laser energy densities above 100mJ/cm^2. Discrete nanoparticles exposed to similar conditions failed to generate microbubbles.

In this study we investigate the evolution of a vapor nuclei cluster exposed to moderate ultrasound irradiation following laser heating of clusters of nanoparticles. Simultaneously applied moderate ultrasound intensities (e.g. 0.2MPa, 1W/cm^2) evolve the nanobubbles cluster into stabilized microbubbles through rectified diffusion while increasing their non-vaporized gas content. A mathematical model that combines momentum, heat and mass transfer is developed for a single bubble in a surrounding liquid.

The developed theoretical model is novel. It simultaneously takes into account three issues: i) the heat transfer and vaporization problem; ii) the bubble dynamics problem; and iii) the dissolved gas transport problem. The model allows us to predict bubble stability and to define conditions for more effective bubble generation in terms of laser power and ultrasound acoustic pressure.

The model is then expanded to handle a cluster of nanoparticles, by simulating a coalesced nanobubble originated form 10 nanobubbles. This study predicts the conditions that are required to induce a stable bubble – a bubble filled with non-vaporized gas that does not grow or shrink. A stable bubble is induced for a specific relationship between the acoustic pressure and the energy absorbed by the particle from the laser pulse. It is predicted that lower ultrasound power density would be required to evolve a stable microbubble from 10 nanobubbles generated near laser irradiated nanoparticles cluster, compared to a single nanoparticle at similar conditions.

Telemanipulation: How does the brain control delayed environment?

Amir Karniel

The Computational Motor Control Laboratory

Department of Biomedical Engineering

Ben-Gurion University of the Negev, Beer-Sheva, Israel

Bilateral (force reflecting) teleoperation allows human operators to determine the motion of a remote slave robot by moving a local master robot and feeling the forces reflected from the slave to the master. Such systems could be useful for telemedicine (e.g., telesurgery and telerehabilitation) however the unavoidable delay prevents truly transparent channel. We assert that understanding the human perception and control of delayed environment could facilitate the design of perceptually transparent telemanipulation and report some of our recent attempts to obtain such understanding.

In a forced choice paradigm subjects were presented with two surfaces and asked to identify the stiffer one. For one surface the force was proportional to the position but in the second the force was proportional to a prior position of the surface a few tens of milliseconds earlier. We found that subjects tend to overestimate delayed stiffness. Additionally, we found that shifting the boundary also modified stiffness perceptions. Interestingly as we observed the human performance in similar adaptation study we observed that the expected stiffness as measured by the motor behavior is not always similar to the expected stiffness as declared by the subject. Moreover, in another study we found that when subjects did not cross a boundary – i.e., when their hand remained inside an elastic field all the time – they tend to underestimate delayed stiffness. We proposed regression based computational models to account for these results, and discuss their possible interpretation for our understanding of the neural control of delayed environments and the potential implications for future teleoperation and telepresence.

Acknowledgements

The studies described in the talk have been conducted with Sandro Mussa-Ivaldi, Assaf Pressman and Ilana Nisky and were supported by the United States-Israel Binational Science Foundation (BSF), Jerusalem, Israel, as well as the National Institute for Psychobiology in Israel – Founded by The Charles E. Smith Family.

OPTICALLY INTERFACING WITH LARGE POPULATIONS OF NEURONS

Shy Shoham

Faculty of Biomedical Engineering, The Technion I.I.T

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Spatiotemporal patterns of activity carried across populations of neurons are the fundamental representation of information within the nervous system, with even the very simplest of neural circuits being composed of thousands to many millions of individual nerve cells. Physical control of complex neural activity patterns can be used experimentally to gain a better understanding of neural information representation and processing, and also medically in neuro-prosthetic interfaces. For example, Retinal neuroprosthetics can potentially be used to address some of the major degenerative disorders that cause blindness, including Retinitis Pigmentosa and Macular Degeneration, by bypassing the degenerated photoreceptor layer, and interfacing directly the largely viable Retinal Ganglion Cells (RGCs).

The talk will focus on describing my lab's efforts to develop an optical approach to interfacing with the retina, as a powerful alternative to micro-electrode array retinal interfaces currently being pursued by a large number of researchers and companies. I will describe different strategies allowing light to stimulate neural activity, the development of several generations of optical systems allowing control of increasingly complex spatiotemporal activity patterns, and potential strategies towards a practical wearable device.

ANTHROPOMETRY OF FETAL VASCULATURE IN THE PLACENTA

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Normal fetal development is dependent on adequate placental blood perfusion. The feto-placental vasculature includes the relatively large chorionic vessels, the intra-placental vessels and the capillaries within the cotyledons. The functional role of the placenta takes place mainly in the capillary system. However, ultrasound imaging of fetal blood flow is commonly performed on the umbilical artery or on its first branches over the chorionic plate. The objective of this study was to evaluate the structural organization of the feto-placental vasculature in the chorionic plate. Plastination of the feto-placental vasculature was performed on 15 full-term placentas. The placental vessels were rinsed immediately after delivery with a solution of saline and heparin sulfate. The casting material was a mixture of a dental polymer mixed with colored ink. The polymeric material was injected via the umbilical vessels by separate syringes, each filled with the casting material mixed with a different color. Hardening of the casting material was allowed for 4 days in a refrigerator, and then, all biological tissues were eroded with a KOH solution. Diameters, lengths and branching angles of the chorionic and intra-placental vessels were measured with a digital caliper. Observations of the cast models revealed that the chorionic vessels' branching architecture is a combination of dichotomous and monopodial patterns, where the first 2-3 generations are always of a dichotomous nature. Analysis of the daughter–to–mother diameter ratios in the chorionic vessels provided a maximum in the range of 0.6-0.8 for the dichotomous branches, while in monopodial branches it was in the range of 0.1-0.3. Similar to previous studies, this study reveals that the vasculature architecture is mostly monopodial for the marginal cord insertion, whereas for the central insertion it is mostly dichotomous. The vasculature of the chorionic plate is designed for optimal perfusion of all placental territories. In case of a central cord insertion, dichotomous networks branch off each umbilical artery for adequate perfusion of the placenta. However, the more marginal the umbilical cord insertion is on the chorionic plate, more monopodial branching patterns are created in order to compensate the dichotomous pattern deficiency to perfuse peripheral placental territories.

MRI GUIDED FOCUSED ULTRASOUND TREATMENT OF MALIGNENT TUMORS

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The concept of "ideal" tumor surgery is to remove or ablate the neoplastic tissue without damaging adjacent normal structures. This concept requires a noninvasive surgical approach. Focused ultrasound surgery (FUS) is such technology. Unlike invasive surgery, it requires no incision and the acoustic energy penetrates the intact skin and through the tissues surrounding the tumor, without causing any significant bioeffects. Energy deposition causes thermal coagulation only at the focal spot where the energy density is high enough. The localization of the target volume requires image guidance. The intraprocedural MRI provides the best possible tumor margin definition and with real-time MR thermometry the closed-loop feedback control of energy deposition is accomplished.

The idea of using focused acoustic energy for thermal coagulation deep within the body is not new. It was first proposed in 1942 (by Lynn et al.). It was recognized that localized high temperatures (>56 deg C) generated at the focal spot of the focused acoustic beam could induce cell damage as a result of protein denaturation and coagulation necrosis. The development of ultrasound induced tissue coagulation as a noninvasive soft tissue ablation method has been delayed due to the lack of an imaging method that can correctly define tumor margins and a temperature-sensitive imaging technique that identify focal temperature elevation. MRI guided focused ultrasound (MRIgFUS) is such technology.

Currently, InSigthec's ExAblate 2000 is the only commercial available MRIgFUS system. It is FDA approved for the treatment of uterine fibroids (a benign tumor of the uterus) and has a CE mark for the treatment of pain palliation caused by bone metastases. It is also used in different stages of clinical studies for treatment of breast cancer, prostate cancer, liver cancer and brain tumors.

MANUFACTURING MINIATURE DEVICES: MEDICAL IMPLANTS AND TOOLS FOR SURGERY

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Minimally invasive surgical (MIS) intervention has been one of the biggest trends in medicine in the last few years. MIS procedures avoid open invasive surgery in favor of closed or local surgery with less trauma.

As surgeons are attempting to perform more procedures as minimally invasive procedures, their progress greatly depends of the development of novel miniature medical devices and specialty accessories that could be inserted into the body through small openings in the skin or via anatomical openings.

STI Laser Industries Ltd. applies cutting-edge high precision laser cutting and welding technologies for the manufacturing of miniature metal parts destined for MIS products. STI processes various biocompatible as well as novel bio-degradable metal alloys. The Company supports medical device companies developing implants and specialty surgical tools from the drawing board through prototyping and onto serial manufacturing. The Company has been instrumental in the development of various types of stents (brain stents, cardio-vascular stents, biliary stents), heart valves, orthopedic devices (expandable spinal support system, nailing system for bone fractures), endoscopes and MIS tools.

CELL MANIPULATION USING MICROFLUIDIC DEVICES

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It has long been recognized that the microenvironment of cells specifically Embryonic Stem Cells is the dominant factor in cell proliferation and sorting mechanisms. Conventional cell culture methods such as culture dishes do not permit the regulation of the cell microenvironment.
Micro-fabricated devices sometimes referred to as BioMEMS chips, facilitate the monitoring and regulation of the microenvironment in terms of local stresses, local concentration of factors or reagents etc.
We have developed, tested and characterized a variety of micro-fabricated devices for the study of cells. One such device is the micro-bioreactor in which cells, including human embryonic cells, are cultured for long periods of time. The bioreactor is analyzed in terms of nutrients diffusive and convective characteristics and shear stress exerted on the cells. The theoretical analysis and experimental results help determine the optimum conditions for culture within micro-bioreactors.
Additional devices for cell culture are characterized in which cells are trapped within micro cavities of different geometries within the bioreactor which help protect them against shear induced by the flow. The diffusive convective characteristic is simulated and the results bear important conclusions regarding the design of such devices.
Another effect known as focused laminar flows is studied both experimentally and theoretically. Due to the laminar flow existing in microfluidics (or low Reynolds numbers) it is possible for two or more streams to flow side by side without any mixing except by diffusion. The flow focusing technique enables the maintenance of a constant nutrients concentration gradient in contrast to the standard culture dish where such a gradient would quickly dissolve due to diffusion. Based on this phenomenon it is possible to regulate the exact concentration of reagents conveyed to cells inside the microfluidic network. It is also demonstrated that the streams location and width could be accurately controlled using a novel apparatus. The system is used to deposit micro-patterns of proteins on the surface of the network which later promote selective cell adhesion.
A detailed analysis of the system demonstrates the mechanisms involved and offers tools for accurately designing such devices.

EXPOSURE OF AIR-LIQUID INTERFACE CULTURED NASAL EPITHELIAL CELLS TO AIRFLOW STRESSES

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The nasal epithelium is continuously exposed to wall shear stresses (WSS) due to airflow during inspiration and expiration and although mucus secretion was widely studied in response to biological, chemical and environmental stimuli, it was only slightly studied in response to WSS. The objective of this work was to explore the response of cultured nasal epithelial cells to airflow induced WSS. Primary human nasal epithelial cells were seeded on either synthetic PTFE filters or denuded human amniotic membranes that were mounted in custom-designed wells. The cells were cultured using the air-liquid interface technique that mimics the *in vivo* conditions of the inner nasal respiratory epithelium. The experimental setup for this study is composed of a special flow chamber which was designed to hold the custom well bottom with the cultured cells and enable application of airflow on the cells, and either steady or oscillatory air source which was connected to the flow chamber and generated airflow on top of the cells. Following the application of WSS on the cells, several of biological tests were performed: quantification of mucus secretion, assessment of morphological changes in the cell cytoskeleton and detection of epithelial goblet cells within the epithelial cell culture. Steady and unsteady airflows were applied on the cultured cells. The results showed increased mucus secretion immediately after exposure to steady WSS of 0.1 and 1.0 dyne/cm^2 for more than 15 minutes, with respect to the unstressed control cell culture. Analysis of cytoskeletal fibers revealed that the actin integrity level was not significantly different in stressed cultures compared with the control cultures. However, the level of β-tubulin integrity was significantly different in the stressed cultures in comparison to the unstimulated ones. Preliminary results from sinusoidal WSS tests in the range of 0-5 dyne/cm^2 showed similar trends as did cultures under exposure to steady WSS, but with moderate strength.

בס"ד

APPLICATION OF THROUGH TRANSMISSION ULTRASONIC WAVES TO BREAST IMAGING

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Breast cancer is a major killer of women in developed countries. The best way to decrease breast cancer mortality is to detect and treat the malignancy while it is still localized to the breast. This calls for a reliable screening method. Presently the main screening and diagnostic modality is X Ray mammography. However, X Ray mammography has three considerable disadvantages: (i) It uses ionizing radiation; (ii) It does not yield good images in dense breasts (a problem for younger women); (iii) Its specificity is low.

Ultrasound offers a hazardless imaging modality that works well in dense breasts. But the most widely used ultrasonic imaging technique is the hand held pulse-echo technique which does not scan the breast systematically, is operator dependent and the scans can hardly be reproduced. Furthermore, pulse-echo imaging does not offer quantitative data on the acoustic properties of the tissue, information which is needed for tumor characterization.

Through transmission ultrasound is much more limited in its imaging application, and the information it provides is integrative. However, it offers a much superior SNR relative to the pulse echo technique and is particularly suitable for automated breast imaging.

We have developed a computerized breast scanning system which scans the breast automatically with through transmission ultrasonic waves. Scanning is systematic and provides quantitative images depicting different acoustic parameters.

In this presentation we shall describe some of the suggested imaging protocols used with this system. This includes: acoustic projection imaging, ultrasonic computerized tomography (UCT), spiral UCT, and contrast enhanced imaging. Some exemplary clinical data demonstrating the potential utility of this method will be shown as well.

PATIENT SPECIFIC MODELS FOR UNDERSTANDING DEEP TISSUE INJURY

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Deep tissue injury (DTI) is a severe pressure ulcer characterized by necrotic tissue mass under intact skin. Systemic infections, sepsis, myocardial infarct and renal failure are a few of the complications associated with DTI. The etiology and biomechanics of DTI are still poorly understood, but in the last years, major progress has taken place. It has been recognized that DTI is distinct from other pressure ulcers in that it originates in deep muscle tissue around the contact region between muscle and bony prominences (particularly the ischial tuberosities or sacrum), rather than at the body surface. Because the site of initial injury is muscle tissue, the focus of our recent research work has been the loads occurring in skeletal muscle tissue adjacent to bony prominences during sitting and lying, and the tolerance of muscle tissue to these loads, in healthy individuals and those with impaired motosensory capacities, particularly patients with spinal cord injury (SCI). We hence developed patient specific computer models of sitting and lying subjects to explore the effects of the anatomy of the individuals - controls and those with SCI - on the internal tissue loading. Additional computer modeling at the muscle fiber microscopic scale was conducted to relate tissue loads at the continuum scale with muscle capillary function, in order to understand the effects on muscle tissue perfusion under sustained loading. It is expected that in the near future, the patient specific modeling approach will allow the establishment of improved clinical criteria and protective means for managing patients with SCI or other patients susceptible to DTI.

NOVEL DRUG-ELUTING FIBERS FOR VARIOUS BIOMEDICAL APPLICATIONS

Meital Zilberman

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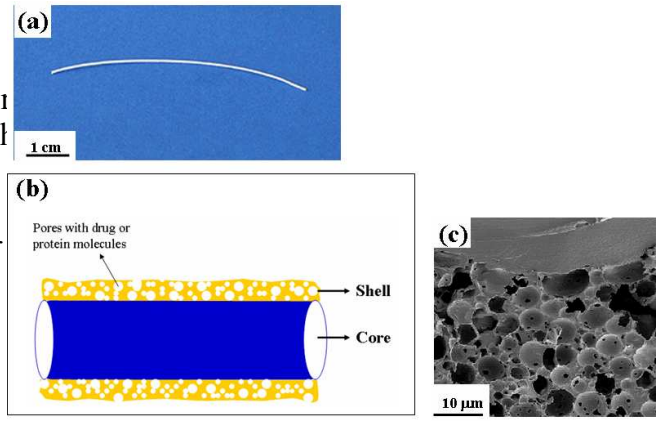
Bioresorbable drug-eluting fibers can be used in many biomedical applications. However, the key problem remains: How can bioactive molecules be incorporated in thin delicate structures that construct devices and scaffolds, without having an adverse effect on their mechanical properties or on the agent's activity. We have recently developed and studied a novel class of bioresorbable, composite (core/shell) fiber structures which successfully overcome these challenges, opening the way for major advances in clinical applications.

Our initial composite fiber structures combine a PLLA core, prepared by melt spinning, and a porous PDLGA shell prepared using the "water-in-oil" emulsion freeze-drying technique. These novel structures are described in Fig. 1. Water-soluble agents can be incorporated into the emulsion's aqueous phase, while the water-insoluble agents can be incorporated into the organic phase.

In our initial studies the shell was loaded with the model enzyme horseradish peroxidase (HRP), which is very sensitive to both solvents and elevated temperature and whose activity is a sensitive monitor of damage during processing. The new fibers displayed both desirable mechanical properties and versatile release profiles (Zilberman 2007). Under mild processing conditions HRP preserved 98-100% of its content and 94-100% of its activity. However, high rates and durations of emulsion homogenization (mixing) should be avoided. Since the incorporated proteins remain highly active, such fibers can be loaded with growth factors and formed into bioactive scaffolds to promote tissue regeneration. We have also studied composite fiber structures loaded with the antiproliferative drug paclitaxel. These fibers can be used as basic elements of biodegradable stents that mechanically support blood vessels while delivering drugs directly to the blood vessel wall, in order to prevent restenosis.

In both cases, the release profiles generally exhibited an initial burst effect accompanied by a decrease in the release rate with time, as is typical for diffusion-controlled systems. It appeared that the O:A emulsion's phase ratio has major effect on HRP release profile, while the emulsion's polymer content has major effect on the paclitaxel release profile. We have demonstrated that appropriate selection of the emulsion's parameters can yield a variety of new core/shell fiber structures with desirable drug/protein release behavior. This will lead to the engineering of new implants and scaffolds, and will advance the field of tissue regeneration and medical implants.

Figure 1:
The structure of the composite fibers:
(a) general look (photograph) of the fiber
(b) a schematic representation showing the core dense fiber and the porous drug-loaded shell.
(c) SEM fractograph of core PLLA fiber coated with HRP loaded PDLGA shell (cross section). Good adhesion between core and shell is shown.



Zilberman, M. (2007). *Acta Biomaterialia*, 3(1), 51-57.

MR BRAIN IMAGE SEGMENTATION AND MULTIPLE-SCLEROSIS LESION DELINEATION

Hayit Greenspan

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Currently no standard software tools exist to quantify brain MRI in Multiple-Sclerosis (MS) patients. In particular, tools are lacking for segmentation, quantification of tissue volumes, to extract lesion burden and to track lesions over time. In this talk I will present an overview of state-of-the-art research in the domain of brain MRI segmentation with initial application towards automated computerized MS lesion delineation.

A state-of-the-art probabilistic framework for brain tissue modeling will be presented. To capture the complex tissue spatial layout, a probabilistic model termed Constrained Gaussian Mixture Model (CGMM) is proposed based on a mixture of multiple spatially-oriented Gaussians per tissue. The intensity of a tissue is considered a global parameter and is constrained, by a parameter-tying scheme, to be the same value for the entire set of Gaussians that are related to the same tissue. MS lesions are identified as outlier Gaussian components, and are grouped to form a new class in addition to the healthy tissue classes. A probability-based curve evolution technique is used to refine delineation of lesion boundaries. The presented algorithm is used to automatically segment 3D MR brain images with an arbitrary number of channels. Experimental results on both standard brain MR simulation data and real data indicate that the proposed method outperforms previously suggested approaches, especially for highly noisy data.

A major focus in recent brain research is on the use of MRI Diffusion Tensor Imaging (DTI) for White Matter (WM) characterization in healthy brain as well as pathology cases, such as MS. An overview will be given on our recent works in the domain of direct inter and intra-subject registration of White Matter (WM) tractographies. The methods presented do not require any previous registration between the brains. They enable automated extraction of fiber tracts of interest within given brain volumes and the generation of fiber tracts atlases.

Research ahead is aimed at utilizing WM tractography connectivity for the analysis of pathological WM in MS. This should enable the investigation of MS influence along fibers that cross with lesions, even at significant distance from the crossing. We expect that the developed algorithms will augment the radiologist-neurologist capabilities in general brain analysis and in the analysis of MRI from MS patients.

Collaborators: Dr. J. Goldberger, A Ruf, O. Friefeld, A. Mayer, O. Zvita

Clinical Collaboration with the Multiple Sclerosis unit, Sheba medical center, Tel-Hashomer.

List of Graduate Students Posters

	Chairmen: **Prof. Dan Adam, Dr. Giora Enden, Dr. Israel Gannot**
1	**Ilana Nisky**, Biomedical Engineering, Ben-Gurion University **Perceptuo-motor transparency in bilateral teleoperation**
2	**Ben Klein**, Biomedical Engineering, Ben-Gurion University **Haptic representation of medical imaging data**
3	**Erez Berkovich**, Biomedical Engineering, Technion **Face recognition with biologically motivated boosted features**
4	**Sima Witman**, Biomedical Engineering, Tel Aviv University **Three dimensional contracting heart based on matrix structural analysis**
5	**Orly Grinberg**, Biomedical Engineering, Tel Aviv University **Highly porous bioresorbable scaffolds with controlled release of bioactive agents for tissue regeneration applications**
6	**Michal Tepper**, Biomedical Engineering, Tel Aviv University **Thermal imaging method for estimating oxygen saturation**
7	**Jonathan Elsner**, Biomedical Engineering, Tel Aviv University **Novel gentamicin-eluting bioresorbable composite fibers for wound healing applications**
8	**Dima Litvak**, Biomedical Engineering, Tel Aviv University **Fall detection of elderly through floor vibrations and sound**
9	**Yael Shifrovitch**, Biomedical Engineering, Tel Aviv University **Metronidazole-loaded bioresorbable films for preventing bacterial infections during gingival healing**
10	**Adi Rachelson**, Biomedical Engineering, Tel Aviv University **Nano-structured bioresorbable films loaded with bioactive agents for biomedical applications**
11	**Amir Kraitzer**, Biomedical Engineering, Tel Aviv University **Long-term in vitro study of paclitaxel-eluting bioresorbable core/shell fibers**
12	**Orly Zvitia**, Biomedical Engineering, Tel Aviv University **White matter tractographies registration using Gaussian mixture modeling**
13	**Sigal Trattner,** Biomedical Engineering, Tel Aviv University **A numerical analysis of the born approximation for image formation modeling of differential interference contrast microscopy for human embryos**
14	**Marina Gaufman**, Biomedical Engineering, Tel Aviv University **Three-dimensional localization and functional detection of tumor labeled with specific fluorescence markers**
15	**J-P Elisha Martinez**, Biomedical Engineering, Tel Aviv University **Hydraulic Pressure enhances LDL but not Ac-LDL intake by BAECs**
16	**Paz Elia**, Biomedical Engineering, Ben-Gurion University **Sonodynamyc of free radicals generated and antioxidants efficacy in high intensity ultrasound energy**
17	**Assaf Hoogi**, Biomedical Engineering, Technion, **Subharmonic response of encapsulated microbubbles: Condition for existence and amplification**
18	**Noa Bachner**, Biomedical Engineering, Technion, **Echocardiographic assessment of transmural myocardial function in normal subjects**
19	**Ayelet Lesman**, Biomedical Engineering, Technion, **Engineering vascularized cardiac muscle tissue from human embryonic stem cells**
20	**Miriam Rubinchik,** Biomedical Engineering, Tel Aviv University **Investigation of platelet activation under shear stress**
21	**Yefim Yashuvaev**, Jerusalem College of Technology **Fiber optic sensor for diabetic plantar pressure monitoring**

2008 ISMBE Annual Meeting

Wednesday, March 12, 2008, Tel Aviv

Abstracts of Posters

PERCEPTUO-MOTOR TRANSPARENCY IN BILATERAL TELEOPERATION

Ilana Nisky	Ferdinando A. Mussa-Ivaldi	Amir Karniel
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In bilateral teleoperation, the operator holds a local robot which determines the motion of a remote robot and continuously receives delayed force feedback. Transparency is a measure of teleoperation system fidelity. The ideal teleoperator system is the identity channel, in which there is neither delay nor distortion.

During the last decades transparency was widely analyzed using two-port hybrid representation of the system in Laplace domain. Such representations define hybrid matrix that maps between the transmission channel inputs and outputs. However, in measuring transparency one should consider also the human operator and therefore we propose a multidimensional measure of transparency which takes into account:

i) Perceptual transparency: The human operator cannot distinguish when the teleoperation channel is being replaced by an identity channel.

ii) Local Motor transparency: The movement of the operator does not change when the teleoperation channel is replaced by an identity channel.

iii) Remote transparency: The movement of the remote robot does not change when the teleoperation channel is replaced by an identity channel.

We hypothesize that by selecting filters and training protocol it is possible to obtain perceptually transparent teleoperation (i) and remote motor transparency (iii) without local motor transparency (ii), namely, to *transparentize* the system. We formally define the transparency error, analyze this process in the linear case and simulate simplified teleoperation system according to typical experimental results in our previous studies about perception of delayed stiffness.

We believe that these tools are essential in developing functional teleoperation systems.

This research was supported by Grant No. 2003021 from the United States-Israel Binational Science Foundation (BSF), Jerusalem, Israel, by the National Institute for Psychobiology in Israel – Founded by the Charles E. Smith Family. The first author is supported by the Kreitman Foundation.

HAPTIC REPRESNTATION OF DATA ORIGINATING IN MEDICAL IMAGING

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For many centuries, illustrations of anatomic structures have been a basis for medical education and practice. Recent development in the field of medical imaging allows fast, reliable and accurate acquisition of anatomic, clinical and pathologic data from a human patient onto a set of 3-dimensional data. Common applications in this field are CT, MRI and nuclear imaging methods. The common way to visualize such data is either through a series of 2D images, or through a reconstructed 3D model of the anatomic structure. While this method is widely used, it leaves all senses but vision unexploited and delivers an experience different from actually interacting with real-life object. We wish to develop a platform that allows the user to interact with a 3 dimensional set of medical data both through vision and through touch.

Today there are several commercially available haptic rendering systems which provide a large user base and flexible development environments. Therefore, such a platform can be deployed easily and with little to none need for modification at the user end. The system will be implemented using a Reachin® virtual reality system with PHANTOM® Desktop™ haptic device and a stereoscopic display. The application development is conducted using the H3D API, an extension to the X3D language for describing 3D objects, with added features for describing the physical properties of the object, such as rigidity, surface textures and compliance. The current version of the application is limited to handling a set of CT images, since the CT imaging maps the relative radiodensity of the tissue to a pixel value in the data set, a property that can be relatively easily linked to the mechanical properties of the tissue. The application will allow the user to explore the data using two main modules: one representing the data through surfaces- a method more suitable for describing rigid objects such as bones, and the other one rendering the data as a volumetric data set that makes it easier for the user explore softer, deformable tissues. At the current phase of our work, pre-processing of the data is required to allow interactive operation and sufficient rendering rate. The pre-processing is implemented using the MATLAB image processing toolbox, with an intention of linking the various components of the application once pilot study will confirm that the solution is stable and satisfactory.

Extending medical imaging to exploit the haptic sense is important and beneficial for a broad range of applications. Among these are medical training and simulation, pre-surgical planning, tele-medicine and minimally invasive procedures.

FACE RECOGNITION WITH BIOLOGICALLY MOTIVATED BOOSTED FEATURES

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Object recognition is the ultimate purpose of the human visual system. It is performed intuitively and spontaneously. A human can identify a variety of objects instantly with no effort based on various perceptual cues and multiple sensory inputs. Unlike computer vision systems, the human visual system is known for its ability to identify an object after spatial transformation and change of viewing and illumination conditions.

Mimicking the visual system, which had the benefit of millions of years of evolution and natural selection to be refined and fine-tuned for the purpose of object recognition, can therefore enhance computational object recognition. The neurophysiological procedures underlying the recognition process are complex and use features such as shape, color, and orientation. The primary visual cortex (V1) generates a unique representation of these features that eventually leads to the perceived object. Hence, in this research, low-level features of the image are extracted by appropriate filters, in a manner similar to the human visual system.

Previously, we have shown that our biologically-motivated model produces improved *categorization* results (e.g., distinguishing between boats, cars, faces, etc.), while being more consistent with physiological mechanisms. In the current work we further analyze the contribution of our biological features to the *recognition* of objects.

We demonstrate our results on the popular problem of face recognition. We analyze color face images (R,G,B channels) from the FERET database and show that recognition performance improves as more biological principles are incorporated into the model. Worst recognition results (95%) are obtained when the images are processed as grayscale (intensity channel); a significant improvement in performance (97.1%) is achieved by representing images in the biological color-space by adding two opponent-color channels (B/Y, R/G) to the intensity channel.

Finally, we use the complete ensemble of biological features—intensity and opponent-color channels shaped by the appropriate biological filters at various scales and orientations. On the ensemble of these features we apply, iteratively, biologically-inspired Boosting. With every iteration, the biological features are used to construct weak face learners on the training data. The best weak learner is weighted by its accuracy and then added to the final strong learner. At the successive iteration, the training data is re-weighted: examples that are misclassified gain weight and examples that are classified correctly lose weight. This boosted technique results in the best recognition performance (98.2%).

THREE DIMENSIONAL CONTRACTING HEART MODEL BASED ON MATRIX STRUCTURAL ANALYSIS

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A new approach for modeling and simulating the contraction of the heart is presented. The model is based on the characteristics of individual myocytes arranged anatomically. The contribution of each myocyte is considered and integrated using matrix structural analysis. Adaptations in the matrix structural analysis were made to make the method suitable for biological material. Three elements are represented, the contractile cardiac myocyte, the elastic passive collagen, and intracardiac blood interacting with the heart's preload and afterload. Incompressibility of each element is preserved. The conduction system is simulated in the model by transferring the activating signal from each element to its neighbor or by Purkinje fibers activation.

The modeling technique is demonstrated by simulating a three-dimensional one-layer geometrical ventricle with helical oriented fibers. Using estimated values of model parameters, we were able to obtain mathematically sound simulations predicting physiological behavior. In our model, which considers solid-fluid interactions we aim at obtaining the overall mechanical behavior of the contracting heart from characteristics of the single myocyte and its interactions with all neighboring myocytes.

Employing the present modeling and mathematical approaches, our model results in blood pressure, that is a function of the contracting myocytes. This model will fill a gap in modeling and will be a link between cellular models of the single myocyte and models at the organ level. It will be applicable, in addition to optimizing biventricular treatment, to gain better understanding of cardiac contraction patterns in different pathological conditions and to study and optimize the interaction of the heart with mechanical assist devices.

HIGHLY POROUS BIORESORBABLE SCAFFOLDS WITH CONTROLLED RELEASE OF BIOACTIVE AGENTS FOR TISSUE REGENERATION APPLICATIONS

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Organ or tissue deficiency or loss is one of the most frequent and devastating problems in human healthcare. Integration of biomaterials, engineering and biology are applied to the development and study of functional substitutes for damaged tissues. Tissue regeneration involves the preparation of polymeric structures that serve as degradable scaffolding for bioactive molecules or cells as well as the study of their structure and properties. The main obstacle to successful drug or protein incorporation and delivery from degradable scaffolds is the inactivation of bioactive molecules by exposure to high temperatures or harsh chemical environments. In the present study we developed and studied novel bioresorbable film structures loaded with bioactive agents. Their high porosity is designed to enable tissue growth into the scaffold. The scaffolds were prepared using the freeze drying of inverted emulsions technique, which enabled to incorporate very sensitive bioactive molecules without affecting their activity. Our study focused on the effect of the emulsion's formulation on the porous shell structure and on the resulting cumulative protein release from the composite fibers for 28 days. Poly(DL-lactic-co-glycolic acid) was used as host polymer and horseradish peroxidase (HRP) was used as the protein source. The release profiles usually exhibited an initial burst effect, accompanied by a decrease in release rate with time, as is typical for diffusion-controlled systems. The Polymer initial molecular weight and the HRP content exhibited significant effects on both the scaffold microstructure and the HRP release profile from the scaffold, whereas the copolymer composition, the emulsion's organic:aqueous phase ratio and the polymer content only affected these characteristics in certain cases. We have investigated the effect of this film composed of PDLGA and HRP on cell adhesion and growth of human fibroblasts in culture. We have observed that cells adhered and grew with characteristics of fibroblasts on the film.

THERMAL IMAGING METHOD FOR ESTIMATING OXYGEN SATURATION

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The objective of this study is to develop a minimal invasive thermal imaging method to determine the oxygenation level of a tissue.
In this method, the tissue is observed by a coherent waveguide bundle in the mid-IR range and a fiber transmitting the excitation NIR laser. As a result of the photo-thermal effect, the tissue temperature rises. This increase depends on the tissue composition, its optical properties and the exciting laser wavelength.
The imaging of the tissue is done with a thermal camera through the coherent bundle. Small temperature changes can be detected because of the high resolution of this system. The tissue is excited using several wavelengths in order to allow us to draw conclusions about the tissue composition in general, and specifically the oxygenation level.
The flexible bundle and adjacent fiber enable imaging within body cavities through a commercial endoscope.
As an intermediate stage, the method will be applied and tested on exposed skin tissue, in order to be compared later with other methods and to simplify the experimental stage.
A theoretical model of this problem was implemented to help design the experiment setup and develop the test procedures. The model simulates the temperature rise in the tissue as a result of the laser excitation in a way that a thermal camera would capture it.
Analysis of the absorption calculations shows that melanin is the main contributor to the temperature rise. In order to develop a method suitable to high melanin concentrations, the most suitable wavelengths range is 400-450nm. For internal applications the range will probably be in the near IR, where the absorption differences between oxygenated and deoxygenates hemoglobin are higher.
The temperature increase function depending on the material concentrations was evaluated using our theoretical model.
The method developed is based on the similarities between the frequency dependence of the temperature function and the hemoglobin absorption.
Since we examine the temperature on a relatively narrow wavelength range, we can derive a simple approximation of the temperature function in it. The approximated temperature function is defined by a set of unknown coefficients and several known parameters (the wavelengths and the absorption coefficients). The saturation is considered as another unknown.
The temperature after the excitation is calculated in several wavelengths. With a curve-fitting algorithm, we find the most suitable values for the unknowns in the temperature function, specifically the saturation value. Using an initial saturation guess, we calculated the estimated saturation in several scenarios varying in the melanin and hemoglobin concentrations and in the saturation values.
Results show the algorithm usually reaches a good estimation of the saturation. Accuracy improves, as expected, when the concentration of melanin decreases or the hemoglobin concentration increases. The worst results were received when the melanin concentration was the highest tested and the hemoglobin concentration was the lowest tested.

NOVEL GENTAMICIN-ELUTING BIORESORBABLE COMPOSITE FIBERS FOR WOUND HEALING APPLICATIONS

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Novel gentamicin-eluting bioresorbable core/shell fiber structures were developed and studied. These structures were composed of a polyglyconate core and a porous PDLGA shell loaded with the antibiotic agent gentamicin, prepared using freeze-drying of inverted emulsions. These unique fibers are designed to be used as basic elements of bioresorbable burn and ulcer dressings. Their investigation focused on the effects of the emulsion's composition (formulation) on the shell's microstructure, on the drug release profile from the fibers and on the bacterial inhibition. The release profiles generally exhibited an initial burst effect accompanied by a decrease in release rates with time. Albumin was found as the most effective surfactant for stabilizing the inverted emulsions. All three formulation parameters had a significant effect on the gentamicin's release profile; an increase in the polymer and organic:aqueous phase ratio or a decrease in the drug content resulted in lower burst release and more moderate release profile. The released gentamicin also resulted in a significant decrease in bacterial viability and practically no bacteria survived after 2 days when bacterial concentrations of 1 x 10^7/ml CFU (Colony Forming units) were used. Hence, our new fiber structures are effective against the relevant bacterial strains and therefore can be used as basic elements of bioresorbable drug eluting wound dressings.

FALL DETECTION OF ELDERLY THROUGH FLOOR VIBRATIONS AND SOUND

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Falls are very prevalent among the elderly especially in their home. The statistics show that approximately one in every three adults 65 years old or older falls each year. Almost 10% of those falls result in serious injuries ranging from hip fractures to head trauma. A serious consequence of older adult falls is also the long period of involuntarily remaining on the ground for an hour or more following a fall. Moreover, Studies have shown that the medical outcome of a fall is largely dependent upon the response and rescue time. Therefore, reliable and immediate fall detection system is important so that adequate medical support could be delivered.

There are different solutions for fall detection that are on research stages. For example: wrist watches that have a combination of accelerometers and tilt sensors, camera based fall detectors, smart carpets and etc. Those solutions have many disadvantages such as: the person has to wear a device on himself; old people intend to forget to wear the wrist watch, many false alarms, etc. Therefore, we have developed a unique inexpensive solution that doesn't demand the person to wear anything. The solution is based on vibration and sound signals. These signals are acquired from vibration sensor (Crossbow's accelerometer) and a small amplified microphone that are attached to the floor. The sensors transmit the analog signals to a portable data acquisition device that samples the signals and transmits them to a PC. Vibration and acoustic features are extracted from these signals, and pattern recognition algorithm classifies between fall events and other events. In case of detected human fall, an alarm is activated.

The proposed algorithm extracts the suspected event by finding when the accelerometer signal energy exceeds a certain threshold, and makes a decision (fall or other event) based on selected features that are extracted from the sound and vibration signals. One problem that we deal with is that a signal of a human fall in a large distance from the accelerometer can be similar to a signal of an object that falls close to the accelerometer. We believe that understanding the physical problem can help us distinguish between events of objects and human falls. Therefore, as part of the algorithm, we use the "shock response spectrum" (SRS) analysis of the shock signal that is recorded by the accelerometer. The SRS is kind of a wavelet transform that assumes that the fall event is a mass-spring system. Moreover, features like energy, spectral content, and duration of the signals are taken into account. The pattern recognition algorithm is based on Gaussian mixture model (GMM).

The training set of data for the algorithm is taken from experiments that are performed using five "popular falling" objects and anthropomorphic dummy with the commercial name "Rescue Randy" that falls forward on a regular tiles floor in distances of 2 to 5 meter from the sensors. The objects are: Heavy bag, book, plastic box, metal box, and a chair. The collected data included 40 falls of "Randy" and 100 falls of the objects. The results of the experiments show that the system can detect any event of a human fall, and 80% of the falling objects events that occurs in a radius of 5 meter. Moreover, the algorithm can distinguish between a human fall and a falling object in a certainty of 96%. Our future plans are to perform the experiments in larger distances (more than 5 meters) and on different kinds of floors, such as concrete and carpet, to understand how it affects the selected features and parameters of the algorithm.

METRONIDAZOLE-LOADED BIORESORBABLE FILMS FOR PREVENTING BACTERIAL INFECTIONS DURING GINGIVAL HEALING

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Periodontal diseases refer to inflammatory conditions in the gums which progress to loss of alveolar bone and loss of teeth. We developed lately bioresorbable poly(DL-lactic - co - glycolic acid) (PDLGA) and poly(DL-lactic acid) (PDLLA) films loaded with the antibiotic agent metronidazole. The films were prepared by solution processing, where film structuring is obtained, according to a specific method of preparation. These films are designed to be inserted into the periodontal pockets and treat infections upon metronidazole controlled release phase, for at least one month. The effects of copolymer composition and drug content on the release profile, on cell growth and on the bacterial inhibition were investigated.

Our results indicate that the copolymer composition affects the release profile, while the drug content did not show any significant effect on the shape of the release curves. For films loaded with 10%wt metronidazole, although the 50/50 PDLGA degrades faster than the PDLLA, the rate of drug release from the latter was faster than from the former, due to differences in drug location/dispersion in the film. While the drug crystals appear to be located mainly on the PDLLA film's surface, in the 50/50 PDLGA films the drug was located in the bulk and also on the surface. Human fibroblast cell growth in vitro was seen on the scaffolds where both 2%wt and 10%wt of metranidazole was applied. Also, at these doses effective inhibition of bacterial growth was observed.

NANO-STRUCTURED BIORESORBABLE FILMS LOADED WITH BIOACTIVE AGENTS FOR BIOMEDICAL APPLICATIONS

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Controlled drug delivery occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other bioactive agent in such a way that the active agent is released from the material in a pre-designed manner. The main ideas in controlled release systems are to achieve more effective therapies, increase patient compliance and minimize the number of administrations. In the present study we developed and studied highly porous nano-structured drug eluting systems loaded with various drugs. The scaffolds were prepared using the inverted emulsion freeze drying technique. Nano emulsions exhibit relatively high stability. In addition, the release profile of bioactive agents from the resulting porous films is strongly affected by the nanostructure.

The goal of the current research was to determine the effect of the nanostructure on the release profile of highly porous films loaded with hydrophilic or hydrophobic drugs. 50/50 poly(DL-lactic-co-glycolic acid) was used as the host polymer of the continuous phase. Paclitaxel and FTS served as the hydrophobic drugs, whereas mafenide acetate and ceftazidime hydrate served as the hydrophilic drugs. Bovine Serum Albumin (BSA) and Horseradish Peroxidase (HRP) were found to be the most effective surface active agents which, together with a high homogenization rate, yielded homogeneously distributed nano pore diameters.

The release profiles usually exhibited an initial burst release, accompanied by a decrease in release rate with time, as typical for diffusion-controlled systems. Nano-structuring had a significant effect on the release profile of hydrophobic drugs from the bioresorbable films. In this case smaller pore size resulted in higher burst effects and higher release rates, due to a decrease in pore size which increases the interfacial area for diffusion. Systems containing hydrophilic drugs were less affected by the nanostructuring. We found that in order to obtain a fine and stable inverted nanoemulsion, a delicate balance of the different formulation parameters is required, the two most critical being high homogenization rate and the incorporation of an appropriate surfactant.

LONG-TERM IN-VITRO STUDY OF PACLITAXEL-ELUTING BIORESORBABLE CORE/SHELL FIBERS

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Paclitaxel-eluting bioresorbable core/shell fiber structures for stent applications and local cancer treatment were developed and studied. These structures were composed of a polyglyconate core and a porous poly (DL-lactic - co - glycolic acid) (PDLGA) shell loaded with the antiproliferative agent paclitaxel, prepared using freeze drying of inverted emulsions. The investigation of these new composite fibers focused on the effects of the emulsion's composition (formulation) and process kinetics on the long-term drug release from the fibers, in light of the shell's morphology and its degradation profile. The emulsion's formulation parameters included the polymer and drug contents of the emulsion, the organic to aqueous (O:A) phase ratio and copolymer composition of the PDLGA host polymer.

The microstructure of the freeze fractured surfaces was characterized using SEM and the in-vitro paclitaxel release profile was determined using High Performance Liquid Chromatography. The degradation behavior of the porous shell structure was investigated using Gel Permeation Chromatography.

The shell's porous structure in all studied specimens based on stable emulsions contained round-shaped pores, usually within the 4-10 μm range, with a porosity in the range of 67-82%. The pores were partially interconnected by smaller inner pores. The paclitaxel release from the porous shell was relatively slow due to its extremely hydrophobic nature. It showed three phases of release, which correspond to the degradation profile of the host PDLGA. It is clear that the first phase (1-10 weeks) was governed by diffusion while the second phase (10-20 weeks) was governed by degradation.

We found that the effect of emulsion formulation on the release profile is more significant than the effect of the process kinetics. Also, emulsions with less hydrophobic nature are favorable for effective controlled release of the hydrophobic paclitaxel from the porous shell. In addition, less hydrophobic formulations do not provide many binding regions for the drug and their higher stability enables to obtain highly porous shell structures with large surface area for diffusion after the freeze drying. The copolymer composition had the most dominant effect on the drug release profile from the composite fibers. An increase in the glycolic acid content (or decrease in lactic acid content) resulted in a tremendous increase in the release rate during the second phase, which was attributed mainly to the increased degradation rate and decreased drug attachment to the host polymer. A decrease in polymer content also resulted in an increase in the release rate during the second phase of release, while the drug content and O:A phase ratio (not shown) in the studied range affected the release profile only during the third phase of release

WHITE MATTER TRACTOGRAPHIES REGISTRAION USING GAUSSIAN MIXTURE MODELING

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The increasing popularity of DT-MRI among brain researchers and clinicians has created the need for robust registration methods for white matter (WM) Tractographies. Registration enables longitudinal (intra-subject) studies, important for evaluating intra-subject structural changes as a result of aging, disease progression, or following medical treatment, as well as population (inter-subjects) studies, that are important for fiber atlas construction, statistical studies over populations and connectivity based surgical planning.

Currently, registration is performed at the tensor level before the Tractographies are computed so that the same ROI can be used in the aligned brains. In comparison to the scalar case, tensor registration involves much more data (6 numbers per voxel) and requires an additional step of tensor reorientation. An alternative is to perform registration between scalar images such as fractional anisotropy and then apply the recovered transform to the fibers. Recently, methods have been proposed for direct registration between fiber sets. WM fibers, which consist of a sequence of connected 3D points, are more informative than the original tensor field and may therefore improve registration robustness.

As fiber-based registration methods rely on Tractography results, they are naturally exposed to common Tractography artifacts such as interrupted or deviating fiber tracts. These issues have not been addressed in previous fiber based registration algorithms.

In the current work we propose an innovative Tractography registration method that is robust to large amounts of interrupted and deviating fiber tracts. The fibers are projected into a high dimensional feature space defined by the sequence of their 3D coordinates. Adaptive mean shift (AMS) clustering is applied to extract a compact set of representative fiber-modes (FM). Each FM is assigned to a multivariate Gaussian distribution according to its population thereby leading to a Mixture of Gaussians (MoG) representation for the entire set of fibers. The registration between two fiber sets is treated as the alignment of two MoGs and is performed by maximizing their correlation ratio. A 9 parameter affine transform is recovered and eventually refined to a 12 parameters affine transform using an innovative mean-shift (MS) based registration refinement scheme. The validation of the algorithm on intra-subject data demonstrates its robustness to interrupted and deviating fiber tracts.

A NUMERICAL ANALYSIS OF THE BORN APPROXIMATION FOR IMAGE FORMATION MODELING OF DIFFERENTIAL INTERFERENCE CONTRAST MICROSCOPY FOR HUMAN EMBRYOS

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The differential interference contrast (DIC) microscope is commonly used for the visualization of live biological specimens. It enables the view of the transparent specimens while preserving their viability, being a non-invasive modality. Fertility clinics often use the DIC microscope for evaluation of human embryos quality.

Towards quantification and reconstruction of the visualized specimens, an image formation model for DIC imaging is sought and the interaction of light waves with biological matter is examined. In many image formation models the light-matter interaction is expressed via the first Born approximation. The validity region of this approximation is defined in a theoretical bound which limits its use to very small specimens with low dielectric contrast.

In this work the Born approximation is investigated via the Helmholtz equation, which describes the interaction between the specimen and light. A solution on the lens field is derived using the Gaussian Legendre quadrature formulation. This numerical scheme is considered both accurate and efficient and has shortened significantly the computation time as compared to integration methods that required a great amount of sampling for satisfying the Whittaker - Shannon sampling theorem. By comparing the numerical results with the theoretical values it is shown that the theoretical bound is not directly relevant to microscopic imaging and is far too limiting. The numerical exhaustive experiments show that the Born approximation is inappropriate for modeling the visualization of thick human embryos.

THREE-DIMENSIONAL LOCALIZATION AND FUNCTIONAL DETECTION OF TUMOR LABELED WITH SPECIFIC FLUORESCENCE MARKERS

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Tumor surface markers are targeted in our method by antigen-fluorophore conjugants. These fluorophores are sensitive to pH changes of the environment they exist in.

Our research deals with fluorescent lifetime imaging. We look at the decay graph of fluorescent emission and analyze it. We study four parameters of this decay curve: maximal intensity, first photon, first moment and lifetime.

We have created a Monte Carlo simulation, programmed in Matlab software that simulates the light propagation in the tissue for inclusions embedded in tissue like phantoms. We compared our simulation to the experimental results from agarose-based tissue like phantom with scattering coefficient, $\mu_s, 10cm^{-1}$ and absorption coefficient, $\mu_a, 0.1cm^{-1}$. The fluorophore's lifetime we simulated was 1.2 ns.

The first stage of this research is a three-dimensional localization of the tumor. For this purpose we used three parameters: maximal intensity, first photon, and first moment. After convolution between the photons propagation equation, Beer-Lambert and exponential decay equation of fluorescence emission we successfully found the physical explanation for the results we got from the experimental set-up and from the simulation. With assistance of the physical model that we developed, we found the first photon and the first moment per tumor's depth dependence. The dependence that was found is linear and doesn't dependent on intensity. This fact enables us to use the above mentioned parameters to detect the correct depth without dependence on fluorophore probe concentration and laser intensity.

The maximal intensity (the maximal number of photons that reach the detector simultaneously) is used to derive the fluorophore location in the XY plane.

First photon (the time pass until the first photon reaches the detector) and first moment (the first moment (area moment) calculated for the decay graph) enabled us to successfully detect the fluorophore's depth with an error $\pm 0.5mm$ .To detect the fluorophore's depth we used the least squares method. In this method, we assumed the initial depth and calculate the sum of the squared residuals (the difference between the predicted and observed values of the first photon and first moment). We search the depth that a sum for it is minimal. Because of the linear dependence, it is enough to find a local minimum in order to stop the iterations. This property economizes the algorithm running time.

The second stage in our research is sensing the environmental conditions, such as pH and temperature. For this purpose we use the forth parameter – lifetime. Fluorescence lifetime is defined as the average time the molecule spends in the excited state following excitation, before returning to the ground state. This parameter is an intrinsic parameter of the fluorophore and independent of the probe concentration. However it does depend on the pH and temperature.

It is well known that the pH in tumor cells decreases and the temperature increases. It is a motivation for us to detect not only the location and morphology, but the functionality of the tissue too. When the environmental conditions are changed, the only part of the fluorophore's molecules undergoes the change and their lifetime is changing. The measured fluorescent signal is composed of the changed lifetime and the unchanged one. The main challenge of this research is to distinguish between the two and calculate the true lifetime. By measuring the change in the fluorescent lifetime it is possible to determine the tissue environmental conditions.

Hydraulic Pressure Enhances LDL but not Acetylated-LDL intake by BAECs

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Introduction: Atherosclerotic plaque formation begins with absorption of fatty materials (LDL-C, triglycerides) from the blood to the artery wall, through the ECs. This intake triggers the recruitment of macrophages to the artery wall, their margination and their infiltration into the media to engulf the fatty materials. Most of the lipid intake by the artery wall is done via diffusion of the lipid molecules between the cells, in particular at regions of the arterial tree where blood flow is disturbed and the endothelium coverage is uneven and poorly organized.

However, there exists another LDL intake pathway - via cellular endocytosis in which LDL molecules which are bound to the membrane-associated LDL receptors (LDL-R), are internalized into endosomes, then released from LDL-R and stored in the lysosomes. At the end point of the process some LDL molecules are oxidized and released by the endothelial cells into the subendothelial space, thereby triggering recruitment of the macrophages.

Blood pressure is considered an important risk factors for atherosclerois However the effects of hydraulic pressure on LDL intake via the intracellular pathway remain unclear.

Hypothesis: Blood pressure significantly affects LDL intracellular intake in a doze and waveform dependent manner.

Method: Bovine artery endothelial cells (BAECs) were cultured on fibronectin-coated cover slips until confluence, submitted to hydraulic pressure of various modes (steady pressure of ~110 mmHg, pulsatile aortic pressure of 80 -120 mmHg (mean ~110 mmHg), and high steady pressure of ~ 190 mmHg) for one hour, then incubated for few hours in the incubator with fluorescently labeled LDL or Ac-LDL (the latter is a marker for endothelial cells which is internalized into ECs by scavenger receptors, not LDL-R). Un-pressurized cells served as control. After incubation, the cells were fixed and analyzed by a confocal microscope.

Results: BAEC incubated with Ac-LDL show intake of labeled acetylated lipid which is significant and independent of the pressure regimens. In contrast, LDL intake by BAEC is pressure-dependent: the no-pressure control cells show very low LDL intake compared to the Ac-LDL control, but pressure significantly enhances LDL intake in a doze and waveform dependent manner in the following order:

steady 190 mmHg > steady 110 mmHg > pulsatile 110 mmHg >>control

Moreover, there was an effect of pressure on the fluorescent distribution and apparent granulation: under steady 110 mmHg pressure, fluorescence was uniformly distributed in the cell and manifested fine granulation, while under pulsatile 110 mmHg pressure, fluorescence localized more around the nucleus with coarser granulation.

Conclusions: Hydraulic pressure enhances LDL but not Ac-LDL intake by BAECs in pressure regimen dependent way and affects the distribution and granulation of the LDL pool in the cells.

SONODYNAMIC OF FREE RADICALS GENERATED AND ANTIOXIDANTS EFFICACY IN HIGH INTENSITY ULTRASOUND ENERGY

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The wide use of high intensity ultrasound energy (HIUE) in the modern medicine raises the question of bio-safety. It has been shown that the effect of HIUE in aqueous biological media may be similar to the effects of ionizing radiation. Exposure of aqueous media to HIUE field is the source of ultrasonic cavitations phenomenon. During the cavitations process local transient "hot spots" are formed with extreme conditions of temperature (~5,000°K), pressure (~1,000atm) and heat transfer rate (~10^{10} °K/s). Cavitations in aqueous media, is followed by the creation of free radicals namely, Hydroxyl radical (•OH) and the super-oxide ion (•O_2-). These highly reactive and hence short-lived oxidizers may be the cause of those harmful effects observed in bio-environments exposed to HIUE field.

The current research, employ electron paramagnetic resonance (EPR) spectroscopy and spin traps to quantify and analyze the dynamics of free radicals creation under exposure to HIUE field. Further more, this study examines and compares the efficiency of water-soluble antioxidants, namely Allicin, Melatonin and Deoxyribose, to suppress the accumulation of those free radicals. Initial results show that among the three, Allicin reduces Hydroxyl concentration with high efficiency.
The course of this research has a direct relation to "Drug Delivery" and "Controlled Drug Release". Therefore, the effect of using antioxidant to neutralize free radicals, and thus reduce their possible harmful effects, will be examined in the near future with regards to specific drugs.

SUBHARMONIC RESPONSE OF ENCAPSULATED MICROBUBBLES: CONDITIONS FOR EXISTENCE AND AMPLIFICATION

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Encapsulated microbubbles are used as ultrasound contrast agents (UCA) and may have potential applications in diagnosis and therapy. Potential utilization of microbubbles for blood pressure measurement is the subject of our study. This application is based on the nonlinear frequency response of UCA to acoustic drive and its sensitivity to ambient pressure. Properly driven, the microbubbles generate a strong subharmonic component, a response which is exclusive for bubbles and differs e.g. from surrounding tissues that transmit only the fundamental frequency and generate a second harmonic component.

The microbubble response depends on the bubble radius. This equilibrium radius depends, among others, on the inward and outward diffusion processes. The resonance frequency of each microbubble, directly relates to its radius.

The size distribution of the microbubbles was optically analyzed by the Coulter LS particle size analyzer. Attenuation of acoustic signals through a bubble solution was tested. Ultrasound pulses of 15 cycles in length were applied at discrete frequencies within the range of 2MHz and 5MHz, at low acoustic pressure of 50kPa. The transmitted signal was measured by a hydrophone.

In addition, backscattering from a tube filled with Definity^{TM} solution was measured for acoustic pressures between 100kPa and 630kPa, and threshold conditions for the appearance of the subharmonic signal were found. Subharmonic to fundamental harmonic ratio was calculated.

Examination of the relationship between the ambient pressure and the desired ratio was performed. The applied acoustic pressure in this experiment was about 250kPa. The ambient pressure amplitude was changed between 9kPa and 15kPa above the atmospheric pressure, at a repetition rate of about 1/3Hz. Resonance frequency of 2.7MHz was determined from the experimental results and according to the theory. At frequency of about 5.5MHz, twice the resonance frequency, a maximal value for the subharmonic to fundamental harmonic ratio was observed. Threshold conditions for existence and the intensity of the subharmonic signal are experimentally found to depend on microbubbles size distribution and shell properties, as well as on the driving field frequency and pressure. When cyclic ambient pressure was applied, it seems that it may be better to transmit ultrasonic signal at frequency which is lower than twice the resonance in order to get higher sensitivity to ambient pressure.

ECHOCARDIOGRAPHIC ASSESSMENT OF TRANSMURAL MYOCARDIAL FUNCTION IN NORMAL SUBJECTS

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Introduction: The heart consists mostly of muscle fibers, a complex fibrous structure that enables its efficient function. The fibers of the Left Ventricle (LV) are wound in a spiral structure around the cavity, generating rotation of the apex and base in counter directions, while producing transmural inhomogeneities of the its mechanical properties. Mathematical models show that LV rotation tends to equalize the sarcomere shortening between the myocardial layers. It has been reported that pathologies that cause LV hypertrophy (e.g. aortic stenosis, congestive heart failure) increase this inhomogeneity.

Aims: The purpose of this study was to measure the transmural distribution of LV rotation, torsion and circumferential strain in normal subjects, in order to establish the normal behavior; deviations from these normal values will allow early detection of different hypertrophy-causing pathologies, as well as small ischemic zones.

Methods: Short-axis echocardiographic cines were acquired from 36 normal subjects at three levels of the LV: apical, papillary muscle and Mitral valve. The data underwent-post processing to obtain the circumferential strain and the myocardial rotation, utilizing '2D strain' program, which is a speckle tracking imaging program (UFI, GE Healthcare Inc., and Technion, Israel) and a novel signal processing method. This new method enables high temporal and spatial resolution measurements of the myocardial velocities, so that the circumferential strain, the myocardial rotation and torsion may be evaluated during a full heart cycle, at 3 myocardial layers.

Results: The results show a significant transmural difference in the myocardial rotation at the apex and Mitral valve levels, and a significant transmural difference in the circumferential strain at all 3 short axis levels. The endocardial rotation is larger and it decreases towards the epicardium, while the apex and base rotate in counter directions. Thus, the endocardial torsion is larger than the epicardial one. Similarly, the endocardial circumferential strain is larger than the epicardial one.

Conclusions: Appropriate image processing of standard 2D echocardiographic cines provides insight of the complex movements that the different myocardial layers perform, and of the contribution of the LV transmural distribution of rotation, torsion and circumferential strain to the cardiac function. This novel measurement tool may serve as the basis of a simple, affordable and commonly available diagnostic modality.

ENGINEERING VASCULARIZED CARDIAC MUSCLE TISSUE FROM HUMAN EMBRYONIC STEM CELLS *IN-VITRO & IN-VIVO* ASSESSMENT

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Tissue- engineering of the heart muscle represents a novel experimental therapeutic paradigm aiming to improve the failing heart function. However, this strategy has been hampered by the lack of sources for human cardiomyocytes and by the significant cell death following cell transplantation. Given the attractive potential of human embryonic stem cell derived cardiomyocytes (hESC-CMs) in future cell therapy for heart failure; we evaluated the ability to form engineered cardiac tissue using these cells.

Survival of the transplanted myocytes may be significantly improved by enrichment of graft vascularization. The later can be induced by co-culture with endothelial cells (EC) and fibroblasts. Additionally, endothelial-cardiomyocyte interactions may also play a key role in enhancing cardiomyocyte and endothelial development, proliferation, maturation, and organization.

In this study we demonstrate that this multi-cellular strategy enables the generation of highly vascularized human engineered cardiac tissue with cardiac-specific ultrastructural, molecular, and functional properties.

hESC-CMs were seeded on 3-dimensional porous scaffolds. To promote *in-vitro* tissue vascularization we constructed multi-cellular scaffold in which hESC-CMs were combined with hESC–derived EC or human umbilical vein EC (HUVEC) with the addition of embryonic fibroblast (EmF). Tissue assessment was carried out using immunostaining, ultrastructural analysis, RT and real time PCR, pharmacological, and calcium imaging studies which revealed the presence of endothelial vessel network embedded within synchronously contracting cardiac construct.

Grafting of this engineered tissue in the rat heart resulted in the formation of long-term stable grafts, which showed structural maturation of the human cardiomyocytes. Electromechanical integration of the human cardiac tissue to the rat heart was examined by immunostaining and electrode recording. Formation of human and rat-derived vasculature within the scaffold was confirmed and their functional perfusion capabilities were examined by the injection of fluorescence microspheres and Lectin-HPA.

The construction of 3-dimensional vascularized human cardiac tissue may have unique applications for studies of cardiac and vascular development, function, cardiovascular regenerative medicine and stem cells research.

INVESTIGATION OF PLATELET ACTIVATION UNDER SHEAR STRESS

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INTRODUCTION

Exposure of the blood to artificial surface leads to cellular and protein deposition, followed by platelet adhesion. Platelet adhesion to artificial surface causes morphological changes leading to a complex series of reactions involving release of platelet granule contents, platelet aggregation, and activation of platelet biochemical processes, all leading to thrombus formation. One of the major parameters influencing platelet adhesion, activation and aggregation is the blood flow rate, or more specifically, the wall shear stress. Therefore, it is essential to consider hemodynamic parameters that can influence experimental design, for better simulation of platelet function under close to physiological conditions and also in pathological conditions.

This work comes to investigate platelet interactions with foreign materials under a variety of shear stress levels. It is expected that platelet activation will increase with the increase in shear stress. In addition, three different materials currently used in cardiovascular implants are investigated to evaluate their hemocompatibility.

METHODS

Impact-R Cone-and-Plate Analyzer (CPA) device was chosen to test artificial material interactions with blood under uniform shear stress. Testing material was placed on the bottom of the well. 130 μl of whole human blood was placed on the plates and subjected to two different shear rates: 250 s^{-1} and 1800 s^{-1} for 2 minutes. Those shear rates correspond to two different mechanisms initiating platelet aggregation one that operates under relatively low shear conditions (less than 1000 s^{-1}) and the other under higher shear conditions (1000 to 10000 s^{-1}). Thin plates, 14 mm in diameter made from three different implantable materials currently used in cardiovascular implants were investigated: 316L Stainless Steel, Titanium and Nitinol were placed on the bottom of the CPA well, for platelet-material interaction investigation. All the samples were polished and examined by Atomic Force Microscopy (AFM) for surface roughness evaluation. Blood samples collected from healthy volunteers were mixed with citrate in order to inhibit spontaneous coagulation. Blood count, blood smear - and FACS (fluorescent activated cell sorter) tests made before and after the experiment for each material. Platelets were fixated to the material surface using 4% Paraformaldehyde for 10 min. Scanning Electron Microscopy (SEM) pictures were taken from each test material for platelet morphology and platelet adhesion visualization.

RESULTS

Platelet count reduction was observed for all the metals at both high and low shear rates indicating platelet adhesion and aggregation on the surface. Blood smear image before the CPA test showed single platelets at the blood, thus after the test, for all three metals platelet aggregation might be observed. The fluorescent labeled antibodies were directed against P-selectin which is increased on the membrane of activated platelets. Platelet P-selectin expression was determined by Mouse Anti CD62P. Increase in P-selectin expression was detected for all the experiments.
SEM images clearly showed that there is a difference in surface reactivity, and the adhesion of platelets to the surface for all three metals. There was almost no surface coverage for Nitinol, a minor coverage fo Titanium and greatest coverage for 316L Stainless Steel.

CONCLUSIONS

This abstract presents the early stage of a thorough investigation. Yet the results of this stage are already stimulating. We will further on evaluate if there is a significant difference between those three metals.

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FIBER OPTIC SENSOR FOR DIABETIC PLANTAR PRESSURE MONITORING

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Medical Introduction

Lower-limb complications associated with diabetes include developing plantar ulcers, which can lead to infection and even amputation. The important component of foot ulcer development is "shearing" forces (pressure) on the sole of the foot.

Problem

To date, no portable units have been designed for continuous round-the-clock monitoring of diabetic patient plantar pressure in non-invasive, un-intrusive, quantitative, and partially objective fashion. The present study reports the potential of measuring localized plantar pressure (as early discovery of the ulcer) with a sensor based on multiple imperfected polymer optical fibers (POF). The bent fiber has been used to create a sensing element with a high resolution over a wide range of the deformation measurements with a linear output characteristic.

Methodology

The bent imperfected fiber can be regarded as a fiber containing dynamic microbends –which increase or decrease in size, depending on the change in macrobending exerted on the fiber. The amount of change and the initial size of the dynamic microbends are determined by the properties and topologies of the imperfections created on the surface of the fiber's core. The imperfections, which are created on the core surface of the fiber, can be theoretically described as identical small V-groves. Imperfections are created at different angles by changing the direction of the abrading. Abrading at a 45, 90, and 135 degree angles (and their combination) to the fiber axis generated multiple overlapping imperfections.

A mechanical system was constructed to measure changes in bending radii. The U-shaped bent plastic optical fiber was held between two parallel walls. The walls were moved by a micrometer screw with a resolution of 10 μm over a range of 25mm. The radius of the bent fiber equals to half the distance between the walls. Measurements were carried out using a 0.5 meter long, poly-methyl-methacrylate resin fiber CK-40, with a 1mm outer diameter (980 μm core diameter) and a step-index profile, manufactured by Mitsubishi.

Light was inputted into the optical fiber from a 650nm light-emitting-diode (LED) and output was measured with a PIN silicon photodetector with a spectral response of 0.45 A/W. In all experiments, an $8mm^2$ area of the fiber was imperfected.

Results

The change of the normalized output as a function of the bending radius is presented. The fiber's sensitivity to bending were evaluate over the radius range of 40mm to 25mm.The results clearly demonstrate the significant increase in sensitivity for sensors based on plastic optical fibers with multiple angular overlapping imperfections. Additional studies showed the possibility of boosting the sensitivity by increasing the scratch depth of the imperfected zone.

Conclusions

These preliminary results may be useful for developing highly sensitive measurement systems using bent polymer optical fibers This increased sensitivity, as well as flexibility and the low price of plastic fibers, make them most suitable for important medical application that involve the measurement of pressure, stress, force, and vibration.