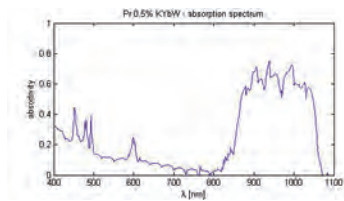


RESULTS OBTAINED TO DATE

For the means of growing the crystals, collaboration with prof. Francesc Diaz, of the FiCMA group in the University Rovira I Virgili in Spain, was established. Using their knowledge of crystal growth and their facilities, a number of crystals were grown.

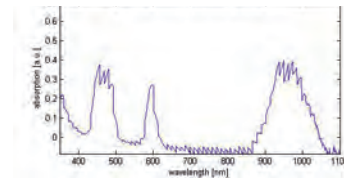
The first set of crystals contained varying concentrations of acceptors (Pr^{3+} & Tb^{3+}), in the medium of 100% Yb^{3+} (Pr/Tb:KYbW). While absorption measurements of these samples showed clear absorption lines fitting the Pr^{3+} and Tb^{3+} absorption spectrum, no detectable emission was registered on the Yb^{3+} emission wavelength.

Furthermore, instead of reading a clear absorption line characteristic to Yb^{3+} absorption spectrum, a wide absorption band was evident in the range of 850-1050nm.

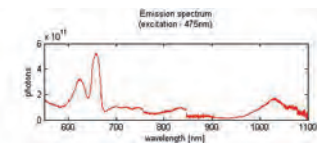


This finding can indicate the existence of energy level splitting as a result of the high Yb^{3+} concentration, and can imply that no emission was evident due to quenching.

Next we grew a crystal with 7% Yb^{3+} and 3% Pr^{3+} (more accurately the crystal was KGdW crystal – a close relative to KYW crystal). This crystal also showed a proper absorption line characteristic to Pr^{3+} , and two absorption bands at 600nm and at 900-1000nm.



When exciting the sample with a light source at 475nm, emissions at 625nm, 660nm & 1032nm were detected. Measuring the external quantum efficiency (QE) of the emission (emission divided to absorbed input power) showed 6.37% QE for emission at 625+660nm, and 6.43% QE for emission at 1032nm this is about 50% internal QE.



CURRENT AND FUTURE DIRECTIONS

The quenching of the Yb should be eliminated (as in Yb lasers). For this we first measure directly the Yb quenching under direct Yb excitation (at 980nm). Best on the quenching results we will design another crystal with lower Yb concentration, and possibly KYW matrix.

As this aspect of the project progresses, we will move forward and optimize the organic materials for the harvesting of a wide band of adequately energetic photons and begin the design and manufacturing of a LSC device for our cause.

FACILITIES

Thermal deposition system with six sources capable of 3 co-deposited materials

The system is inside a set of three glove boxes which include:

1. the thermal deposition system
2. spin coater and sample preparation box
3. optical characterization box with light source and optical detection



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PROJECT

Interactions of slow fullerene ion beams with carbon nanotube based devices. Annealing and repairing, effect on properties and control of device performance

Launch year:

2011

Principal investigators:

Prof. Eli Kolodney - *Technion IIT, Schulich Faculty of Chemistry*
Prof. Francesc Perez-Murano - *IMB-CNM, CSIC*

Participating students:

2

SCIENTIFIC GOAL

Study the effect of fullerene C_{60}^- irradiation on carbon nanotube (CNT) electronic devices. Develop a novel approach for tuning and improving performance of CNT based devices using C_{60} molecules as an all-carbon weld and repair material.

82

ABSTRACT

The basic idea of the proposal was to exploit the tendency of energetic fullerene molecules (C_{60}) to merge efficiently with single-wall and multi-wall CNTs incorporated within nano-electronic devices such as a single CNT based field effect transistor (CNT-FET). *The electrical response of the device constitutes an ultra-sensitive probe of the CNT quality and integrity before, during and after irradiation.* This unique approach has remarkable fundamental and technological value. To the best of our knowledge, it has never been reported or tested elsewhere. Studies reported in the literature regarding interactions of

ion beams with carbon nanotube based devices are limited to damage induced by atomic inert (Ar^+) ion beams. The tendency of C_{60} to coalesce with the CNT wall is based on "family relations" and affinity derived from similar bonding interactions and configurations of these all-carbon nano structures. Using low energy ion beams (negative C_{60}^- ions at 50 - 300 eV) will enable us also to control the energy density at the impact zone. "Soft landing" type interactions can be probed by using effusive molecular beams (neutral C_{60}).

RESULTS OBTAINED TO DATE

The collaboration is based on the unique and complementary expertise of the two partners: CNT based nano electronic devices on chips developed and fabricated by the CNM team, and controlled irradiation with fullerene ion beam at the Technion. The CNM team fabricated and provided portable chips with multiple CNT-FETs (arrays of thousands of CNT-FETs). These were C_{60}^- beam irradiated inside the high vacuum chamber at the Technion (mounted

on an especially designed and built manipulator). Controlled beam parameters were impact energy and total flux. Characteristic electrical properties (as for example, drain-to-source current versus gate voltage I/V curves) were measured at CNM for all the transistors, before and after exposure with the C_{60}^- ion beam, thus enabling statistical analysis using a large number of devices.

FACILITIES

At the Technion we have built the special exposure stage mounted on a precision manipulator. We have used this setup for all the C_{60} irradiation experiments. All other measurements were carried out in the Instituto de Microelectronica de Barcelona - Centro Nacional de Microelectronica (IMB-CNM). These included HRSEM and electrical characterization of the CNT-FETs arrays.



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nanoGUNE-Technion**

PROJECT

**Preparation, application and characterization
of a ReRAM type nonvolatile memory device
made of nanopolycrystalline oxide layer**

Launch year:

2011

Principal investigators:

Prof. Yoed Tsur - *Technion IIT, Dept. of Chemical Engineering*
Prof. Felix Casanova - *NanoGune, Spain*
Prof. Luis Hueso - *NanoGune, Spain*

Participating students:

Emanuelle Goren - *MSc student, Technion IIT*
Omri Mazar - *PhD student, Technion IIT*

SCIENTIFIC GOAL

1. Producing switchable resistive switch random access memories (ReRAMs) using low cost chemical fabrication methods, comparing with the high cost physical techniques that are common today.
2. Studying the effect of nanoparticles properties in the resistive switching behavior, in order to control the synthesis, and be able to optimize the device properties.
3. Comparing the performances of standard device with oxide thin films prepared by physical routes, and the device which was fabricated from oxide nanopolycrystalline layers.
4. Studying the electrical mechanism of resistive switching by impedance spectroscopy.

ABSTRACT

Recently, a promising candidate for future non-volatile memory applications has emerged in the form of the resistance random access memory (ReRAM), which can also be described as so-called memristor. This element is based on the resistive switching phenomenon. A ReRAM memory cell has typically a capacitor-like structure, composed of an insulating oxide nanometric layer, sandwiched

between two metal electrodes and can be electrically switched between different resistance states. The ReRAM mechanism is based on a significant reversible change in the resistance of the structure that can be set to a desired value (either ON or OFF) by applying the appropriate voltage pulse. These two states can be translated into a binary code.

RESULTS OBTAINED TO DATE

1. Titania layers were synthesized using both sol-gel and atomic layer deposition (ALD), to compose stable reproducible working ReRAM device.
2. The layers morphology and crystalline state was characterized using HR-TEM, HR-SEM, XRD, and EELS, to find relation between the layer state to its switching ability.
3. Sol-gel and ALD layers has shown different hysteresis loop when measuring the I-V curve.
4. Impedance spectroscopy was performed on ALD TiO_x ReRAMs, in order to understand the dominant process in the resistive switch phenomenon.
5. Sol-gel ReRAMs were demonstrated for the first time. Still, there is a long way to go, as the samples show leaky behavior (cannot retain its resistance state for a long time, as seen in the remnant current experiments) comparing with ALD, which retain stable for both resistance states.

FIGURES

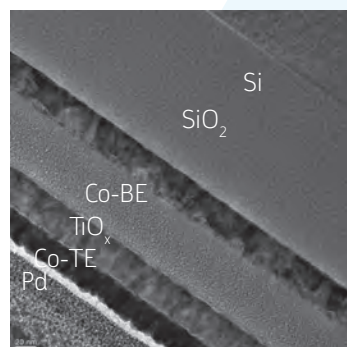
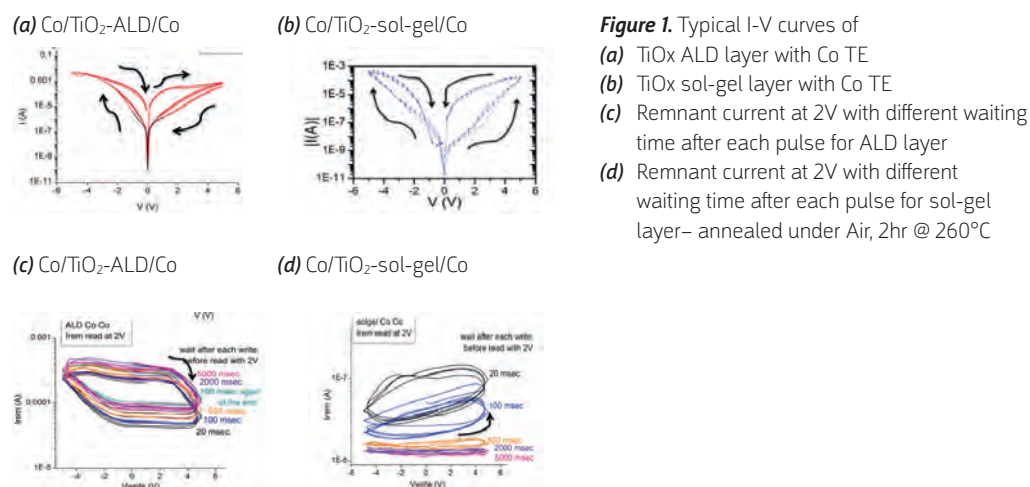


Figure 2. HRTEM images of sol-gel titania- calcined at 260°C, air. Was taken by Yaron Kauffmann, from up to down Si/SiO₂/Co/TiO_x/Co/Pd and Pt sputtered to protect the structure.

FACILITIES

X-ray Diffraction (XRD), high resolution Scanning electron microscope (HR-SEM), high-resolution transmission electron microscopy (HR-SEM), electron energy loss spectroscopy (EELS), energy-dispersive

X-ray spectroscopy (EDS), differential scanning calorimetry (DSC), electrochemical Impedance Spectroscopy (EIS), electrical I-V characterization



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PROJECT

Nonlinear Dynamics, Bifurcations, and Non-Stationary Response in Nano-and Micro-Cantilever Arrays for Multiple Sensor Detection

Launch year:

2011

Principal investigators:

Prof. Oded Gottlieb - *Technion IIT, Dept. of Mechanical Engineering*
Prof. Nuria Barniol, *Autonomous University of Barcelona, Dept. of Electrical Engineering*

Participating students:

1 PhD student, 1 MSc student and 1 postdoctoral research associate

SCIENTIFIC GOAL

The main objective of this collaboration is to develop and analyze a theoretical quasi-continuum model for a mass sensor array derived on the basis of a controlled set of experiments in the nonlinear operation regime.

ABSTRACT

Arrays of nano- and micro electromechanical cantilevers have been proposed over a decade ago for fast imaging in atomic force microscopy and more recently for multiple detection of mass sensing with attogram resolution. To allow for increased sensitivity and robustness of measurements it is crucial to understand the nonlinear dynamics of these arrays as their resonant dynamics can exhibit a complex bifurcation structure that includes synchronous periodic or de-synchronized non-stationary dynamics. We investigate an electrodynamic array of coupled conductive cantilevers which can be excited externally or parametrically via alternative configurations of electrodes. Calibration of individual element thermo-visco-elastic material properties is done via an asymptotic model-based estimation procedure [1] based on measurements (Fig.1) obtained from a five element CMOS array coupled with a common overhang. Derivation of a coupled set of initial-boundary-value problems for the array enables construction of a reduced-order dynamical

system which is integrated numerically to yield periodic solutions with both in-phase and out-of-phase synchronization between the elements (Fig.2). We note that de-synchronized non-stationary dynamics can then be shown to exist following loss of orbital stability and intermittent switching between coexisting solutions in ultra-high vacuum conditions [2]. External excitation of the end element in the array reveals bi-stable behavior in both response amplitude and phase (Fig.3). This effect can be estimated analytically via multiple-scale asymptotics (Fig.4) which highlight the importance of unstable solutions that separate the domains of attraction of the bi-stable solutions. Future research will focus on non-stationary energy transfer between array elements that may enable decomposition of multiple frequency components required for simultaneous sensing of additional system parameters for both electrodynamic mass sensing [2] and for resonance based detection of magnetic properties [3].

RESULTS OBTAINED TO DATE

- [1] Hollander, E. and Gottlieb, O., "Self-excited chaotic dynamics of a nonlinear thermo-visco elastic system that is subject to laser irradiation", *Applied Physics Letters*, 101, 133507, 1-5, 2012.
- [2] Gottlieb, O., Torres, F., Mintz, I., Vidal, G., Hollander, E., Barniol, N., "Nonlinear dynamics of thermo-visco-elastic cantilever sensor arrays", Int. Conf. Nonlinear Dynamics in Engineering, Aberdeen, UK, August 21-23, 2013.
- [3] Hacker, E., Ruiz-Oliveras, F., Gottlieb, O., "Nonlinear dynamics and stability of a microcantilever for magnetic resonance force microscopy", *Nonlinear Theory and its Applications*, IEICE, 4, 3, 272-283, 2013.

FIGURES

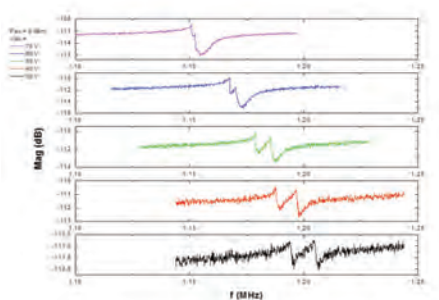


Figure 1. Response measurement of a five equal element cantilever array experiment.

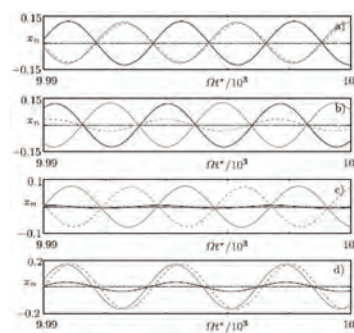
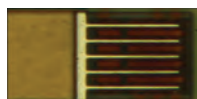


Figure 2. Numerical integration of vibration modes of periodic solution branches (overlaid time-histories of a central array element and its nearest neighbors) from a three element reduced-order model.

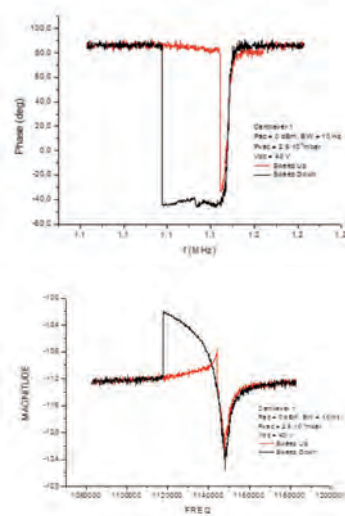


Figure 3. Response magnitude (top) and phase (bottom) of bi-stable solutions in a cantilever experiment (red-sweep up vs. black-sweep down).

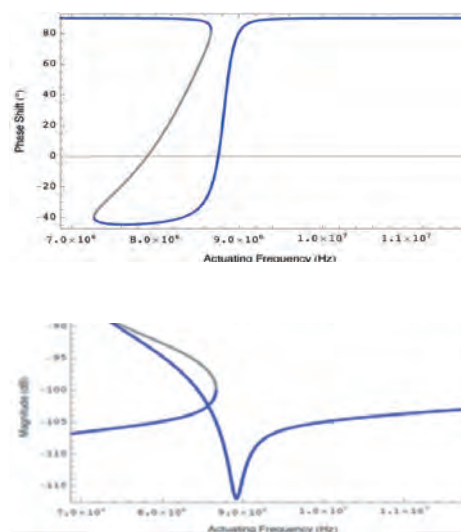


Figure 4. Asymptotic response magnitude (top) and phase (bottom) of a single cantilever in a reduced-order model (blue solutions are stable and grey solutions are unstable).



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PROJECT

**Epitaxial growth of Nb-doped SrTiO_3
films by pulsed laser deposition**

Launch year:

2011

Principal investigators:

Prof. Avner Rothschild - *Technion IIT, Dept. of Materials Science and Engineering*
Prof. Jose Santiso, *Research Center for Nanoscience & Nanotechnology,
Bellaterra, Barcelona*

Participating students:

Miri Markovich

SCIENTIFIC GOAL

**Study the effect of point defects and interfaces on mixed ionic
electronic transport properties of SrTiO_3 -based heterostructures.**

ABSTRACT

Nb-doped SrTiO_3 thin films are potential candidates for transparent conducting oxide electrodes and other applications in oxide electronics and optoelectronics. In this work we grew epitaxial films of Nb-doped SrTiO_3 on (0 0 1)-oriented SrTiO_3 single crystal substrates and examined their crystal structure, defects and strain state by means of high-resolution X-ray diffraction (mapping in reciprocal space) and complementary methods. The films were deposited by pulsed laser deposition (PLD) under oxygen flow (60 mTorr) or in vacuum (5×10^{-3} mTorr). The substrate temperature was 700°C and the substrate-to-target distance was 55 or 70 mm, respectively. Strained epitaxial films with homogeneous concentration of point

defects and dopants were obtained in both cases as long as the film thickness did not exceed 200 nm. Films deposited in oxygen displayed considerably higher concentration of point defects (presumably cation vacancies) than their vacuum-deposited counterparts. Films of intermediate thickness (between 200 and 1000 nm) exhibited significant structural inhomogeneity accompanied by strain relaxation via redistribution of point defects across the film. Thicker films (>1000 nm) grown in oxygen exhibited changes in the film growth mode and the resultant microstructure, providing a complementary mechanism for strain relaxation.

RESULTS OBTAINED TO DATE

The results obtained in this work manifest the effect of the deposition conditions, specifically the gas atmosphere and pressure during film growth and the substrate-to-target distance, on the structural quality of Nb-doped STO films grown by PLD on (0 0 1)-oriented STO substrates. Highly strained epitaxial films with homogeneous concentration of point defects and dopants were obtained both in oxygen (60 mTorr) and vacuum conditions (5×10^{-3} mTorr), as long as the film thickness did not exceed a critical value of about 200 nm. Films deposited in oxygen displayed higher concentration of point defects, presumably cation vacancies, than films deposited in vacuum.

Thicker films (>200 nm) displayed significantly more defective structures as a result of more complicated mechanisms of strain accommodation and relief. Thick films grown in oxygen displayed two distinctive spatial regions, one almost fully strained and the second one almost completely relaxed. The point defect concentration in the strained region was

found to be larger (by a factor of 1.4) than in the strain-relaxed region. TEM micrographs revealed that the strain accommodation correlates with changes in the film growth mode and the resultant microstructure, from fully coherent epitaxial region at the bottom of the film (<200 nm from the substrate) to columnar structure at intermediate thickness and eventually dendritic growth in micron-thick films.

Films grown in vacuum conditions remained coherent and highly strained at larger thicknesses (500 nm) than the ones deposited in oxygen, and had lower concentrations of point defects. Strain accommodation in thick films (500 nm) deposited in vacuum causes redistribution of point defects across the film, resulting in two highly-strained regions with different point defect concentrations.

Epitaxial growth of Nb-doped SrTiO₃ films by pulsed laser deposition. *Applied Surface Science* 258 (2012). M. Markovicha, J. Roquetab, J. Santisob, E. Lakina, E. Zolotoyabkoa, A. Rothschild.

FIGURES

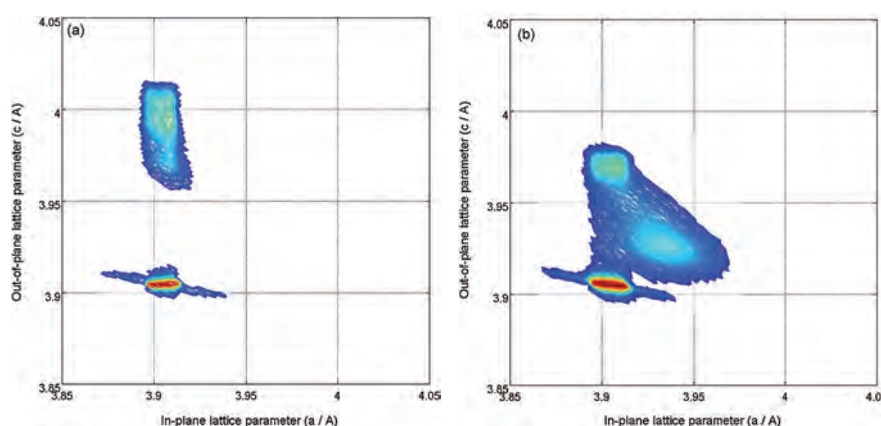


Figure 1. RSM (logarithm of intensity) taken in the vicinity of the (3 0 3) reflection from a 300 nm (a) or 650 nm thick (b) Nb-doped STO films grown in oxygen atmosphere. The intense peaks centered at $3.905^\circ 2\theta$ originated in the STO substrates, whereas the less intense ones originated in the films.

FACILITIES

PLD (EMD lab); HRTEM (Titan, MIKA); HRXRD (Mater. Eng.); ToF-SIMS (Surface Science lab)



**multidisciplinary
research
collaboration
within Technion**

PROJECT

Nonlinear Induction Detection of Electron Spin Resonance

Launch year:

2012

Principal investigators:

Prof. Eyal Buks - *Technion IIT, Department of Electrical Engineering*
Prof. Aharon Blank - *Technion IIT, Department of Chemistry*

Participating students:

Itai Katz, *PhD student*

SCIENTIFIC GOAL

The purpose of this project is to suggest, test, and implement a new approach to the sensitive detection and high resolution imaging of paramagnetic materials.

ABSTRACT

Imaging and spectroscopy of paramagnetic species using electron spin resonance (ESR) is widely employed in many fields of science. Here we propose a new approach for induction detection of ESR, which is based on two discoveries that were recently made in our laboratories. One is related to the nonlinear microwave properties of flat superconducting

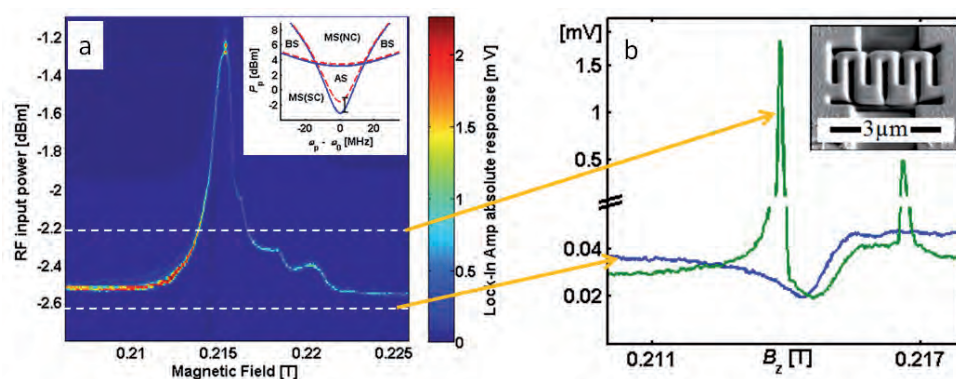
structures and the other is a new approach to the efficient concentration of microwave magnetic fields in a small volume. The proposed research will potentially allow significant enhancement of sensitivity of ESR detection and open the way for nano-scale spatial resolution of ESR imaging and spectroscopy.

RESULTS OBTAINED TO DATE

In a recent experiment we were able to detect very strong ESR signals based on nonlinear phenomenon. The figure below shows the ESR spectrum of a paramagnetic sample obtained with this method using a superconducting microstrip resonator operated in the linear and nonlinear regimes at 4.2 K and ~ 6.2 GHz. Part (a) in the figure shows the reflected power from the resonator, as a function of both the static magnetic field and the input power. Part (b) presents cuts from the two dotted lines in (a), showing linear and nonlinear response, respectively. At a relatively low input power the response is linear and a conventional derivative-like CW ESR spectrum is obtained (the blue line in (b)). At higher input powers the nonlinear bursts start to appear, with

the resulting ESR spectrum being an admixture of the conventional spectrum with nonlinear spikes (green line in (b)). When covering the entire relevant power-static field plane (in a), a distinct maximum pattern is evident and the ESR spectrum can be obtained from the nonlinear response readings (local maxima of the 2D image). The phenomena observed in this experiment are related to changes in the resonator's properties, moving from a stable to an astable state, as can be explained through the phase diagram shown in the insert of (a). The insert in panel (b) shows a SEM image of the central part of the microstrip resonator used in our experiments that was fabricated in the RBNI clean rooms facility.

FIGURES



FACILITIES

MNFU (Photolithography, FIB)



**multidisciplinary
research
collaboration
within Technion**

PROJECT

***In vitro* microfluidic models for inhaled
nanoparticle deposition assays**

Launch year:

2012

Principal investigators:

Prof. Josué Sznitman - *Technion IIT, Dept. of Biomedical Eng.*
Prof. Yael Dubowski - *Technion IIT, Dept. of Civil & Environmental Eng.*

Participating students:

4

SCIENTIFIC GOAL

The long-term aim is to design, develop and test *in vitro* microfluidic models of alveolated airways that mimic both morphologically and physiologically the deep regions of the lung (i.e., pulmonary acinus) in an effort to assess quantitatively the dynamics of fine and ultrafine inhaled aerosols inside the smallest airways of the lungs, characterized by the presence of sub-millimeter alveoli (gas exchange cavities). The development of such assays are critical in understanding (i) the transport and deposition characteristics of inhaled aerosols, (ii) potential cytotoxicity effects of nanoparticles on airway epithelial cells, and (iii) devise a screening platform for airway deposition targeting.

ABSTRACT

Inhaled ultrafine nano-particles (UFP) have the ability to reach the most distal regions of the lung, and deposit on the acinar airways where alveoli are abundant. Once deposited, such aerosols can bypass the lung's clearance mechanisms and translocate across alveolar epithelial cells, ultimately entering the systemic circulation and other organs. In particular, high concentrations of inhaled toxic UFPs have been linked to increased pulmonary and cardiovascular morbidity. However, due to microscale dimensions, UFP deposition remains prohibitively difficult to assess *in vivo* within the pulmonary acinus. As a result, our understanding of (toxic) UFP transport often relies on coarse-scale data, and a quantitative mapping of acinar deposition patterns is still lacking. The proposed research is aimed at

elucidating detailed deposition characteristics of inhaled UFPs directly at the acinar scale, using *in vitro* microfluidic models of acinar airway trees that capture physiological respiratory airflows. To bridge physical models with biological functionality, our microfluidic networks will mimic cellular aspects of the acinar environment by integrating confluent monolayers of alveolar epithelial cells. This latter strategy is essential to investigate potential toxic effects of deposited UFPs on airways and unravel the biological processes regulating UFP cellular uptake. This work represents a crucial step towards determining how UFPs associated with adverse health effects ultimately access into the systemic circulation.

RESULTS OBTAINED TO DATE

Our work has been geared towards two specific targets. (i) First, we have successfully completed the design and study of flow patterns that exist inside micro-cavities (in analogy to pulmonary alveoli), in an effort to map the diverse range of flow topologies that exist in the viscous regime (i.e., low Reynolds number); see *Figs. 1 and 2*. This work was recently published in the journal *Microfluidics and Nanofluidics* (Fishler et al., 2013).

Next, (ii) we have been integrating monolayer cultures of alveolar epithelial cells into simple microfluidic devices (i.e., straight channels) and investigating surfactant secretion functions in such cells under various perfusion conditions (i.e., shear stress); see *Figs. 3 and 4*. This work is currently under revision for publication (Mahto et al., "Microfluidic shear-stress-regulated surfactant secretion in alveolar epithelial type II cells *in vitro*").

In parallel, we have designed microfluidic models of pulmonary acinar trees featuring five generations of alveolated airways that incorporate cyclic wall motion (i.e., expansion-contraction displacements) to mimic lung breathing movements and effectively

yield a form of microfluidic-based artificial breathing; see *Figs. 5 and 6*. We have recently submitted this work for publication (Fishler et al., "Acinus-on-a-chip: a microfluidic platform for pulmonary acinar flows"). This microfluidic platform was recently submitted for a provisional patent through the Technion Technology Transfer (T³) office (inventors: R. Fishler and J. Sznitman).

We are also currently conducting the first airborne studies of nanoparticle transport and deposition in our pulmonary alveolar microfluidic structures –this latter research is extremely challenging and still requires substantial efforts in both the experimental setup and control of various parameters. We have first attempted preliminary studies in single straight channels and are now beginning to use the microfluidic alveolated airway tree platform; *Figs. 7 and 8*.

Finally, we are in the process of drafting a manuscript reviewing the development and use of microfluidic systems for *in vitro* assessments of nanoparticle cytotoxicity on cells (Mahto et al., "Microfluidic platforms for advanced risk assessments of nanomaterial").

FIGURES

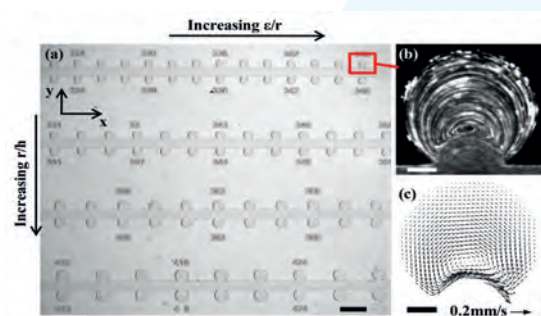


Figure 1. (a) Snapshot of the microfluidic screening device. Scale bar = 1 mm. (b) Streamline visualization of steady flow based on digital averaging over a sequence of 200 images acquired at 50 Hz ($Re=0.1$, $r/h=1.14$, $\epsilon/r=0.967$). Scale bar = 60 μm . (c) Corresponding PIV velocity map. Scale bar = 60 μm .

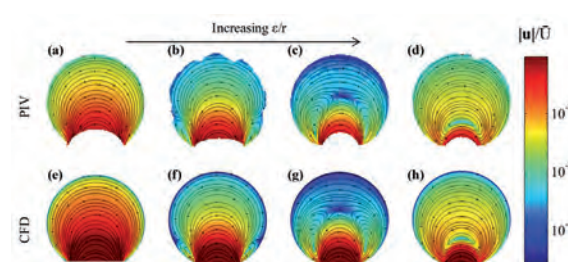


Figure 2. Normalized velocity magnitude and corresponding streamlines for PIV experiments (top row) and CFD simulations (bottom row). Values of ϵ/r increase from left to right (experiments: $\epsilon/r=0.905, 0.937, 0.953, 0.977$; simulations: $\epsilon/r=0.86, 0.92, 0.935, 0.965$). For all cases $r/h=1.89$ and $Re=0.1$, and ductal flow is from left to right. With increasing ϵ/r , the cavity flow evolves from being attached (left) to exhibiting two side vortices that eventually give rise to a "cat's eye" configuration, before coalescing into a single vortex (right).

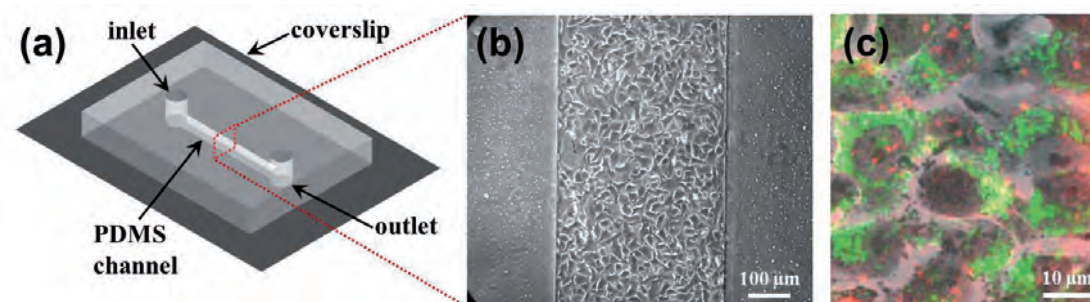


Figure 3. (a) Schematic illustration of a PDMS-based microfluidic device consisting of a straight channel (0.4 mm wide, 4.5 mm long, 0.08 mm high). (b) Phase-contrast image shows a monolayer of type II alveolar epithelial (A549) cells cultured inside the microfluidic channel (>80% confluency).

(c) A549 cells were subjected to a flow rate of 20 $\mu\text{L}/\text{min}$ (approximately 4 dyn/cm^2) for 20 min and thereafter stained with fluorescent dyes, quinacrine (green) and MM 1-43 (red), for the detection of (i) lamellar bodies (LBs) and (ii) fusion of LBs with the plasma membrane, respectively.

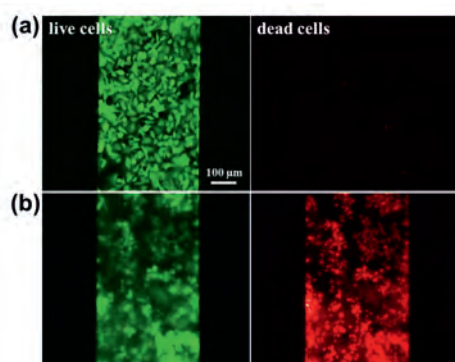


Figure 4. Effects of fluid shear stress on cell viability. (a) Cells subjected to a maximal flow rate of 100 $\mu\text{L}/\text{min}$ for 20 min were tested for viability using fluorescent dyes, calcein AM (green) and propidium iodide (red). (b) As a negative control, cells were treated with 70% ethanol for 5 min and thereafter stained with the same combination of dyes to measure the specificity of the assay.

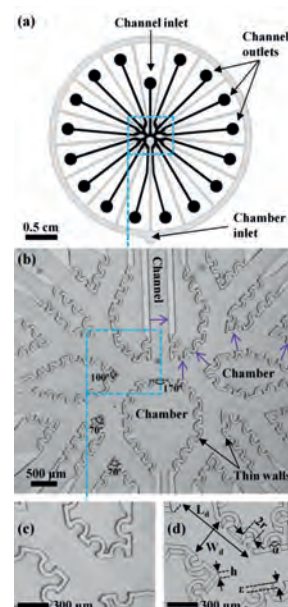


Figure 5. Microfluidic model of the acinar tree network. (a) CAD drawing of the full device. (b,c) Close-up snapshots of the acinar tree structure showing the channels, the chambers, and the thin walls separating them. Purple arrows indicate the corresponding locations and positive y-directions of the flow profiles presented in Fig. 4. (d) 3D CAD drawing illustrating the shape of the thin lateral acinar walls; nomenclature for the acinar geometry is included for clarity.

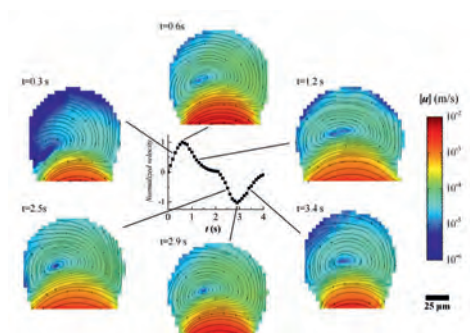


Figure 6. Velocity magnitudes and corresponding streamlines obtained from micro-PIV inside an alveolus located at generation 1. Data are shown for a projection of the flow at the midplane and sampled at several time instances along the breathing flow cycle. Velocity magnitudes are shown on a logarithmic scale.

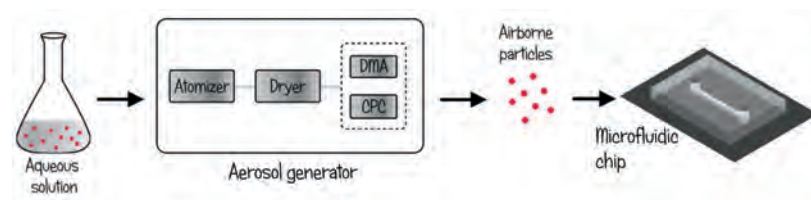


Figure 7. Schematic of the microfluidic aerosol exposure setup featuring an aerosol generator that includes an (i) aerosol atomizer, where (ii) particles are then dried with two tubular dryers filled with silica gel, and then (iii) directed in a sizing mobility particle system (differential mobility analyzer - DMA) attached to a condensation particle counter (CPC) to measure particle size distributions. Particle-laden airflows are then directed and fed into the microfluidic chip.

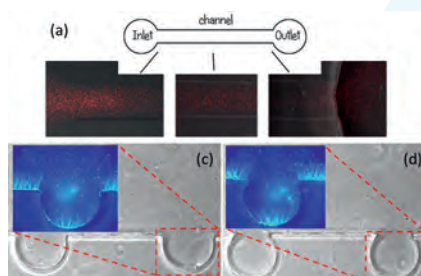


Figure 8. (a) Deposition pattern of monodisperse fluorescent polystyrene latex beads (500 nm diameter) in simple straight microchannels using the particle exposure setup of Fig. S6. Deposition of polydisperse smoke particles (<1 μm to ~7 μm) for (b) attached flow conditions in an alveolus, and (c) recirculating flow conditions. Note that for attached flow (c), particle deposition reaches into the depth of the cavity but not under recirculating flow conditions.

FACILITIES

Photolithography and deep reactive ion etching (DRIE) were conducted at the Micro-Nanofabrication Unit (MNFU) of the Russell Berrie Nanotechnology Institute (RBNI). Soft-lithography PDMS-based microfluidic chip manufacturing was conducted in the Technion Biofluids Laboratory (PI Sznitman) as well as all flow visualization experiments. Preliminary airborne deposition assays inside microfluidic channels were conducted at the Aerosol Laboratory (PI Dubowski).



**multidisciplinary
research
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PROJECT

The Nanostructure-Function Connection in Cancer-Related Circulating Microparticles

Launch year:

2012

Principal investigators:

Dr. Anat Aharon Ph.D. - *The Thrombosis and Hemostasis Research Laboratory, Thrombosis and Hemostasis Unit, Rambam Health Care Campus*
Prof. Benjamin Brenner, M.D. *Dept. of Medicine, The Hematology Institute, and The Thrombosis and Hemostasis Unit, Rambam Health Care Campus*
Prof. Yeschayahu Talmon, Ph.D. - *Technion IIT, Dept. of Chemical Engineering*

Participating students:

1 M.Sc. finished (*Mr. Liron Issman*)
1 Ph.D. in progress (*Ms. Na'ama Koifman*)

SCIENTIFIC GOAL

We aim to find a correlation between the nanostructure of specific microparticles (MPs) subgroups to their biological role in both physiological and pathological conditions. MPs nanostructure and content of coagulation- and angiogenic-markers are evaluated by cryogenic- and room-temperature transmission electron microscopy (TEM) and scanning electron microscope (SEM), including immunogold labeling, and compared with data acquired by FACS. These studies should provide insight into MPs and better understanding of the mechanisms related to chemotherapy effects.

ABSTRACT

Microvesicles (MPs) are membrane vesicles (50-1000 nm dia.) shed from cells upon activation or apoptosis. MPs are found in blood circulation under normal physiological conditions; their level increases in a variety of diseases, such as cancer and diabetes, and during pregnancy. MPs bearing tissue factor (TF), the main activator of the coagulation cascade, play a role in pathogenesis of pro-thrombotic state in cancer patients. Despite increasing scientific and clinical interest, there are no standard procedures for isolation, detection and characterization of MPs. MPs size is at the edge of the detection range of conventional methods. As MPs affect and reflect physiological and pathological states, and since their

clinical properties (size, concentration, morphology, biochemical composition and cellular origin) are extremely important, we are in the process of establishing a new methodology centered around nano-imaging, which will open new possibilities in this area, and that provides significant new data on MPs nanostructure, their composition and function. We isolate and characterize the nanostructure of cancer breast cell line MPs. We strive to identify the biological contents encapsulated in the MVs, and those bound to their membranes. These studies will provide insight into MVs and better understanding of the mechanisms related to chemotherapy effects.

RESULTS OBTAINED TO DATE

We have developed a new methodology based on nano-imaging that provides significant new data on MPs nanostructure, their composition and function. We are among the first to characterize by direct-imaging cryogenic transmitting electron microscopy (cryo-TEM) the near-to-native nanostructure of MP systems isolated from different cell types and stimulation procedures. We found that there are no major differences between the MP systems we have studied, as most particles were spherical, with diameters from 200 to 400 nm. However, each MP population is very heterogeneous, showing diverse morphologies. We investigated by cryo-TEM the effects of standard techniques used to isolate and store MPs, and found that either high-g centrifugation of MPs for isolation purposes, or slow freezing to

-80 °C for storage, introduce morphological artifacts, which can influence MP nanostructure, and thus affect the efficiency of these particles as future diagnostic tools. We are still trying to find an effective labeling procedure in the liquid state to allow the identification of proteins on the MP membrane. A paper describing this work is under review in PLOS 1.

In addition we have looked at whole cells in the process of shedding MPs. Those critical-point-dried cells show very well the formation of MPs and transmission nanotubes (TNTs). Immunogold labeling works well on those cells. We would like to extend this part of our work to cryo-SEM imaging of the same cells in their native state.

FIGURES

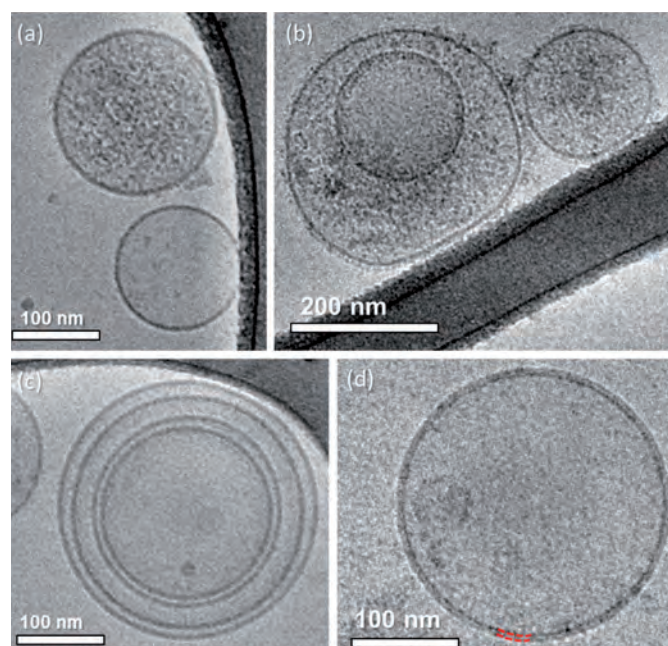


Figure 1. Cryo-TEM images of MPs derived from MDA-231 cancer cells: (a) Grnulated and smooth MPs; (b) bilayered MP with nanoparticle decoration on its membrane; (c) multilayered MP with three inner vesicles; (d) two dashed lines clearly show the phospholipid bilayer stucture of the MP membrane.

FACILITIES

The Electron Microscopy of Soft Matter Laboratory



**multidisciplinary
research
collaboration
within Technion**

PROJECT

Enhanced OLED and novel OLASER with plasmonic nanostructures

Launch year:

2012

Principal investigators:

Prof. Meir Orenstein - *Technion IIT, Faculty of Electrical Engineering*
Prof. Nir Tessler - *Technion IIT, Faculty of Electrical Engineering*

Participating students:

Ariel Epstein, Ofir Sorias, Zahi Lati

SCIENTIFIC GOAL

The major research goal is to study the combination of organic semiconductor with phosphors, nano-photonics and especially nano-plasmonics in order to mitigate simultaneously some of the major factors impeding OLED efficiency. This includes: Enhancement of radiative decay rate, especially of the auxiliary phosphors; enhancing the time response (modulation rate) of the whole device; improving the out-coupling efficiency, by designed forward scattering, adjust the transmission directionality. The embedded scientific goal is the understanding of the intricate structure comprised of doped organic semiconductors, phosphorous, metallic and nonmetallic conductors – in an intimate ultrathin structure.

A secondary, but more scientifically challenging goal is to study the feasibility of plasmonic enhanced organic diode lasers.

ABSTRACT

Organic light emitters OLEDs are intensively penetrating into the application fields of displays, lighting and sensors. Their intrinsic low efficiency of utilizing the current injection and especially of the external efficiency can be improved – and any percent of improvement that can be achieved in an affordable manner is of a potential giant impact.

Yet another important perspective for OLED is their growing use in short range optical communication due to their preferable properties over regular LEDs. However some disadvantages exist and the major one is the modulation speed. To get high bit-rate the

OLED needs short lifetime which it lacks due to long phosphors transition times.

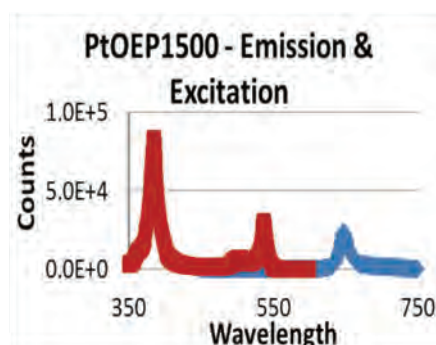
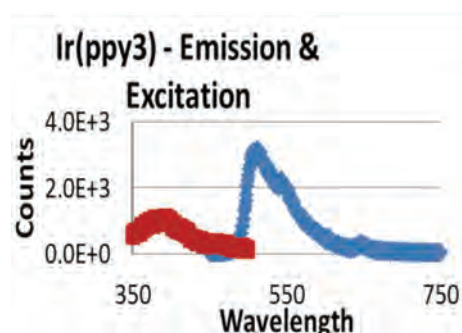
In the proposed research – two complimentary groups – one expert in OLED and the second in nano-photonics are teamed to present a comprehensive approach utilizing metallic nano structures within the OLED layers to enhance simultaneously the emission from the auxiliary phosphor, the efficient out-coupling of the generated light and modifying the emission angular pattern to a desired cone.

In addition the incorporation of metallic nano structures will result in a significant shorter lifetime of the phosphor transitions which will results in faster response of the OLED, faster modulation and higher communication speed.

In parallel the more exotic of plasmonic enhanced organic laser OSPASER will be explored – with the metallic structure enhancing the lasing rate as well as assisting in separating the emission and absorption bands of the organic semiconductor – a major hurdle in diode lasers based on organic materials.

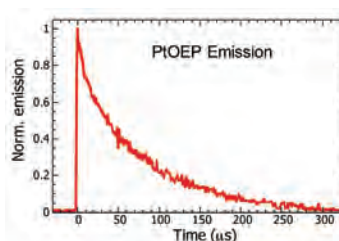
RESULTS OBTAINED TO DATE

At first we would like to show the enhancement of radiative decay rate of phosphorescent substances, so appropriate material was selected, and absorption and emission measurements were done.

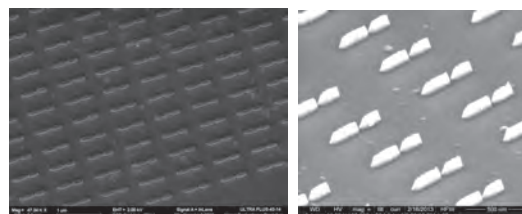


Life time measurements on the bare organic material were performed (Figure 33) and found to be 50msec for PtOEP1500 and 3msec for Irppy3. The results

show a long life time, which can be shortened by nano-antennas.



Nano antennas with appropriate resonance were designed and fabricated:



Deposition of the phosphor over the nanoantennas was done. The deposition process needs to be carefully calibrated so organic material will get into the gaps between antennas.

Measurements of resonances inside the organic material were done.

Next, life time and spectrum measurements with the nano-antennas will be performed. The results we expect to get include shorter life time and stronger emission.

FACILITIES

Electron-Beam-Lithography, Clean room, SEM, HR-SEM, Micro-nano-photonics laboratory, Organic materials laboratories



**multidisciplinary
research
collaboration
within Technion**

PROJECT

**Controlled light-matter coupling through
deterministic positioning of a quantum
dot in a photonic microcavity**

Launch year:

2012

Principal investigators:

Prof. David Gershoni - *Technion IIT, The Physics Department
and the Solid State Institute*
Prof. Gad Bahir - *Technion IIT, The Department of Electrical Engineering
and the Solid State Institute*

Participating students: 1

SCIENTIFIC GOAL

We proposed to use far-field optical lithography to position single QD in a particularly designed photonic structure, which spectrally matches a specific QD.

ABSTRACT

In this work we demonstrated far-field optical lithography to position single QD in a particularly designed photonic structure, which spectrally matches a specific QD. *In situ* lithography was used while measuring the QD emission in a low-temperature micro photoluminescence-setup. The positioning was

achieved using a specific single QD as a probe for a focused Gaussian laser beam and the spectral matching between the optical characteristics of the QD and the photonic structure is done during the same lithographical step utilizing the nonlinearity of the resist exposure process.

RESULTS OBTAINED TO DATE

We developed the technology and modeling for the design and fabrication of a three dimensional microcavity containing a single semiconductor quantum dot in its center. This is a crucial step towards fabricating efficient single photon sources.

FIGURES

The following figures demonstrate the main steps in the technology that we developed:

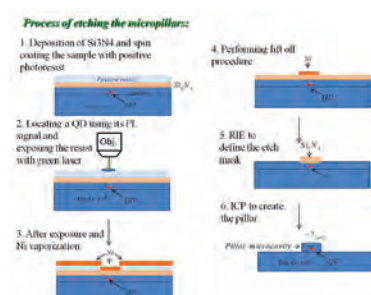
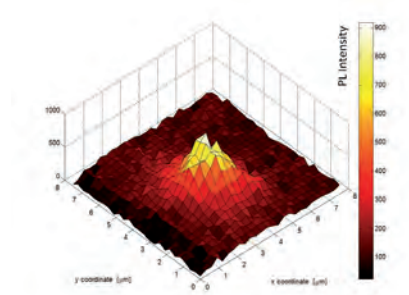


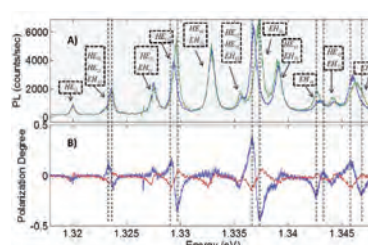
Figure 1 (Left). Schematic description of the in-situ lithography processing for fabricating the photonic structure with embedded quantum dot.



(Right). PL intensity of a single QD spectral line under red laser excitation as a function of the sample position beneath the microscope objective. Exposing the photoresist to green laser at the point of the maximum PL intensity insures the central alignment of the QD inside the photonic cavity.



Figure 2 (Left). Scanning electron microscope image of a single photonic pillar containing single QD. **(Right)** Polarization sensitive PL spectra from the micropillar under high excitation power. The blue (green) line presents H (V) linear polarization.



(Right B). Rectilinear (blue) and circular (red) degree of polarization spectra. The cavity modes are clearly observed. The identification of the various modes was made by comparing the measurements with the analytical model presented in the left panel of Fig. 3.

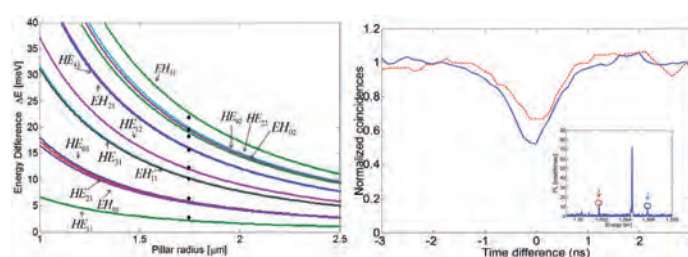


Figure 3 (left). calculated energies of the electromagnetic modes of a cylindrical pillar as a function of its radius. Symbols represent the measured values from Fig.2. **(right)** Time resolved intensity correlation measurements between the spectral lines observed in the PL from the single QD in the micropillar under excitation.

The blue line represents autocorrelation measurement of the PL from the spectral line in the inset marked by the blue arrow. The red line represents cross-correlation measurement between the two spectral lines marked by arrows. **The clear minimum at zero time difference (antibunching) indicates that the PL comes from a single photon light source.**

FACILITIES

Clean rooms, E-Beam Lithography, Near Field Scanning Optical Microscopy (NSOM) laboratory at Solid State Institute.



**multidisciplinary
research
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between Ben-Gurion
University-Technion**

PROJECT

Design of plasmonic photoelectrodes for water splitting

Launch year:

2012

Principal investigators:

Prof. Maya Bar-Sadan - Ben Gurion University, Department of Chemistry
Prof. Avner Rothschild - Technion IIT, Faculty of Materials Engineering

Participating students:

1

SCIENTIFIC GOAL

Our proposed research concerned the fundamental understanding of the interaction of light with a device containing metal nanoparticles, by directly probing the spatial distribution of the optical excitation around the particles. Using electron energy loss spectroscopy (EELS) in the low-loss region ($< 10\text{eV}$) to directly compare the structure of the device (the distribution of metal particles over the thin semiconductor layer) with its electronic properties in order to verify the corresponding calculations and modeling of the same configuration.

RESULTS OBTAINED TO DATE

$\alpha\text{-Fe}_2\text{O}_3$ thin film photoanodes with gold nanoparticles (Au-NPs) buried between the $\alpha\text{-Fe}_2\text{O}_3$ film and the FTO back electrode were obtained by dewetting of gold thin films, as illustrated in Fig. 1. The Au-NPs sensitized photoanodes display enhanced

water photoelectrolysis current density compared to pristine $\alpha\text{-Fe}_2\text{O}_3$ photoanodes, as shown in Fig. 2. The key aspect of the project was developing the know-how of low-loss measurement within a TEM microscope, in a large field of view and with good

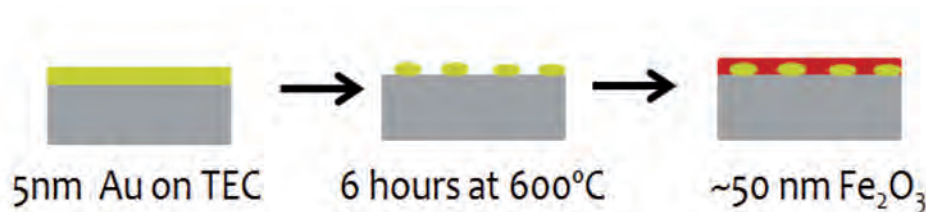


Fig.1

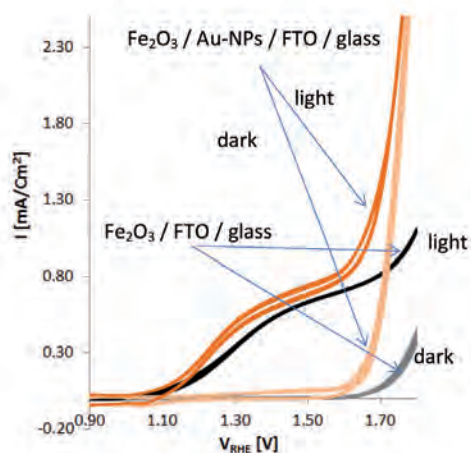


Fig. 2

energy resolution. For that matter we synthesized gold nanoparticles (5-8 nm) in large arrays, with the aim of measuring the electronic properties of the array. Typical results are presented in Fig.3. The different images show the energy losses across the field of view in 3 different energies: (a) 7.40 eV, (b) 5.10

eV, (c) 2.10 eV. The intensity of the image is correlated with the magnitude of energy loss.

It can be seen that at certain energies, such as 5.10 eV, the interaction between the electron beam and the particles causes energy absorption within the close surrounding of the particles.

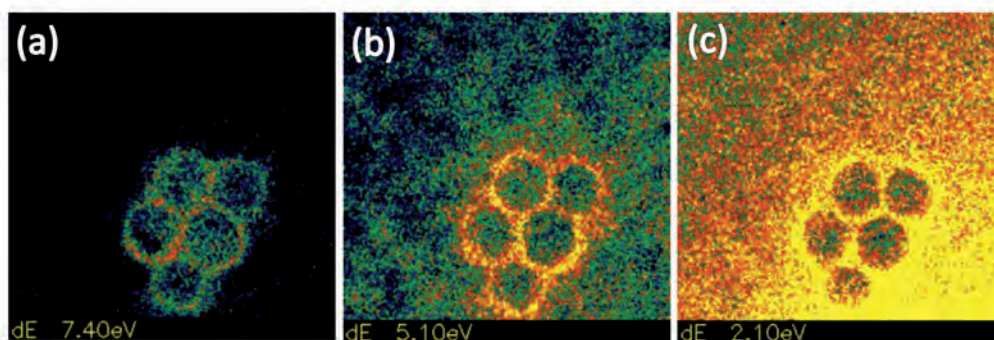


Fig.3

While these preliminary results show that the method allows probing of the electronic properties of the array, we could not expand it to larger structures because of a technical reason. The imaging of large fields of view requires an electron beam which is homogenous across the field of view, and for the purpose of this project this would require a few 100s of nm². Currently, it was not possible to achieve such a situation, without hampering the energy resolution. During the project time we have tried to develop image processing schemes that allow correcting for the inhomogeneity, but we could not implement them for an array of large particles.

It is foreseen that new hardware, now being installed in the ER-C in Juelich, will allow the fast acquisition of spectrum images by STEM-EELS. In that case, large fields of view will be available and the project may be resumed. A possible obstacle might be contamination of the samples with small organic molecules, which is a known problem in STEM measurements. For that we built a home-made apparatus to clean samples under inert environment and installed it in the electron microscopy center of the IKI.



**multidisciplinary
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between Ben-Gurion
University-Technion**

PROJECT

**Chromatic nanoparticle-based
cardiovascular diagnostic technology**

Launch year:

2011

Principal investigators:

Prof. Michael Aviram - *Technion Rappaport Faculty of Medicine*
Prof. Jelinek Raz - *Ben Gurion University, Department of Natural Sciences*

Participating students:

2

SCIENTIFIC GOAL

To refined the methodology and to acquire and analyze data obtained through application of the PDA chromatic data on blood plasma collected from **healthy**, **diabetics**, and **hypercholesterolemics** patients, as well as from hypercholesterolemic patients treated with **statins** or with **statins** combined with **pomegranate extract**.

ABSTRACT

The colorimetric nanoparticle assay can indeed *distinguish among biomedical conditions*. Basically each “flower” corresponds to a particular lipid composition [indicated below the flower]. Each radial axis corresponds to the extent of color change [the higher the number - the more significant blue-red

transition of the liposome]. The “circumference lines” correspond to the number of plasma samples (and repeats). The different colors correspond to the different conditions [normal, diabetics, hypercholesterolemics].

RESULTS OBTAINED TO DATE

We are currently analyzing the chromatic data to identify patterns correlating the color response to the biomedical conditions, and particularly predicting development of pathological conditions based upon the colorimetric differences.

Specific tasks accomplished so far:

1. Collection and isolation of sera from healthy individuals and from patients;

Sera were obtained from patients diagnosed

as suffering from type 2 diabetes, hypercholesterolemia or hypertension, as well as healthy control group. The three study groups consisted of 50 patients with type 2 diabetes (serum glucose levels above 160 mg% and blood hemoglobin A1c levels above 7.5%), 50 patients with hypercholesterolemia (serum cholesterol levels > 250 mg/dl), and 50 patients with hypertension (blood pressure higher than 140/90 mm Hg). Since these three diseases are

considered as risk factors to CVD, some of the recruited patients are expected to develop CVD during the time of the study. As they are all followed in the clinic (Prof. Tony Hayek, Technion faculty of Medicine), additional serum aliquot will be taken for further analyses following the CVD event.

2. Processing of chromatic data:
Below depicted a representative “radar plot”, underscoring that the colorimetric nanoparticle assay can indeed **distinguish among biomedical**

conditions. Basically each “flower” corresponds to a particular lipid composition [indicated below the flower]. Each radial axis corresponds to the extent of color change [the higher the number - the more significant blue-red transition of the liposome]. The “circumference lines” correspond to the number of plasma samples (and repeats). The different colors correspond to the different conditions [normal, diabetics, hypercholesterolemics].

FIGURES

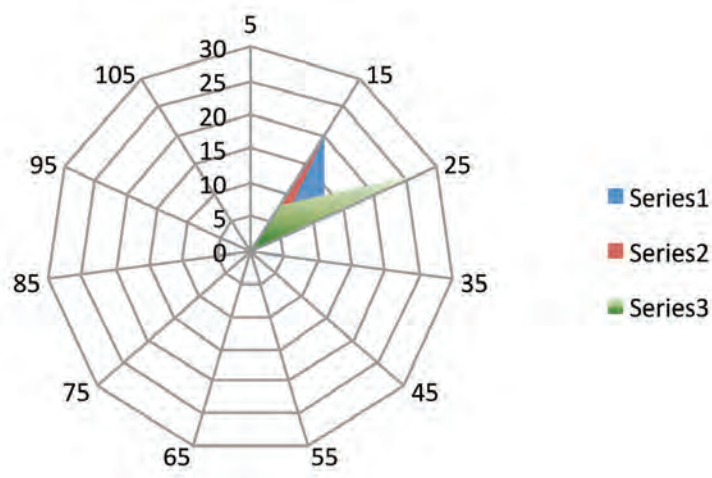


Figure 1. Chromatic data analysis: DMPC/PS/PDA vesicular nano particles in a sol-gel matrix. Series 1: healthy control; series 2: diabetic patients; series 3: hypercholesterolemic patients.

FACILITIES

Aviram biochemical / cell biology lab and Jelinek chemistry lab



**multidisciplinary
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PROJECT

Mapping of nucleosomal interactions during activation of the LH gene, using nanometer-resolution optical force spectroscopy

Launch year:

2013

Principal investigators:

Prof. Ariel Kaplan - *Technion IIT, Faculty of Biology and Faculty of Physics*
Prof. Philippa Melamed - *Technion IIT, Faculty of Biology*

Participating students:

1

SCIENTIFIC GOAL

- (i) To characterize, at the single molecule level, the nucleosome positioning at the LH β genepromoter and to map the *interactions* between DNA and histones.
- (ii) To characterize how these are affected by post-translational histone modifications.
- (iii) To characterize the kinetics of competition between nucleosome dynamics and binding of gene-specific transcription factors.

ABSTRACT

DNA within the nucleus of eukaryotic cells is compacted into chromatin, a hierarchical assembly of DNA and protein whose basic unit is the nucleosome, which consists of ~147 base pairs (bp) of DNA wrapped 1.65 times around an octamer of histone. Previous studies have shown that the accessibility of DNA is modulated by nucleosome structural dynamics and positioning. However, the complex and dynamic character of chromatin presents a challenge for detailed structural studies with classical “bulk” methods, because of an inherent ensemble-averaging of unsynchronized molecular populations. Remarkably, single-molecule techniques such as optical-tweezers, offer the unique ability both to detect the inherent heterogeneities of biomolecules and to monitor directly dynamic processes in real time, and are thus the method of choice for understanding various biological systems. In particular, it has been shown that by force-unwinding the DNA it is possible to generate a detailed histone–DNA interaction energy landscape (Hall et.al. 2009).

Luteinizing hormone (LH) is a glycoprotein secreted by the anterior pituitary, which plays an important role in regulating development and function of the gonads. It is positively regulated by the gonadotropin-releasing hormone (GnRH) which is synthesized and secreted from hypothalamic neurons. During development, gonadotropin hormone levels are highly dynamic and the genes that encode these hormones are repressed soon after birth as a result of insufficient GnRH release. Reinitiation of their expression occurs at puberty following stimulation of GnRH synthesis and release.

A probabilistic sequence-based algorithm (Segal and Widom, 2009) to predict the relative nucleosome occupancy of different regions along the LH β promoter reveals that DNA sequences which are predicted to be highly occupied by the nucleosomes include transcription factors binding sites; i.e. nucleosomes physically block the access of these factors to the DNA. As a result, LH β gene transcription initiation requires changes in its promoter chromatin structure. In the project, we

intend to characterize the mechanism of chromatin remodeling required for the expression of LH. We will characterize at the single molecule level the position of the nucleosome and the strength of its interactions, and how these parameters are affected

by histone post-translational modifications and competition with transcription factor binding.

RESULTS OBTAINED TO DATE

We have successfully reconstituted the LH β promoter chromatin with histones purified from T3⁻¹ and LBT2 cell lines and mouse LH β promoter DNA. The resulting pattern assayed with MNase-qPCR mapping analysis (Fig. 1A), closely resembles the LH β nucleosomal occupancy, predicted by the sequence based algorithm and by LH β promoter nucleosome occupancy mapping data obtained from cell lines. Currently, we are working on preparation of dsDNA handles which we will use in unzipping experiments described in Fig. 1B.

To our knowledge, our work for the first time will try to characterize mammalian biologically active promoter chromatin with its system-specific biological components such as promoter DNA sequence, cellular histone proteins and transcription factors on a single-molecule-single-base-pair resolution. Our study will help to understand the fundamental physical mechanisms of the mammalian regulation of gene expression, through focusing on events that regulate the mammalian reproductive potential.

FIGURES

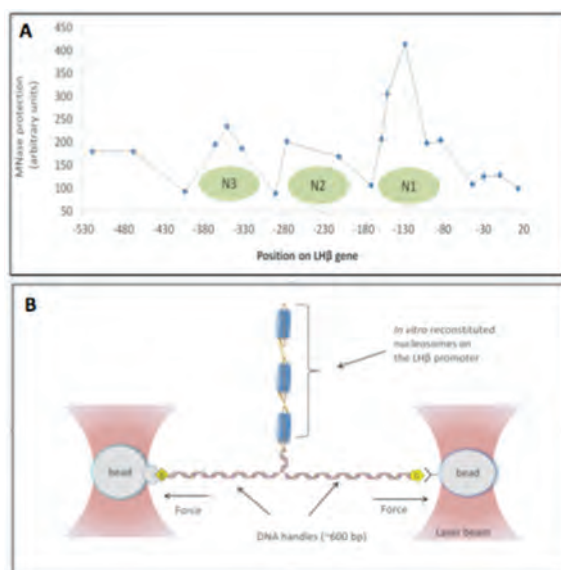


Figure 1. (A) Nucleosomal distribution for the LH β promoter sequence which was in vitro reconstituted with histones purified from aT3-1 cells. The reconstituted nucleosomes were "mapped" using MNase-qPCR (blue line). (B) Illustration of the experimental geometry: The template for single-molecule experiments consists of three parts: (a) the in vitro reconstituted chromatin segment, (b) digoxigenin-labeled dsDNA handle connected to a polystyrene bead via Dig/anti-Dig interaction, and (c) biotin-labeled dsDNA handle connected to a polystyrene bead via biotin-streptavidin interaction. Optical traps are used to apply force and mechanically unzip the DNA through the nucleosome.

FACILITIES

High-resolution optical tweezers (Kaplan Lab)



**multidisciplinary
research
collaboration
within Technion**

PROJECT

Quantum Dot Light Sources Probed by Superconducting Nanowires

Launch year:

2013

Principal investigators:

Prof. Eyal Buks - *Technion IIT, Department of Electrical Engineering*
Prof. David Gershoni - *Technion IIT, Department of Physics and the Solid State Institute*

Participating students:

1 PhD student and 1 postdoctoral scholar

SCIENTIFIC GOAL

Our main objective is to develop fast and sensitive superconducting single photon detectors and to use them in order to develop and characterize novel optical emitters of non-classical radiative states.

ABSTRACT

Based on recent progress in the fields of semi-conducting quantum structures and superconducting single photon detectors, we develop and characterize novel non-classical optical emitters for applications in the field of quantum information processing. The project is based on a collaboration of two research groups in the Technion, each with its own expertise. The Gershoni group - in charge of developing the optical emitters - has a well-established track-record

in the field of semiconductor quantum structures of lower dimensionality, such as quantum wires and quantum dots. The Buks group - in charge of developing fast and sensitive photon detectors - brings knowledge on the design, fabrication, and operation of superconducting nanowire single photon detectors (SNSPD).

RESULTS OBTAINED TO DATE

We have developed two types of SNSPDs, the first is fabricated directly on the tip of a single mode optical fiber (SMOF) (*see Figs. 1 and 2*), and the second is based on a fixed alignment between a SNSPD

made on a sapphire wafer and a SMOF (*see Figs. 3 and 4*). An extensive effort has been devoted to optimization of superconducting material properties and nanofabrication of the nanowires.

FIGURES

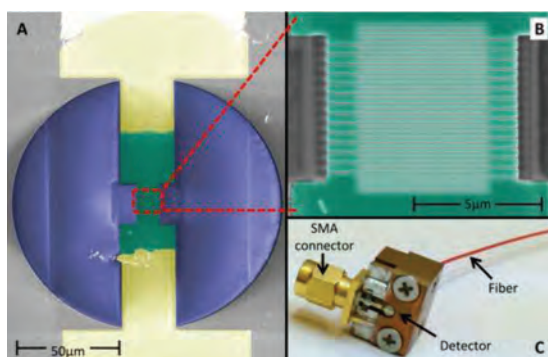


Figure 1. On-fiber SNSPD [1]. (A) A low magnification scanning electron microscope (SEM) micrograph of a SNSPD on a tip of a fiber (colored for clarity): the detector (green), the gold contacts (yellow) and the fiber (purple circle). (B) A higher magnification image. The thin 120nm wide lines are folded in a meander form. The meander covers an area of $25\mu\text{m}^2$. (C) A photo of a mounted device.

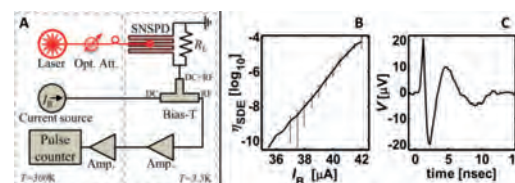


Figure 2. (A) Characterization of on-fiber SNSPD [1]. We use CW monochromatic laser at 1550nm as a light source. The light is attenuated at room temperature to 10nW and sent into a cryostat where the device is cooled to 3.5K. (B) The system detection efficiency of one of our devices as a function of the bias current. (C) An electrical pulse from the detector after an event of single photon detection.

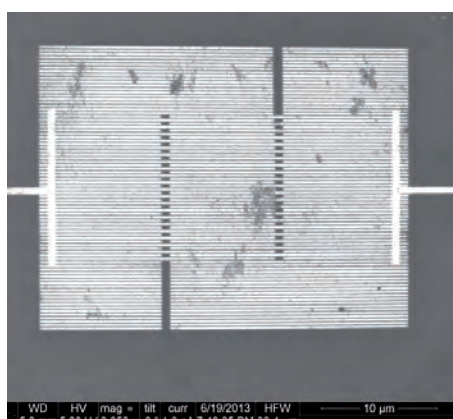


Figure 3. SNSPD nanowire folded in a meander pattern of size $10\mu\text{m} \times 10\mu\text{m}$. The grey area is a NbN thin film ($\approx 4\text{nm}$ thick) deposited on a sapphire substrate, and the white area is the sapphire substrate.

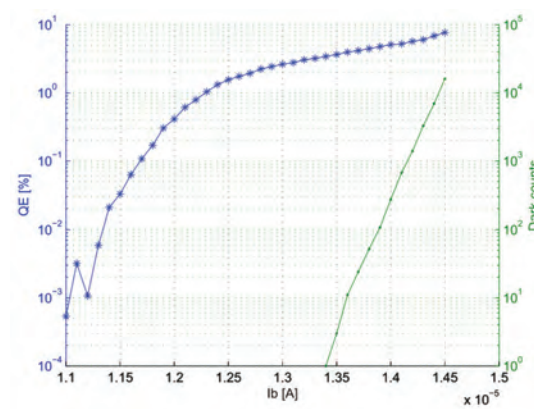


Figure 4. SNSPD dark count rate (green points) and photon detection efficiency (blue points) as a function of bias-current.

FACILITIES

MNFU, FIB



**multidisciplinary
research
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between Ben-Gurion
University-Technion**

PROJECT

Engineering of a Protein Nanocage for Biotechnological Applications

Launch year:

2013

Principal investigators:

Prof. Raz Zarivach - *Ben-Gurion University, Dept. of Life Sciences*
Prof. Ayelet Fishman - *Technion IIT, Faculty of Biotechnology and Food Eng.*

Participating students:

Dr. Mor Goldfeder, Dr. Margarita Kanteev, Samuel Cronin

SCIENTIFIC GOAL

The overall goal of this research is to create hollow protein nanocages stable in solution, for biotechnological applications. As a feasibility study, we plan to encapsulate the enzyme tyrosinase for biosensing phenol.

ABSTRACT

The Zarivach group from Ben Gurion recently discovered that MamA, a magnetosome associated protein, can form a 14-nanometer hollow nanocage in crystal form. The Fishman group from the Technion has been working on the characterization and engineering of tyrosinase from *Bacillus megaterium* (TyrBm). In the present study, we will join forces to modulate MamA so that it forms nanocages (Figure

1) in solution for the encapsulation of TyrBm as a potential nanosensor of phenol. We also plan to encapsulate γ -3 linolenic acid and study its protection from oxidation for a potential application as a delivery vehicle of this important nutraceutical. Thus, the combined efforts of our groups will pave the way for biotechnological applications using a novel nano-delivery system.

RESULTS OBTAINED TO DATE

We are investigating variants of MamA which will form stable nanocages in solution. The latest mutation, E68L, has been successfully crystallized and its structure solved. We have confirmed that this protein still assembles into a nanocage when crystallized. The mutation has resulted in a slight re-organization of the structure, leading to a somewhat tighter packing. Furthermore, it has illuminated potential locations for the application of the next mutations. First and foremost will be E68M, as the structure shows a void in the hydrophobic patch

which methionine may fill, further tightening the structure. With regard to the bacterial tyrosinase (TyrBm) which we are attempting to entrap within the nanocage, a monomer has been successfully designed in order to increase the chances for entrapment of the protein. TyrBm variants W41A and F48A were shown to be monomers by both gel filtration and DSC measurements. They have similar activity to wild-type at 35°C but have lower stability at higher temperatures indicating that the native dimer is more stable than the monomers. We anticipate

that the TyrBm monomers will be more stable once entrapped within the nanocages.

We continue our attempt to capture TyrBm variant W41A in the crystallized nanocage and to validate its presence via SDS-PAGE. This is being done via

the co-crystallization of tyrosinase with MamA, at different ratios. The crystals formed are then sequentially washed, to remove any excess tyrosinase on the surface, and are then run on a gel.

FIGURES

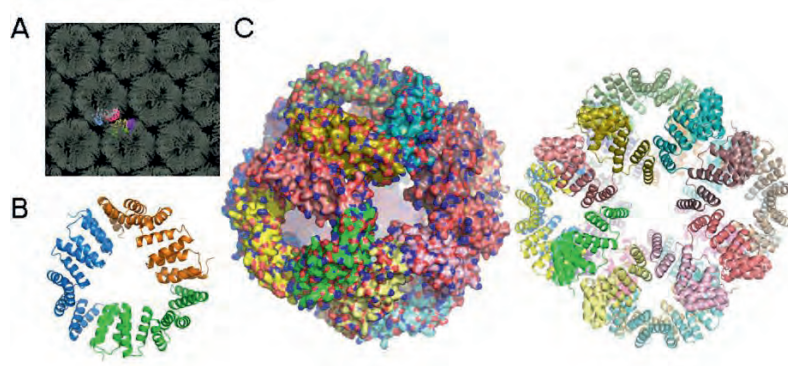


Figure 1: Crystal structure of a modified MamA. *A)* MamA structure crystallised as a perfect sphere packing within the protein crystal. The asymmetric unit is coloured and the generated symmetry molecules are coloured in grey. *B)* MamA assembled as trimeric ring with ~1.5 nm inner void.

The trimer is the minimal unit for sphere formation. *C)* A single empty sphere has an inner hollow ~8 nm core. The sphere is composed of 8 trimeric rings as represented by surface (left) and ribbon (right). Source: Zarivach, unpublished.

FACILITIES

In the present study we are using the dynamic light scattering (DSC) equipment in Ben-Gurion University. We are also using the equipment in the Russell Berrie Nanoparticles & Nanometric Systems Characterization Center. Furthermore we are making use of the Technion Center for Structural Biology for obtaining crystal structures of wild type tyrosinase and its mutants. We are thankful to the Nevet program for supporting this collaborative research.



**multidisciplinary
research
collaboration
between Ben-Gurion
University-Technion**

PROJECT

Self-assembled Janus cyclic peptide nano- tubes with controllable length

Launch year:

2013

Principal investigators:

Prof. Dganit Danino - *Technion IIT, Department of Biotechnology and Food Eng.*
Prof. Nurit Ashkenasy - *Ben-Gurion University of the Negev, Department of Materials Engineering*

Participating students:

2

SCIENTIFIC GOAL

Spatial control of nanoparticles' physiochemical properties is of great importance for many device applications, including electronic devices and sensors. Here we propose a novel co-assembly approach in which several different monomeric units are assembled into a single structure to achieve these goals. D,L α -cyclic peptides will be employed, since their self-assembly occurs by backbone hydrogen bonding, making it easy to control the properties of the resulting nanotubes by the choice of the sequence. **The main aim of the suggested project is to develop methodologies for the formation of peptide nanotubes with controllable length, and spatially controlled physiochemical properties.** The specific aims are to: 1. Study the kinetics of cyclic-peptide nanotubes self-assembly; 2. Develop methodologies to control the length of nanotubes by capping molecules; 3. Prepare and characterize Janus nanotubes designed with localized regions for binding or nucleating the growth of metals.

ABSTRACT

Peptides' self-assembly into fibrous and tubular structures with nanometric dimensions, which is a key process in diverse biological processes, can open the way to the construction of functional peptide nanostructures. Suggested applications, e.g. in electronic devices, require the ability to control the physico-chemical properties along the fibers –i.e. the formation of Janus nanotubes, which is hard to implement in common self-assembly processes that use a single monomer. Additionally, controlling the final length is not easy due to the inherent spontaneous nature of the self-assembly process. The aim of the suggested project is to develop a

novel strategy for the formation of Janus peptide nanotubes with controllable length. This goal will be achieved using hetero-meric mixtures of D,L α -cyclic peptides. Self-assembly of these peptides will form nanotubes with (a) controlled dimensions, primarily length, by using backbone-methylated peptides that hinder further self-assembly by steric effects; and (b) spatial control of properties. The great potential of this unique approach will be demonstrated by the formation of Janus metallic-peptide nano-hybrids, which can be used to develop electronic devices in a bottom-up approach.

RESULTS OBTAINED TO DATE

The control of self-assembly in this work is based on backbone hydrogen bonding of alternating D-L cyclic octa peptide. The hypothesis is that electrostatic interactions between negatively and positively charged peptides, can be used to control the self-assembly, in similar to layer-by-layer deposition processes. In order to study this process two peptides were synthesized: cyclic (D-Glu-L-Trp)₄, abbreviated as c(EW)₄, and cyclic(D-Lys-L-Tyr)₄, abbreviated as c(KY)₄.

Both peptides were found to be soluble at pH 7, based on solution clarity. To promote assembly each of the peptides was assembled at a suitable pH. Cryo-TEM images revealed the formation of

fibrous material, showing the formation of fibres for c(EW)₄, and more crystallite type assembly for c(KY)₄. Co-assembly of a 1:1 molar ratio mixture of the two peptides was performed at room temperature in a MOPS buffer pH 7.2. Cryo-TEM imaging of the mixture (*Figure 1*) revealed ordered crystalline structures, having characteristic striations of 2-nm step (*see the intensity profile in the figure insert*). These striations were spaced at a distance that corresponds to the van der Waals width of a single flat ring-shaped cyclic peptide and represent images of individual nanotubes packed side by side in parallel. These results demonstrate the applicability of the suggested assembly approach- opening the way to pursuing the next steps of the project.

FIGURES

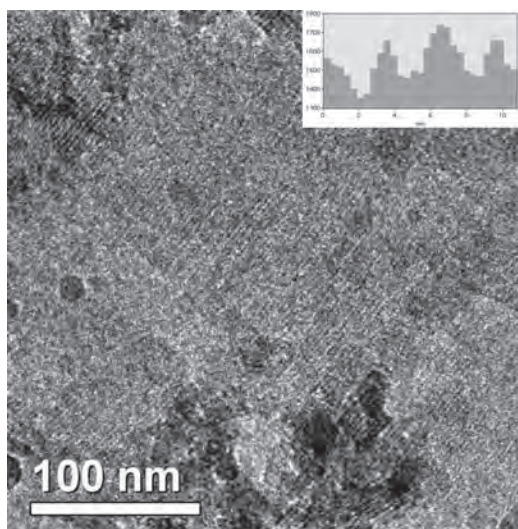


Figure 1. High resolution cryo-TEM image of mixture at 1:1 molar ratio mixture of c(EW)₄ and c(KY)₄. Assembly was performed at room temperature in a MOPS buffer pH 7.2

FACILITIES

Cryo-EM Center of Soft-Matter



**multidisciplinary
research
collaboration
between RBNI-
Life Sciences and
Engineering Unit**

PROJECT

Towards Functional Mapping of Neural Activity with Novel Nanoparticle Markers

Launch year:

2013

Principal investigators:

Prof. Lilac Amirav - *Technion IIT, Schulich Faculty of Chemistry*
Prof. Itamar Kahn - *Technion IIT, Department of Physiology and Biophysics*
The Ruth and Bruce Rappaport Faculty of Medicine

Participating students:

One postdoc and one student

SCIENTIFIC GOAL

We propose to establish the research platform and first steps that will enable a dynamic, *in situ*, functional study of population of neurons at a single cell resolution, while in their natural circuit environment and in the intact animal.

ABSTRACT

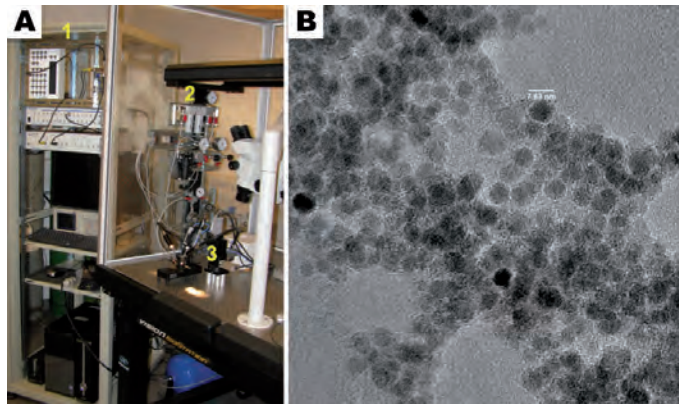
Designing effective nanoparticles that can passively or actively label fine biological structures in various functional states is a central goal of medicine-oriented nanotechnology development. Here we aim to establish a platform for the development of a class of particles that will be compatible with and visible in a magnetic resonance imaging (MRI) environment. Although several attempts have been successful in this domain, a paucity of particles optimized for the intracellular environment in the intact animals exists. We will focus on materials built as spheres that can carry encapsulated sensors or drugs and strategies that can introduce these materials to the intracellular environment of mammalian neurons. We propose a development scheme that will allow us to rapidly test these materials in both cultured

cells as well as the intact animal, thereby shortening the cycle of development between a chemically suitable prototype and tests in an animal model. A novel aspect of the platform we propose is the use of electroporation to introduce impermeable materials directly into selected individual cells. This approach will allow us to track precisely the fate of the particles and cells. Leveraging the complementary expertise of the two participating groups, we expect to establish a robust platform for the development of nanoparticles for structural intracellular labeling and basic functional sensing in the short term and develop first-in-class novel nanoparticles for large-scale brain mapping in the medium term.

RESULTS OBTAINED TO DATE

This project has only now commenced.

FIGURES



[A] Computer controlled micromanipulator ("autopatcher"). Autopatcher system capable of automatically achieve juxtacellular configuration recording and electroporation. Key components: (1) recording amplifier, labview control computer, and custom-built dedicated controller computer; (2) pneumatic system capable of achieving juxtacellular (and patch) configuration; (3) software controlled micromanipulator and a modified stereotactic holder.

[B] Iron oxide nanoparticles as MRI contrast agents. The project has commenced with the synthesis of iron oxide nanoparticles, which are known to be excellent contrast agents for MRI. This is a convenient starting point for demonstrating compatibility with single cell in vivo measurements.



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PROJECT

Microfluidic chip for probing immune cell functionality on a single cell level

Launch year:

2013

Principal investigators:

Prof. Prof. Moran Bercovici - *Technion IIT, Faculty of Mechanical Eng.*
Prof. Shai Shen-Orr - *Technion IIT, Faculty of Medicine*

Participating students:

2

SCIENTIFIC GOAL

1. Develop microfluidic platform for capturing single cell pairs and measuring their interactions.
2. Demonstrate performance of simultaneous 500 functional killing assays at the single cell level.
3. Measure variability in killing assay and correlate with phenotypic markers.

ABSTRACT

We are developing a novel microfluidic chip which would enable high throughput studies of immune cell functionality on a single-cell level. Given the heterogeneity of immune cell population, the ultimate goal of the proposed project is to provide insight into the functionality of different sub-populations of immune cells and to understand the underlying mechanisms of cellular communication at sub-

population level. Based on numerical simulations, we have designed a microfluidic platform capable of capturing single cells. We are now focusing on microfabrication of the chip and its use for the demonstration of a "cell killing assay" multiplexed to perform 500 independent single-cell killing events in parallel.

RESULTS OBTAINED TO DATE

We are working on the optimization of the first design for capturing cells in isolated conditions. COMSOL-based simulations are being used for this round of optimization. We have simulated several design parameters to understand their effect on

the efficiency of cell capturing. Currently, we have obtained the first working design which will be used to develop our first cell capture system. Illustrations from those simulations have been added in the figures category.

FIGURES

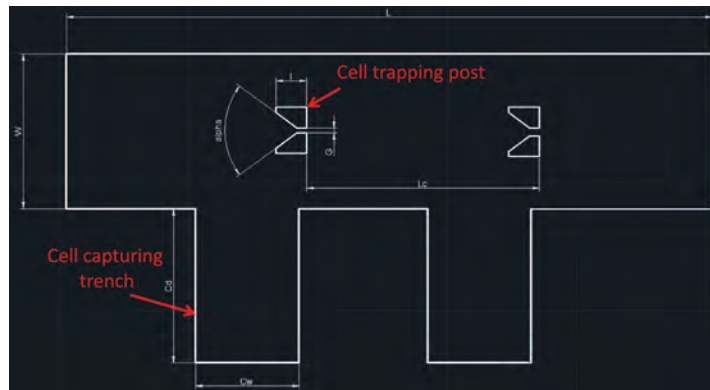
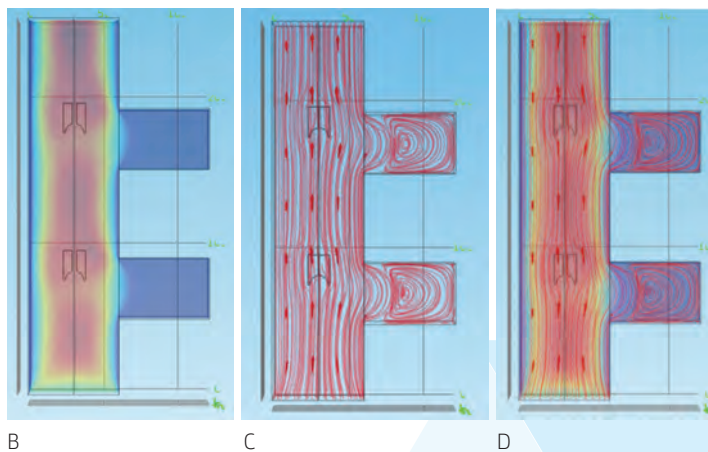


Figure 1. Simulation-based design of the microfluidic chip for single cell capture. (A) depicts a section of the chip which possess cell trapping posts along the width of the channel 'W'. The cells trapped in these posts will then be directed to trenches at the same axis by flipping the chip. B and C illustrate the profiles of velocity and streamlines of liquid in the channel, respectively; while in D an overlap of corresponding profiles of velocity and streamlines is presented.



B

C

D

FACILITIES

We have not used any technical facilities yet, as the current phase of the project was solely based on numerical simulations.



**multidisciplinary
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Life Sciences and
Engineering Unit**

PROJECT

**Selective regulation of protein synthesis
during innate immune response -
from single molecules to live cells**

Launch year:

2013

Principal investigators:

Prof. Amit Meller - *Technion IIT, Faculty of Biomedical Engineering*
Prof. Amir Orian - *Technion IIT, Faculty of Medicine*

Participating students:

2

SCIENTIFIC GOAL

The control of gene expression involved in immune responses are highly selective and are likely determined by protein-protein interactions as a mean to achieve this selectivity. The goal of our research is to elucidate the precise mechanism at which selectivity in immunity arises at the translational level and is regulated by posttranscriptional modifications by STBL and Ubiquitin SUMO pathways. This selective regulation stems from the recognition of individual proteins and specific mRNAs that act cooperatively to enhance selective gene translation. Therefore this system must be investigated with appropriate Nanotechnological tools, intimately linked to the immune biological context.

ABSTRACT

Translation initiation is the rate-limiting step for all protein synthesis in Eukaryotic cells and involves the activity of the eIF4F translation initiation complex, which can bind to the 5' end of the mRNA, marked by the m7GpppN or alternatively at internal 5' UTR sites called Internal Ribosome Entry Sites (IRES)1. The binding to internal sites, which differ in primary and secondary structure among gens, provides an opportunity for selective activation of specific genes. However, the way in which selective translation initiation is achieved have seldom been investigated, presumably due lack of nano-technological tools that allow single-molecule observations of these molecular processes.

Recent findings from our laboratories identified that the Drosophila SUMO-Targeted Ubiquitin Ligase (STUbl) protein, Dgrn, serves as a molecular selector

that determines selective co-factors recruitment during development. Moreover, we recently identified Dgrn as the key regulator of eukaryotic translation initiation factor 4A (eIF4A) – a primary member of the eIF4F complex. Presumably, the specific ubiquitylation of eIF4A mediated by Dgrn tags the former enzyme in a way that results in a marked reduction in the protein level of Akirin - an obligatory co-activator protein of the NFkB-related Imd pathway. Our results show that Dgrn performs this function without affecting Akirin's half-life or its mRNA level. Subsequently the reduction in Akirin protein level inhibits Imd-dependent gene expression. Yet, Dgrn effect is limited to Akirin/Imd pathway and not co-activators within the second NFkB-related Toll pathway. These results may thus suggest a pathway wherein Dgrn specifically controls selectively the translation efficiency of Akirin.

In parallel, our groups have developed a high sensitivity single molecule Fluorescence Resonance Energy Transfer (sm-FRET) apparatus that was used to study the binding and helicase activity of eIF4A and its associated factors in real time. We recently find that when coupled to an accessory protein eIF4H, eIF4A can tightly bind mRNA loop structures and perform unwinding of stem structures in a repetitive manner. Here we propose to first utilize this high-sensitivity setup to investigate the activity of the ubiquitinated eIF4A by Dgrn specifically using mRNA sequences associated with 5'UTR of the Akirin gene.

Second, we will further enhance our technologies to detect these processes in live cells, with specific tagging of the eIF4A and the mRNA transcript in fly cell lines. By combining classical cell biology and genetics using *Drosophila* as a model organisms with single-molecule investigations in vitro and in live cells we propose to study, for the first time to our knowledge, the hypothesis that gene-specific protein synthesis is controlled at the translation initiation step and is key to generate selective immune gene expression signatures.

RESULTS OBTAINED TO DATE

Research started this past week. We have already been able to transfect cells in Orian's laboratory

with the eIF4A plasmids produced in Meller's lab. Microscopy measurements have commenced.

FIGURES

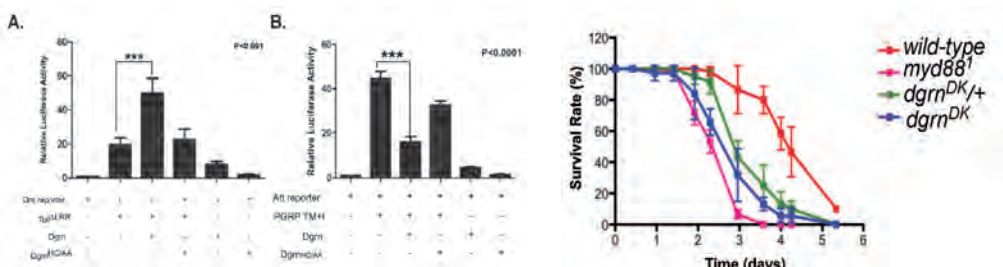
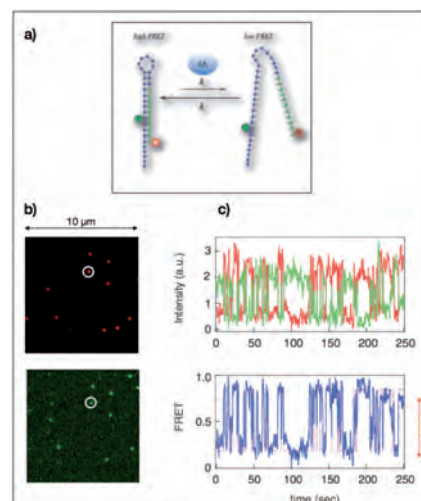


Figure 1. Luciferase-based reporter assay in S2 cells. Expression of the relevant receptor (Toll^{ALRR} and PGRP-TM-I) activated the Toll or Imd pathway specific reporter. (A.) Dgrn but not Dgrn catalytic mutant (Dgrn^{HC/AA}) enhances the transcription a Toll pathway specific reporter. (B.) Expression

of Dgrn inhibits the transcription derived of an Imd-pathway specific reporter. (C.) Survival of adult flies infected with *Beauveria Bassiana* spores that activates the Toll pathway is compromised in Dgrn^{DK} mutants. myd88 serves as a positive control for the Toll pathway.

Figure 2. Single-molecule FRET assays for the study of eIF4A binding and unwinding activity. Typical single molecule results are shown in b and c.





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Life Sciences and
Engineering Unit**

PROJECT

Designing Anti-Fungal Nano- Textured Surfaces

Launch year:

2013

Principal investigators:

Prof. Boaz Pokroy - *Technion IIT, Department of Materials Science and Engineering*
Prof. Ester Segal - *Technion IIT, Department of Biotechnology and Food Engineering*

Participating students:

Sasha Pechook, Maksym Krupker

SCIENTIFIC GOAL

The aim of the proposed research is to design nano and micro-structured surfaces that mitigate or prevent fungal colonization or infection with subsequent biofilm formation.

ABSTRACT

The aim of the proposed research is to design nanostructured surfaces that mitigate or prevent fungal colonization or infection with subsequent biofilm formation. We propose to combine materials science, nanobiotechnology, and biology in order to study the ability of superhydrophobic/superoleophobic coatings to prevent the growth of different fungi on surfaces. Our approach is to use thin-filmed nano-crystals of paraffin and fluorinated waxes on different substrates as the source of self-cleaning elements, which have already demonstrated their outstanding bacterial anti-

biofilm characteristics. We will study whether these surfaces also have anti-fungal properties and which materials and surface characteristics are needed for this specific function. The approach we are proposing has significant advantages, as the resulting "passive" surfaces are non-leaching and they are completely inert to biological systems as well as ecosystems. This bio-nanotechnological study is by definition a multidisciplinary study that ties together materials science and biology and by such also brings together two PI's from these two disciplines.

RESULTS OBTAINED TO DATE

Various coatings were applied on polyethylene and paper via thermal evaporation of various waxes ($C_{36}H_{74}$, $C_{50}H_{102}$ and $C_{24}F_{50}$) and spray coating of fluorinated wax ($C_{24}F_{50}$). The different waxes formed textured surfaces as described in *figure 1*. As a model fungus, we used *Alternaria alternate* ATCC 11680 using an experimental setup as described in *figure 2*. The fungi growth on polyethylene was very moderate and thus the polyethylene substrates were replaced by paper (Whatman filter paper No. 1).

All examined surfaces demonstrated significant reduction of fungi over a 7 day period under 100% humidity conditions (*figures 3 and 4*) comparing with the reference samples.

Best results were obtained for thermally evaporated $C_{36}H_{74}$ and $C_{24}F_{50}$. These results will be further investigated.

FIGURES

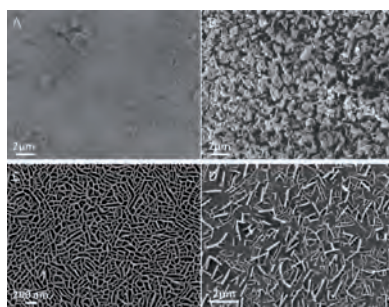


Figure 1. HRSEM micrographs of
A) spray coated $C_{24}F_{50}$, thermally
evaporated B) $C_{24}F_{50}$, C) $C_{50}H_{102}$
and D) $C_{36}H_{74}$

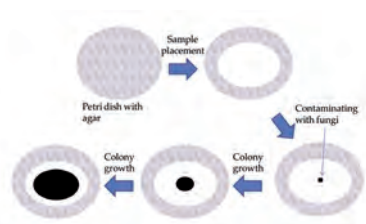


Figure 2. Experimental setup

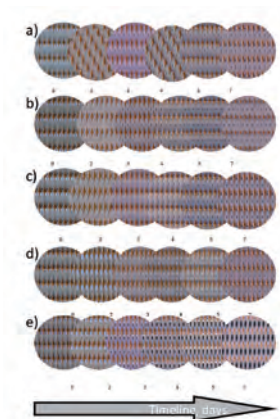


Figure 3. Fungi growth as a
function of time: a) $C_{24}F_{50}$,
b) $C_{24}F_{50}$ spray, c) $C_{50}H_{102}$, d)
 $C_{36}H_{74}$ and e) uncoated paper
(reference).

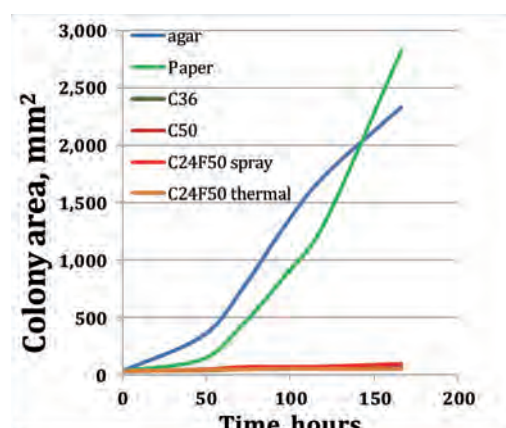


Figure 4. Colony area vs. time

FACILITIES

Preparation and characterization of textured coatings:

Thermal deposition: Moorfield MiniLab evaporator. Spray coating: A commercial Air Brush system.

Characterization: Wax powder and crystalline thin films were characterized structurally and microstructurally by XRD with a Cu anode sealed tube (Rigaku, SmartLab, X-Ray Diffractometer). Surface imaging was performed by HR-SEM (Zeiss Ultra Plus). Roughness and in situ time-dependent roughness were measured under materials confocal microscopy (Leica 3D DCM).

Antimicrobial (antifungal and comparative antibacterial) studies:

Each coated (and control) sample was inoculated with between 10^3 and 10^4 *Alternaria alternate* spores. Plates are incubated at 30 °C for various times. Antifungal activity was assessed by the colorimetric MTT assay. In this assay growth is assessed by the reduction of the tetrazolium dye 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT), allowing quantitative characterization of fungal growth inhibition on the different surfaces.

Observation of fungi growth on the different coatings over time was characterized by optical and fluorescence microscopy. Variation in colony morphology, growth and spore production was assessed compared to the control plates. In addition, at different time points, the cultured surfaces were stained with FungaLight (a fluorescent live/dead assay), and studied by fluorescence microscope in order to determine cells viability.