Patients with Alzheimer’s disease (AD) run a high risk of seizures. While the amyloid-beta protein (Aβ) involved in the development and progression of Alzheimer’s seems the most likely cause for this neuronal hyperactivity, how and why this elevated activity takes place has not yet been explained. Our recent study, published in Cell Reports, pinpoints the precise molecular mechanism that may trigger an enhancement of neuronal activity in Alzheimer’s patients, which subsequently damages memory and learning functions. Our research team, led by PhD student Hilla Fogel and Postdoctoral fellow Samuel Frere, discovered that the amyloid precursor protein (APP), in addition to its well-known role in producing Aβ, also constitutes the receptor for Aβ. According to the study, the binding of Aβ to dimers of APP molecules triggers a signaling cascade, which causes elevated neuronal activity.

Building on earlier research

Accumulation of Aβ in the extracellular space of the brain appears to be critical for developing synaptic and cognitive deficits in AD. Aβ is produced by sequential limited proteolysis of the amyloid precursor protein (APP) by two aspartyl proteases, β- and γ-secretases. Normally, γ-secretase cleavage results in variable 38 to 43 amino acids Aβ peptides, with Aβ40 monomers as the predominant species. The biophysical and biochemical properties of Aβ strongly depend on its concentration, length and primary structure. Gradual elevation of Aβ monomers in limbic and association cortices leads to their aggregation into oligomers, pre-fibrillar assemblies (protofibrils) and amyloid fibrils. All these Aβ forms can be in dynamic equilibrium, leading to a high variety of synaptic and circuit dysfunctions that underlie progressive cognitive impairments in AD.

While pathological Aβ concentrations and assembly forms depress neuronal activity, an increase in endogenous Aβ levels induced by inhibition of Aβ degradation causes presynaptic enhancement. Specifically, inhibition of the Aβ-degrading enzyme neprilysin augmented glutamate release and reduced synaptic plasticity in hippocampal circuits. As hippocampal and cortical hyperactivity are common in various transgenic AD mouse models, humans with mild-cognitive impairments and AD patients, elucidating synaptic mechanisms of hyperactivity is critical for understanding AD-associated cognitive impairments.

APP homodimer constitutes a receptor for Aβ

In our recent study, we explored the mechanism initiating augmentation of synaptic vesicle release at hippocampal synapses by Aβ. Utilizing a combination of fluorescence resonance energy transfer (FRET) spectroscopy, a single-molecule imaging, two-photon excitation laser scanning microscopy combined with fluorescence lifetime imaging (2pFLIM), biochemistry, imaging of synaptic vesicle recycling and calcium, we searched for the presynaptic Aβ receptor mediating regulation of release probability at hippocampal synapses. We found that APP binds Aβ40 monomers and dimers and increases the fraction of APP homodimers at the plasma membrane. Utilizing FRET spectroscopy and 2pFLIM-FRET, we were able to identify molecular mechanisms that trigger hyperactivity of brain circuits in early stages of Alzheimer’s disease.
to monitor APP-APP interactions at individual presynaptic boutons of live neurons in hippocampal slices. Interestingly, APP-APP interactions were directly altered by Aβ (Figure 1). Specifically, inhibition of Aβ degradation or addition of Aβ boosted FRET between APP molecules.

How does Aβ exert its presynaptic effect? Following secretion, Aβ forms the Aβ:APP complex that triggers APP-APP conformational changes, leading to an increase in the presynaptic Ca2+ flux via G-protein dependent signaling and subsequent potentiation of synaptic vesicle release. We identified the APP growth-factor-like domain as a critical determinant of Aβ40-induced changes in APP-APP interactions and release probability. These data highlight the role of APP as a *bona fide* surface Aβ40 receptor.

**Figure 1: Aβ40 promotes APP-APP interactions at mossy fiber terminals in acute hippocampal slices.** APPmEGFP and APPmCherry expression in the CA3 and dentate gyrus (DG) of APP−/− mice injected with lentiviral vectors to the DG (A1). Zoom in to the DG expression (A2). Scale bars: 0.5 mm (A1), 0.1 mm (A2). In CA3 area, mEGFP and mCherry fluorescence is localized in the stratum lucidum where the mossy fibers project. Mossy fiber terminals positive for mEGFP and mCherry fluorescence and color-coded APPmEGFP decay constant. Scale bar: 10 µm. (C–E) Left: Application of Aβ40 in hippocampal slices of APP−/− mice expressing APPmEGFP and APPmCherry accelerated the decay constant of the interacting molecules (C, τAD, p < 0.01), increased FRET efficiency between APPmEGFP and APPmCherry co-expressed at mossy fibers (D, Ei, p < 0.01), while did not alter the fraction of interacting APPmEGFP and APPmCherry (E, p = 0.3). Right: Thiorphan treatment accelerated τAD (C, p < 0.0001), increased Ei (D, p < 0.0001), but did not affect the binding fraction (E, p = 0.48).

From APP homodimer activation to Alzheimer’s disease

Based on the current work, we propose that increase in the extracellular levels of Aβ monomers and dimers in the early stages of AD development may augment signaling via APP homodimers, leading to hyperactivity of hippocampal synapses (Figure 2). Potentiation of synaptic vesicle release, in turn, causes a subsequent increase in Aβ40 production and release13,14, leading to a positive feedback loop between the extracellular Aβ concentration and the basal glutamate release. Under physiological conditions, an increase in Aβ-mediated APP homodimerization may induce a feedback inhibition of Aβ production15 to maintain steady-state Aβ levels and the basal glutamate release. Disruption of this negative feedback loop by genetic-/experience-dependent factors may cause a gradual increase in the extracellular levels of Aβ monomers and dimers during the early AD stages, leading to excessive activation of APP homodimers at the plasma membrane and subsequent synaptic hyperactivity. The described presynaptic augmentation may initiate neural dysfunctions by two possible ways: first, it may cause deficits in short-term synaptic plasticity and second, it may facilitate the kinetics of Aβ oligomerization, thus depress synapses and induce...
synapse loss. Such an Aβ-induced synaptic reorganization may promote homeostasis of synaptic output across the dendrites, but reduce the ability of synaptic networks to undergo experience-dependent modifications. It remains to be seen whether excessive activation of APP homodimers by Aβ emerges as the first molecular step is contributing to hippocampal hyperactivity in the most frequent, sporadic AD.

Currently, in collaboration with Prof. Joel Hirsch from the Faculty of Life Sciences, we are working on identifying the exact spot where the Aβ binds to APP and how it modifies the structure of the APP molecule. If we can change the APP structure and engineer molecules that interfere with the binding of Aβ to APP, then we can break up the process leading to hippocampal hyperactivity. Similar to previous studies by Prof. Lennart Mucke laboratory strongly which suggest that a reduction in the expression level of “tau” (microtubule-associated protein), another key player in Alzheimer’s pathogenesis, rescues synaptic deficits and decreases abnormal brain activity in animal models, we will explore the missing link between APP and ‘tau’-mediated signaling pathways leading to hyperactivity of hippocampal circuits. Disruption of the positive signaling loop between Aβ and neuronal activity may rescue cognitive decline and the conversion to Alzheimer’s disease.

References

Figure 2: Proposed model of Aβ-mediated functions and dysfunctions at excitatory synapses. Under physiological conditions, a positive feedback loop between basal glutamate release and Aβ secretion may be compensated through a feedback inhibition of Aβ production, maintaining the basal extracellular glutamate and Aβ levels. Under pathological conditions, this negative feedback may be disrupted, resulting in hyperactivity of excitatory boutons and reduction in short-term synaptic facilitation. A remaining positive feedback between glutamate and Aβ release may lead to accumulation of the extracellular Aβ and subsequent Aβ oligomerization, resulting in postsynaptic depression and spine loss.
The field of plasmonics has attracted great interest in the last decade and surface-plasmon-polariton waves have been utilized in many novel applications, such as sub-wavelength optics, nonlinear plasmonics, sensing, optical trapping, and more. Controlling the shape and trajectory of these waves is a key feature in enabling all of the above, and a challenging task. In the last couple of years, efforts to control the plasmonic wave properties have been made, and unique plasmonic beams such as "self-accelerating" Airy beams and "diffraction-free" Cosine-Gauss beam, have been realized. However, each one of these realizations was based on a different ad-hoc method, specifically tailored, and therefore limited only to that specific plasmonic beam. Hence, finding a general approach, which will enable complete control over the plasmonic wavefront, still remains a challenge.

This fundamental challenge resides in the different wave properties of surface-plasmon waves, in comparison to free-space waves: first, coupling a free-space wave into a surface-plasmon wave requires a compensation of momentum to match the two beam wave-vectors. Second, due to the limited propagation length of surface-plasmons and the limited range of their characterization tools, the resulting beams should be formed directly in the near-field, before they decay. Third, unlike planar phase plates, surface-plasmons are excited over a finite propagation distance and therefore their phase cannot be simply defined at a specific one-dimensional plane. Fourth, dynamic tools for controlling a beam's wavefront, like spatial-light-modulators, do not exist for surface-plasmons. This year, we introduced a new class of binary plasmonic holograms, which are designed specifically

Figure 1: Near-field intensity measurements of: (a)self-similar plasmonic Hermite-Gauss(1,0) beam[1], (c)non-paraxial, self-accelerating plasmonic Mathieu beam with an elliptic trajectory[3], (d)plasmonic bottle-beam, formed by two counter-accelerating beams[4], (b)SEM image the Hermite-Gauss plasmonic hologram shown in(a).
for the near-field, and allow overcoming all of the above challenges. This robust holographic scheme provides complete control over the amplitude and phase of surface-plasmons, thereby enabling the generation of any desired plasmonic beam.

The standard method in optics for generating a beam with desired amplitude and phase profiles is holography. Typically one uses a Fourier-hologram, in which the desired beam is obtained in the first diffraction order at the far-field, separated spatially from other undesired diffraction orders. In our new scheme, the plasmonic hologram is directly encoded with the target amplitude and phase, rather than its Fourier-transform, and is therefore formed in the near-field. Moreover, only the desired beam is reconstructed as a surface-plasmon, thereby inherently separating it from the other undesired diffraction orders of the hologram.

Using these holograms, we have demonstrated a variety of plasmonic beams, such as "self-similar", "non-diffracting", "self-healing", arbitrary "self-accelerating" and non-paraxial plasmonic beams, as well as plasmonic bottle-beams. We expect this new class of plasmonic near-field holograms to enable the realization of new ideas and applications in plasmonics and nanoscale technologies.

References

Insight from wave patterns in fluids inspires a new scheme for designing periodic and aperiodic soft-matter crystals

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Quasicrystals are aperiodic crystals that readily form in intermetallic alloys, where they usually possess 5-fold or 10-fold symmetry, yet current research is exploring their formation in soft matter, where they typically exhibit 12-fold symmetry. Armed with insights from similar 12-fold patterns, called Faraday waves, that appear on the surfaces of vibrated fluids, a recent study published in Physical Review Letters sheds new light on how polymers and other macromolecules order in the plane. In a combined computational and theoretical study, Kobi Barkan and Ron Lifshitz from the School of Physics & Astronomy at Tel Aviv University, together with Michael Engel from the University of Michigan, have demonstrated a scheme to control the formation of periodic and aperiodic crystals made of clusters of molecules by designing the way the molecules interact. The central idea is mapping the frequencies of the vibrating fluid to length scales in the designed interaction between the molecules. Past research has established the existence of simple periodic cluster crystals, but with the new scheme it is now possible to induce the assembly of higher-symmetry patterns, including the 12-fold quasicrystals observed in experiments. The ability to control the self-assembly of periodic and aperiodic soft-matter crystals could contribute to the development of novel photonic or other applications based on self-assembled metamaterials.


Figure 1: Five cluster crystals that were assembled spontaneously in computer simulations using the new design scheme for the intermolecular interaction. Molecules are represented by red particles in the main figures, while the gray-scale figures in the corners display the corresponding Faraday-wave-like patterns that inspired the new design scheme. From left to right: stripes, 4-fold and 6-fold periodic crystals, and 10-fold and 12-fold quasicrystals. Reprinted with permission from Phys. Rev. Lett. 113 (2014) 098304.
Highly efficient, wide angle and broadband holograms using optical nano-antennas

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Since its inception by Gabor in the late 1940s\(^1\), holography has captured the public imagination as the key to genuine 3D projection with applications in medicine, design, and entertainment. Most contemporary computer generated holograms rely on transmitting light waves through a transparent medium of varying thickness or refractive index. These slight changes in the optical path translate to changes in the phase-front of the wave allowing, in principle, for the generation of beams with arbitrary profiles. Due to fabrication methods and shading effects the phase resolution of these elements is limited and the resulting holograms exhibit low efficiency and narrow angular coverage.

Nano-antennas are natural candidates for high efficient holography. In very recent years, researchers have demonstrated the use of coupled nano-antenna structures for controlling the optical phase of light\(^2\), and demonstrate a wide range of applications such as lensing and complex waveform generation. However, most of the studies focused on transmission mode, resulting in low efficiencies (i.e. the fraction of the impinging power which is channeled into the hologram).

In our work\(^3\) we demonstrate phase-front shaping and holography using patch-dipole nano-antennas. These elements are fabricated over a gold backplane reflector and a \(\text{SiO}_2\) buffer, yielding dramatic improvement in the hologram efficiency. Moreover, our design methodology which is based on optimization of the nano-antennas in groups rather than individually (as was done previously) reduces the power scattered into spurious beams and further improves the efficiency.

The strength of this approach was demonstrated by designing and fabricating an array of nano-antennas which generates a hologram, in our case the logo of Tel Aviv University, and projects it at wide angles of 20° and 45° relative to the impinging beam. We used the Gerchberg-Saxton\(^4\) algorithm to determine the required phase map and realized it by writing the appropriate antenna at each position using e-beam lithography.

The figure below shows the antenna design as well as an SEM image of the fabricated array, the experimental setup, and the resulting hologram. The efficiency of the hologram in the range of 1440 – 1640 nm exceeds 40% at both angles. Our approach is applicable to any wavelength range and can be used for generating an arbitrary, highly-efficient, omni-directional hologram. The next step is incorporating techniques to activate the antennas, allowing for dynamic holography and beam-steering.

Efficient particle accelerators are in the heart of various applications for high energy physics, medicine, material science, and more. Particularly, they can be utilized to generate bright, short duration and high intensity X-Ray and particle beams which can revolutionize the way researches investigate these fields. Nevertheless, contemporary RF based technologies, which are limited to ~100MV/m acceleration gradients, coerce devices lengths of tens and even thousands of meters for most high-end applications. This limits the implementation of these devices to few research centers world-wide. Hence, to enable widespread research, applicable for implementation in many existing facilities, revolutionary accelerator concepts are required.

Laser-driven particle accelerators provide efficient acceleration, potentially reducing the required device length to micrometer scales. Due to its transverse nature, the electric field of a laser pulse co-propagating with the particles cannot be utilized for their acceleration. Consequently, several techniques have been suggested to rotate the field and gain a synchronized component that can be used. Nonetheless, most of them are not very efficient for ultra-short pulse laser utilization, which is attractive for acceleration applications due to the very large electric fields which can be attained. The most efficient structure presented for this purpose consisted of a periodic dielectric structure, which was considered favorable over metallic structures due to metallic losses at optical wavelengths. However, metallic structures exhibiting plasmonic resonances can be utilized for compensating these losses and attaining a substantial acceleration.

The use of plasmonic metasurfaces for enhancing optical applications was studied extensively in the last decade. These structures can focus electro-magnetic energy into an ultra-small volume, resulting in a large enhancement of the local field. Furthermore, the field amplitude, phase, and polarization in their vicinity can be controlled as desired. A recent study in the nano-photonics group in Tel-Aviv University has suggested, for the first time, an efficient metasurfaces laser-driven accelerator (MLA) apparatus. Using a periodic structure consisting of a unique slot-patch unit cell (see figure), the suggested structure manipulates the field profile to yield efficient acceleration, reaching 11.6GV/m at 16fsec for relativistic particle acceleration. Furthermore, the design versatility of the suggested concept paves the way for researches from the plasmonic community to explore and suggest additional particle accelerators, e.g. for slower particle beams. This versatility, efficient ultra-short pulse operation and a high acceleration gradient, render the MLA a promising concept for future laser accelerators operating at the ultra-short pulse regime, thus constituting an important step towards cost-effective table-top devices.


Figure 1: MLA Structure; (a) Top view; (b) Unit cell structure [nm]; (c) Unit cell dimensions [nm]; (d) An SEM image of an MLA facet fabricated in TAU nano-center, red line - the normalized acceleration field at resonance as experienced by a relativistic particle with the maximally accelerating phase.
Prof. Dan Peer has received the Breakthrough Award in Inflammatory Bowel Diseases from the Kenneth Rainin Foundation.

Itai Epstein, from the research group of Prof. Adi Arie, has won the SPIE Optics and Photonics Education Scholarship, the KLA-Tencor Research excellence award, the David and Paulina Trozky Graduate Degree Award, and the Weinstein Signal Processing Award for Outstanding Student Paper.

Doron Bar-Lev, from the research group of Prof. Koby Scheuer, has been awarded the Ministry of Science and Technology travel scholarship.

Prof. Karen B. Avraham has received the Teva Founders Prize on Breakthroughs in “Discovery of new molecular mechanisms and targets that would lead to new therapeutic approaches”.

Gali Pichman, from the research group of Prof. Ehud Gazit and Dr. Michal Shuman from the research group of Dr. Tal Dvir, have won the Na’amat Scholarship.

Prof. Dan Peer and Prof. Rimona Margalit have received an award from the Untold News Awards on their groundbreaking development in cancer treatment.

Dr. Haim Suchowski from the school of Physics and Astronomy has received the prestigious ERC-StG grant for 2014-2019.

Prof. Noam Eliaz has received the Technical Achievement award from the NACE International.

Dr. Yoav Linzon graduated with his bachelor degree from the Technion, Israel Institute of Technology, in the program of applied physics and electrical engineering. He conducted his graduate studies at Tel Aviv University school of physics and astronomy, and received his PhD in 2009 for his research on ‘Propagation and interactions of waves in homogeneous, periodically modulated and locally modulated non-linear waveguides’, conducted under the supervision of Prof. Shimshon Bar-Ad. During his PhD studies, he worked on spatiotemporal solitons and their interactions among themselves and among structural defects. He also participated in the implementation of a setup for secure transmission of information in fibers using single-photon protocols. During April 2008 – April 2009 Dr. Linzon conducted a research at the University of Quebec in Montreal relating to magneto-optical phenomena.
Dr. Haim Suchowski, School of Physics and Astronomy

Dr. Suchowski received his PhD in 2011 from the Weizmann institute of Science, for his research on 'Spatio-temporal coherent control of nonlinear interactions', conducted under the supervision of Prof. Yaron Silberberg. In his PhD, he worked on quantum coherent control of atoms and molecules with ultra-short laser pulses, and analogous schemes in nonlinear optics. In July 2011 Dr. Suchowski joined the group of Prof. Xiang Zhang at The University of California at Berkeley as a postdoctoral associate, where he studied the application of micro- and nano-electromechanical resonators for sensitive vapor sensors and new optomechanical imaging systems. In October 2014 Dr. Suchowski joined the school of Mechanical engineering in the faculty of Engineering to establish the optomechanics research laboratory.

The Linzon group will develop novel nano- and micro-opto-electro-mechanical systems (NOEMS and MOEMS) for fundamental and applicative studies.
New equipment at the center

**Ion Milling System – AJA International, INC.**

A specially designed milling (dry etching) system suitable for substrates up to 6” in diameter for a wide range of process applications is expected to arrive to the MNCF labs soon. The system, designated for etching, and is capable of physically etching various materials, some not etch-able in other chemical or physical methods (e.g. metals, glasses, and ceramic compounds). The system utilizes an Ar ion source with a high current density which creates a broad ion beam directed at the substrate. The ions are accelerated into the beam with well-defined and controlled direction, due to the source remote location from the substrate. The ions are accelerated to the substrate and then are neutralized by electrons in the substrate proximity, physically sputtering the exposed areas on the substrate. The chuck, substrate holder, can be rotate and titled to allow milling in different angles. A vacuum load lock will enable keeping the main chamber in high vacuum. The system is expected to arrive to TAU during March 2015 and will be installed in the engineering clean room of MNCF. In the picture – the new system.

New faces at the Center

**Mickey Shenhar**

Michal (Mickey) Shenhar joined TAU Nanocenter in August 2014 to be the Nano center administrative director. Mickey joined TAU after working for Kenes International, as a registration and accommodation manager, organizing conventions in various locations around the world. Mickey holds a BA degree in Political Science and Geography from Bar Ilan University. She has an extensive experience in fiscal management after working in the finance department of Elad Group for several years and is already utilizing her experience in managing the Nano and MNCF budget, as well as organizing the XIN winter school and the Fred Chaoul 10th annual workshop, both will take place in February 2015.

**Yuval Kupitz**

Yuval Kupitz joined the Nano center in May 2014 to manage the Center’s international collaborations, in particular to lead the activity of the recently-inaugurated XIN center, the joint collaboration with Tsinghua University. Yuval holds a master degree in Business Management and Industrial Chemistry and an additional master degree in Biochemistry from the Hebrew University in Jerusalem. Yuval worked as the Technology business development manager of the Biotechnology National Institute of Ben Gurion University, where he founded new biotechnology startup companies, facilitated research and service agreements, and more. Between the years 1999 and 2010 he worked for Hadasit Research Services in Jerusalem as a business development manager and became the VP of IP there. Yuval has extensive background in business development and he will be involved in the center’s commercialization efforts.
A ceremony for Intel Electronics was held, January 12, 2015, at TAU. Intel Electronics has donated expensive equipment to TAU from Fab18 which closed down in Qiryat Gat. Ms. Maxin Fassberg, the President of Intel Israel and the Vice President of the Global Intel company has received an honor certificate from TAU President, Prof. Yosef Klafter.

The Fred Chaoul 10th Annual workshop will be held in Ha’Goshrim resort hotel during 15-17 of February 2015. The key note speaker will be Prof. Miles Padget from the University of Glasgow. More information can be found on the Nano website.

The XIN Center International Winter School on Nano-Photonics will take place during February 1-5, 2015 at Tel-Aviv University. Over a hundred participants from TAU, Tsinghua University as well as other Israeli and International Universities are expected. Novel topics in nano-photonics will be presented and discussed including: transformation optics, meta-materials & meta-surfaces, nano-antennas and plasmonics, quantum dots, beam shaping and nano-imaging.

Tel Aviv University and Tsinghua University XIN Center conducted the 2014 Autumn Innovation Forum during October 23-25, 2014 at Tsinghua University, Beijing, China. Top academics and students from both universities, entrepreneurs, investors and major government, business and industry leaders from China and Israel joined together to discuss the universities new initiatives in the nano-field. The forum also included early stage technologies evaluation for further development under the XIN Center and initiated some student exchanges between collaborating PIs.

Dreidels for Hanukah, carved in glass by the Laser Micromachining, operated by Dr. Yigal Lilach