Controlled Orientations of Neighboring Tetracene Units by Mixed Self-Assembled Monolayers on Gold Nanoclusters for High-Yield and Long-Lived Triplet Excited States through Singlet Fission

Although tetracene (Tc) is well-known as a good candidate for singlet fission (SF), the number of high-yield and long-lived triplet excited states through SF is extremely limited because of the relative acceleration of the reverse triplet-triplet annihilation (TTA) considering the energy matching between a singlet and two triplet states. Systematic control of electronic interactions between two neighboring units using conventional covalent linkages and molecular assembly methods to optimize these kinetic processes is quite difficult because of the complicated synthesis and random orientations. In this study, we propose a novel supramolecular strategy utilizing mixed self-assembled monolayers (SAMs) with two different chain lengths. Specifically, mixed Tc-SAMs on gold nanoclusters, which are prepared using Tc-modified heterodisulfides with two different chain lengths, attain high-yield SF (ΦSF ≈ 90%) and individual triplet yields (ΦT ≈ 160%). The obtained ΦSF is the highest value among Tc derivatives in homogeneous solution to the best of our knowledge.

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Contributors: Saegusa, T., Sakai, H., Nagashima, H., Kobori, Y., Tkachenko, N. V., Hasobe, T.
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An efficient auxin-inducible degron system with low basal degradation in human cells

Auxin-inducible degron technology allows rapid and controlled protein depletion. However, basal degradation without auxin and inefficient auxin-inducible depletion have limited its utility. We have identified a potent auxin-inducible degron system composed of auxin receptor F-box protein AtAFB2 and short degron miniIAA7. The system showed minimal basal degradation and enabled rapid auxin-inducible depletion of endogenous human transmembrane, cytoplasmic and nuclear proteins in 1 h with robust functional phenotypes.

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Contributors: Li, S., Prasanna, X., Salo, V. T., Vattulainen, I., Ikonen, E.
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Behavior of the DPH fluorescence probe in membranes perturbed by drugs

1,6-Diphenyl-1,3,5-hexatriene (DPH) is one of the most commonly used fluorescent probes to study dynamical and structural properties of lipid bilayers and cellular membranes via measuring steady-state or time-resolved fluorescence anisotropy. In this study, we present a limitation in the use of DPH to predict the order of lipid acyl chains when the lipid bilayer is doped with itraconazole (ITZ), an antifungal drug. Our steady-state fluorescence anisotropy measurements showed a significant decrease in fluorescence anisotropy of DPH embedded in the ITZ-containing membrane, suggesting a substantial increase in membrane fluidity, which indirectly indicates a decrease in the order of the hydrocarbon chains. This result or its interpretation is in disagreement with the fluorescence recovery after photobleaching measurements and molecular dynamics (MD) simulation data. The results of these experiments and calculations indicate an increase in the hydrocarbon chain order. The MD simulations of the bilayer containing both ITZ and DPH provide explanations for these observations. Apparently, in the presence of the drug, the DPH molecules are pushed deeper into the hydrophobic membrane core below the lipid double bonds, and the probe predominately adopts the orientation of the ITZ molecules that is parallel to the membrane surface, instead of orienting parallel to the lipid acyl chains. For this reason, DPH anisotropy provides information related to the less ordered central region of the membrane rather than reporting the properties of the upper segments of the lipid acyl chains.

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Influence of ions to modulate hydrazone and oxime reaction kinetics to obtain dynamically cross-linked hyaluronic acid hydrogels

Dynamic covalent chemistry forming hydrazone and oxime linkages is attractive due to its simplicity, selectivity and compatibility under aqueous conditions. However, the low reaction rate at physiological pH hampers its use in biomedical applications. Herein, we present different monovalent and bivalent aqueous salt solutions as bio-friendly, non-toxic catalysts which can drive the hydrazone and oxime reactions with excellent efficacy at physiological pH. Direct comparison of hydrazone and oxime reactions using a small molecule model, without any salt catalysis, indicated that oxime formation is 6-times faster than hydrazone formation. Addition of different salts (NaCl, NaBr, KCl, LiCl, $LiClO_4$, Na_2SO_4, $MgCl_2$ and $CaCl_2$) accelerated the pseudo-first-order reaction kinetics by ~1.2-4.9-fold for acylhydrazone formation and by ~1.5-6.9-fold for oxime formation, in a concentration-dependent manner. We further explored the potential of such catalysts to develop acylhydrazone and oxime cross-linked hyaluronic acid (HA) hydrogels with different physicochemical properties without changing the degree of chemical modification. Analogous to the small molecule model system, the addition of monovalent and divalent salts as catalysts significantly reduced the gelling time. The gelling time for the acylhydrazone cross-linked HA-hydrogel (1.6 wt%) could be reduced from 300 min to 1.2 min by adding 100 mM $CaCl_2$, while that for the oxime cross-linked HA-hydrogel (1.2 wt%) could be reduced from 68 min to 1.1 min by adding 50 mM $CaCl_2$. This difference in the gelling time also resulted in hydrogels with differential swelling properties as measured after 24 h. Our results are the first to demonstrate the use of salts, for catalyzing hydrogel formation under physiologically relevant conditions.

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Contributors: Wang, S., Nawale, G. N., Oommen, O. P., Hilborn, J., Varghese, O. P.
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Characterisation and in vitro and in vivo evaluation of supercritical-CO2-foamed β-TCP/PLCL composites for bone applications
Most synthetic bone grafts are either hard and brittle ceramics or paste-like materials that differ in applicability from the gold standard autologous bone graft, which restricts their widespread use. Therefore, the aim of the study was to develop an elastic, highly porous and biodegradable β-tricalciumphosphate/poly(L-lactide-co-ε-caprolactone) (β-TCP/PLCL) composite for bone applications using supercritical CO2 foaming. Ability to support osteogenic differentiation was tested in human adipose stem cell (hASC) culture for 21 d. Biocompatibility was evaluated for 24 weeks in a rabbit femur-defect model. Foamed composites had a high ceramic content (50 wt%) and porosity (65-67 %). After 50 % compression, in an aqueous environment at 37 °C, tested samples returned to 95 % of their original height. Hydrolytic degradation of β-TCP/PLCL composite, during the 24-week follow-up, was very similar to that of porous PLCL scaffold both in vitro and in vivo. Osteogenic differentiation of hASCs was demonstrated by alkaline phosphatase activity analysis, alizarin red staining, soluble collagen analysis, immunocytochemical staining and qRT-PCR. In vitro, hASCs formed a pronounced mineralised collagen matrix. A rabbit femur defect model confirmed biocompatibility of the composite. According to histological Masson-Goldner's trichrome staining and micro-computed tomography, β-TCP/PLCL composite did not elicit infection, formation of fibrous capsule or cysts. Finally, native bone tissue at 4 weeks was already able to grow on and in the β-TCP/PLCL composite. The elastic and highly porous β-TCP/PLCL composite is a promising bone substitute because it is osteoconductive and easy-to-use and mould intraoperatively.

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Contributors: Pitkänen, S., Paakinaho, K., Pihlman, H., Ahola, N., Hannula, M., Asikainen, S., Manninen, M., Morelius, M., Keränen, P., Hyttinen, J., Kellomäki, M., Laitinen-Vapaavuori, O., Miettinen, S.
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An architectural understanding of natural sway frequencies in trees

The relationship between form and function in trees is the subject of a longstanding debate in forest ecology and provides the basis for theories concerning forest ecosystem structure and metabolism. Trees interact with the wind in a dynamic manner and exhibit natural sway frequencies and damping processes that are important in understanding wind damage. Tree-wind dynamics are related to tree architecture, but this relationship is not well understood. We present a comprehensive view of natural sway frequencies in trees by compiling a dataset of field measurement spanning conifers and broadleaves, tropical and temperate forests. The field data show that a cantilever beam approximation adequately predicts the fundamental frequency of conifers, but not that of broadleaf trees. We also use structurally detailed tree dynamics simulations to test fundamental assumptions underpinning models of natural frequencies in trees. We model the dynamic properties of greater than 1000 trees using a finite-element approach based on accurate three-dimensional model trees derived from terrestrial laser scanning data. We show that (1) residual variation, the variation not explained by the cantilever beam approximation, in fundamental frequencies of broadleaf trees is driven by their architecture; (2) slender trees behave like a simple pendulum, with a single natural frequency dominating their motion, which makes them vulnerable to wind damage and (3) the presence of leaves decreases both the fundamental frequency and the damping ratio. These findings demonstrate the value of new three-dimensional measurements for understanding wind impacts on trees and suggest new directions for improving our understanding of tree dynamics from conifer plantations to natural forests.

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Organisations: Computing Sciences, University of Oxford, SCION, University of Connecticut, Delft University of Technology, Wageningen University and Research Centre, University of Massachusetts Amherst, National Parks Board, University of Melbourne, Oregon State University, Universiteit Gent, National Physical Laboratory, University College London, NERC National Centre for Earth Observation (NCEO), 16 Center for International Forestry Research (CIFOR), Swedish University of Agricultural Sciences, INRA
Contributors: Jackson, T., Shenkin, A., Moore, J., Bunce, A., van Emmerik, T., Kane, B., Burcham, D., James, K., Selker, J., Calders, K., Origo, N., Disney, M., Burt, A., Wilkes, P., Raumonen, P., Gonzalez de Tanago Menaca, J., Lau, A., Herold, M., Goodman, R. C., Fourcaud, T., Malhi, Y.
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Methods for simultaneous robot-world-hand–eye calibration: A comparative study

In this paper, we propose two novel methods for robot-world-hand-eye calibration and provide a comparative analysis against six state-of-the-art methods. We examine the calibration problem from two alternative geometrical interpretations, called 'hand-eye' and 'robot-world-hand-eye', respectively. The study analyses the effects of specifying the objective function as pose error or reprojection error minimization problem. We provide three real and three simulated datasets with rendered images as part of the study. In addition, we propose a robotic arm error modeling approach to be used along with the simulated datasets for generating a realistic response. The tests on simulated data are performed in both ideal cases and with pseudo-realistic robotic arm pose and visual noise. Our methods show significant improvement and

robustness on many metrics in various scenarios compared to state-of-the-art methods.

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Connection of Collimation, Asymmetric Beaming, and Independent Transmission-Reflection Processes in Concentric-Groove Gratings Supporting Spoof Surface Plasmons

Transmission through subwavelength apertures enables separation of the incidence half-space and the exit half-space, which leads to that the spatial distribution of the field in the latter is not affected by the distribution in the former. The distribution in the exit half-space is mainly determined by the properties of surface plasmons (SPs) at the exit-side interface. In this paper, for the microwave structures with one-side concentric corrugations around a single annular hole, we demonstrate the possible connections between asymmetric transmission in the beaming regime and collimation of the waves incident at different angles, which can be considered as two sides of the same phenomenon occurring due to the common effect of such a separation and the radiation shaping effect being possible due to the spoof SPs at the corrugated exit interface. Collimation manifests itself in that the waves incident at different angles from a wide range contribute to the single outgoing beam so that a far-zone observer cannot distinguish between the contributions of different angles of arrival. Asymmetry in transmission manifests itself in that the spatial shaping of radiation (beaming) in the exit half-space appears only for one of the two opposite incidence directions. Moreover, even in the structures with the same corrugations on both sides, i.e., without asymmetric transmission, spatial separation of two wave processes, e.g., two symmetric or asymmetric collimation processes, can be obtained for a wide range of nonzero angles of incidence.

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Organisations: Photonics, Bilkent University, KU Leuven, Adam Mickiewicz University
Contributors: Habib, M., Serebryannikov, A. E., Caglayan, H., Vandenbosch, G. A., Ozbay, E.
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Bioimpedance Sensor Array for Long-Term Monitoring of Wound Healing from Beneath the Primary Dressings and Controlled Formation of H_2O_2 Using Low-Intensity Direct Current

Chronic wounds impose a significant financial burden for the healthcare system. Currently, assessment and monitoring of hard-to-heal wounds are often based on visual means and measuring the size of the wound. The primary wound dressings must be removed before assessment can be done. We have developed a quasi-monopolar bioimpedance-measurement-based method and a measurement system to determine the status of wound healing. The objective of this study was to demonstrate that with an appropriate setup, long-term monitoring of wound healing from beneath the primary dressings is feasible. The developed multielectrode sensor array was applied on the wound area and left under the primary dressings for 142 h. The impedance of the wounds and the surrounding intact skin area was measured regularly during the study at 150 Hz, 300 Hz, 1 kHz, and 5 kHz frequencies. At the end of the follow-up period, the wound impedance had reached the impedance of the intact skin at the higher frequencies and increased significantly at the lowest frequencies. The measurement frequency affected the measurement sensitivity in wound monitoring. The skin impedance remained stable over the measurement period. The sensor array also enabled the administration of periodical low-intensity direct current (LIDC) stimulation in order to create an antimicrobial environment across the wound area via the controlled formation of hydrogen peroxide (H2O2).

General information

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Organisations: BioMediTech, Turku University Hospital, Kaarinantie 700, Åbo Akademi University
Contributors: Kekonen, A., Bergelin, M., Johansson, M., Kumar Joon, N., Bobacka, J., Viik, J.
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Alpha radiation-induced luminescence by am-241 in aqueous nitric acid solution

When exposed to air, alpha particles cause the production of light by exciting the molecules surrounding them. This light, the radioluminescence, is indicative of the presence of alpha radiation, thus allowing for the optical sensing of alpha radiation from distances larger than the few centimeters an alpha particle can travel in air. While the mechanics of radioluminescence in air and other gas compositions is relatively well understood, the same cannot be said about the radioluminescence properties of liquids. Better understanding of the radioluminescence properties of liquids is essential to design methods for the detection of radioactively contaminated liquids by optical means. In this article, we provide radioluminescence images of Am-241 dissolved in aqueous nitric acid (HNO_3) solution and present the recorded radioluminescence spectrum with a maximum between and, and a steep decrease at the short wavelength side of the maximum. The shape of the spectrum resembles a luminescence process rather than Cerenkov light, bremsstrahlung, or other mechanisms with broadband emission. We show that the amount of light produced is about 150 times smaller compared to that of the same amount of Am-241 in air. The light production in the liquid is evenly distributed throughout the sample volume with a slight increase on the surface of the liquid. The radioluminescence intensity is shown to scale linearly with the Am-241 concentration and not be affected by the HNO_3concentration.

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Contributors: Kerst, T., Malmbeck, R., lal Banik, N. L., Toivonen, J.
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Research output: Contribution to journal › Article › Scientific › peer-review

Positioning information privacy in intelligent transportation systems: An overview and future perspective
Today, the Intelligent Transportation Systems (ITS) are already in deep integration phase all over the world. One of the most significant enablers for ITS are vehicle positioning and tracking techniques. Worldwide integration of ITS employing Dedicated Short Range Communications (DSRC) and European standard for vehicular communication, known as ETSI ITS-G5, brings a variety of options to improve the positioning in areas where GPS connectivity is lacking precision. Utilization of the ready infrastructure, next-generation cellular 5G networks, and surrounding electronic devices together with conventional positioning techniques could become the solution to improve the overall ITS operation in vehicle-to-everything (V2X) communication scenario. Nonetheless, effective and secure communication protocols between the vehicle and roadside units should be both analyzed and improved in terms of potential attacks on the transmitted positioning-related data. In particular, said information might be misused or stolen at the infrastructure side conventionally assumed to be trusted. In this paper, we first survey different methods of vehicle positioning, which is followed by an overview of potential attacks on ITS systems. Next, we propose potential improvements allowing mutual authentication between the vehicle and infrastructure aiming at improving positioning data privacy. Finally, we propose a vision on the development and standardization aspects of such systems.

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Contributors: Ometov, A., Bezzateev, S., Davydov, V., Shchesniak, A., Masek, P., Lohan, E. S., Koucheryavy, Y.
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Iterative unsupervised domain adaptation for generalized cell detection from brightfield z-stacks

Background: Cell counting from cell cultures is required in multiple biological and biomedical research applications. Especially, accurate brightfield-based cell counting methods are needed for cell growth analysis. With deep learning, cells can be detected with high accuracy, but manually annotated training data is required. We propose a method for cell detection that requires annotated training data for one cell line only, and generalizes to other, unseen cell lines. Results: Training a deep learning model with one cell line only can provide accurate detections for similar unseen cell lines (domains). However, if the new domain is very dissimilar from training domain, high precision but lower recall is achieved. Generalization capabilities of the model can be improved with training data transformations, but only to a certain degree. To further improve the detection accuracy of unseen domains, we propose iterative unsupervised domain adaptation method. Predictions of unseen cell lines with high precision enable automatic generation of training data, which is used to train the model together with parts of the previously used annotated training data. We used U-Net-based model, and three consecutive focal planes from brightfield image z-stacks. We trained the model initially with PC-3 cell line, and used LNCaP, BT-474 and 22Rv1 cell lines as target domains for domain adaptation. Highest improvement in accuracy was achieved for 22Rv1 cells. F_1-score after supervised training was only 0.65, but after unsupervised domain adaptation we achieved a score of 0.84. Mean accuracy for target domains was 0.87, with mean improvement of 16 percent. Conclusions: With our method for generalized cell detection, we can train a model that accurately detects different cell lines from brightfield images. A new cell line can be introduced to the model without a single manual annotation, and after iterative domain adaptation the model is ready to detect these cells with high accuracy.

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Contributors: Liimatainen, K., Kananen, L., Latonen, L., Ruusuvuori, P.
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Regulation of asymmetries in the kinetics and protein numbers of bacterial gene expression

Genetic circuits change the status quo of cellular processes when their protein numbers cross thresholds. We investigate the regulation of RNA and protein threshold crossing propensities in Escherichia coli. From in vivo single RNA time-lapse microscopy data from multiple promoters, mutants, induction schemes and media, we study the asymmetry and tailedness (quantified by the skewness and kurtosis, respectively) of the distributions of time intervals between transcription events. We find that higher thresholds can be reached by increasing the skewness and kurtosis, which is shown to be achievable without affecting mean and coefficient of variation, by regulating the rate-limiting steps in transcription initiation. Also, they

propagate to the skewness and kurtosis of the distributions of protein expression levels in cell populations. The results suggest that the asymmetry and tailedness of RNA and protein numbers in cell populations, by controlling the propensity for threshold crossing, and due to being sequence dependent and subject to regulation, may be key regulatory variables of decision-making processes in E. coli.

General information

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Contributors: Startceva, S., Kandavalli, V. K., Visa, A., Ribeiro, A. S.
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Advances in Human Stem Cell-Derived Neuronal Cell Culturing and Analysis

This chapter provides an overview of the current stage of human in vitro functional neuronal cultures, their biological application areas, and modalities to analyze their behavior. During the last 10 years, this research area has changed from being practically non-existent to one that is facing high expectations. Here, we present a case study as a comprehensive short history of this process based on extensive studies conducted at NeuroGroup (University of Tampere) and Computational Biophysics and Imaging Group (Tampere University of Technology), ranging from the differentiation and culturing of human pluripotent stem cell (hPSC)-derived neuronal networks to their electrophysiological analysis. After an introduction to neuronal differentiation in hPSCs, we review our work on their functionality and approaches for extending cultures from 2D to 3D systems. Thereafter, we discuss our target applications in neuronal developmental modeling, toxicology, drug screening, and disease modeling. The development of signal analysis methods was required due to the unique functional and developmental properties of hPSC-derived neuronal cells and networks, which separate them from their much-used rodent counterparts. Accordingly, a line of microelectrode array (MEA) signal analysis methods was developed. This work included the development of action potential spike detection methods, entropy-based methods and additional methods for burst detection and quantification, joint analysis of spikes and bursts to analyze the spike waveform compositions of bursts, assessment methods for network synchronization, and computational simulations of synapses and neuronal networks.

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Organisations: Research group: Computational Biophysics and Imaging Group, BioMediTech, NeuroGroup, Danish Research Institute of Translational Neuroscience - DANDRITE, Aarhus Universitet, Department of Biomedicine, Tampere University
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SCIP: a single-cell image processor toolbox

Summary: Each cell is a phenotypically unique individual that is influenced by internal and external processes, operating in parallel. To characterize the dynamics of cellular processes one needs to observe many individual cells from multiple points of view and over time, so as to identify commonalities and variability. With this aim, we engineered a software, 'SCIP', to analyze multi-modal, multi-process, time-lapse microscopy morphological and functional images. SCIP is capable of automatic and/or manually corrected segmentation of cells and lineages, automatic alignment of different microscopy channels, as well as detect, count and characterize fluorescent spots (such as RNA tagged by MS2-GFP), nucleoids, Z rings, Min system, inclusion bodies, undefined structures, etc. The results can be exported into *mat files and all results can be jointly analyzed, to allow studying not only each feature and process individually, but also find potential relationships. While we exemplify its use on Escherichia coli, many of its functionalities are expected to be of use in analyzing other prokaryotes and eukaryotic cells as well. We expect SCIP to facilitate the finding of relationships between cellular processes, from small-scale (e.g. gene expression) to large-scale (e.g. cell division), in single cells and cell lineages. Availability and implementation: http://www.ca3-uninova.org/project_scip. Supplementary information: Supplementary data are available at Bioinformatics online.

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Organisations: Faculty of Biomedical Sciences and Engineering, Campus FCT-UNL
Contributors: Martins, L., Neeli-Venkata, R., Oliveira, S. M., Häkkinen, A., Ribeiro, A. S., Fonseca, J. M.
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M2M Communication Assessment in Energy-Harvesting and Wake-Up Radio Assisted Scenarios Using Practical Components

Techniques for wireless energy harvesting (WEH) are emerging as a fascinating set of solutions to extend the lifetime of energy-constrained wireless networks, and are commonly regarded as a key functional technique for almost perpetual communications. For example, with WEH technology, wireless devices are able to harvest energy from different light sources or Radio Frequency (RF) signals broadcast by ambient or dedicated wireless transmitters to support their operation and communications capabilities. WEH technology will have increasingly wider range of use in upcoming applications such as wireless sensor networks, Machine-to-Machine (M2M) communications, and the Internet of Things. In this paper, the usability and fundamental limits of joint RF and solar cell or photovoltaic harvesting based M2M communication systems are studied and presented. The derived theoretical bounds are in essence based on the Shannon capacity theorem, combined with selected propagation loss models, assumed additional link nonidealities, diversity processing, as well as the given energy harvesting and storage capabilities. Fundamental performance limits and available capacity of the communicating link are derived and analyzed, together with extensive numerical results evaluated in different practical scenarios, including realistic implementation losses and state-of-the-art printed supercapacitor performance figures with voltage doubler-based voltage regulator. In particular, low power sensor type communication applications using passive and semi-passive wake-up radio (WuR) are addressed in the study. The presented analysis principles and results establish clear feasibility regions and performance bounds for wireless energy harvesting based low rate M2M communications in the future IoT networks.

General information

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Contributors: Rinne, J., Keskinen, J., Berger, P. R., Lupo, D., Valkama, M.
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Research output: Contribution to journal › Article › Scientific › peer-review

Molecular-Scale Ligand Effects in Small Gold-Thiolate Nanoclusters

Because of the small size and large surface area of thiolate-protected Au nanoclusters (NCs), the protecting ligands are expected to play a substantial role in modulating the structure and properties, particularly in the solution phase. However, little is known on how thiolate ligands explicitly modulate the structural properties of the NCs at atomic level, even though this information is critical for predicting the performance of Au NCs in application settings including as a catalyst interacting with small molecules and as a sensor interacting with biomolecular systems. Here, we report a combined experimental and theoretical study, using synchrotron X-ray spectroscopy and quantum mechanics/molecular mechanics simulations, that investigates how the protecting ligands impact the structure and properties of small $Au_{18}(SR)_{14}$ NCs. Two representative ligand types, smaller aliphatic cyclohexanethiolate and larger hydrophilic glutathione, are selected, and their structures are followed experimentally in both solid and solution phases. It was found that cyclohexanethiolate ligands are significantly perturbed by toluene solvent molecules, resulting in structural changes that cause disorder on the surface of $Au_{18}(SR)_{14}$ NCs. In particular, large surface cavities in the ligand shell are created by interactions between toluene and cyclohexanethiolate. The appearance of these small molecule-accessible sites on the NC surface demonstrates the ability of Au NCs to act as a catalyst for organic phase reactions. In contrast, glutathione ligands encapsulate the Au NC core via intermolecular interactions, minimizing structural changes caused by interactions with water molecules. The much better protection from glutathione ligands imparts a rigidified surface and ligand structure,

making the NCs desirable for biomedical applications due to the high stability and also offering a structural-based explanation for the enhanced photoluminescence often reported for glutathione-protected Au NCs.

General information

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Organisations: Physics, Dalhousie University, Universitat Autonoma de Barcelona, Spain, Catalan Institute for Research and Advanced Studies (ICREA), Carnegie Mellon University, National University of Singapore, Norwegian Univ. of Sci. and Technol.
Contributors: Chevrier, D. M., Raich, L., Rovira, C., Das, A., Luo, Z., Yao, Q., Chatt, A., Xie, J., Jin, R., Akola, J., Zhang, P.
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Research output: Contribution to journal › Article › Scientific › peer-review

How to minimize dye-induced perturbations while studying biomembrane structure and dynamics: PEG linkers as a rational alternative

Organic dye-tagged lipid analogs are essential for many fluorescence-based investigations of complex membrane structures, especially when using advanced microscopy approaches. However, lipid analogs may interfere with membrane structure and dynamics, and it is not obvious that the properties of lipid analogs would match those of non-labeled host lipids. In this work, we bridged atomistic simulations with super-resolution imaging experiments and biomimetic membranes to assess the performance of commonly used sphingomyelin-based lipid analogs. The objective was to compare, on equal footing, the relative strengths and weaknesses of acyl chain labeling, headgroup labeling, and labeling based on poly-ethyl-glycol (PEG) linkers in determining biomembrane properties. We observed that the most appropriate strategy to minimize dye-induced membrane perturbations and to allow consideration of Brownian-like diffusion in liquid-ordered membrane environments is to decouple the dye from a membrane by a PEG linker attached to a lipid headgroup. Yet, while the use of PEG linkers may sound a rational and even an obvious approach to explore membrane dynamics, the results also suggest that the dyes exploiting PEG linkers interfere with molecular interactions and their dynamics. Overall, the results highlight the great care needed when using fluorescent lipid analogs, in particular accurate controls.

General information

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Organisations: Physics, University of Helsinki, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Max Planck Institute of Molecular Cell Biology and Genetics, Weatherall Institute of Molecular Medicine, Friedrich-Schiller-University Jena, Leibniz Institute of Photonic Technology e.V., MEMPHYS - Center for Biomembrane Physics (www.memphys.dk), Laboratory of Physics
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Alzheimer's disease and alpha-synuclein pathology in the olfactory bulbs of infants, children, teens and adults ≤40 years in Metropolitan Mexico City. APOE4 carriers at higher risk of suicide accelerate their olfactory bulb pathology

There is growing evidence that air pollution is a risk factor for a number of neurodegenerative diseases, most notably Alzheimer's (AD) and Parkinson's (PD). It is generally assumed that the pathology of these diseases arises only later in life and commonly begins within olfactory eloquent pathways prior to the onset of the classical clinical symptoms. The present study demonstrates that chronic exposure to high levels of air pollution results in AD- and PD-related pathology within the olfactory bulbs of children and relatively young adults ages 11 months to 40 years. The olfactory bulbs (OBs) of 179 residents of highly polluted Metropolitan Mexico City (MMC) were evaluated for AD- and alpha-synuclein-related pathology. Even in toddlers, hyperphosphorylated tau (hTau) and Lewy neurites (LN) were identified in the OBs. By the second decade, 84% of the bulbs exhibited hTau (48/57), 68% LNs and vascular amyloid (39/57) and 36% (21/57) diffuse amyloid plaques. OB active endothelial phagocytosis of red blood cell fragments containing combustion-derived nanoparticles (CDNPs) and the neurovascular unit damage were associated with myelinated and unmyelinated axonal damage. OB hTau neurites were associated mostly with pretangle stages 1a and 1b in subjects ≤ 20 years of age, strongly suggesting olfactory deficits could potentially be an early guide of AD pretangle subcortical and cortical hTau. APOE4 versus APOE3 carriers were 6–13 times more likely to exhibit OB vascular amyloid, neuronal amyloid accumulation, alpha-synuclein aggregates, hTau neurofibrillary tangles, and neurites. Remarkably, APOE4 carriers were 4.57 times more likely than non-carriers to die by suicide. The present findings, along with previous data that over a third of clinically healthy MMC teens and young adults exhibit low scores on an odor identification test, support the concept that olfactory testing may aid in identifying young people at high risk for neurodegenerative diseases. Moreover, results strongly support early neuroprotective interventions in fine particulate matter ($PM_{2.5}$) and CDNP's exposed individuals ≤ 20 years of age, and the critical need for air pollution control.

General information

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Organisations: Physics, The University of Montana, Universidad del Valle de México, Instituto Nacional de Pediatría, Lake Erie College of Osteopathic Medicine, Boise State University, Department of Electrical Engineering, University of Pennsylvania
Contributors: Calderón-Garcidueñas, L., González-Maciel, A., Reynoso-Robles, R., Kulesza, R. J., Mukherjee, P. S., Torres-Jardón, R., Rönkkö, T., Doty, R. L.
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Source: Scopus

Source ID: 85048709486
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Comparative analysis of tissue reconstruction algorithms for 3D histology

Motivation: Digital pathology enables new approaches that expand beyond storage, visualization or analysis of histological samples in digital format. One novel opportunity is 3D histology, where a three-dimensional reconstruction of the sample is formed computationally based on serial tissue sections. This allows examining tissue architecture in 3D, for example, for diagnostic purposes. Importantly, 3D histology enables joint mapping of cellular morphology with spatially resolved omics data in the true 3D context of the tissue at microscopic resolution. Several algorithms have been proposed for the reconstruction task, but a quantitative comparison of their accuracy is lacking. Results: We developed a benchmarking framework to evaluate the accuracy of several free and commercial 3D reconstruction methods using two whole slide image datasets. The results provide a solid basis for further development and application of 3D histology algorithms and indicate that methods capable of compensating for local tissue deformation are superior to simpler approaches.

General information

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Contributors: Kartasalo, K., Latonen, L., Vihinen, J., Visakorpi, T., Nykter, M., Ruusuvuori, P.
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Physiologically-relevant levels of sphingomyelin, but not GM1, induces a β-sheet-rich structure in the amyloid-β(1-42) monomer

To resolve the contribution of ceramide-containing lipids to the aggregation of the amyloid-β protein into β-sheet rich toxic oligomers, we employed molecular dynamics simulations to study the effect of cholesterol-containing bilayers comprised of POPC (70% POPC, and 30% cholesterol) and physiologically relevant concentrations of sphingomyelin (SM) (30% SM, 40% POPC, and 30% cholesterol), and the GM1 ganglioside (5% GM1, 70% POPC, and 25% cholesterol). The increased bilayer rigidity provided by SM (and to a lesser degree, GM1) reduced the interactions between the SM-enriched bilayer and the N-terminus of Aβ42 (and also residues Ser26, Asn27, and Lys28), which facilitated the formation of a β-sheet in the normally disordered N-terminal region. Aβ42 remained anchored to the SM-enriched bilayer through hydrogen bonds with the side chain of Arg5. With β-sheets in the at the N and C termini, the structure of Aβ42 in the sphingomyelin-enriched bilayer most resembles β-sheet-rich structures found in higher-ordered Aβ fibrils. Conversely, when bound to a bilayer comprised of 5% GM1, the conformation remained similar to that observed in the absence of GM1, with Aβ42 only making contact with one or two GM1 molecules. This article is part of a Special Issue entitled: Protein Aggregation and Misfolding at the Cell Membrane Interface edited by Ayyalusamy Ramamoorthy.

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Organisations: Physics, Forschungszentrum Jülich (FZJ), Masaryk University, Heinrich Heine University Düsseldorf
Contributors: Owen, M. C., Kulig, W., Poojari, C., Rog, T., Strodel, B.
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Acquiring respiration rate from photoplethysmographic signal by recursive bayesian tracking of intrinsic modes in time-frequency spectra
Respiration rate (RR) provides useful information for assessing the status of a patient. We propose RR estimation based on photoplethysmography (PPG) because the blood perfusion dynamics are known to carry information on breathing, as respiration-induced modulations in the PPG signal. We studied the use of amplitude variability of transmittance mode finger PPG signal in RR estimation by comparing four time-frequency (TF) representation methods of the signal cascaded with a particle filter. The TF methods compared were short-time Fourier transform (STFT) and three types of synchrosqueezing methods. The public VORTAL database was used in this study. The results indicate that the advanced frequency reallocation methods based on synchrosqueezing approach may present improvement over linear methods, such as STFT. The best results were achieved using wavelet synchrosqueezing transform, having a mean absolute error and median error of 2.33 and 1.15 breaths per minute, respectively. Synchrosqueezing methods were generally more accurate than STFT on most of the subjects when particle filtering was applied. While TF analysis combined with particle filtering is a promising alternative for real-time estimation of RR, artefacts and non-respiration-related frequency components remain problematic and impose requirements for further studies in the areas of signal processing algorithms an PPG instrumentation.

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Contributors: Pirhonen, M., Peltokangas, M., Vehkaoja, A.
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Evaluation of dry electrodes in canine heart rate monitoring
The functionality of three dry electrocardiogram electrode constructions was evaluated by measuring canine heart rate during four different behaviors: Standing, sitting, lying and walking. The testing was repeated (n = 9) in each of the 36 scenarios with three dogs. Two of the electrodes were constructed with spring-loaded test pins while the third electrode was a molded polymer electrode with Ag/AgCl coating. During the measurement, a specifically designed harness was used to attach the electrodes to the dogs. The performance of the electrodes was evaluated and compared in terms of heartbeat detection coverage. The effect on the respective heart rate coverage was studied by computing the heart rate coverage from the measured electrocardiogram signal using a pattern-matching algorithm to extract the R-peaks and further the beat-to-beat heart rate. The results show that the overall coverage ratios regarding the electrodes varied between 45-95% in four different activity modes. The lowest coverage was for lying and walking and the highest was for standing and sitting.

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Contributors: Virtanen, J., Somppi, S., Törnqvist, H., Jeyhani, V., Fiedler, P., Gizatdinova, Y., Majaranta, P., Väätäjä, H., Cardó, A. V., Lekkala, J., Tuukkanen, S., Surakka, V., Vainio, O., Vehkaoja, A.
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Photo-antimicrobial efficacy of zinc complexes of porphyrin and phthalocyanine activated by inexpensive consumer LED lamp
The properties and antimicrobial efficacies of zinc complexes of tetrakis(N-methylpyridinium-4-yl) tetraiodide porphyrin and tetrakis(N-methylpyridinium-4-yl) tetraiodide phthalocyanine impregnated to paper were evaluated. Photo-inactivation of microbes using inexpensive consumer light-emitting diode lamp was assessed on surface of dyed papers. Antimicrobial experiments of phthalocyanine-dyed paper by live cell assessment through colony forming units counting demonstrated 3.72 and 4.01 log reduction against Escherichia coli (E. coli) and Acinetobacter baylyi (A. baylyi) respectively after 1 h of illumination with 35 mW/cm^2 light. The porphyrin-dyed paper exhibited 1.66 and 2.01 log reduction in colony forming units against E. coli and A. baylyi respectively after 1 h exposure with 4 mW/cm^2 light. Both dyed papers were photo-stable after 64 h of continuous exposure with 42 mW/cm^2 light, while phthalocyanine-dyed paper exhibited superior leaching stability in phosphate-buffered saline.

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Non-intersecting leaf insertion algorithm for tree structure models
We present an algorithm and an implementation to insert broadleaves or needleleaves into a quantitative structure model according to an arbitrary distribution, and a data structure to store the required information efficiently. A structure model contains the geometry and branching structure of a tree. The purpose of this work is to offer a tool for making more realistic simulations of tree models with leaves, particularly for tree models developed from terrestrial laser scanning (TLS) measurements. We demonstrate leaf insertion using cylinder-based structure models, but the associated software implementation is written in a way that enables the easy use of other types of structure models. Distributions controlling leaf location, size and angles as well as the shape of individual leaves are user definable, allowing any type of distribution. The leaf generation process consist of two stages, the first of which generates individual leaf geometry following the input distributions, while in the other stage intersections are prevented by carrying out transformations when required. Initial testing was carried out on English oak trees to demonstrate the approach and to assess the required computational resources. Depending on the size and complexity of the tree, leaf generation takes between 6 and 18 min. Various leaf area density distributions were defined, and the resulting leaf covers were compared with manual leaf harvesting measurements. The results are not conclusive, but they show great potential for the method. In the future, if our method is demonstrated to work well for TLS data from multiple tree types, the approach is likely to be very useful for three-dimensional structure and radiative transfer simulation applications, including remote sensing, ecology and forestry, among others.

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Contributors: Åkerblom, M., Raumonen, P., Casella, E., Disney, M. I., Danson, F. M., Gaulton, R., Schofield, L. A., Kaasalainen, M.
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Research output: Contribution to journal › Article › Scientific › peer-review

Uncertainty in multispectral lidar signals caused by incidence angle effects

Multispectral terrestrial laser scanning (TLS) is an emerging technology. Several manufacturers already offer commercial dual or three wavelength airborne laser scanners, while multispectral TLS is still carried out mainly with research instruments. Many of these research efforts have focused on the study of vegetation. The aim of this paper is to study the uncertainty of the measurement of spectral indices of vegetation with multispectral lidar. Using two spectral indices as examples, we find that the uncertainty is due to systematic errors caused by the wavelength dependency of laser incidence angle effects. This finding is empirical, and the error cannot be removed by modelling or instrument modification. The discovery and study of these effects has been enabled by hyperspectral and multispectral TLS, and it has become a subject of active research within the past few years. We summarize the most recent studies on multi-wavelength incidence angle effects and present new results on the effect of specular reflection from the leaf surface, and the surface structure, which have been suggested to play a key role. We also discuss the consequences to the measurement of spectral indices with multispectral TLS, and a possible correction scheme using a synthetic laser footprint.

General information

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Organisations: Mathematics, Department of Navigation and Positioning, FGI
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Weighing trees with lasers: Advances, challenges and opportunities

Terrestrial laser scanning (TLS) is providing exciting new ways to quantify tree and forest structure, particularly above-ground biomass (AGB). We show how TLS can address some of the key uncertainties and limitations of current approaches to estimating AGB based on empirical allometric scaling equations (ASEs) that underpin all large-scale estimates of AGB. TLS provides extremely detailed non-destructive measurements of tree form independent of tree size and shape. We show examples of three-dimensional (3D) TLS measurements from various tropical and temperate forests and describe how the resulting TLS point clouds can be used to produce quantitative 3D models of branch and trunk size, shape and distribution. These models can drastically improve estimates of AGB, provide new, improved large-scale ASEs, and deliver insights into a range of fundamental tree properties related to structure. Large quantities of detailed measurements of individual 3D tree structure also have the potential to open new and exciting avenues of research in areas where difficulties of measurement have until now prevented statistical approaches to detecting and understanding

underlying patterns of scaling, form and function. We discuss these opportunities and some of the challenges that remain to be overcome to enable wider adoption of TLS methods.

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Soft hydrazone crosslinked hyaluronan- and alginate-based hydrogels as 3D supportive matrices for human pluripotent stem cell-derived neuronal cells
Regenerative medicine, especially cell therapy combined with a supportive biomaterial scaffold, is considered to be a potential treatment for various deficits in humans. Here, we have produced and investigated the detailed properties of injectable hydrazone crosslinked hyaluronan-polyvinyl alcohol (HA-PVA) and alginate-polyvinyl alcohol (AL-PVA) hydrogels to be used as a supportive biomaterial for 3D neural cell cultures. To the best of our knowledge, this is the first time the polymerization and properties of hydrazone crosslinked AL-PVA hydrogel have been reported. The effect of the degree of substitution and molecular weight of the polymer components as well as the polymer concentration of the hydrogel on the swelling, degradation and mechanical properties of the hydrogels is reported. Furthermore, we studied the effect of the above parameters on the growth of human pluripotent stem cell-derived neuronal cells. The most neural cell supportive HA-PVA hydrogel was composed of high molecular weight HA component with brain-mimicking mechanical properties and decreased polymer concentration. AL-PVA hydrogel, with stiffness quite similar to brain tissue, was also shown to be similarly supportive. Neuronal spreading and 3D network formation was enhanced inside the softest hydrogels.

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Organisations: Faculty of Biomedical Sciences and Engineering, Research group: Biomaterials and Tissue Engineering Group, BioMediTech Institute and Faculty of Medicine and Life Sciences
Contributors: Karvinen, J., Joki, T., Ylä-Outinen, L., Koivisto, J. T., Narkilahti, S., Kellomäki, M.
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Research output: Contribution to journal › Article › Scientific › peer-review

An activity recognition framework deploying the random forest classifier and a single optical heart rate monitoring and triaxial accelerometer wrist-band

Wrist-worn sensors have better compliance for activity monitoring compared to hip, waist, ankle or chest positions. However, wrist-worn activity monitoring is challenging due to the wide degree of freedom for the hand movements, as well as similarity of hand movements in different activities such as varying intensities of cycling. To strengthen the ability of wrist-worn sensors in detecting human activities more accurately, motion signals can be complemented by physiological signals such as optical heart rate (HR) based on photoplethysmography. In this paper, an activity monitoring framework using an optical HR sensor and a triaxial wrist-worn accelerometer is presented. We investigated a range of daily life activities including sitting, standing, household activities and stationary cycling with two intensities. A random forest (RF) classifier was exploited to detect these activities based on the wrist motions and optical HR. The highest overall accuracy of 89.6 ± 3.9% was achieved with a forest of a size of 64 trees and 13-s signal segments with 90% overlap. Removing the HR-derived features decreased the classification accuracy of high-intensity cycling by almost 7%, but did not affect the classification accuracies of other activities. A feature reduction utilizing the feature importance scores of RF was also carried out and resulted in a shrunken feature set of only 21 features. The overall accuracy of the classification utilizing the shrunken feature set was 89.4 ± 4.2%, which is almost equivalent to the above-mentioned peak overall accuracy.

General information

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Molecular mechanism for inhibition of twinfilin by phosphoinositides

Membrane phosphoinositides control organization and dynamics of the actin cytoskeleton by regulating the activities of several key actin-binding proteins. Twinfilin is an evolutionarily conserved protein that contributes to cytoskeletal dynamics by interacting with actin monomers, filaments, and the heterodimeric capping protein. Twinfilin also binds phosphoinositides, which inhibit its interactions with actin, but the underlying mechanism has remained unknown. Here, we show that the high-affinity binding site of twinfilin for phosphoinositides is located at the C-terminal tail region, whereas the two actin-depolymerizing factor (ADF)/cofilin-like ADF homology domains of twinfilin bind phosphoinositides only with low affinity. Mutagenesis and biochemical experiments combined with atomistic molecular dynamics simulations reveal that the C-terminal tail of twinfilin interacts with membranes through a multivalent electrostatic interaction with a preference toward phosphatidylinositol 3,5-bisphosphate ($PI(3,5)P_2$), $PI(4,5)P_2$, and $PI(3,4,5)P_3$. This initial interaction places the actin-binding ADF homology domains of twinfilin in close proximity to the membrane and subsequently promotes their association with the membrane, thus leading to inhibition of the actin interactions. In support of this model, a twinfilin mutant lacking the C-terminal tail inhibits actin filament assembly in a phosphoinositide-insensitive manner. Our mutagenesis data also reveal that the phosphoinositide- and capping protein- binding sites overlap in the C-terminal tail of twinfilin, suggesting that phosphoinositide binding additionally inhibits the interactions of twinfilin with the heterodimeric capping protein. The results demonstrate that the conserved C-terminal tail of twinfilin is a multifunctional binding motif, which is crucial for interaction with the heterodimeric capping protein and for tethering twinfilin to phosphoinositide-rich membranes.

General information

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Organisations: Physics, University of Helsinki Institute of Biotechnology, Laboratory of Physics, MEMPHYS, University of Southern Denmark, University of Helsinki
Contributors: Hakala, M., Kalimeri, M., Enkavi, G., Vattulainen, I., Lappalainen, P.
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A Bioscreening Technique for Ultraviolet Irradiation Protective Natural Substances

Ultraviolet radiation (UV-R) causes genotoxic and aging effects on skin, and sunscreens are used to alleviate the damage. However, sunscreens contain synthetic shielding agents that can cause harmful effects in the environment. Nature-derived substances may have potential as replacement materials for the harmful sunscreen chemicals. However, screening of a broad range of samples is tedious, and often requires a separate genotoxicity assessment. We describe a simple microplate technique for the screening of UV protective substances using a recombinant Escherichia coli biosensor. Both absorbance-based and bioactivity-based shields can be detected with simultaneous information about the sample genotoxicity. With this technique, a controversial sunscreen compound, oxybenzone offers physical or absorbance-based shield but appears genotoxic at higher concentrations (3.3 mg/mL). We also demonstrate that pine needle extract (Pi_{Ne}) shields the biosensor from UV-R in a dose-dependent manner without showing genotoxicity. The physical shield of 5 mg/mL Pi_{Ne} was similar to that of one of the most common UV-shielding compound TiO_2 concentration 0.80 mg/mL. The bioactivity-based shield of Pi_{Ne} also reaches the extent of the physical shield with the highest concentration (3.3 mg/mL). We conclude that our technique is suitable in detecting the UV-shielding potential of natural substances, and gives simultaneous information on genotoxicity.

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Contributors: Tienaho, J., Poikulainen, E., Sarjala, T., Muilu-Mäkelä, R., Santala, V., Karp, M.
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INT=keb,"Poikulainen, Emmi"
Source: Scopus
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Research output: Contribution to journal › Article › Scientific › peer-review

Bioactive glass induced osteogenic differentiation of human adipose stem cells is dependent on cell attachment mechanism and mitogen-activated protein kinases
Bioactive glasses (BaGs) are widely utilised in bone tissue engineering (TE) but the molecular response of cells to BaGs is poorly understood. To elucidate the mechanisms of cell attachment to BaGs and BaG-induced early osteogenic differentiation, we cultured human adipose stem cells (hASCs) on discs of two silica-based BaGs S53P4 (23.0 Na_2O-20.0 CaO-4.0 P_2O_5-53.0 SiO_2 (wt-%)) and 1-06 (5.9 Na_2O-12.0 K_2O-5.3 MgO-22.6 CaO-4.0 P_2O_5-0.2 B_2O_3-50.0 SiO_2) in the absence of osteogenic supplements. Both BaGs induced early osteogenic differentiation by increasing alkaline phosphatase activity (ALP) and the expression of osteogenic marker genes RUNX2a and OSTERIX. Based on ALP activity, the slower reacting 1-06 glass was a stronger osteoinducer. Regarding the cell attachment, cells cultured on BaGs had enhanced integrinβ1 and vinculin production, and mature focal adhesions were smaller but more dispersed than on cell culture plastic (polystyrene). Focal adhesion kinase (FAK), extracellular signal-regulated kinase (ERK1/2) and c-Jun N-terminal kinase (JNK)-induced c-Jun phosphorylations were upregulated by glass contact. Moreover, the BaG-stimulated osteoinduction was significantly reduced by FAK and mitogen-activated protein kinase (MAPK) inhibitors, indicating an important role for FAK and MAPKs in the BaG-induced early osteogenic commitment of hASCs. Upon indirect insert culture, the ions released from the BaG discs could not reproduce the observed cellular changes, which highlighted the role of direct cell-BaG interactions in the osteopotential of BaGs. These findings gave valuable insight into the mechanism of BaG-induced osteogenic differentiation and therefore provided knowledge to aid the future design of new functional biomaterials to meet the increasing demand for clinical bone TE treatments.

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Organisations: Faculty of Biomedical Sciences and Engineering, The National Science Centre, Poland, Tampere University Hospital, Johan Gadolin Process Chemistry Centre, Abo Akademi University, University of Tampere
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EXT="Ojansivu, M."
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Effect of N/S ratio on anoxic thiosulfate oxidation in a fluidized bed reactor: Experimental and artificial neural network model analysis

Anoxic thiosulfate ($S_2O_3^{2-}$) oxidation using autotrophic denitrification by a mixed culture of nitrate reducing, sulfur oxidizing bacteria (NR-SOB) was studied in a fluidized bed reactor (FBR). The long-term performance of the FBR was evaluated for 306 days at three nitrogen-to-sulfur (N/S) molar ratios (0.5, 0.3 and 0.1) and a hydraulic retention time (HRT) of 5 h. $S_2O_3^{2-}$ removal efficiencies >99% were obtained at a N/S ratio of 0.5 and a $S_2O_3^{2-}$ and nitrate (NO_3^-) loading rate of 820 (±84) mg S-$S_2O_3^{2-}$ L^{-1} d^{-1} and 173 (±10) mg N-NO_3^- L^{-1} d^{-1}, respectively. The $S_2O_3^{2-}$ removal efficiency decreased to 76% and 26% at N/S ratios of 0.3 and 0.1, respectively, and recovered to 80% within 3 days after increasing the N/S ratio from 0.1 back to 0.5. The highest observed half-saturation (K_s) and inhibition (K_I) constants of the biofilm-grown NR-SOB obtained from batch cultivations were 172 and 800 mg S-$S_2O_3^{2-}$ L^{-1}, respectively. Thiobacilus denitrificans was the dominant microorganism in the FBR. Artificial neural network modeling successfully predicted $S_2O_3^{2-}$ and NO_3^- removal efficiencies and SO_4^{2-} production in the FBR. Additionally, results from the sensitivity analysis showed that the effluent pH was the most influential parameter affecting the $S_2O_3^{2-}$ removal efficiency.

General information
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Organisations: Chemistry and Bioengineering, Hydraulic and Environmental Engineering (IHE) Inst. for Water Education, University of Cassino and Southern Lazio, ENEA/CREATE/Università Degli Studi Napoli Federico II
Contributors: Khanongnuch, R., Di Capua, F., Lakaniemi, A., Rene, E. R., Lens, P. N.
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Gloriosa superba Mediated Synthesis of Platinum and Palladium Nanoparticles for Induction of Apoptosis in Breast Cancer

Green chemistry approaches for designing therapeutically significant nanomedicine have gained considerable attention in the past decade. Herein, we report for the first time on anticancer potential of phytogenic platinum nanoparticles (PtNPs)

and palladium nanoparticles (PdNPs) using a medicinal plant Gloriosa superba tuber extract (GSTE). The synthesis of the nanoparticles was completed within 5 hours at 100°C which was confirmed by development of dark brown and black colour for PtNPs and PdNPs, respectively, along with enhancement of the peak intensity in the UV-visible spectra. High-resolution transmission electron microscopy (HRTEM) showed that the monodispersed spherical nanoparticles were within a size range below 10 nm. Energy dispersive spectra (EDS) confirmed the elemental composition, while dynamic light scattering (DLS) helped to evaluate the hydrodynamic size of the particles. Anticancer activity against MCF-7 (human breast adenocarcinoma) cell lines was evaluated using MTT assay, flow cytometry, and confocal microscopy. PtNPs and PdNPs showed 49.65 ± 1.99% and 36.26 ± 0.91% of anticancer activity. Induction of apoptosis was most predominant in the underlying mechanism which was rationalized by externalization of phosphatidyl serine and membrane blebbing. These findings support the efficiency of phytogenic fabrication of nanoscale platinum and palladium drugs for management and therapy against breast cancer.

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Organisations: Faculty of Biomedical Sciences and Engineering, Modern College of Arts, Savitribai Phule Pune University , Indian Institute of Science, Bangalore, Department of Biomedical Sciences and Engineering, Defense Institute of Advanced Technology, Indian Institute of Technology Bombay, RK University
Contributors: Rokade, S. S., Joshi, K. A., Mahajan, K., Patil, S., Tomar, G., Dubal, D. S., Parihar, V. S., Kitture, R., Bellare, J. R., Ghosh, S.
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Azopolymer photopatterning for directional control of angiogenesis

Understanding cellular behavior in response to microenvironmental stimuli is central to tissue engineering. An increasing number of reports emphasize the high sensitivity of cells to the physical characteristics of the surrounding milieu and in particular, topographical cues. In this work, we investigated the influence of dynamic topographic signal presentation on sprout formation and the possibility to obtain a space–time control over sprouting directionality without growth factors, in order to investigate the contribution of just topography in the angiogenic process. To test our hypothesis, we employed a 3D angiogenesis assay based on the use of spheroids derived from human umbilical vein endothelial cells (HUVECs). We then modulated the in situ presentation of topographical cues during early-stage angiogenesis through real-time photopatterning of an azobenzene-containing polymer, poly (Disperse Red 1 methacrylate) (pDR1m). Pattern inscription on the polymer surface was made using the focused laser of a confocal microscope. We demonstrate that during early-stage angiogenesis, sprouts followed the pattern direction, while spheroid cores acquired a polarized shape. These findings confirmed that sprout directionality was influenced by the photo-inscribed pattern, probably through contact guidance of leader cells, thus validating the proposed platform as a valuable tool for understanding complex processes involved in cell-topography interactions in multicellular systems. Statement of Significance The complex relationship between endothelial cells and the surrounding environment that leads to formation of a newly formed vascular network during tissue repair is currently unknown. We have developed an innovative in vitro platform to study these mechanisms in a space and time controlled fashion simulating what happens during regeneration. In particular, we combine a “smart” surface, namely a polymer film, with a three-dimensional living cell aggregate. The polymer is activated by light through which we can design a path to guide cells toward the formation of a new vessel. Our work lies at the intersection of stimuli-responsive biointerfaces and cell biology and may be particularly inspiring for those interested in designing biomaterial surface related to angiogenesis.

General information

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Contributors: Fedele, C., De Gregorio, M., Netti, P. A., Cavalli, S., Attanasio, C.
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Comparison of different coating techniques on the properties of FucoPol films
Plasma deposition, liquid flame spray (LFS) and atomic layer deposition (ALD) were used to form inorganic coatings in new exopolysaccharide (FucoPol) biodegradable films. Coated films were characterised in terms of surface, optical and barrier properties in order to evaluate their potential use in food packaging. FucoPol films presented dense and homogeneous surface with instant water contact angle of 95. Plasma deposition of perfluorohexane (PFH) on FucoPol surface has not shown significant improvement in the hydrophobic behaviour over the time. The FucoPol coating of SiO_2 nanoparticles deposited by LFS and plasma deposition of PFH have shown higher instant water contact angle (135°) caused by coating surface roughness, but this hydrophobic behaviour was not stable over time. FucoPol films coated only with TiO_2 deposited by ALD and combination of that with plasma deposition of PFH have shown stable water contact angle during time (90 and 115, respectively), transparency in the same order of magnitude and significantly lower permeability to water vapour (3.45×10^{-11} mol/m s Pa and 3.45×10^{-11} mol/m s Pa when compared to uncoated films with 5.32×10^{-11} mol/m s Pa). Moreover, films coated with TiO_2-PFH have also shown a permeability to oxygen of 1.70×10^{-16} molm/m^2s Pa which is 67% lower than uncoated films.

General information
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MoE publication type: A1 Journal article-refereed
Organisations: Physics, Research group: Aerosol Synthesis, Campus FCT-UNL, Centre for Molecular Medicine Norway, Nordic European Molecular Biology Laboratory Partnership, University of Oslo, SP Technical Research Institute of Sweden, Universidade de Lisboa
Contributors: Ferreira, A. R., Haapanen, J., Mäkelä, J. M., Bratvold, J. E., Nilsen, O., Tuominen, M., Alves, V. D., Coelhoso, I. M.
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Inhibition of Aβ Amyloid Growth and Toxicity by Silybins: The Crucial Role of Stereochemistry

The self-assembling of the amyloid β (Aβ) peptide into neurotoxic aggregates is considered a central event in the pathogenesis of Alzheimer's disease (AD). Based on the "amyloid hypothesis", many efforts have been devoted to designing molecules able to halt disease progression by inhibiting Aβ self-assembly. Here, we combine biophysical (ThT assays, TEM and AFM imaging), biochemical (WB and ESI-MS), and computational (all-atom molecular dynamics) techniques to investigate the capacity of four optically pure components of the natural product silymarin (silybin A, silybin B, 2,3-dehydrosilybin A, 2,3-dehydrosilybin B) to inhibit Aβ aggregation. Despite TEM analysis demonstrated that all the four investigated flavonoids prevent the formation of mature fibrils, ThT assays, WB and AFM investigations showed that only silybin B was able to halt the growth of small-sized protofibrils thus promoting the formation of large, amorphous aggregates. Molecular dynamics (MD) simulations indicated that silybin B interacts mainly with the C-terminal hydrophobic segment ^{35}MVGGVV^{40} of Aβ40. Consequently to silybin B binding, the peptide conformation remains predominantly unstructured along all the simulations. By contrast, silybin A interacts preferentially with the segments ^{17}LVFF^{20} and ^{27}NKGAII^{32} of Aβ40 which shows a high tendency to form bend, turn, and β-sheet conformation in and around these two domains. Both 2,3-dehydrosilybin enantiomers bind preferentially the segment ^{17}LVFF^{20} but lead to the formation of different small-sized, ThT-positive Aβ aggregates. Finally, in vivo studies in a transgenic Caenorhabditis elegans strain expressing human Aβ indicated that silybin B is the most effective of the four compounds in counteracting Aβ proteotoxicity. This study underscores the pivotal role of stereochemistry in determining the neuroprotective potential of silybins and points to silybin B as a promising lead compound for further development in anti-AD therapeutics.

General information

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MoE publication type: A1 Journal article-refereed
Organisations: Physics, Centro S3, ENEA/CREATE/Università Degli Studi Napoli Federico II, STMicroelectronics, Università degli Studi di Catania, IRCCS-Istituto di Ricerche Farmacologiche Mario Negri
Contributors: Sciacca, M. F., Romanucci, V., Zarrelli, A., Monaco, I., Lolicato, F., Spinella, N., Galati, C., Grasso, G., D'Urso, L., Romeo, M., Diomede, L., Salmona, M., Bongiorno, C., Di Fabio, G., La Rosa, C., Milardi, D.
Number of pages: 12
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Publication information

Journal: ACS Chemical Neuroscience
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Original language: English
ASJC Scopus subject areas: Physiology, Biochemistry, Cognitive Neuroscience, Cell Biology
Keywords: Alzheimer's disease, Chiral drugs, natural compounds, neurodegeneration, neuroprotection
DOIs:

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Source ID: 85027418392
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sgnesR: An R package for simulating gene expression data from an underlying real gene network structure considering delay parameters

Background: sgnesR (Stochastic Gene Network Expression Simulator in R) is an R package that provides an interface to simulate gene expression data from a given gene network using the stochastic simulation algorithm (SSA). The package allows various options for delay parameters and can easily included in reactions for promoter delay, RNA delay and Protein delay. A user can tune these parameters to model various types of reactions within a cell. As examples, we present two network models to generate expression profiles. We also demonstrated the inference of networks and the evaluation of association measure of edge and non-edge components from the generated expression profiles. Results: The purpose of sgnesR is to enable an easy to use and a quick implementation for generating realistic gene expression data from biologically relevant networks that can be user selected. Conclusions: sgnesR is freely available for academic use. The R package has been tested for R 3.2.0 under Linux, Windows and Mac OS X.

General information

Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: BioMediTech, Faculty of Biomedical Sciences and Engineering, Signal Processing, Research group: Laboratory of Biosystem Dynamics-LBD, Research group: Computational Systems Biology, Research group: Computational Medicine and Statistical Learning Laboratory (CMSL), Harvard T.H. Chan School of Public Health, Harvard School of Public Health, Mathematics and Operations Research
Contributors: Tripathi, S., Lloyd-Price, J., Ribeiro, A., Yli-Harja, O., Dehmer, M., Emmert-Streib, F.
Publication date: 4 Jul 2017
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Publication information
Journal: BMC Bioinformatics
Volume: 18
Issue number: 1
Article number: 325
ISSN (Print): 1471-2105
Ratings:

Scopus rating (2017): CiteScore 2.49 SJR 1.479 SNIP 0.896
Original language: English
ASJC Scopus subject areas: Structural Biology, Biochemistry, Molecular Biology, Computer Science Applications, Applied Mathematics
Keywords: Gene expression data, Gene network, Simulation
Electronic versions:

sgnesR
DOIs:

10.1186/s12859-017-1731-8
URLs:

http://urn.fi/URN:NBN:fi:tty-201708041653
Source: Scopus
Source ID: 85021637056
Research output: Contribution to journal › Article › Scientific › peer-review

Dynamics of a True Moving Bed separation process: Linear model identification and advanced process control
The control of Simulated Moving Bed (SMB) units is challenging due to their complex dynamic behaviour and the difficulty of measuring their main properties. Furthermore, for the SMB units, the transfer function identification when the unit is operating at its optimal point is not easy to be done through the usual way. This work presents the development of a novel strategy to identify transfer functions of TMB/SMB and its application on classical linear model predictive controllers (MPC). However, for the process in study, due its unique dynamics, only the identification of the linear model is not enough to solve its control problem. Therefore, it is proposed a modification in the MPC prediction, that consists in a strategy based on a switching system where the most adequate transfer function is employed in the controller to overcome the problems related with the process dynamic behaviour. The results show that the used methodology enables the easy identification of transfer functions at the process optimal operating point and that the MPC can control the process in both the servo and regulator problem cases. It is also showed that the transfer function identified can be applied in the control of a SMB unit with four columns, under its optimal conditions.

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MoE publication type: A1 Journal article-refereed
Organisations: Automation and Hydraulic Engineering, Research area: Information Systems in Automation
Contributors: Nogueira, I. B., Ribeiro, A. M., Martins, M. A., Rodrigues, A. E., Koivisto, H., Loureiro, J. M.
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Journal: Journal of Chromatography A
Volume: 1504
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Ratings:

Scopus rating (2017): CiteScore 3.81 SJR 1.378 SNIP 1.23
Original language: English
ASJC Scopus subject areas: Analytical Chemistry, Biochemistry, Organic Chemistry
Keywords: Enantiomers separation, Model predictive control, Process transfer function, Simulated moving bed
DOIs:

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Source: Scopus
Source ID: 85019248239
Research output: Contribution to journal › Article › Scientific › peer-review

Calcium Assists Dopamine Release by Preventing Aggregation on the Inner Leaflet of Presynaptic Vesicles

In this study, the dopamine-lipid bilayer interactions were probed with three physiologically relevant ion compositions using atomistic molecular dynamics simulations and free energy calculations. The in silico results indicate that calcium is able to decrease significantly the binding of dopamine to a neutral (zwitterionic) phosphatidylcholine lipid bilayer model mimicking the inner leaflet of a presynaptic vesicle. We argue that the observed calcium-induced effect is likely in crucial role in the neurotransmitter release from the presynaptic vesicles docked in the active zone of nerve terminals. The inner leaflets of presynaptic vesicles, which are responsible for releasing neurotransmitters into the synaptic cleft, are mainly composed of neutral lipids such as phosphatidylcholine and phosphatidylethanolamine. The neutrality of the lipid head group region, enhanced by a low pH level, should limit membrane aggregation of transmitters. In addition, the simulations suggest that the high calcium levels inside presynaptic vesicles prevent even the most lipophilic transmitters such as dopamine from adhering to the inner leaflet surface, thus rendering unhindered neurotransmitter release feasible.

General information

Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Physics, Research group: Biological Physics and Soft Matter, Structural Bioinformatics Laboratory, Abo Akad Univ, Abo Akademi University, Dept Phys, University of Helsinki, MEMPHYS, University of Southern Denmark
Contributors: Mokkila, S., Postila, P. A., Rissanen, S., Juhola, H., Vattulainen, I., Róg, T.
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Original language: English
ASJC Scopus subject areas: Physiology, Biochemistry, Cognitive Neuroscience, Cell Biology
Keywords: binding free energy, dopamine, molecular dynamics simulations, neurotransmitter release, phosphatidylcholine , presynaptic vesicle, Synaptic neurotransmission
DOIs:

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Bibliographical note

INT=fys,"Mokkila, Sini"
EXT="Postila, Pekka A."
Source: Scopus
Source ID: 85021076435
Research output: Contribution to journal › Article › Scientific › peer-review

Long-chain GM1 gangliosides alter transmembrane domain registration through interdigitation

Extracellular and cytosolic leaflets in cellular membranes are distinctly different in lipid composition, yet they contribute together to signaling across the membranes. Here we consider a mechanism based on long-chain gangliosides for coupling the extracellular and cytosolic membrane leaflets together. Based on atomistic molecular dynamics simulations, we find that long-chain GM1 in the extracellular leaflet exhibits a strong tendency to protrude into the opposing bilayer leaflet. This interdigitation modulates the order in the cytosolic monolayer and thereby strengthens the interaction and coupling across a membrane. Coarse-grained simulations probing longer time scales in large membrane systems indicate that GM1 in the extracellular leaflet modulates the phase behavior in the cytosolic monolayer. While short-chain GM1 maintains phase-symmetric bilayers with a strong membrane registration effect, the situation is altered with long-chain GM1. Here, the significant interdigitation induced by long-chain GM1 modulates the behavior in the cytosolic GM1-free leaflet, weakening and slowing down the membrane registration process. The observed physical interaction mechanism provides a possible means to mediate or foster transmembrane communication associated with signal transduction.

General information

Publication status: Published
MoE publication type: A1 Journal article-refereed

Organisations: Research area: Computational Physics, Physics, Research group: Biological Physics and Soft Matter, University of Helsinki, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Ludwig Maximilian University, MEMPHYS - Centre for Biomembrane Physics, University of Southern Denmark
Contributors: Manna, M., Javanainen, M., Martinez-Seara Monne, H., Gabius, H., Rog, T., Vattulainen, I.
Number of pages: 9
Pages: 870-878
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Peer-reviewed: Yes

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Volume: 1859
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Scopus rating (2017): CiteScore 3.64 SJR 1.495 SNIP 1.113
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ASJC Scopus subject areas: Biophysics, Biochemistry, Cell Biology
Keywords: cholesterol, computer simulations, Glycosphingolipid, membrane domain, membrane registry, molecular dynamics
Electronic versions:

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URLs:

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Source: Scopus
Source ID: 85012110513
Research output: Contribution to journal › Article › Scientific › peer-review

Tunable Plasmonic Silver Nanodomes for Surface-Enhanced Raman Scattering
Surface-enhanced Raman scattering (SERS) is an emerging analytical method used in biological and non-biological structure characterization. Since the nanostructure plasmonic properties is a significant factor for SERS performance, nanostructure fabrication with tunable plasmonic properties are crucial in SERS studies. In this study, a novel method for fabrication of tunable plasmonic silver nanodomes (AgNDs) is presented. The convective-assembly method is preferred for the deposition of latex particles uniformly on a regular glass slide and used as a template for polydimethylsiloxane (PDMS) to prepare nanovoids on a PDMS surface. The obtained nanovoids on the PDMS are used as a mold for AgNDs fabrication. The nanovoids are filled with Ag deposition by the electrochemical method to obtain metallic AgNDs. Scanning electron microscopy (SEM) and atomic force microscopy (AFM) are used for characterization of the structural properties of all fabricated AgNDs. The optical properties of AgNDs are characterized with the evaluation of SERS activity of 4-aminothiphonel and rhodamine 6G. In addition to experimental characterizations, the finite difference time domain (FDTD) method is used for the theoretical plasmonic properties calculation of the AgNDs. The experimental and theoretical results show that the SERS performance of AgNDs is strongly dependent on the heights and diameters of the AgNDs.

General information
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MoE publication type: A1 Journal article-refereed
Organisations: Gaziantep University, Bingöl University, Bilkent University
Contributors: Kahraman, M., Ozbay, A., Yuksel, H., Solmaz, R., Demir, B., Caglayan, H.
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Journal: Plasmonics
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Scopus rating (2017): CiteScore 2.13 SJR 0.679 SNIP 0.805
Original language: English
ASJC Scopus subject areas: Biotechnology, Biophysics, Biochemistry
Keywords: Electrochemical deposition, FDTD method, Plasmonic, SERS, Silver Nanodomes, Tunable
DOIs:

10.1007/s11468-017-0573-6

Bibliographical note
EXT="Caglayan, Humeyra"
Source: Scopus
Source ID: 85017133474
Research output: Contribution to journal › Article › Scientific › peer-review

Hexaphyrin as a Potential Theranostic Dye for Photothermal Therapy and ^{19}F Magnetic Resonance Imaging

Two features of meso-Aryl-substituted expanded porphyrins suggest suitability as theranostic agents. They have excellent absorption in near infrared (NIR) region, and they offer the possibility of introduction of multiple fluorine atoms at structurally equivalent positions. Here, hexaphyrin (hexa) was synthesized from 2,6-bis(trifluoromethyl)-4-formyl benzoate and pyrrole and evaluated as a novel expanded porphyrin with the above features. Under NIR illumination hexa showed intense photothermal and weak photodynamic effects, which were most likely due to its low excited states, close to singlet oxygen. The sustained photothermal effect caused ablation of cancer cells more effectively than the photodynamic effect of indocyanine green (a clinical dye). In addition, hexa showed potential for use in the visualization of tumors by ^{19}F magnetic resonance imaging (MRI), because of the multiple fluorine atoms. Our results strongly support the utility of expanded porphyrins as theranostic agents in both photothermal therapy and ^{19}F MRI.

General information
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MoE publication type: A1 Journal article-refereed
Organisations: Chemistry and Bioengineering, Research group: Chemistry & Advanced Materials, Kyoto Women's University, Toyama Prefectural University
Contributors: Higashino, T., Nakatsuji, H., Fukuda, R., Okamoto, H., Imai, H., Matsuda, T., Tochio, H., Shirakawa, M., Tkachenko, N. V., Hashida, M., Murakami, T., Imahori, H.
Number of pages: 9
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Journal: ChemBioChem
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Original language: English
ASJC Scopus subject areas: Biochemistry, Molecular Medicine, Molecular Biology, Organic Chemistry
Keywords: expanded porphyrin, fluorine, MRI, NMR spectroscopy, photochemistry, theranostics
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Source ID: 85016610793
Research output: Contribution to journal › Article › Scientific › peer-review

Calcium Directly Regulates Phosphatidylinositol 4,5-Bisphosphate Headgroup Conformation and Recognition

The orchestrated recognition of phosphoinositides and concomitant intracellular release of Ca^{2+} is pivotal to almost every aspect of cellular processes, including membrane homeostasis, cell division and growth, vesicle trafficking, as well as secretion. Although Ca^{2+} is known to directly impact phosphoinositide clustering, little is known about the molecular basis for this or its significance in cellular signaling. Here, we study the direct interaction of Ca^{2+} with phosphatidylinositol 4,5-bisphosphate ($PI(4,5)P_2$), the main lipid marker of the plasma membrane. Electrokinetic potential measurements of $PI(4,5)P_2$ containing liposomes reveal that Ca^{2+} as well as Mg^{2+} reduce the zeta potential of liposomes to nearly background levels of pure phosphatidylcholine membranes. Strikingly, lipid recognition by the default $PI(4,5)P_2$ lipid sensor, phospholipase C delta 1 pleckstrin homology domain (PLC δ1-PH), is completely inhibited in the presence of Ca^{2+}, while Mg^{2+} has no effect with 100 nm liposomes and modest effect with giant unilamellar vesicles. Consistent with biochemical data, vibrational sum frequency spectroscopy and atomistic molecular dynamics simulations reveal how Ca^{2+} binding to the $PI(4,5)P_2$ headgroup and carbonyl regions leads to confined lipid headgroup tilting and conformational rearrangements. We rationalize these findings by the ability of calcium to block a highly specific interaction between PLC δ1-PH and $PI(4,5)P_2$, encoded within the conformational properties of the lipid itself. Our studies demonstrate the possibility that switchable phosphoinositide conformational states can serve as lipid recognition and controlled cell signaling mechanisms.

General information
Publication status: Published

MoE publication type: A1 Journal article-refereed
Organisations: Physics, German Center for Diabetes Research (DZD e.V.), Institute of Experimental Botany of the Academy of Sciences of the Czech Republic, Pennsylvania State University, University of Wrocław, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, J. Heyrovský Institute of Physical Chemistry, University of Helsinki, MEMPHYS, University of Southern Denmark
Contributors: Bilkova, E., Pleskot, R., Rissanen, S., Sun, S., Czogalla, A., Cwiklik, L., Róg, T., Vattulainen, I., Cremer, P. S., Jungwirth, P., Coskun, Ü.
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Original language: English
ASJC Scopus subject areas: Catalysis, Chemistry(all), Biochemistry, Colloid and Surface Chemistry
DOIs:

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Bibliographical note
EXT="Cwiklik, Lukasz"
Source: Scopus
Source ID: 85016148911
Research output: Contribution to journal › Article › Scientific › peer-review

Hierarchical Self-Assembly of Halogen-Bonded Block Copolymer Complexes into Upright Cylindrical Domains
Self-assembly of block copolymers into well-defined, ordered arrangements of chemically distinct domains is a reliable strategy for preparing tailored nanostructures. Microphase separation results from the system, minimizing repulsive interactions between dissimilar blocks and maximizing attractive interactions between similar blocks. Supramolecular methods have also achieved this separation by introducing small-molecule additives binding specifically to one block by noncovalent interactions. Here, we use halogen bonding as a supramolecular tool that directs the hierarchical self-assembly of low-molecular-weight perfluorinated molecules and diblock copolymers. Microphase separation results in a lamellar-within-cylindrical arrangement and promotes upright cylindrical alignment in films upon rapid casting and without further annealing. Such cylindrical domains with internal lamellar self-assemblies can be cleaved by solvent treatment of bulk films, resulting in separated and segmented cylindrical micelles stabilized by halogen-bond-based supramolecular crosslinks. These features, alongside the reversible nature of halogen bonding, provide a robust modular approach for nanofabrication.

General information
Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Chemistry and Bioengineering, Research group: Supramolecular photochemistry, VTT Technical Research Centre of Finland, Aalto University, Politecnico di Milano, Italian Institute of Technology, Università del Salento
Contributors: Milani, R., Houbenov, N., Fernandez-Palacio, F., Cavallo, G., Luzio, A., Haataja, J., Giancane, G., Saccone, M., Priimägi, A., Metrangolo, P., Ikkala, O.
Number of pages: 10
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Peer-reviewed: Yes

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Ratings:

Scopus rating (2017): CiteScore 7.23 SJR 5.295 SNIP 2.263
Original language: English
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Keywords: block copolymers, halogen bond, hierarchical self-assembly, nanofabrication, supramolecular complexes
Electronic versions:

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Source: Scopus
Source ID: 85014778403
Research output: Contribution to journal › Article › Scientific › peer-review

Atomistic Molecular Dynamics Simulations of Mitochondrial DNA Polymerase γ: Novel Mechanisms of Function and Pathogenesis

DNA polymerase γ (Pol γ) is a key component of the mitochondrial DNA replisome and an important cause of neurological diseases. Despite the availability of its crystal structures, the molecular mechanism of DNA replication, the switch between polymerase and exonuclease activities, the site of replisomal interactions, and functional effects of patient mutations that do not affect direct catalysis have remained elusive. Here we report the first atomistic classical molecular dynamics simulations of the human Pol γ replicative complex. Our simulation data show that DNA binding triggers remarkable changes in the enzyme structure, including (1) completion of the DNA-binding channel via a dynamic subdomain, which in the apo form blocks the catalytic site, (2) stabilization of the structure through the distal accessory β-subunit, and (3) formation of a putative transient replisome-binding platform in the "intrinsic processivity" subdomain of the enzyme. Our data indicate that noncatalytic mutations may disrupt replisomal interactions, thereby causing Pol γ-associated neurodegenerative disorders.

General information
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MoE publication type: A1 Journal article-refereed
Organisations: Physics, University of Helsinki, MEMPHYS - Centre for Biomembrane Physics, University of Southern Denmark, Helsinki University Central Hospital, University of Helsinki Institute of Biotechnology
Contributors: Euro, L., Haapanen, O., Róg, T., Vattulainen, I., Suomalainen, A., Sharma, V.
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Peer-reviewed: Yes

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Journal: Biochemistry
Volume: 56
Issue number: 9
ISSN (Print): 0006-2960
Ratings:

Scopus rating (2017): CiteScore 2.92 SJR 1.685 SNIP 0.855
Original language: English
ASJC Scopus subject areas: Biochemistry
DOIs:

10.1021/acs.biochem.6b00934
Source: Scopus
Source ID: 85014731062
Research output: Contribution to journal › Article › Scientific › peer-review

Polarization resolved photoluminescence in $GaAs_{1-x}Bi_x$/GaAs quantum wells

We have investigated polarization resolved photoluminescence (PL) of $GaAs_{1-x}Bi_x$/GaAs quantum wells (QWs) with different Bi concentrations in the dilute range (x1−xBi_x/GaAs QWs increase with the increase of Bi concentration. Excitonic g_{ex}-factors of 4 and 10 were obtained at 15 T for as-grown $GaAs_{1-x}Bi_x$/GaAs QWs with 1.2% and 1.9% Bi concentration, respectively. These values evidence an important increase of electron and hole g-factors with the introduction of Bi in GaAs.

General information
Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Optoelectronics Research Centre, Research group: Semiconductor Technology and Applications, Universid ade Federal de São Carlos, University of Nottingham, Universidade Federal de São Carlos
Contributors: Balanta, M. A. G., Orsi Gordo, V., Carvalho, A. R. H., Puustinen, J., Alghamdi, H. M., Henini, M., Galeti, H. V. A., Guina, M., Galvão Gobato, Y.

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Peer-reviewed: Yes
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Journal: Journal of Luminescence
Volume: 182
ISSN (Print): 0022-2313
Ratings:

Scopus rating (2017): CiteScore 2.72 SJR 0.694 SNIP 1.075
Original language: English
ASJC Scopus subject areas: Biophysics, Chemistry(all), Atomic and Molecular Physics, and Optics, Biochemistry, Condensed Matter Physics
DOIs:

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Source ID: 84992707527
Research output: Contribution to journal › Article › Scientific › peer-review

GSAR: Bioconductor package for Gene Set analysis in R

Background: Gene set analysis (in a form of functionally related genes or pathways) has become the method of choice for analyzing omics data in general and gene expression data in particular. There are many statistical methods that either summarize gene-level statistics for a gene set or apply a multivariate statistic that accounts for intergene correlations. Most available methods detect complex departures from the null hypothesis but lack the ability to identify the specific alternative hypothesis that rejects the null. Results: GSAR (Gene Set Analysis in R) is an open-source R/Bioconductor software package for gene set analysis (GSA). It implements self-contained multivariate non-parametric statistical methods testing a complex null hypothesis against specific alternatives, such as differences in mean (shift), variance (scale), or net correlation structure. The package also provides a graphical visualization tool, based on the union of two minimum spanning trees, for correlation networks to examine the change in the correlation structures of a gene set between two conditions and highlight influential genes (hubs). Conclusions: Package GSAR provides a set of multivariate non-parametric statistical methods that test a complex null hypothesis against specific alternatives. The methods in package GSAR are applicable to any type of omics data that can be represented in a matrix format. The package, with detailed instructions and examples, is freely available under the GPL (> = 2) license from the Bioconductor web site.

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Organisations: Faculty of Biomedical Sciences and Engineering, University of Arkansas for Medical Sciences, Computational Medicine and Statistical Learning Laboratory
Contributors: Rahmatallah, Y., Zybailov, B., Emmert-Streib, F., Glazko, G.
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ASJC Scopus subject areas: Structural Biology, Biochemistry, Molecular Biology, Computer Science Applications, Applied Mathematics
Keywords: Gene set analysis, Kolmogorov-Smirnov, Minimum spanning tree, Non-parametric, Pathways, Wald Wolfowitz
Electronic versions:

GSAR - Bioconductor package for Gene Set analysis in R
DOIs:

10.1186/s12859-017-1482-6
URLs:

http://urn.fi/URN:NBN:fi:tty-201703151179
Source: Scopus

Source ID: 85010460642
Research output: Contribution to journal › Article › Scientific › peer-review

Dynamics and energetics of the mammalian phosphatidylinositol transfer protein phospholipid exchange cycle

Phosphatidylinositol-transfer proteins (PITPs) regulate phosphoinositide signaling in eukaryotic cells. The defining feature of PITPs is their ability to exchange phosphatidylinositol (PtdIns) molecules between membranes, and this property is central to PITP-mediated regulation of lipid signaling. However, the details of the PITP-mediated lipid exchange cycle remain entirely obscure. Here, all-atom molecular dynamics simulations of the mammalian StART-like PtdIns/phosphatidylcholine (PtdCho) transfer protein PITP, both on membrane bilayers and in solvated systems, informed downstream biochemical analyses that tested key aspects of the hypotheses generated by the molecular dynamics simulations. These studies provided five key insights into the PITP lipid exchange cycle: (i) interaction of PITP with the membrane is spontaneous and mediated by four specific protein substructures; (ii) the ability of PITP to initiate closure around the PtdCho ligand is accompanied by loss of flexibility of two helix/loop regions, as well as of the C-terminal helix; (iii) the energy barrier of phospholipid extraction from the membrane is lowered by a network of hydrogen bonds between the lipid molecule and PITP; (iv) the trajectory of PtdIns or PtdCho into and through the lipid-binding pocket is chaperoned by sets of PITP residues conserved throughout the StART-like PITP family; and (v) conformational transitions in the C-terminal helix have specific functional involvements in PtdIns transfer activity. Taken together, these findings provide the first mechanistic description of key aspects of the PITP PtdIns/PtdCho exchange cycle and offer a rationale for the high conservation of particular sets of residues across evolutionarily distant members of the meta-zoan StART-like PITP family.

General information

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Organisations: Physics, Research area: Computational Physics, Texas A and M Health Science Center, Department of Physics and Energy, University of Limerick, University of Helsinki, Department of Physics and Chemistry, University of Southern Denmark, Texas A and M University, Laboratory of Physics
Contributors: Grabon, A., Orłowski, A., Tripathi, A., Vuorio, J., Javanainen, M., Róg, T., Lönnfors, M., McDermott, M. I., Siebert, G., Somerharju, P., Vattulainen, I., Bankaitis, V. A.
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Publication information

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Original language: English
ASJC Scopus subject areas: Biochemistry, Molecular Biology, Cell Biology
Electronic versions:

J. Biol. Chem.-2017-Grabon-jbc.M117.791467
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URLs:

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Source: Scopus
Source ID: 85028808808
Research output: Contribution to journal › Article › Scientific › peer-review

Synthesis, Structural Characterization, Hirshfeld Surface and Antioxidant Activity Analysis of a Novel Organic Cation Antimonate Complex

A new organic–inorganic hybrid material of formula $(C_{10}H_{15}N_2)_7\ Sb_2Cl_{10}\ Sb_2Cl_9\ (SbCl_5)_2\ SbCl_4\ 2Cl{\cdot}7H_2O$ was synthesized and characterized by an X-ray diffraction analysis. It crystallizes in the triclinic system with the P(Formula presented.) space group and the following unit cell parameters a = 11.8127(3) Å, b = 15.7557(4) Å, c = 35.4511(8) Å, α = 89.409(1)°, β = 84.04(1)°, γ = 71.116(1)°, Z = 2 and V = 6207.3(3) $Å^3$. The examination of the structure shows that the two dimensional frameworks are produced by O–H Cl, N–H···Cl and N–H···O hydrogen bonding. In addition, the most important features of crystal packing and intermolecular interactions in the title complex were quantified via Hirshfeld surface analysis. Differential scanning calorimetry has revealed a dehydration phenomenon at around 348 K. The investigation of the antioxidant activity of the title compound was carried out using the 2,2-diphenyl-1-picrylhydrazyl and ferrous iron chelating methods.

General information
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Organisations: Chemistry and Bioengineering, Carthage University
Contributors: Lahbib, I., Valkonen, A., Rzaigui, M., Smirani, W.
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Keywords: Antimonates, Antioxidant activity, Crystal structure, Hirshfeld surface, Photoluminescence
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SamExploreR: Exploring reproducibility and robustness of RNA-seq results based on SAM files
Motivation: Data from RNA-seq experiments provide us with many new possibilities to gain insights into biological and disease mechanisms of cellular functioning. However, the reproducibility and robustness of RNA-seq data analysis results is often unclear. This is in part attributed to the two counter acting goals of (i) a cost efficient and (ii) an optimal experimental design leading to a compromise, e.g. in the sequencing depth of experiments. Results: We introduce an R package called samExploreR that allows the subsampling (m out of n bootstraping) of short-reads based on SAM files facilitating the investigation of sequencing depth related questions for the experimental design. Overall, this provides a systematic way for exploring the reproducibility and robustness of general RNA-seq studies. We exemplify the usage of samExploreR by studying the influence of the sequencing depth and the annotation on the identification of differentially expressed genes.

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Organisations: Department of Signal Processing, BioMediTech, Queen's University, Belfast, Northern Ireland, University of Arkansas for Medical Sciences, Nankai University
Contributors: Stupnikov, A., Tripathi, S., De Matos Simoes, R., McArt, D., Salto-Tellez, M., Glazko, G., Dehmer, M., Emmert-Streib, F.
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Original language: English
ASJC Scopus subject areas: Statistics and Probability, Medicine(all), Biochemistry, Molecular Biology, Computer Science Applications, Computational Theory and Mathematics, Computational Mathematics
DOIs:

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Source ID: 84994666672
Research output: Contribution to journal › Article › Scientific › peer-review

Effects of σ factor competition are promoter initiation kinetics dependent

In Escherichia coli, the expression of a σ factor is expected to indirectly down-regulate the expression of genes recognized by another σ factor, due to σ factor competition for a limited pool of RNA polymerase core enzymes. Evidence suggests that the sensitivity of genes to indirect down-regulation differs widely. We studied the variability in this sensitivity in promoters primarily recognized by RNAP holoenzymes carrying σ^{70}. From qPCR and live single-cell, single-RNA measurements of the transcription kinetics of several σ^{70}-dependent promoters in various conditions and from the analysis of σ factors population-dependent models of transcription initiation, we find that, the smaller is the time-scale of the closed complex formation relative to the open complex formation, the weaker is a promoter's responsiveness to changes in σ^{38} numbers. We conclude that, in E. coli, a promoter's responsiveness to indirect regulation by σ factor competition is determined by the sequence-dependent kinetics of the rate limiting steps of transcription initiation.

General information

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Organisations: Department of Signal Processing, Research group: Laboratory of Biosystem Dynamics-LBD
Contributors: Kandavalli, V. K., Tran, H., Ribeiro, A. S.
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ASJC Scopus subject areas: Biochemistry, Biophysics, Genetics, Molecular Biology, Structural Biology
Keywords: Closed Complex Formation, In vivo Transcription dynamics, Open Complex Formation, Single RNA detection, σ Factors competition
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Source ID: 84979503502
Research output: Contribution to journal › Article › Scientific › peer-review

Identifying involvement of Lys251/Asp252 pair in electron transfer and associated proton transfer at the quinone reduction site of Rhodobacter capsulatus cytochrome bc_1

Describing dynamics of proton transfers in proteins is challenging, but crucial for understanding processes which use them for biological functions. In cytochrome bc_1, one of the key enzymes of respiration or photosynthesis, proton transfers engage in oxidation of quinol (QH_2) and reduction of quinone (Q) taking place at two distinct catalytic sites. Here we evaluated by site-directed mutagenesis the contribution of Lys251/Asp252 pair (bacterial numbering) in electron transfers and associated with it proton uptake to the quinone reduction site (Q_i site). We showed that the absence of protonable group at position 251 or 252 significantly changes the equilibrium levels of electronic reactions including the Q_i-site mediated oxidation of heme b_H, reverse reduction of heme b_H by quinol and heme b_H/Q_i semiquinone equilibrium. This implicates the role of H-bonding network in binding of quinone/semiquinone and defining thermodynamic properties of $Q/SQ/QH_2$ triad. The Lys251/Asp252 proton path is disabled only when both protonable groups are removed. With just one protonable residue from this pair, the entrance of protons to the catalytic site is sustained, albeit at lower rates, indicating that protons can travel through parallel routes, possibly involving water molecules. This shows that proton paths display engineering tolerance for change as long as all the elements available for functional cooperation secure efficient proton delivery to the catalytic site.

General information

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Organisations: Department of Physics, Uniwersytet Jagiellonski w Krakowie, Structural Bioinformatics Laboratory, Abo Akad Univ, Abo Akademi University, Dept Phys, University of Helsinki
Contributors: Kuleta, P., Sarewicz, M., Postila, P., Róg, T., Osyczka, A.
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Original language: English
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Keywords: Cytochrome bc, Electron transfer, Mitochondrial complex III, Proton transfer, Quinone
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Bibliographical note
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Source ID: 84979609847
Research output: Contribution to journal › Article › Scientific › peer-review

Lipid membranes: Theory and simulations bridged to experiments

General information
Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Department of Physics, University of Helsinki, MEMPHYS - Centre for Biomembrane Physics, University of Southern Denmark
Contributors: Vattulainen, I., Róg, T.
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Source ID: 84982897384
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Efficient preparation and analysis of membrane and membrane protein systems

Molecular dynamics (MD) simulations have become a highly important technique to consider lipid membrane systems, and quite often they provide considerable added value to laboratory experiments. Rapid development of both software and hardware has enabled the increase of time and size scales reachable by MD simulations to match those attainable by several accurate experimental techniques. However, until recently, the quality and maturity of software tools available for building membrane models for simulations as well as analyzing the results of these simulations have seriously lagged behind.Here, we discuss the recent developments of such tools from the end-users' point of view. In particular, we review the software that can be employed to build lipid bilayers and other related structures with or without embedded membrane proteins to be employed in MD simulations. Additionally, we provide a brief critical insight into force fields and MD packages commonly used for membrane and membrane protein simulations. Finally, we list analysis tools that can be used to study the properties of membrane and membrane protein systems. In all these points we comment on the

respective compatibility of the covered tools.We also share our opinion on the current state of the available software. We briefly discuss the most commonly employed tools and platforms on which new software can be built. We conclude the review by providing a few ideas and guidelines on how the development of tools can be further boosted to catch up with the rapid pace at which the field of membrane simulation progresses. This includes improving the compatibility between software tools and promoting the openness of the codes on which these applications rely.This article is part of a Special Issue entitled: Biosimulations edited by Ilpo Vattulainen and Tomasz Róg.

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Contributors: Javanainen, M., Martinez-Seara, H.
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Source: Scopus
Source ID: 84959908239
Research output: Contribution to journal › Article › Scientific › peer-review

Functionalized lipids and surfactants for specific applications

Synthetic lipids and surfactants that do not exist in biological systems have been used for the last few decades in both basic and applied science. The most notable applications for synthetic lipids and surfactants are drug delivery, gene transfection, as reporting molecules, and as support for structural lipid biology. In this review, we describe the potential of the synergistic combination of computational and experimental methodologies to study the behavior of synthetic lipids and surfactants embedded in lipid membranes and liposomes. We focused on select cases in which molecular dynamics simulations were used to complement experimental studies aiming to understand the structure and properties of new compounds at the atomistic level. We also describe cases in which molecular dynamics simulations were used to design new synthetic lipids and surfactants, as well as emerging fields for the application of these compounds. This article is part of a Special Issue entitled: Biosimulations edited by Ilpo Vattulainen and Tomasz Róg.

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Organisations: Department of Physics, Research area: Computational Physics, Uniwersytet Jagiellonski w Krakowie, University of Helsinki
Contributors: Kepczynski, M., Róg, T.
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Research output: Contribution to journal › Article › Scientific › peer-review

Distribution and dynamics of quinones in the lipid bilayer mimicking the inner membrane of mitochondria

Quinone and its analogues (Q) constitute an important class of compounds that perform key electron transfer reactions in oxidative- and photo-phosphorylation. In the inner membrane of mitochondria, ubiquinone molecules undergo continuous redox transitions enabling electron transfer between the respiratory complexes. In such a dynamic system undergoing continuous turnover for ATP synthesis, an uninterrupted supply of substrate molecules is absolutely necessary. In the current work, we have performed atomistic molecular dynamics simulations and free energy calculations to assess the structure, dynamics, and localization of quinone and its analogues in a lipid bilayer, whose composition mimics the one in the inner mitochondrial membrane. The results show that there is a strong tendency of both quinone and quinol molecules to localize in the vicinity of the lipids' acyl groups, right under the lipid head group region. Additionally, we observe a second location in the middle of the bilayer where quinone molecules tend to stabilize. Translocation of quinone through a lipid bilayer is very fast and occurs in 10–100 ns time scale, whereas the translocation of quinol is at least an order of magnitude slower. We suggest that this has important mechanistic implications given that the localization of Q ensures maximal occupancy of the Q-binding sites or Q-entry points in electron transport chain complexes, thereby maintaining an optimal turnover rate for ATP synthesis.

General information

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Organisations: Department of Physics, Research area: Computational Physics, University of Helsinki, MEMPHYS - Centre for Biomembrane Physics, University of Southern Denmark, Department of Physics
Contributors: Kaurola, P., Sharma, V., Vonk, A., Vattulainen, I., Róg, T.
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Keywords: Biological energy transduction, Electron transport chain, Free energy calculations, Molecular dynamics simulations
DOIs:

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INT=fys,"Kaurola, Petri"
INT=fys,"Vonk, Amanda"
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Research output: Contribution to journal › Article › Scientific › peer-review

The role of the K-channel and the active-site tyrosine in the catalytic mechanism of cytochrome c oxidase

The active site of cytochrome c oxidase (CcO) comprises an oxygen-binding heme, a nearby copper ion (Cu_B), and a tyrosine residue that is covalently linked to one of the histidine ligands of Cu_B. Two proton-conducting pathways are observed in CcO, namely the D- and the K-channels, which are used to transfer protons either to the active site of oxygen reduction (substrate protons) or for pumping. Proton transfer through the D-channel is very fast, and its role in efficient

transfer of both substrate and pumped protons is well established. However, it has not been fully clear why a separate K-channel is required, apparently for the supply of substrate protons only. In this work, we have analysed the available experimental and computational data, based on which we provide new perspectives on the role of the K-channel. Our analysis suggests that proton transfer in the K-channel may be gated by the protonation state of the active-site tyrosine (Tyr244) and that the neutral radical form of this residue has a more general role in the CcO mechanism than thought previously. This article is part of a Special Issue entitled 'EBEC 2016: 19th European Bioenergetics Conference, Riva del Garda, Italy, July 2-6, 2016', edited by Prof. Paolo Bernardi.

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Contributors: Sharma, V., Wikström, M.
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ASJC Scopus subject areas: Biochemistry, Biophysics, Cell Biology
Keywords: Electron transfer, Neutral tyrosyl radical, Proton pumping
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Research output: Contribution to journal › Article › Scientific › peer-review

Robust statistical approaches for RSS-based floor detection in indoor localization
Floor detection for indoor 3D localization of mobile devices is currently an important challenge in the wireless world. Many approaches currently exist, but usually the robustness of such approaches is not addressed or investigated. The goal of this paper is to show how to robustify the floor estimation when probabilistic approaches with a low number of parameters are employed. Indeed, such an approach would allow a building-independent estimation and a lower computing power at the mobile side. Four robustified algorithms are to be presented: a robust weighted centroid localization method, a robust linear trilateration method, a robust nonlinear trilateration method, and a robust deconvolution method. The proposed approaches use the received signal strengths (RSS) measured by the Mobile Station (MS) from various heardWiFi access points (APs) and provide an estimate of the vertical position of the MS, which can be used for floor detection. We will show that robustification can indeed increase the performance of the RSS-based floor detection algorithms.

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Organisations: Department of Electronics and Communications Engineering, Research group: Wireless Communications and Positioning
Contributors: Razavi, A., Valkama, M., Lohan, E. S.
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Original language: English
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Source ID: 84971596811
Research output: Contribution to journal › Article › Scientific › peer-review

Characterizing rate limiting steps in transcription from RNA production times in live cells

Motivation: Single-molecule measurements of live Escherichia coli transcription dynamics suggest that this process ranges from sub- to super-Poissonian, depending on the conditions and on the promoter. For its accurate quantification, we propose a model that accommodates all these settings, and statistical methods to estimate the model parameters and to select the relevant components. Results: The new methodology has improved accuracy and avoids overestimating the transcription rate due to finite measurement time, by exploiting unobserved data and by accounting for the effects of discrete sampling. First, we use Monte Carlo simulations of models based on measurements to show that the methods are reliable and offer substantial improvements over previous methods. Next, we apply the methods on measurements of transcription intervals of different promoters in live E. coli, and show that they produce significantly different results, both in low- and high-noise settings, and that, in the latter case, they even lead to qualitatively different results. Finally, we demonstrate that the methods can be generalized for other similar purposes, such as for estimating gene activation kinetics. In this case, the new methods allow quantifying the inducer uptake dynamics as opposed to just comparing them between cases, which was not previously possible. We expect this new methodology to be a valuable tool for functional analysis of cellular processes using single-molecule or single-event microscopy measurements in live cells.

General information

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Contributors: Häkkinen, A., Ribeiro, A. S.
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Original language: English
ASJC Scopus subject areas: Biochemistry, Molecular Biology, Computational Theory and Mathematics, Computer Science Applications, Computational Mathematics, Statistics and Probability
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Source ID: 84966359423
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Human Adipose Stem Cells Differentiated on Braided Polylactide Scaffolds is a Potential Approach for Tendon Tissue Engineering

Growing number of musculoskeletal defects increases the demand for engineered tendon. Our aim was to find an efficient strategy to produce tendon-like matrix in vitro. To allow efficient differentiation of human adipose stem cells (hASCs) toward tendon tissue, we tested different medium compositions, biomaterials, and scaffold structures in preliminary tests. This is the first study to report that medium supplementation with 50 ng/mL of growth and differentiation factor-5 (GDF-5) and 280 μM l-ascorbic acid are essential for tenogenic differentiation of hASCs. Tenogenic medium (TM) was shown to significantly enhance tendon-like matrix production of hASCs compared to other tested media groups. Cell adhesion, proliferation, and tenogenic differentiation of hASCs were supported on braided poly(l/d)lactide (PLA) 96l/4d copolymer

filament scaffolds in TM condition compared to foamed poly(l-lactide-co-ε-caprolactone) (PLCL) 70L/30CL scaffolds. A uniform cell layer formed on braided PLA 96/4 scaffolds when hASCs were cultured in TM compared to maintenance medium (MM) condition after 14 days of culture. Furthermore, total collagen content and gene expression of tenogenic marker genes were significantly higher in TM condition after 2 weeks of culture. The elastic modulus of PLA 96/4 scaffold was more similar to the elastic modulus reported for native Achilles tendon. Our study showed that the optimized TM is needed for efficient and rapid in vitro tenogenic extracellular matrix production of hASCs. PLA 96/4 scaffolds together with TM significantly stimulated hASCs, thus demonstrating the potential clinical relevance of this novel and emerging approach to tendon injury treatments in the future.

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Organisations: Department of Electronics and Communications Engineering, Research group: Biomaterials and Tissue Engineering Group, BioMediTech, Tampere University Hospital, Univ Helsinki, Helsinki University Central Hospital, University of Helsinki, Cent Hosp, Dept Med, Div Nephrol, University of Twente
Contributors: Vuornos, K., Björninen, M., Talvitie, E., Paakinaho, K., Kellomäki, M., Huhtala, H., Miettinen, S., Seppänen-Kaijansinkko, R., Haimi, S.
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Original language: English
ASJC Scopus subject areas: Bioengineering, Biochemistry, Biomedical Engineering, Biomaterials
DOIs:

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Bibliographical note
EXT="Vuornos, Kaisa"
Source: Scopus
Source ID: 84961782193
Research output: Contribution to journal › Article › Scientific › peer-review

Cholesterol oxidation products and their biological importance
The main biological cause of oxysterols is the oxidation of cholesterol. They differ from cholesterol by the presence of additional polar groups that are typically hydroxyl, keto, hydroperoxy, epoxy, or carboxyl moieties. Under typical conditions, oxysterol concentration is maintained at a very low and precisely regulated level, with an excess of cholesterol. Like cholesterol, many oxysterols are hydrophobic and hence confined to cell membranes. However, small chemical differences between the sterols can significantly affect how they interact with other membrane components, and this in turn can have a substantial effect on membrane properties. In this spirit, this review describes the biological importance and the roles of oxysterols in the human body. We focus primarily on the effect of oxysterols on lipid membranes, but we also consider other issues such as enzymatic and nonenzymatic synthesis processes of oxysterols as well as pathological conditions induced by oxysterols.

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Organisations: Department of Physics, Research area: Computational Physics, Research group: Biological Physics and Soft Matter, J. Heyrovský Institute of Physical Chemistry, Academy of Sciences of the Czech Republic
Contributors: Kulig, W., Cwiklik, L., Jurkiewicz, P., Rog, T., Vattulainen, I.
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ASJC Scopus subject areas: Biochemistry, Molecular Biology, Organic Chemistry, Cell Biology
Keywords: Biological membranes, Biophysical properties, Cholesterol, Oxidation, Oxidative stress, Oxysterols, Reactive oxygen species
DOIs:
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EXT="Cwiklik, Lukasz"
Source: Scopus
Source ID: 84959894259
Research output: Contribution to journal › Article › Scientific › peer-review

Morphological Differentiation Towards Neuronal Phenotype of SH-SY5Y Neuroblastoma Cells by Estradiol, Retinoic Acid and Cholesterol

Human SH-SY5Y neuroblastoma cells maintain their potential for differentiation and regression in culture conditions. The induction of differentiation could serve as a strategy to inhibit cell proliferation and tumor growth. Previous studies have shown that differentiation of SH-SY5Y cells can be induced by all-trans-retinoic-acid (RA) and cholesterol (CHOL). However, signaling pathways that lead to terminal differentiation of SH-SY5Y cells are still largely unknown. The goal of this study was to examine in the RA and CHOL treated SH-SY5Y cells the additive impacts of estradiol (E_2) and brain-derived neurotrophic factor (BDNF) on cell morphology, cell population growth, synaptic vesicle recycling and presence of neurofilaments. The above features indicate a higher level of neuronal differentiation. Our data show that treatment for 10 days in vitro (DIV) with RA alone or when combined with E_2 (RE) or CHOL (RC), but not when combined with BDNF (RB), significantly ($p < 0.01$) inhibited the cell population growth. Synaptic vesicle recycling, induced by high-K^+ depolarization, was significantly increased in all treatments where RA was included (RE, RC, RB, RCB), and when all agents were added together (RCBE). Specifically, our results show for the first time that E_2 treatment can alone increase synaptic vesicle recycling in SH-SY5Y cells. This work contributes to the understanding of the ways to improve suppression of neuroblastoma cells' population growth by inducing maturation and differentiation.

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Organisations: Department of Signal Processing, Research group: Computational Neuro Science-CNS, University of Tampere, St. George's University School of Medicine
Contributors: Teppola, H., Sarkanen, J. R., Jalonen, T. O., Linne, M.
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Source: Scopus
Source ID: 84945586344
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Non-Brownian diffusion in lipid membranes: Experiments and simulations

The dynamics of constituents and the surface response of cellular membranes-also in connection to the binding of various particles and macromolecules to the membrane-are still a matter of controversy in the membrane biophysics community, particularly with respect to crowded membranes of living biological cells. We here put into perspective recent single particle tracking experiments in the plasma membranes of living cells and supercomputing studies of lipid bilayer model membranes with and without protein crowding. Special emphasis is put on the observation of anomalous, non-Brownian diffusion of both lipid molecules and proteins embedded in the lipid bilayer. While single component, pure lipid bilayers in

simulations exhibit only transient anomalous diffusion of lipid molecules on nanosecond time scales, the persistence of anomalous diffusion becomes significantly longer ranged on the addition of disorder-through the addition of cholesterol or proteins-and on passing of the membrane lipids to the gel phase. Concurrently, experiments demonstrate the anomalous diffusion of membrane embedded proteins up to macroscopic time scales in the minute time range. Particular emphasis will be put on the physical character of the anomalous diffusion, in particular, the occurrence of ageing observed in the experiments-the effective diffusivity of the measured particles is a decreasing function of time. Moreover, we present results for the time dependent local scaling exponent of the mean squared displacement of the monitored particles. Recent results finding deviations from the commonly assumed Gaussian diffusion patterns in protein crowded membranes are reported. The properties of the displacement autocorrelation function of the lipid molecules are discussed in the light of their appropriate physical anomalous diffusion models, both for non-crowded and crowded membranes. In the last part of this review we address the upcoming field of membrane distortion by elongated membrane-binding particles. We discuss how membrane compartmentalisation and the particle-membrane binding energy may impact the dynamics and response of lipid membranes. For SI: Biosimulations - This article is part of a Special Issue entitled: Biosimulations.

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Organisations: Department of Physics, Universitat Potsdam
Contributors: Metzler, R., Jeon, J. H., Cherstvy, A. G.
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Original language: English
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Bibliographical note
EXT="Jeon, J. H."
Source: Scopus
Source ID: 84958559500
Research output: Contribution to journal › Review Article › Scientific › peer-review

Role of charged lipids in membrane structures: Insight given by simulations
Lipids and proteins are the main components of cell membranes. It is becoming increasingly clear that lipids, in addition to providing an environment for proteins to work in, are in many cases also able to modulate the structure and function of those proteins. Particularly charged lipids such as phosphatidylinositols and phosphatidylserines are involved in several examples of such effects. Molecular dynamics simulations have proved an invaluable tool in exploring these aspects. This so-called computational microscope can provide both complementing explanations for the experimental results and guide experiments to fruitful directions. In this paper, we review studies that have utilized molecular dynamics simulations to unravel the roles of charged lipids in membrane structures. We focus on lipids as active constituents of the membranes, affecting both general membrane properties as well as non-lipid membrane components, mainly proteins. This article is part of a Special Issue entitled: Biosimulations edited by Ilpo Vattulainen and Tomasz Róg.

General information
Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Department of Physics, Research area: Computational Physics, Research group: Biological Physics and Soft Matter, University of Helsinki, University of Southern Denmark
Contributors: Pöyry, S., Vattulainen, I.
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ASJC Scopus subject areas: Biochemistry, Cell Biology, Biophysics
Keywords: Cardiolipin, Lipid membrane, Lipid-protein interactions, Phosphatidylinositol, Phosphatidylserine
DOIs:

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Source ID: 84961924291
Research output: Contribution to journal › Article › Scientific › peer-review

The biophysical properties of ethanolamine plasmalogens revealed by atomistic molecular dynamics simulations
Given the importance of plasmalogens in cellular membranes and neurodegenerative diseases, a better understanding of how plasmalogens affect the lipid membrane properties is needed. Here we carried out molecular dynamics simulations to study a lipid membrane comprised of ethanolamine plasmalogens (PE-plasmalogens). We compared the results to the PE-diacyl counterpart and palmitoyl-oleyl-phosphatidylcholine (POPC) bilayers. Results show that PE-plasmalogens form more compressed, thicker, and rigid lipid bilayers in comparison with the PE-diacyl and POPC membranes. The results also point out that the vinyl-ether linkage increases the ordering of sn-1 chain substantially and the ordering of the sn-2 chain to a minor extent. Further, the vinyl-ether linkage changes the orientation of the lipid head group, but it does not cause changes in the head group and glycerol backbone tilt angles with respect to the bilayer normal. The vinyl-ether linkage also packs the proximal regions of the sn-1 and sn-2 chains more closely together which also decreases the distance between the rest of the sn-1 and sn-2 chains.

General information
Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Department of Physics, Research area: Computational Physics, Tampere University of Technology, VTT Technical Research Centre of Finland
Contributors: Rog, T., Koivuniemi, A.
Number of pages: 7
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Publication date: 2016
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Journal: Biochimica et Biophysica Acta: Biomembranes
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Issue number: 1
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Original language: English
ASJC Scopus subject areas: Biochemistry, Cell Biology, Biophysics
Keywords: Lipid membrane, Molecular dynamics, Neurodegenerative diseases, Plasmalogens
DOIs:

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Bibliographical note
EXT="Koivuniemi, Artturi"
Source: Scopus
Source ID: 84946197363
Research output: Contribution to journal › Article › Scientific › peer-review

Gene expression analysis upon lncRNA DDSR1 knockdown in human fibroblasts
Long non-coding RNAs (lncRNAs) play important roles in regulating diverse biological processes including DNA damage and repair. We have recently reported that the DNA damage inducible lncRNA DNA damage-sensitive RNA1 (DDSR1) regulates DNA repair by homologous recombination (HR). Since lncRNAs also modulate gene expression, we identified gene expression changes upon DDSR1 knockdown in human fibroblast cells. Gene expression analysis after RNAi

treatment targeted against DDSR1 revealed 119 genes that show differential expression. Here we provide a detailed description of the microarray data (NCBI GEO accession number GSE67048) and the data analysis procedure associated with the publication by Sharma et al., 2015 in EMBO Reports [1].

General information

Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Computational Science X (CompX), National Cancer Institute, Frederick National Laboratory for Cancer Research
Contributors: Jia, L., Sun, Z., Wu, X., Misteli, T., Sharma, V.
Number of pages: 3
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ISSN (Print): 2213-5960
Ratings:

Scopus rating (2015): CiteScore 0.42 SJR 0.227 SNIP 0.088
Original language: English
ASJC Scopus subject areas: Molecular Medicine, Biochemistry, Biotechnology, Genetics
Keywords: DDSR1, LncRNA
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Source: Scopus
Source ID: 84945932080
Research output: Contribution to journal › Article › Scientific › peer-review

Tuning the Plasmonic Extinction Resonances of Hexagonal Arrays of Ag Nanoparticles

Plasmonically enhanced effects on a self-assembled, hexagonal array layer of ~4-nm silver nanoparticles are analyzed using three-dimensional finite-difference time-domain (3D FDTD) simulations and compared against experimentally measured extinction spectra. The effect of particle size, lattice spacing, and lack of monodispersity of the hexagonal array of silver nanoparticles on the extinction resonance was investigated to help determine optimal design specifications for efficient organic solar power harvesting.

General information

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MoE publication type: A1 Journal article-refereed
Organisations: Augmented Human Activities (AHA), Ohio State University, Department of Electrical and Computer Engineering
Contributors: Ravi, A., Luthra, A., Teixeira, F. L., Berger, P. R., Coe, J. V.
Number of pages: 8
Pages: 1505-1512
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Publication information

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ISSN (Print): 1557-1955
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Scopus rating (2015): CiteScore 2.07 SJR 0.755 SNIP 0.834
Original language: English
ASJC Scopus subject areas: Biochemistry, Biophysics, Biotechnology
Keywords: Active plasmonics, Metamaterials, Nanoparticles, Organic solar panels, Plasmon resonance
DOIs:

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Source ID: 84947019436
Research output: Contribution to journal › Article › Scientific › peer-review

A BRCA1-interacting lncRNA regulates homologous recombination

Long non-coding RNAs (lncRNAs) are important players in diverse biological processes. Upon DNA damage, cells activate a complex signaling cascade referred to as the DNA damage response (DDR). Using a microarray screen, we identify here a novel lncRNA, DDSR1 (DNA damage-sensitive RNA1), which is induced upon DNA damage. DDSR1 induction is triggered in an ATM-NF-κB pathway-dependent manner by several DNA double-strand break (DSB) agents. Loss of DDSR1 impairs cell proliferation and DDR signaling and reduces DNA repair capacity by homologous recombination (HR). The HR defect in the absence of DDSR1 is marked by aberrant accumulation of BRCA1 and RAP80 at DSB sites. In line with a role in regulating HR, DDSR1 interacts with BRCA1 and hnRNPUL1, an RNA-binding protein involved in DNA end resection. Our results suggest a role for the lncRNA DDSR1 in modulating DNA repair by HR.

General information

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MoE publication type: A1 Journal article-refereed
Organisations: Computational Science X (CompX), National Cancer Institute, National Institute on Aging
Contributors: Sharma, V., Khurana, S., Kubben, N., Abdelmohsen, K., Oberdoerffer, P., Gorospe, M., Misteli, T.
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ASJC Scopus subject areas: Biochemistry, Molecular Biology, Genetics
Keywords: BRCA1, hnRNPUL1, p53, RAP80, repair
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Source ID: 84946489384
Research output: Contribution to journal › Article › Scientific › peer-review

Submolecular Plasticization Induced by Photons in Azobenzene Materials

We demonstrate experimentally for the first time that the illumination of azobenzene derivatives leads to changes in molecular environment similar to those observed on heating but that are highly heterogeneous at the submolecular scale. This localized photoplasticization, which can be associated with a free volume gradient, helps to understand the puzzling phenomenon of photoinduced macroscopic material flow and photoexpansion upon illumination far below the glass transition temperature (T_g). The findings stem from the correlation of infrared (IR) spectral band shifts measured upon illumination with those measured at controlled temperatures for two amorphous DR1-functionalized azo derivatives, a polymer, pDR1A, and a molecular glass, gDR1. This new approach reveals that IR spectroscopy can be used as an efficient label-free molecular-scale thermometer that allows the assignment of an effective temperature (T_{eff}) to each moiety in these compounds when irradiated. While no band shift is observed upon illumination for the vibrational modes assigned to backbone moieties of pDR1A and gDR1 and a small band shift is found for the spacer moiety, dramatic band shifts are recorded for the azo moiety, corresponding to an increase in T_{eff} of up to nearly 200 °C and a molecular environment that is equivalent to thermal heating well above the bulk T_g of the material. An irradiated azo-containing material thus combines characteristic properties of amorphous materials both below and above its bulk T_g. The direct measurement of T_{eff} is a powerful probe of the local environment at the submolecular scale, paving the way toward better rationalization of photoexpansion and the athermal malleability of azo-containing materials upon illumination below their T g.

General information

Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Frontier Photonics, Département de Chimie, Succ. Centre-Ville, Royal Military College of Canada
Contributors: Vapaavuori, J., Laventure, A., Bazuin, C. G., Lebel, O., Pellerin, C.
Number of pages: 8
Pages: 13510-13517

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Journal: Journal of the American Chemical Society
Volume: 137
Issue number: 42
ISSN (Print): 0002-7863
Ratings:

Scopus rating (2015): CiteScore 12.81 SJR 6.775 SNIP 2.6
Original language: English
ASJC Scopus subject areas: Catalysis, Chemistry(all), Biochemistry, Colloid and Surface Chemistry
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Source ID: 84946020103
Research output: Contribution to journal › Article › Scientific › peer-review

Cancer incidence and mortality in patients treated either with RAI or thyroidectomy for hyperthyroidism
Context: Some previous studies have suggested increased cancer risk in hyperthyroid patients treated with radioactive iodine (RAI). It is unclear whether the excess cancer risk is attributable to hyperthyroidism, its treatment, or the shared risk factors of the two diseases. Objective: The objective was to assess cancer morbidity and mortality in hyperthyroid patients treated with either RAI or surgery. Patients: We identified 4334 patients treated surgically for hyperthyroidism in Finland during 1986-2007 from the Hospital Discharge Registry and 1814 patients treated with RAI for hyperthyroidism at Tampere University Hospital. For each patient, three age-and gender-matched controls were chosen. Informationoncancer diagnoses was obtained from the Cancer Registry. The follow-up began 3 months after the treatment and ended at cancer diagnosis, death, emigration, or the common closing date (December 31, 2009). Results: The overall cancer incidence was not increased among the hyperthyroid patients compared to their controls (rate ratio [RR], 1.05;95%confidence interval [CI], 0.96-1.15). However, the risk of cancers of the respiratory tract (RR, 1.46; 95% CI, 1.05-2.02) and the stomach (RR, 1.64; 95% CI, 1.01-2.68) was increased among the patients. The overall cancer mortality did not differ between the patients and the controls (RR, 1.08; 95% CI, 0.94-1.25). The type of treatment did not affect the overall risk of cancer (hazard ratio for RAI vs thyroidectomy, 1.03; 95% CI, 0.86-1.23) or cancer mortality (hazard ratio, 1.04; 95% CI, 0.91-1.21). Conclusions: In this cohort of Finnish patients with hyperthyroidism treated with thyroidectomy or RAI, the overall risk of cancer was not increased, although an increased risk of gastric and respiratory tract cancers was seen in hyperthyroid patients. Based on this large-scale, long-term follow-up study, the increased cancer risk in hyperthyroid patients is attributable to hyperthyroidismandshared risk factors, not the treatment modality.

General information
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MoE publication type: A1 Journal article-refereed
Organisations: Prostate cancer research center (PCRC), Tampere University Hospital, Central Hospital of Seinäjoki, School of Health Sciences, Helsinki University Central Hospital
Contributors: Ryödi, E., Metso, S., Jaatinen, P., Huhtala, H., Saaristo, R., Välimäki, M., Auvinen, A.
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Journal: Journal of Clinical Endocrinology and Metabolism
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Scopus rating (2015): CiteScore 5.68 SJR 3.071 SNIP 2.011
Original language: English
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Source ID: 84943774041
Research output: Contribution to journal › Article › Scientific › peer-review

Surface Modified Biodegradable Electrospun Membranes as a Carrier for Human Embryonic Stem Cell-Derived Retinal Pigment Epithelial Cells

Human embryonic stem cell-derived retinal pigment epithelial (hESC-RPE) cells are currently undergoing clinical trials to treat retinal degenerative diseases. Transplantation of hESC-RPE cells in conjuction with a supportive biomaterial carrier holds great potential as a future treatment for retinal degeneration. However, there has been no such biodegradable material that could support the growth and maturation of hESC-RPE cells so far. The primary aim of this work was to create a thin porous poly (L-lactide-co-caprolactone) (PLCL) membrane that could promote attachment, proliferation, and maturation of the hESC-RPE cells in serum-free culture conditions. The PLCL membranes were modified by atmospheric pressure plasma processing and coated with collagen IV to enhance cell growth and maturation. Permeability of the membranes was analyzed with an Ussing chamber system. Analysis with scanning electron microscopy, contact angle measurement, atomic force microscopy, and X-ray photoelectron spectroscopy demonstrated that plasma surface treatment augments the surface properties of the membrane, which enhances the binding and conformation of the protein. Cell proliferation assays, reverse transcription-polymerase chain reaction, indirect immunofluoresence staining, trans-epithelial electrical resistance measurements, and in vitro phagocytosis assay clearly demonstrated that the plasma treated PLCL membranes supported the adherence, proliferation, maturation and functionality of hESC-RPE cells in serum-free culture conditions. Here, we report for the first time, how PLCL membranes can be modified with atmospheric pressure plasma processing to enable the formation of a functional hESC-RPE monolayer on a porous biodegradable substrate, which have a potential as a tissue-engineered construct for regenerative retinal repair applications.

General information

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Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), University of Ulster
Contributors: Sorkio, A., Porter, P. J., Juuti-Uusitalo, K., Meenan, B. J., Skottman, H., Burke, G. A.
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Peer-reviewed: Yes

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Original language: English
ASJC Scopus subject areas: Bioengineering, Biochemistry, Biomedical Engineering, Biomaterials, Medicine(all)
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Source: Scopus
Source ID: 84940705576
Research output: Contribution to journal › Article › Scientific › peer-review

Bioactive glass ions as strong enhancers of osteogenic differentiation in human adipose stem cells

Bioactive glasses are known for their ability to induce osteogenic differentiation of stem cells. To elucidate the mechanism of the osteoinductivity in more detail, we studied whether ionic extracts prepared from a commercial glass S53P4 and from three experimental glasses (2-06, 1-06 and 3-06) are alone sufficient to induce osteogenic differentiation of human adipose stem cells. Cells were cultured using basic medium or osteogenic medium as extract basis. Our results indicate that cells stay viable in all the glass extracts for the whole culturing period, 14 days. At 14 days the mineralization in osteogenic medium extracts was excessive compared to the control. Parallel to the increased mineralization we observed a decrease in the cell amount. Raman and Laser Induced Breakdown Spectroscopy analyses confirmed that the mineral consisted of calcium phosphates. Consistently, the osteogenic medium extracts also increased osteocalcin production and collagen Type-I accumulation in the extracellular matrix at 13 days. Of the four osteogenic medium extracts, 2-06 and 3-06 induced the best responses of osteogenesis. However, regardless of the enhanced mineral formation, alkaline phosphatase activity was not promoted by the extracts. The osteogenic medium extracts could potentially provide a fast and effective way to differentiate human adipose stem cells in vitro.

General information
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MoE publication type: A1 Journal article-refereed
Organisations: Department of Electronics and Communications Engineering, Research group: Biomaterials and Tissue Engineering Group, BioMediTech, Integrated Technologies for Tissue Engineering Research (ITTE), Tampere University Hospital, BioMediTech, University of Jyväskylä, Pirkanmaa Hospital District and School of Health Sciences, Adult Stem Cell Research Group, Regenerative Medicine, Adult Stem Cell Group, Johan Gadolin Process Chemistry Centre, Åbo Akademi University, National Center for Nanoscience and Technology (NCNST), Peking, China
Contributors: Ojansivu, M., Vanhatupa, S., Björkvik, L., Häkkänen, H., Kellomäki, M., Autio, R., Ihalainen, J. A., Hupa, L., Miettinen, S.
Number of pages: 14
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Publication date: 15 Jul 2015
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Volume: 21
ISSN (Print): 1742-7061
Ratings:

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Original language: English
ASJC Scopus subject areas: Biomaterials, Biomedical Engineering, Biotechnology, Biochemistry, Molecular Biology
Keywords: Bioactive glass, Bone tissue engineering, Mesenchymal stem cell, Mineralization, Osteogenic differentiation
DOIs:

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Bibliographical note
EXT="Autio, Reija"
Source: Scopus
Source ID: 84929951673
Research output: Contribution to journal › Article › Scientific › peer-review

A robust AMMI model for the analysis of genotype-by-environment data
Motivation: One of the most widely used models to analyse genotype-by-environment data is the additive main effects and multiplicative interaction (AMMI) model. Genotype-by-environment data resulting from multi-location trials are usually organized in two-way tables with genotypes in the rows and environments (location-year combinations) in the columns. The AMMI model applies singular value decomposition (SVD) to the residuals of a specific linear model, to decompose the genotype-by-environment interaction (GEI) into a sum of multiplicative terms. However, SVD, being a least squares method, is highly sensitive to contamination and the presence of even a single outlier, if extreme, may draw the leading principal component towards itself resulting in possible misinterpretations and in turn lead to bad practical decisions. Since, as in many other real-life studies the distribution of these data is usually not normal due to the presence of outlying observations, either resulting from measurement errors or sometimes from individual intrinsic characteristics, robust SVD methods have been suggested to help overcome this handicap. Results: We propose a robust generalization of the AMMI model (the R-AMMI model) that overcomes the fragility of its classical version when the data are contaminated. Here, robust statistical methods replace the classic ones to model, structure and analyse GEI. The performance of the robust extensions of the AMMI model is assessed through a Monte Carlo simulation study where several contamination schemes are considered. Applications to two real plant datasets are also presented to illustrate the benefits of the proposed methodology, which can be broadened to both animal and human genetics studies. Availability and implementation: Source code implemented in R is available in the supplementary material under the function r-AMMI.

General information
Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Research Community on Data-to-Decision (D2D), Centro de Matemática e Aplicações (CMA, NOVA University of Lisbon
Contributors: Rodrigues, P. C., Monteiro, A., Lourenço, V. M.
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Pages: 58-66
Publication date: 1 Jul 2015
Peer-reviewed: Yes

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Volume: 32

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ISSN (Print): 1367-4803
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Original language: English
ASJC Scopus subject areas: Biochemistry, Molecular Biology, Computational Theory and Mathematics, Computer Science Applications, Computational Mathematics, Statistics and Probability, Medicine(all)
DOIs:

10.1093/bioinformatics/btv533
URLs:

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Source: Scopus
Source ID: 84959872026
Research output: Contribution to journal › Article › Scientific › peer-review

Cholesterol under oxidative stress: How lipid membranes sense oxidation as cholesterol is being replaced by oxysterols

The behavior of oxysterols in phospholipid membranes and their effects on membrane properties were investigated by means of dynamic light scattering, fluorescence spectroscopy, NMR, and extensive atomistic simulations. Two families of oxysterols were scrutinized - tail-oxidized sterols, which are mostly produced by enzymatic processes, and ring-oxidized sterols, formed mostly via reactions with free radicals. The former family of sterols was found to behave similar to cholesterol in terms of molecular orientation, roughly parallel to the bilayer normal, leading to increasing membrane stiffness and suppression of its membrane permeability. In contrast, ring-oxidized sterols behave quantitatively differently from cholesterol. They acquire tilted orientations and therefore disrupt the bilayer structure with potential implications for signaling and other biochemical processes in the membranes.

General information

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MoE publication type: A1 Journal article-refereed
Organisations: Department of Physics, Research area: Computational Physics, Research group: Biological Physics and Soft Matter, Computational Science X (CompX), University of Oulu, Tallinn Technical University, Institute of Chemistry, University of Southern Denmark, J. Heyrovský Institute of Physical Chemistry, Academy of Sciences of the Czech Republic, Department of Physics and Chemistry, Weill Cornell Medical College, Fritz Haber Research Center, Hebrew University of Jerusalem
Contributors: Kulig, W., Olzyńska, A., Jurkiewicz, P., Kantola, A. M., Komulainen, S., Manna, M., Pourmousa, M., Vazdar, M., Cwiklik, L., Rog, T., Khelashvili, G., Harries, D., Telkki, V. V., Hof, M., Vattulainen, I., Jungwirth, P.
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Original language: English
ASJC Scopus subject areas: Biochemistry, Physiology (medical)
Keywords: Phospholipid bilayers, Oxysterols, Molecular dynamics simulations, DPH anisotropy, NMR measurements, Laurdan fluorescence, Liposomes, Tilt modulus, FLUORESCENCE SOLVENT RELAXATION, MOLECULAR-DYNAMICS METHOD, MODEL MEMBRANES, FOURIER TRANSFORMATION, POTENTIAL FUNCTIONS, SOLVATION DYNAMICS , BENDING RIGIDITY, ORDER PARAMETERS, BILAYERS, PROTEINS
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Source: WOS
Source ID: 000355896500004
Research output: Contribution to journal › Article › Scientific › peer-review

Apolipoprotein A-I mimetic peptide 4F blocks sphingomyelinase-induced LDL aggregation

Lipolytic modification of LDL particles by SMase generates LDL aggregates with a strong affinity for human arterial proteoglycans and may so enhance LDL retention in the arterial wall. Here, we evaluated the effects of apoA-I mimetic peptide 4F on structural and functional properties of the SMase-modified LDL particles. LDL particles with and without 4F

were incubated with SMase, after which their aggregation, structure, and proteoglycan binding were analyzed. At a molar ratio of L-4F to apoB-100 of 2.5 to 20:1, 4F dose-dependently inhibited SMase-induced LDL aggregation. At a molar ratio of 20:1, SMase-induced aggregation was fully blocked. Binding of 4F to LDL particles inhibited SMase-induced hydrolysis of LDL by 10% and prevented SMase-induced LDL aggregation. In addition, the binding of the SMase-modified LDL particles to human aortic proteoglycans was dose-dependently inhibited by pretreating LDL with 4F. The 4F stabilized apoB-100 conformation and inhibited SMase-induced conformational changes of apoB-100. Molecular dynamic simulations showed that upon binding to protein-free LDL surface, 4F locally alters membrane order and fluidity and induces structural changes to the lipid layer. Collectively, 4F stabilizes LDL particles by preventing the SMase-induced conformational changes in apoB-100 and so blocks SMase-induced LDL aggregation and the resulting increase in LDL retention.

General information

Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Department of Physics, Research group: Biological Physics and Soft Matter, Computational Science X (CompX), Department of Molecular and Cellular Medicine, University of California, Los Angeles, University of Southern Denmark, Wihuri Research Institute, Biomedicum Helsinki, University of Helsinki Institute of Biotechnology, Science Service Center, Kuopio University Hospital, David Geffen School of Medicine at UCLA, A.I. Virtanen Institute for Molecular Sciences, Department of Biotechnology and Molecular Medicine, Univ Eastern Finland, University of Eastern Finland, Inst Photon
Contributors: Nguyen, S. D., Javanainen, M., Rissanen, S., Zhao, H., Huusko, J., Kivelä, A. M., Ylä-Herttuala, S., Navab, M., Fogelman, A. M., Vattulainen, I., Kovanen, P. T., Öörni, K.
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Original language: English
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Keywords: Apolipoprotein B-100, Atherosclerosis, Conformation, Interaction, Low density lipoprotein, Proteoglycans, Retention
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URLs:

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Source: Scopus
Source ID: 84937161010
Research output: Contribution to journal › Article › Scientific › peer-review

Using shRNA experiments to validate gene regulatory networks

Quantitative validation of gene regulatory networks (GRNs) inferred from observational expression data is a difficult task usually involving time intensive and costly laboratory experiments. We were able to show that gene knock-down experiments can be used to quantitatively assess the quality of large-scale GRNs via a purely data-driven approach (Olsen et al. 2014). Our new validation framework also enables the statistical comparison of multiple network inference techniques, which was a long-standing challenge in the field.In this Data in Brief we detail the contents and quality controls for the gene expression data (available from NCBI Gene Expression Omnibus repository with accession number GSE53091) associated with our study published in Genomics (Olsen et al. 2014). We also provide R code to access the data and reproduce the analysis presented in this article.

General information

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MoE publication type: A1 Journal article-refereed
Organisations: Department of Signal Processing, BioMediTech, Research Community on Data-to-Decision (D2D), BioMediTech - Institute of Biosciences and Medical Technology, University of Toronto, Canada, Machine Learning Group, Interuniversity Institute of Bioinformatics in Brussels (IB), Computational Biology and Functional Genomics Laboratory, Dana-Farber Cancer Institute, Harvard School of Public Health, Bioinformatics and Computational Genomics Laboratory, Princess Margaret Cancer Centre, University Health Network University of Toronto, Department of Medical Biophysics, University of Toronto, Embedded Electronics research unit of the Bio Electro and Mechanical Systems (BEAMS) department of the Université Libre de Bruxelles

Contributors: Olsen, C., Fleming, K., Prendergast, N., Rubio, R., Emmert-Streib, F., Bontempi, G., Quackenbush, J., Haibe-Kains, B.
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Keywords: Colon cancer, Gene expression, Knock-down, Microarray, ShRNA
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Role of subunit III and its lipids in the molecular mechanism of cytochrome c oxidase

The terminal respiratory enzyme cytochrome c oxidase (CcO) reduces molecular oxygen to water, and pumps protons across the inner mitochondrial membrane, or the plasma membrane of bacteria. A two-subunit CcO harbors all the elements necessary for oxygen reduction and proton pumping. However, it rapidly undergoes turnover-induced irreversible damage, which is effectively prevented by the presence of subunit III and its tightly bound lipids. We have performed classical atomistic molecular dynamics (MD) simulations on a three-subunit CcO, which show the formation of water wires between the polar head groups of lipid molecules bound to subunit III and the proton uptake site Asp91 (Bos taurus enzyme numbering). Continuum electrostatic calculations suggest that these lipids directly influence the proton affinity of Asp91 by 1-2 pK units. We surmise that lipids bound to subunit III influence the rate of proton uptake through the D-pathway, and therefore play a key role in preventing turnover-induced inactivation. Atomistic MD simulations show that subunit III is rapidly hydrated in the absence of internally bound lipids, which is likely to affect the rate of O<inf>2</inf> diffusion into the active-site. The role of subunit III with its indigenous lipids in the molecular mechanism of CcO is discussed.

General information
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MoE publication type: A1 Journal article-refereed
Organisations: Department of Physics, Research area: Computational Physics, Tampere University of Technology, Research group: Biological Physics and Soft Matter, Computational Science X (CompX), University of Southern Denmark, Institute of Molecular Biotechnology, Jena, Germany, Helsinki Bioenergetics Group, University of Helsinki Institute of Biotechnology
Contributors: Sharma, V., Ala-Vannesluoma, P., Vattulainen, I., Wikström, M., Róg, T.
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Original language: English
ASJC Scopus subject areas: Biochemistry, Biophysics, Cell Biology
Keywords: Cardiolipin, Continuum electrostatic, Molecular dynamics simulation, Oxygen diffusion, Water molecule
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Bibliographical note

AUX=fys,"Ala-Vannesluoma, Pauliina"
Source: Scopus
Source ID: 84929657652
Research output: Contribution to journal › Article › Scientific › peer-review

Multi-stable dynamics of the non-adiabatic repressilator

The assumption of the fast binding of transcription factors (TFs) to promoters is a typical point in studies of synthetic genetic circuits functioning in bacteria. Although the assumption is effective for simplifying the models, it becomes questionable in the light of in vivo measurements of the times TF spends searching for its cognate DNA sites. We investigated the dynamics of the full idealized model of the paradigmatic genetic oscillator, the repressilator, using deterministic mathematical modelling and stochastic simulations. We found (using experimentally approved parameter values) that decreases in the TF binding rate changes the type of transition between steady state and oscillation. As a result, this gives rise to the hysteresis region in the parameter space, where both the steady state and the oscillation coexist. We further show that the hysteresis is persistent over a considerable range of the parameter values, but the presence of the oscillations is limited by the low rate of TF dimer degradation. Finally, the stochastic simulation of the model confirms the hysteresis with switching between the two attractors, resulting in highly skewed period distributions. Moreover, intrinsic noise stipulates trains of large-amplitude modulations around the stable steady state outside the hysteresis region, which makes the period distributions bimodal.

General information

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MoE publication type: A1 Journal article-refereed
Organisations: Department of Mathematics, Research group: MAT Inverse Problems, Mathematical modelling with wide societal impact (MathImpact), Department of Theoretical Physics, Lebedev Physical Institution
Contributors: Potapov, I., Zhurov, B., Volkov, E.
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ASJC Scopus subject areas: Biophysics, Biotechnology, Bioengineering, Biomedical Engineering, Biomaterials, Biochemistry
Keywords: Adiabatic, Bimodality, Genetic oscillator, Hysteresis, Multi-stability
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Research output: Contribution to journal › Article › Scientific › peer-review

Oxidation half-reaction of aqueous nucleosides and nucleotides via photoelectron spectroscopy augmented by ab initio calculations

Oxidative damage to DNA and hole transport between nucleobases in oxidized DNA are important processes in lesion formation for which surprisingly poor thermodynamic data exist, the relative ease of oxidizing the four nucleobases being one such example. Theoretical simulations of radiation damage and charge transport in DNA depend on accurate values for vertical ionization energies (VIEs), reorganization energies, and standard reduction potentials. Liquid-jet photoelectron spectroscopy can be used to directly study the oxidation half-reaction. The VIEs of nucleic acid building blocks are measured in their native buffered aqueous environment. The experimental investigation of purine and pyrimidine nucleotides, nucleosides, pentose sugars, and inorganic phosphate demonstrates that photoelectron spectra of nucleotides arise as a spectral sum over their individual chemical components; that is, the electronic interactions between each component are effectively screened from one another by water. Electronic structure theory affords the assignment of the lowest energy photoelectron band in all investigated nucleosides and nucleotides to a single ionizing transition centered solely on the nucleobase. Thus, combining the measured VIEs with theoretically determined reorganization energies allows for the spectroscopic determination of the one-electron redox potentials that have been difficult to establish via electrochemistry.

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MoE publication type: A1 Journal article-refereed
Organisations: Computational Science X (CompX), University of Southern California, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Max-Planck-Institut für Dynamik und Selbstorganisation, Department of Physical Chemistry, Helmholtz Center Berlin
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Research output: Contribution to journal › Article › Scientific › peer-review

Estimation of GFP-tagged RNA numbers from temporal fluorescence intensity data
Motivation: MS2-GFP-tagging of RNA is currently the only method to measure intervals between consecutive transcription events in live cells. For this, new transcripts must be accurately detected from intensity time traces. Results: We present a novel method for automatically estimating RNA numbers and production intervals from temporal data of cell fluorescence intensities that reduces uncertainty by exploiting temporal information. We also derive a robust variant, more resistant to outliers caused e.g. by RNAs moving out of focus. Using Monte Carlo simulations, we show that the quantification of RNA numbers and production intervals is generally improved compared with previous methods. Finally, we analyze data from live Escherichia coli and show statistically significant differences to previous methods. The new methods can be used to quantify numbers and production intervals of any fluorescent probes, which are present in low copy numbers, are brighter than the cell background and degrade slowly. Availability: Source code is available under Mozilla Public License at http://www.cs.tut.fi/%7ehakkin22/jumpdet/. Contact:

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MoE publication type: A1 Journal article-refereed
Organisations: Department of Signal Processing, Research group: Laboratory of Biosystem Dynamics-LBD, Multi-scaled biodata analysis and modelling (MultiBAM)
Contributors: Häkkinen, A., Ribeiro, A. S.
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ASJC Scopus subject areas: Biochemistry, Molecular Biology, Computational Theory and Mathematics, Computer Science Applications, Computational Mathematics, Statistics and Probability, Medicine(all)
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Source ID: 396
Research output: Contribution to journal › Article › Scientific › peer-review

Efficient preparation of shuffled DNA libraries through recombination (Gateway) cloning
Efficient and robust subcloning is essential for the construction of high-diversity DNA libraries in the field of directed evolution. We have developed a more efficient method for the subcloning of DNAshuffled libraries by employing recombination cloning (Gateway). The Gateway cloning procedure was performed directly after the gene reassembly reaction, without additional purification and amplification steps, thus simplifying the conventional DNA shuffling protocols. Recombination-based cloning, directly from the heterologous reassembly reaction, conserved the high quality of the library and reduced the time required for the library construction. The described method is generally compatible for the construction of DNA-shuffled gene libraries.

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Organisations: Multi-scaled biodata analysis and modelling (MultiBAM), Fimlab Laboratories Ltd, Next Biomed Technologies NBT Oy, Karolinska University Hospital, Tampere University Hospital
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Original language: English
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Keywords: Directed evolution, DNA library, DNA shuffling, Phage display recombination cloning
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Source: Scopus
Source ID: 84983121996
Research output: Contribution to journal › Article › Scientific › peer-review

Experimental determination and computational interpretation of biophysical properties of lipid bilayers enriched by cholesteryl hemisuccinate
Cholesteryl hemisuccinate (CHS) is one of the cholesterol-mimicking detergents not observed in nature. It is, however, widely used in protein crystallography, in biochemical studies of proteins, and in pharmacology. Here, we performed an extensive experimental and theoretical study on the behavior of CHS in lipid membranes rich in unsaturated phospholipids. We found that the deprotonated form of CHS (that is the predominant form under physiological conditions) does not mimic cholesterol very well. The protonated form of CHS does better in this regard, but also its ability to mimic the physical effects of cholesterol on lipid membranes is limited. Overall, although ordering and condensing effects characteristic to cholesterol are present in systems containing any form of CHS, their strength is appreciably weaker compared to cholesterol. Based on the considerable amount of experimental and atomistic simulation data, we conclude that these differences originate from the fact that the ester group of CHS does not anchor it in an optimal position at the water-membrane interface. The implications of these findings for considerations of protein-cholesterol interactions are briefly discussed.

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Organisations: Department of Physics, Research group: Biological Physics and Soft Matter, Computational Science X (CompX), Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, J. Heyrovský Institute of Physical Chemistry, Academy of Sciences of the Czech Republic, University of Southern Denmark
Contributors: Kulig, W., Jurkiewicz, P., Olzyńska, A., Tynkkynen, J., Javanainen, M., Manna, M., Rog, T., Hof, M., Vattulainen, I., Jungwirth, P.
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Keywords: Cholesterol-mimicking detergents, DPH, Dynamic light scattering, Laurdan, Molecular dynamics simulations, Time-dependent fluorescence shift
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AUX=fys,"Tynkkynen, Joona"
Source: Scopus
Source ID: 84912099904
Research output: Contribution to journal › Article › Scientific › peer-review

Interaction with serum albumin as a factor of the photodynamic efficacy of novel bacteriopurpurinimide derivatives
Optimization of the chemical structure of antitumor photosensitizers (PSs) is aimed at increasing their affinity to a transport protein, albumin and irreversible light-induced tumor cell damage. Bacteriopurpurinimide derivatives are promising PSs thanks to their ability to absorb light in the near infrared spectral region. Using spectrophotometry, we show that two new bacteriopurpurinimide derivatives with different substituents at the N atoms of the imide exocycle and the pyrrole ring A are capable of forming non-covalent complexes with human serum albumin (HSA). The association constant (calculated with the Benesi-Hildebrand equation) for N-ethoxybacteriopurpurinimide ethyloxime (compound 1) is higher than that for the methyl ether of methoxybacteriopurpurinimide (compound 2) (1.18×10^{5} M^{-1} vs. 1.26×10^{4} M^{-1}, respectively). Molecular modeling provides details of the atomic interactions between 1 and 2 and amino acid residues in the FA1 binding site of HSA. The ethoxy group stabilizes the position of 1 within this site due to hydrophobic interaction with the protein. The higher affinity of 1 for HSA makes this compound more potent than 2 in photodynamic therapy for cultured human colon carcinoma cells. Photoactivation of 1 and 2 in cells induces rapid (within a few minutes of irradiation) necrosis. This mechanism of cell death may be efficient for eliminating tumors resistant to other therapies.

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Organisations: Emanuel' Institute of Biochemical Physics, Russian Academy of Sciences, St. Petersburg State Polytechnical University, M.V. Lomonosov Moscow State University of Fine Chemical Technologies, N.N. Blokhin Russian Cancer Research Center, Russian Academy of Medical Sciences, Georgian Technical University
Contributors: Akimova, A. V., Rychkov, G. N., Grin, M. A., Filippova, N. A., Golovina, G. V., Durandin, N. A., Vinogradov, A. M., Kokrashvili, T. A., Mironov, A. F., Shtil, A. A., Kuzmin, V. A.
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Keywords: Albumin, Association constant, Cancer, Necrosis, Photodynamic therapy, Photosensitizers
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Research output: Contribution to journal › Article › Scientific › peer-review

Comparative evaluation of gene set analysis approaches for RNA-Seq data

Background: Over the last few years transcriptome sequencing (RNA-Seq) has almost completely taken over microarrays for high-throughput studies of gene expression. Currently, the most popular use of RNA-Seq is to identify genes which are differentially expressed between two or more conditions. Despite the importance of Gene Set Analysis (GSA) in the interpretation of the results from RNA-Seq experiments, the limitations of GSA methods developed for microarrays in the context of RNA-Seq data are not well understood. Results: We provide a thorough evaluation of popular multivariate and gene-level self-contained GSA approaches on simulated and real RNA-Seq data. The multivariate approach employs multivariate non-parametric tests combined with popular normalizations for RNA-Seq data. The gene-level approach utilizes univariate tests designed for the analysis of RNA-Seq data to find gene-specific -values and combines them into a pathway -value using classical statistical techniques. Our results demonstrate that the Type I error rate and the power of multivariate tests depend only on the test statistics and are insensitive to the different normalizations. In general standard multivariate GSA tests detect pathways that do not have any bias in terms of pathways size, percentage of differentially expressed genes, or average gene length in a pathway. In contrast the Type I error rate and the power of gene-level GSA tests are heavily affected by the methods for combining -values, and all aforementioned biases are present in detected pathways. Conclusions: Our result emphasizes the importance of using self-contained non-parametric multivariate tests for detecting differentially expressed pathways for RNA-Seq data and warns against applying gene-level GSA tests, especially because of their high level of Type I error rates for both, simulated and real data.

General information

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Organisations: Research Community on Data-to-Decision (D2D), University of Arkansas for Medical Sciences, Computational Biology and Machine Learning, Queen's University, Belfast, Northern Ireland
Contributors: Rahmatallah, Y., Emmert-Streib, F., Glazko, G.
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Research output: Contribution to journal › Article › Scientific › peer-review

Connection between absorption properties and conformational changes in Deinococcus radiodurans phytochrome

Phytochromes consist of several protein domains and a linear tetrapyrrole molecule, which interact as a red-light-sensing system. In this study, size-exclusion chromatography and light-scattering techniques are combined with UV-vis spectroscopy to investigate light-induced changes in dimeric Deinococcus radiodurans bacterial phytochrome (DrBphP) and its subdomains. The photosensory unit (DrCBD-PHY) shows an unusually stable Pfr state with minimal dark reversion, whereas the histidine kinase (HK) domain facilitates dark reversion to the resting state. Size-exclusion chromatography reveals that all phytochrome fragments remain as dimers in the illuminated state and dark state. Still, the

elution profiles of all phytochrome fragments differ between the illuminated and dark states. The differences are observed reliably only when the whole UV-vis spectrum is characterized along the elution profile and show more Pfr-state characteristics at later elution volumes in DrBphP and DrCBD-PHY fragments. This implies that the PHY domain has an important role in amplifying and relaying light-induced conformational changes to the HK domain. In the illuminated state, the HK domain appears partially unfolded and prone to form oligomers. The oligomerization of DrBphP can be diminished by converting the molecule back to the resting Pr state by using far-red light.

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Organisations: Multi-scaled biodata analysis and modelling (MultiBAM), University of Gothenburg, Department of Biological and Environmental Science, Jyväskylän yliopisto, Univ Jyvaskyla, University of Jyvaskyla, Dept Psychol, University of Texas, School of Medicine, Department of Epidemiology and Biostatistics, San Antonio, USA, School of Management (JKK), Fimlab Laboratories Ltd
Contributors: Takala, H., Lehtivuori, H., Hammarén, H., Hytönen, V. P., Ihalainen, J. A.
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Original language: English
ASJC Scopus subject areas: Biochemistry
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Global analysis of human nonreceptor tyrosine kinase specificity using high-density peptide microarrays
Protein kinases phosphorylate substrates in the context of specific phosphorylation site sequence motifs. The knowledge of the specific sequences that are recognized by kinases is useful for mapping sites of phosphorylation in protein substrates and facilitates the generation of model substrates to monitor kinase activity. Here, we have adapted a positional scanning peptide library method to a microarray format that is suitable for the rapid determination of phosphorylation site motifs for tyrosine kinases. Peptide mixtures were immobilized on glass slides through a layer of a tyrosine-free Y33F mutant avidin to facilitate the analysis of phosphorylation by radiolabel assay. A microarray analysis provided qualitatively similar results in comparison with the solution phase peptide library "macroarray" method. However, much smaller quantities of kinases were required to phosphorylate peptides on the microarrays, which thus enabled a proteome scale analysis of kinase specificity. We illustrated this capability by microarray profiling more than 80% of the human nonreceptor tyrosine kinases (NRTKs). Microarray results were used to generate a universal NRTK substrate set of 11 consensus peptides for in vitro kinase assays. Several substrates were highly specific for their cognate kinases, which should facilitate their incorporation into kinase-selective biosensors.

General information
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Organisations: Multi-scaled biodata analysis and modelling (MultiBAM), Yale School of Medicine, Bio21 Molecular Science and Biotechnology Institute, Fimlab Laboratories Ltd
Contributors: Deng, Y., Alicea-Velázquez, N. L., Bannwarth, L., Lehtonen, S. I., Boggon, T. J., Cheng, H. C., Hytönen, V. P., Turk, B. E.
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ASJC Scopus subject areas: Chemistry(all), Biochemistry
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Source: Scopus
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Calcium transients closely reflect prolonged action potentials in iPSC models of inherited cardiac arrhythmia
Long-QT syndrome mutations can cause syncope and sudden death by prolonging the cardiac action potential (AP). Ion channels affected by mutations are various, and the influences of cellular calcium cycling on LQTS cardiac events are unknown. To better understand LQTS arrhythmias, we performed current-clamp and intracellular calcium ($[Ca^{2+}]_i$) measurements on cardiomyocytes differentiated from patient-derived induced pluripotent stem cells (iPS-CM). In myocytes carrying an LQT2 mutation (HERG-A422T), APs and $[Ca^{2+}]_i$ transients were prolonged in parallel. APs were abbreviated by nifedipine exposure and further lengthened upon releasing intracellularly stored Ca^{2+}. Validating this model, control iPS-CM treated with HERG-blocking drugs recapitulated the LQT2 phenotype. In LQT3 iPS-CM, expressing $Na_V1.5$-N406K, APs and $[Ca^{2+}]_i$ transients were markedly prolonged. AP prolongation was sensitive to tetrodotoxin and to inhibiting Na^+-Ca^{2+} exchange. These results suggest that LQTS mutations act partly on cytosolic Ca^{2+} cycling, potentially providing a basis for functionally targeted interventions regardless of the specific mutation site.

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Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Gladstone Institute of Cardiovascular Disease, University of California San Francisco, Berkeley, University of Wisconsin School of Medicine and Public Health, Kyoto Women's University
Contributors: Spencer, C. I., Baba, S., Nakamura, K., Hua, E. A., Sears, M. A. F., Fu, C. C., Zhang, J., Balijepalli, S., Tomoda, K., Hayashi, Y., Lizarraga, P., Wojciak, J., Scheinman, M. M., Aalto-Setälä, K., Makielski, J. C., January, C. T., Healy, K. E., Kamp, T. J., Yamanaka, S., Conklin, B. R.
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ASJC Scopus subject areas: Biochemistry, Cell Biology, Developmental Biology, Genetics, Medicine(all)
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Research output: Contribution to journal › Article › Scientific › peer-review

Blood microRNA profile associates with the levels of serum lipids and metabolites associated with glucose metabolism and insulin resistance and pinpoints pathways underlying metabolic syndrome. The cardiovascular risk in Young Finns Study.

Since metabolic syndrome (MetS) is a collection of cardiovascular risk factors involving multiple signaling systems, we related the metabolic abnormalities associated with MetS with circulating microRNA profiles to pinpoint the affected signaling pathways. The blood microRNA profile, genome wide gene expression and serum NMR metabolomics were analyzed from 71 participants of the Young Finns Study.We found nine microRNAs that associated significantly with metabolites connected to MetS. MicroRNA-144-5p concentration correlated with glucose levels, hsa-1207-5p with glycosylated hemoglobin and hsa-miR-484 with metabolites related to insulin resistance. Hsa-miR-625-3p correlated with cholesterol levels, hsa-miR-1237-3p and hsa-miR-331-3p expression with certain fatty acids levels and hsa-miR-129-1-3p, -129-2-3p, and -1288-3p with glycerol levels. The down-regulated targets of miR-1207-5p and -129-2-3p were enriched in PI3K and MAPK pathways and 8 out of the 12 enriched pathways were down-regulated in individuals with MetS. In conclusion microRNAs associated with several aspects of MetS, possibly regulating glucose and lipid metabolism.

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Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Department of Clinical Chemistry, Tampere University Hospital, Turun Yliopisto/Turun Biomateriaalikeskus, University of Bristol, Ita-Suomen yliopisto, German Research Center for Environmental Health, Hannover Medical School, National Public Health Institute
Contributors: Raitoharju, E., Seppälä, I., Oksala, N., Lyytikäinen, L. P., Raitakari, O., Viikari, J., Ala-Korpela, M., Soininen, P., Kangas, A. J., Waldenberger, M., Klopp, N., Illig, T., Leiviskä, J., Loo, B. M., Hutri-Kähönen, N., Kähönen, M., Laaksonen, R., Lehtimäki, T.
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Light-fuelled transport of large dendrimers and proteins
This work presents a facile water-based supramolecular approach for light-induced surface patterning. The method is based upon azobenzene- functionalized high-molecular weight triazine dendrimers up to generation 9, demonstrating that even very large globular supramolecular complexes can be made to move in response to light. We also demonstrate light-fuelled macroscopic movements in native biomolecules, showing that complexes of apoferritin protein and azobenzene can effectively form light-induced surface patterns. Fundamentally, the results establish that thin films comprising both flexible and rigid globular particles of large diameter can be moved with light, whereas the presented material concepts offer new possibilities for the yet marginally explored biological applications of azobenzene surface patterning.

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Organisations: Frontier Photonics, COMP Centre of Excellence, Department of Applied Physics, Aalto University, Aalto University, Texas Christian University
Contributors: Koskela, J. E., Liljeström, V., Lim, J., Simanek, E. E., Ras, R. H. A., Priimagi, A., Kostiainen, M. A.
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Research output: Contribution to journal › Article › Scientific › peer-review

AROS has a context-dependent effect on SIRT1

The modulation of protein deacetylase SIRT1 has a vast therapeutic potential in treatment of several aging-associated diseases. Active regulator of SIRT1 (AROS) is a small endogenous protein which was originally reported to activate SIRT1 through a direct interaction in cancer cells. We show that the interaction between the two proteins is weak and does not alter the activity of SIRT1 in non-cancerous human cells. The results of different in vitro SIRT1 activity assays disclosed AROS as an inhibitor of SIRT1. The functional relationship between AROS and SIRT1 proved to be dependent on the biological context and experimental setting.

General information

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Organisations: Multi-scaled biodata analysis and modelling (MultiBAM), Ita-Suomen yliopisto
Contributors: Kokkola, T., Suuronen, T., Molnár, F., Määttä, J., Salminen, A., Jarho, E. M., Lahtela-Kakkonen, M.
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Research output: Contribution to journal › Article › Scientific › peer-review

NetBioV: An R package for visualizing large network data in biology and medicine

NetBioV (Network Biology Visualization) is an R package that allows the visualization of large network data in biology and medicine. The purpose of NetBioV is to enable an organized and reproducible visualization of networks by emphasizing or highlighting specific structural properties that are of biological relevance.

General information

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Organisations: Research Community on Data-to-Decision (D2D), Prostate cancer research center (PCRC), Queen's University, Belfast, Northern Ireland, Universität der Bundeswehr München, Computational Biology and Machine Learning
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Small-molecule induction promotes corneal epithelial cell differentiation from human induced pluripotent stem cells
Human induced pluripotent stem cells (hiPSCs) offer unique opportunities for developing novel cell-based therapies and disease modeling. In this study, we developed a directed differentiation method for hiPSCs toward corneal epithelial progenitor cells capable of terminal differentiation toward mature corneal epithelial-like cells. In order to improve the efficiency and reproducibility of our method, we replicated signaling cues active during ocular surface ectoderm development with the help of two small-molecule inhibitors in combination with basic fibroblast growth factor (bFGF) in serum-free and feeder-free conditions. First, small-molecule induction downregulated the expression of pluripotency markers while upregulating several transcription factors essential for normal eye development. Second, protein expression of the corneal epithelial progenitor marker p63 was greatly enhanced, with up to 95% of cells being p63 positive after 5 weeks of differentiation. Third, corneal epithelial-like cells were obtained upon further maturation.

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Contributors: Mikhailova, A., Ilmarinen, T., Uusitalo, H., Skottman, H.
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Gene Sets Net Correlations Analysis (GSNCA): A multivariate differential coexpression test for gene sets
Motivation: To date, gene set analysis approaches primarily focus on identifying differentially expressed gene sets (pathways). Methods for identifying differentially coexpressed pathways also exist but are mostly based on aggregated

pairwise correlations or other pairwise measures of coexpression. Instead, we propose Gene Sets Net Correlations Analysis (GSNCA), a multivariate differential coexpression test that accounts for the complete correlation structure between genes.Results: In GSNCA, weight factors are assigned to genes in proportion to the genes' cross-correlations (intergene correlations). The problem of finding the weight vectors is formulated as an eigenvector problem with a unique solution. GSNCA tests the null hypothesis that for a gene set there is no difference in the weight vectors of the genes between two conditions. In simulation studies and the analyses of experimental data, we demonstrate that GSNCA captures changes in the structure of genes' cross-correlations rather than differences in the averaged pairwise correlations. Thus, GSNCA infers differences in coexpression networks, however, bypassing method-dependent steps of network inference. As an additional result from GSNCA, we define hub genes as genes with the largest weights and show that these genes correspond frequently to major and specific pathway regulators, as well as to genes that are most affected by the biological difference between two conditions. In summary, GSNCA is a new approach for the analysis of differentially coexpressed pathways that also evaluates the importance of the genes in the pathways, thus providing unique information that may result in the generation of novel biological hypotheses.

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Contributors: Rahmatallah, Y., Emmert-Streib, F., Glazko, G.
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Research output: Contribution to journal › Article › Scientific › peer-review

Structure and barrier properties of human embryonic stem cell-derived retinal pigment epithelial cells are affected by extracellular matrix protein coating
Extracellular matrix (ECM) interactions play a vital role in cell morphology, migration, proliferation, and differentiation of cells. We investigated the role of ECM proteins on the structure and function of human embryonic stem cell-derived retinal pigment epithelial (hESC-RPE) cells during their differentiation and maturation from hESCs into RPE cells in adherent differentiation cultures on several human ECM proteins found in native human Bruch's membrane, namely, collagen I, collagen IV, laminin, fibronectin, and vitronectin, as well as on commercial substrates of xeno-free CELLstart™ and Matrigel™. Cell pigmentation, expression of RPE-specific proteins, fine structure, as well as the production of basal lamina by hESC-RPE on different protein coatings were evaluated after 140 days of differentiation. The integrity of hESC-RPE epithelium and barrier properties on different coatings were investigated by measuring transepithelial resistance. All coatings supported the differentiation of hESC-RPE cells as demonstrated by early onset of cell pigmentation and further maturation to RPE monolayers after enrichment. Mature RPE phenotype was verified by RPE-specific gene and protein expression, correct epithelial polarization, and phagocytic activity. Significant differences were found in the degree of RPE cell pigmentation and tightness of epithelial barrier between different coatings. Further, the thickness of self-assembled basal lamina and secretion of the key ECM proteins found in the basement membrane of the native RPE varied between hESC-RPE cultured on compared protein coatings. In conclusion, this study shows that the cell culture substrate has a major effect on the structure and basal lamina production during the differentiation and maturation of hESC-RPE potentially influencing the success of cell integrations and survival after cell transplantation.

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Contributors: Sorkio, A., Hongisto, H., Kaarniranta, K., Uusitalo, H., Juuti-Uusitalo, K., Skottman, H.
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ASJC Scopus subject areas: Bioengineering, Biochemistry, Biomaterials, Biomedical Engineering
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Research output: Contribution to journal › Article › Scientific › peer-review

Antioxidant supplementation reduces genomic aberrations in human induced pluripotent stem cells
Somatic cells can be reprogrammed to induced pluripotent stem cells (iPSCs) using oncogenic transcription factors. However, this method leads to genetic aberrations in iPSCs via unknown mechanisms, which may limit their clinical use. Here, we demonstrate that the supplementation of growth media with antioxidants reduces the genome instability of cells transduced with the reprogramming factors. Antioxidant supplementation did not affect transgene expression level or silencing kinetics. Importantly, iPSCs made with antioxidants had significantly fewer de novo copy number variations, but not fewer coding point mutations, than iPSCs made without antioxidants. Our results suggest that the quality and safety of human iPSCs might be enhanced by using antioxidants in the growth media during the generation and maintenance of iPSCs.

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Organisations: Computational Science X (CompX), Zhejiang University, Ontario Institute for Cancer Research, National Cancer Institute, Shanghai Institute of Ceramics Chinese Academy of Sciences, Key Laboratory of Regenerative Biology of the Chinese Academy of Sciences, University of Toronto, Canada
Contributors: Ji, J., Sharma, V., Qi, S., Guarch, M. E., Zhao, P., Luo, Z., Fan, W., Wang, Y., Mbabaali, F., Neculai, D., Esteban, M. A., McPherson, J. D., Batada, N. N.
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Natural thermal adaptation increases heat shock protein levels and decreases oxidative stress

Heat shock proteins (HSPs), originally identified as heat-inducible gene products, are a family of highly conserved proteins that respond to a wide variety of stress including oxidative stress. Although both acute and chronic oxidative stress have been well demonstrated to induce HSP responses, little evidence is available whether increased HSP levels provide enhanced protection against oxidative stress under elevated yet sublethal temperatures. We studied relationships between oxidative stress and HSPs in a physiological model by using Garra rufa (doctor fish), a fish species naturally acclimatized to different thermal conditions. We compared fish naturally living in a hot spring with relatively high water temperature (34.4±0.6. °C) to those living in normal river water temperature (25.4±4.7. °C), and found that levels of all the studied HSPs (HSP70, HSP60, HSP90, HSC70 and GRP75) were higher in fish living in elevated water temperature compared with normal river water temperature. In contrast, indicators of oxidative stress, including protein carbonyls and lipid hydroperoxides, were decreased in fish living in the elevated temperature, indicating that HSP levels are inversely associated with oxidative stress. The present results provide evidence that physiologically increased HSP levels provide protection against oxidative stress and enhance cytoprotection.

General information

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MoE publication type: A1 Journal article-refereed
Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), University of Tampere, Medical School, University of Hacettepe, University of Düzce, Ita-Suomen yliopisto, University Central Hospital Kuopio
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Source ID: 84912102339
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Shiga-like toxin binds with high avidity to multivalent O-linked blood group P1 determinants on mucin-type fusion proteins

The binding of Shiga-like toxin 1 (Stx1) and Shiga-like toxin 2 (Stx2) to a mucin-like fusion protein, P-selectin glycoprotein ligand-1/mouse IgG $_{2b}$ (PSGL-1/mIgG$_{2b}$), carrying multiple copies of the blood group P1 determinant on O-glycans was investigated with western blot and the biosensor Biacore. Chinese hamster ovary K-1 (CHO-K1) cells were stably transfected with linearized plasmids encoding the PSGL-1/mIgG$_{2b}$ fusion protein, the pigeon α1,4-galactosyltransferase (α4Gal-T) and the core 2 β1,6-N-acetylglucosaminyltransferase (C2GnT-I). Western blot analyses of purified PSGL-1/mIgG$_{2b}$ and liquid chromatography - mass spectrometry (LC-MS) of released O-glycans confirmed the presence of the P1 determinant. Western blot analysis indicated strong binding of Stx1, but not Stx2, to PSGL-1/mIgG$_{2b}$. In a Biacore assay, Stx1 and Stx2 were immobilized on a dextran chip and the binding of purified PSGL-1/mIgG $_{2b}$ and a P^k-albumin neoglycoprotein was analyzed. Stx1 and Stx2 bound with high avidity to both PSGL-1/mIgG$_{2b}$ and P^k-albumin, while the Stx1 binding was the strongest. In summary, we have shown that the pigeon α4Gal-T can be aberrantly expressed in CHO cells together with the core 2 enzyme to generate multiple, O-linked P1 determinants on a simultaneously expressed mucin-type fusion protein. P1-decorated PSGL-1/mIgG$_{2b}$ bound with high avidity to both Stx1 and Stx2, and as such constitutes a potential therapeutic inhibitor of these toxins.

General information

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Contributors: Maria Cherian, R., Gaunitz, S., Nilsson, A., Liu, J., Karlsson, N. G., Holgersson, J.
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Electrophoretic mobilities of neutral analytes and electroosmotic flow markers in aqueous solutions of Hofmeister salts
Small neutral organic compounds have traditionally the role of EOF markers in electrophoresis, as they are expected to have zero electrophoretic mobility in external electric fields. The BGE contains, however, ions that have unequal affinities to the neutral molecules, which in turn results in their mobilization. In this study we focused on two EOF markers-thiourea and DMSO, as well as on N-methyl acetamide (NMA) as a model of the peptide bond. By means of CE and all atom molecular dynamics simulations we explored mobilization of these neutral compounds in large set of Hofmeister salts. Employing a statistical mechanics approach, we were able to reproduce by simulations the experimental electrophoretic mobility coefficients. We also established the role of the chemical composition of marker and the BGE on the measured electrophoretic mobility coefficient. For NMA, we interpreted the results in terms of the relative affinities of cations versus anions to the peptide bond.

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Organisations: Computational Science X (CompX), Charles University in Prague, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Soft Matter and Functional Materials, Helmholtz-Zentrum Berlin
Contributors: Křížek, T., Kubíčková, A., Hladílková, J., Coufal, P., Heyda, J., Jungwirth, P.
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Functional and genetic analysis of the colon cancer network.

Cancer is a complex disease that has proven to be difficult to understand on the single-gene level. For this reason a functional elucidation needs to take interactions among genes on a systems-level into account. In this study, we infer a colon cancer network from a large-scale gene expression data set by using the method BC3Net. We provide a structural and a functional analysis of this network and also connect its molecular interaction structure with the chromosomal locations of the genes enabling the definition of cis- and trans-interactions. Furthermore, we investigate the interaction of genes that can be found in close neighborhoods on the chromosomes to gain insight into regulatory mechanisms. To our knowledge this is the first study analyzing the genome-scale colon cancer network.

General information

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Contributors: Emmert-Streib, F., de Matos Simoes, R., Glazko, G., McDade, S., Haibe-Kains, B., Holzinger, A., Dehmer, M., Campbell, F.
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Research output: Contribution to journal › Article › Scientific › peer-review

Kinetics of bioconjugate nanoparticle label binding in a sandwich-type immunoassay

Nanoparticle labels have enhanced the performance of diagnostic, screening, and other measurement applications and hold further promise for more sensitive, precise, and costeffective assay technologies. Nevertheless, a clear view of the biomolecular interactions on the molecular level is missing. Controlling the ratio of molecular recognition over undesired nonspecific adhesion is the key to improve biosensing with nanoparticles. To improve this ratio with an aim to disallow nonspecific binding, a more detailed perspective into the kinetic differences between the cases is needed. We present the application of two novel methods to determine complex binding kinetics of bioconjugate nanoparticles, interferometry, and force spectroscopy. Force spectroscopy is an atomic force microscopy technique and optical interferometry is a direct method to monitor reaction kinetics in second-hour timescale, both having steadily increasing importance in nanomedicine. The combination is perfectly suited for this purpose, due to the high sensitivity to detect binding events and the ability to investigate biological samples under physiological conditions. We have attached a single biofunctionalized nanoparticle to the outer tip apex and studied the binding behavior of the nanoparticle in a sandwich-type immunoassay using dynamic force spectroscopy in millisecond timescale. Utilization of the two novel methods allowed characterization of binding kinetics in a time range spanning from 50 ms to 4 h. These experiments allowed detection and demonstration of differences between specific and nonspecific binding. Most importantly, nonspecific binding of a nanoparticle was reduced at contact times below 100 ms with the solid-phase surface.

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Contributors: Näreoja, T., Ebner, A., Gruber, H. J., Taskinen, B., Kienberger, F., Hänninen, P. E., Hytönen, V. P., Hinterdorfer, P., Härmä, H.
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Novel derivatives of bacteriochlorophyll a: Complex formation with albumin and the mechanism of tumor cell photodamage

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MoE publication type: A1 Journal article-refereed
Organisations: Frontier Photonics, Emanuel' Institute of Biochemical Physics, Russian Academy of Sciences, M.V. Lomonosov Moscow State University of Fine Chemical Technologies, Georgian Technical University, St. Petersburg State Polytechnical University, N.N. Blokhin Russian Cancer Research Center, Russian Academy of Medical Sciences
Contributors: Akimova, A. V., Grin, M. A., Golovina, G. V., Kokrashvili, T. A., Vinogradov, A. M., Mironov, A. F., Rychkov, G. N., Shtil, A. A., Kuzmin, V. A., Durandin, N. A.
Number of pages: 4
Pages: 17-20
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Peer-reviewed: Yes

Publication information
Journal: DOKLADY BIOCHEMISTRY AND BIOPHYSICS
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Scopus rating (2014): CiteScore 0.38 SJR 0.208 SNIP 0.312
Original language: English
ASJC Scopus subject areas: Biophysics, Chemistry(all), Medicine(all), Biochemistry
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Source: Scopus
Source ID: 84896349301
Research output: Contribution to journal › Article › Scientific › peer-review

Recurrent thyroid cancers have more peritumoural lymphatic vasculature than nonrecurrent thyroid cancers

Background: The goal of the study was to evaluate angiogenesis and lymphangiogenesis in differentiated thyroid cancer and recurrences. Methods: Twenty-seven patients with recurrent differentiated thyroid cancer (20 papillary and seven follicular thyroid carcinomas) and 24 nonrecurrent thyroid cancers were included in this study. Additionally, 24 thyroid adenomas were included as benign controls. All thyroid cancer recurrences were operatively managed, and local recurrences in cervical lymph nodes or cervical soft tissue were histologically confirmed. Altogether, a total of 108 samples were evaluated using CD31 and D2-40 immunohistochemical staining and microscopy. Results: As measured in primary tumours, the median density of CD31-positive vascular structures was 327 vessels (v)/mm^2 for recurrent cancers, 362 v/mm^2 for nonrecurrent cancers and 484 v/mm^2 for thyroid adenomas (P = 0·017). Among the subgroups, the lowest median vascular density of 316 v/mm^2 was found in recurrent papillary cancers and the highest vascular density of 604 v/mm^2 was observed in nonrecurrent follicular cancers (P = 0·018). The median density of D2-40-positive peritumoural lymphatic vessels was 101/mm^2 in recurrent cancers, 56·1/mm^2 in nonrecurrent cancers and 53·9/mm^2 for adenomas (P = 0·015). In the subgroups, peritumoural lymphatic vascular density was 102 v/mm^2 in recurrent papillary cancers and

56·0 v/mm^2 in nonrecurrent papillary cancers (P = 0·044). Conclusions: Recurrent thyroid cancers expressed less intratumoural microvessels than thyroid adenomas. A high density of peritumoural lymphatic vessels was found in recurrent papillary cancers. High blood vessel density may be a marker for less aggressive tumours, while high peritumoural lymphatic vasculature is a marker for more aggressive and recurrence-prone tumours.

General information
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MoE publication type: A1 Journal article-refereed
Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Tampere University Hospital
Contributors: Hakala, T., Sand, J., Kellokumpu-Lehtinen, P. L., Huhtala, H., Leinonen, R., Kholová, I.
Number of pages: 8
Pages: 825-832
Publication date: 2014
Peer-reviewed: Yes

Publication information
Journal: European Journal of Clinical Investigation
Volume: 44
Issue number: 9
ISSN (Print): 0014-2972
Ratings:

Scopus rating (2014): CiteScore 2.74 SJR 1.252 SNIP 0.973
Original language: English
ASJC Scopus subject areas: Medicine(all), Clinical Biochemistry, Biochemistry
Keywords: Angiogenesis, Head and neck cancer, Histopathology, Lymphangiogenesis, Thyroid, Thyroid cancer
DOIs:

10.1111/eci.12301
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Source ID: 84906777634
Research output: Contribution to journal › Article › Scientific › peer-review

Report from the 2nd Summer School in Computational Biology organized by the Queen's University of Belfast
In this paper, we present a meeting report for the 2nd Summer School in Computational Biology organized by the Queen's University of Belfast. We describe the organization of the summer school, its underlying concept and student feedback we received after the completion of the summer school.

General information
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MoE publication type: A1 Journal article-refereed
Organisations: Research Community on Data-to-Decision (D2D), Computational Biology and Machine Learning, Queen's University, Belfast, Northern Ireland
Contributors: Emmert-Streib, F., Zhang, S. D., Hamilton, P.
Number of pages: 3
Pages: 37-39
Publication date: 2014
Peer-reviewed: Yes

Publication information
Journal: Genomics Data
Volume: 2
ISSN (Print): 2213-5960
Ratings:

Scopus rating (2014): CiteScore 0.33 SJR 0.238 SNIP 0.111
Original language: English
ASJC Scopus subject areas: Molecular Medicine, Biochemistry, Biotechnology, Genetics
Keywords: Computational biology, Genomics data, High-throughput data
DOIs:

10.1016/j.gdata.2013.12.001
URLs:

http://www.scopus.com/inward/record.url?scp=84920678698&partnerID=8YFLogxK (Link to publication in Scopus)
Source: Scopus
Source ID: 84920678698

Analysis of free, mono- and diacetylated polyamines from human urine by LC-MS/MS

Polyamines are promising biochemical markers of cancer and many other pathophysiological conditions, and thus their concentrations in biological fluids are a matter of interest. However, since the concentrations of these compounds are low, their quantitation is typically based on methods requiring laborious sample preparation. Here we developed and validated an LC-MS/MS method to analyze simultaneously free (DAP, PUT, CAD, SPD, SPM) monoacetylated (AcPUT, AcCAD, N^1AcSPD, N^8AcSPD, N^1AcSPM) and diacetylated (DiAcPUT, DiAcCAD, DiAcSPD, DiAcSPM) polyamines from human urine without the need for derivatization. Deuterium labeled polyamines were the internal standards for each analyte. Diluted urine samples spiked with internal standards were filtered through a strong anion exchange resin prior to LC-MS/MS analysis. The chromatographic separation of 14 polyamines was achieved in 12min on C18 column with 0.1% HFBA (v/v) as the ion-pairing agent and a water-acetonitrile gradient. Ionization was performed with positive electrospray ionization (ESI) and detection was with a triple quadrupole mass spectrometer with selected reaction monitoring. Calibration curves ranged from up to 5 to 10,000nM. The accuracy and precision of the method were determined using urine based quality control samples, and matrix effects were examined by using standard addition methods. This novel method is suitable for elucidating differences in urinary polyamine excretion in cancer patients and healthy humans.

General information

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MoE publication type: A1 Journal article-refereed
Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Ita-Suomen yliopisto, Tampere University Hospital, Karolinska University Hospital, School of Management (JKK)
Contributors: Häkkinen, M. R., Roine, A., Auriola, S., Tuokko, A., Veskimäe, E., Keinänen, T. A., Lehtimäki, T., Oksala, N. , Vepsäläinen, J.
Number of pages: 9
Pages: 81-89
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Publication information

Journal: JOURNAL OF CHROMATOGRAPHY B: ANALYTICAL TECHNOLOGIES IN THE BIOMEDICAL AND LIFE SCIENCES
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Scopus rating (2013): CiteScore 2.78 SJR 1.061 SNIP 1.278
Original language: English
ASJC Scopus subject areas: Analytical Chemistry, Biochemistry, Clinical Biochemistry, Cell Biology
Keywords: Cancer diagnostic markers, Liquid chromatography-tandem mass spectrometry, N-acetylated, Polyamines, Prostate cancer, Urine
DOIs:

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URLs:

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Source: Scopus
Source ID: 84887097655
Research output: Contribution to journal › Article › Scientific › peer-review

Mechanisms of acceleration and retardation of water dynamics by ions

There are fundamental and not yet fully resolved questions concerning the impact of solutes, ions in particular, on the structure and dynamics of water, which can be formulated as follows: Are the effects of ions local or long-ranged? Is the action of cations and anions on water cooperative or not? Here, we investigate how the reorientation and hydrogen-bond dynamics of water are affected by ions in dilute and concentrated aqueous salt solutions. By combining simulations and analytic modeling, we first show that ions have a short-ranged influence on the reorientation of individual water molecules and that depending on their interaction strength with water, they may accelerate or slow down water dynamics. A simple additive picture combining the effects of the cations and anions is found to provide a good description in dilute solutions. In concentrated solutions, we show that the average water reorientation time ceases to scale linearly with salt concentration due to overlapping hydration shells and structural rearrangements which reduce the translational displacements induced by hydrogen-bond switches and increase the solution viscosity. This effect is not ion-specific and explains why all concentrated salt solutions slow down water dynamics. Our picture, which is demonstrated to be robust vis-a-vis a change in the force-field, reconciles the seemingly contradictory experimental results obtained by ultrafast infrared and NMR spectroscopies, and suggests that there are no long-ranged cooperative ion effects on the dynamics of individual water molecules in dilute solutions.

General information
Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Computational Science X (CompX), Columbia University in the City of New York, Lund University, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, UMR ENS-CNRS-UPMC 8640
Contributors: Stirnemann, G., Wernersson, E., Jungwirth, P., Laage, D.
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Original language: English
ASJC Scopus subject areas: Chemistry(all), Catalysis, Biochemistry, Colloid and Surface Chemistry
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Source: Scopus
Source ID: 84882270662
Research output: Contribution to journal › Article › Scientific › peer-review

Identification, prioritization, and evaluation of glycoproteins for aggressive prostate cancer using quantitative glycoproteomics and antibody-based assays on tissue specimens
Prostate cancer is highly heterogeneous in nature; while the majority of cases are clinically insignificant, some cases are lethal. Currently, there are no reliable screening methods for aggressive prostate cancer. Since most established serum and urine biomarkers are glycoproteins secreted or leaked from the diseased tissue, the current study seeks to identify glycoprotein markers specific to aggressive prostate cancer using tissue specimens. With LC-MS/MS glycoproteomic analysis, we identified 350 glycopeptides with 17 being altered in aggressive prostate cancer. ELISA assays were developed/purchased to evaluate four candidates, that is, cartilage oligomeric matrix protein (COMP), periostin, membrane primary amine oxidase (VAP-1), and cathepsin L, in independent tissue sets. In agreement with the proteomic analysis, we found that COMP and periostin expressions were significantly increased in aggressive prostate tumors while VAP-1 expression was significantly decreased in aggressive tumor. In addition, the expression of these proteins in prostate metastases also follows the same pattern observed in the proteomic analysis. This study provides a workflow for biomarker discovery, prioritization, and evaluation of aggressive prostate cancer markers using tissue specimens. Our data suggest that increase in COMP and periostin and decrease in VAP-1 expression in the prostate may be associated with aggressive prostate cancer.

General information
Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Prostate cancer research center (PCRC), Johns Hopkins University, School of Management (JKK)
Contributors: Chen, J., Xi, J., Tian, Y., Bova, G. S., Zhang, H.
Number of pages: 10
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Journal: Proteomics
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Issue number: 15
ISSN (Print): 1615-9853
Ratings:

Scopus rating (2013): CiteScore 3.88 SJR 1.488 SNIP 0.978
Original language: English
ASJC Scopus subject areas: Molecular Biology, Biochemistry
Keywords: Aggressive, Biomarker, Glycoproteomics, OCT, Prostate cancer
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Source: Scopus
Source ID: 84881222169
Research output: Contribution to journal › Article › Scientific › peer-review

Development and characterization of poly(ε-caprolactone) hollow fiber membranes for vascular tissue engineering

The fabrication of tissue-engineered scaffolds for small-caliber blood vessels still remains a challenge. In the present work, we prepared poly(ε-caprolactone) (PCL) hollow fiber (HF) membranes, suitable for small-diameter blood vessel regeneration, by a phase separation spinning technique. The difficulty of processing PCL, a highly elastic material prone to suffer die swelling by extrusion, was overcome by tailoring the dope solution temperature and extrusion flow rate during the spinning procedure. The influence of the composition of the coagulation bath (water, ethanol, isopropanol) on the HF membrane physico-chemical properties (morphology, transport and mechanical properties) and cell attachment and proliferation was studied. The HF membranes fabricated using ethanol as coagulation bath had the most uniform morphology, good mechanical and transport properties and showed human adipose stem cell attachment and proliferation. Therefore, these fibers are promising scaffolds for small-caliber blood vessel regeneration.

General information

Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), University of Cantabria, University of Twente
Contributors: Diban, N., Haimi, S., Bolhuis-Versteeg, L., Teixeira, S., Miettinen, S., Poot, A., Grijpma, D., Stamatialis, D.
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Publication information

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Volume: 438
ISSN (Print): 0376-7388
Ratings:

Scopus rating (2013): CiteScore 5.38 SJR 2.451 SNIP 1.98
Original language: English
ASJC Scopus subject areas: Physical and Theoretical Chemistry, Materials Science(all), Biochemistry, Filtration and Separation
Keywords: Adipose stem cell, Hollow fiber, Phase-inversion, Poly(ε-caprolactone), Vascular regeneration
DOIs:

10.1016/j.memsci.2013.03.024
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Source: Scopus
Source ID: 84876440642
Research output: Contribution to journal › Article › Scientific › peer-review

The highly dynamic oligomeric structure of bradavidin II is unique among avidin proteins

Bradavidin II is a biotin-binding protein from Bradyrhizobium japonicum that resembles chicken avidin and bacterial streptavidin. A biophysical characterization was carried out using dynamic light scattering, native mass spectrometry, differential scanning calorimetry, and isothermal titration calorimetry combined with structural characterization using X-ray crystallography. These observations revealed that bradavidin II differs from canonical homotetrameric avidin protein family members in its quaternary structure. In contrast with the other avidins, bradavidin II appears to have a dynamic (transient) oligomeric state in solution. It is monomeric at low protein concentrations but forms higher oligomeric assemblies at higher concentrations. The crystal structure of bradavidin II revealed an important role for Phe42 in shielding the bound ligand from surrounding water molecules, thus functionally replacing the L7,8 loop essential for tight ligand binding in avidin and streptavidin. This bradavidin II characterization opens new avenues for oligomerizationindependent biotin-binding protein development.

General information

Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Multi-scaled biodata analysis and modelling (MultiBAM), Institute of Biomedical Technology, Tampere University Hospital, Hebrew University of Jerusalem, BioMediTech, Ita-Suomen yliopisto, Fimlab Laboratories Ltd

Contributors: Leppiniemi, J., Meir, A., Kahkonen, N., Kukkurainen, S., Maatta, J. A., Ojanen, M., Janis, J., Kulomaa, M. S. , Livnah, O., Hytonen, V. P.
Number of pages: 15
Pages: 980-994
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Peer-reviewed: Yes

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Volume: 22
Issue number: 7
ISSN (Print): 0961-8368
Ratings:

Scopus rating (2013): CiteScore 2.96 SJR 1.995 SNIP 0.813
Original language: English
ASJC Scopus subject areas: Biochemistry, Molecular Biology
Keywords: Dynamic structure, Ligand binding, Oligomeric state, Structural cooperativity
DOIs:

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Source: Scopus
Source ID: 84881284521
Research output: Contribution to journal › Article › Scientific › peer-review

Non-coding RNAs in DNA damage and repair
Non-coding RNAs (ncRNAs) are increasingly recognized as central players in diverse biological processes. Upon DNA damage, the DNA damage response (DDR) elicits a complex signaling cascade, which includes the induction of multiple ncRNA species. Recent studies indicate that DNA-damage induced ncRNAs contribute to regulation of cell cycle, apoptosis and DNA repair, and thus play a key role in maintaining genome stability. This review summarizes the emerging role of ncRNAs in DNA damage and repair.

General information
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MoE publication type: A2 Review article in a scientific journal
Organisations: Computational Science X (CompX), National Cancer Institute
Contributors: Sharma, V., Misteli, T.
Number of pages: 8
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Peer-reviewed: Yes

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Volume: 587
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ISSN (Print): 0014-5793
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Scopus rating (2013): CiteScore 3.71 SJR 2.356 SNIP 0.982
Original language: English
ASJC Scopus subject areas: Biochemistry, Biophysics, Cell Biology, Genetics, Molecular Biology, Structural Biology
Keywords: Non-coding RNA DNA damage Repair miRNA Long non-coding RNA Genome integrity
DOIs:

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Source: Scopus
Source ID: 84878919248
Research output: Contribution to journal › Review Article › Scientific › peer-review

Resonance assignments of the 56 kDa chimeric avidin in the biotin-bound and free forms
Avidin is a homotetrameric ~56 kDa protein found in chicken egg white. Avidin's ability to bind biotin with a very high affinity has widely been exploited in biotechnological applications. Protein engineering has further diversified avidin's feasibility. ChiAVD(I117Y) is a product of rational protein engineering. It is a hyperthermostable synthetic hybrid of avidin

and avidin-related protein 4 (AVR4). In this chimeric protein a 23-residue segment in avidin has been replaced with the corresponding sequence found in AVR4, and a point mutation at subunit interface 1-3 (and 2-4) has been introduced. Here we report the backbone and sidechain resonance assignments of the biotin-bound form of ChiAVD(I117Y) as well as the backbone resonance assignments of the free form.

General information

Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Multi-scaled biodata analysis and modelling (MultiBAM), University of Helsinki Institute of Biotechnology, School of Management (JKK), BioMediTech
Contributors: Tossavainen, H., Helppolainen, S. H., Määttä, J. A. E., Pihlajamaa, T., Hytönen, V. P., Kulomaa, M. S., Permi, P.
Number of pages: 4
Pages: 35-38
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Peer-reviewed: Yes

Publication information

Journal: BIOMOLECULAR NMR ASSIGNMENTS
Volume: 7
Issue number: 1
ISSN (Print): 1874-2718
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Original language: English
ASJC Scopus subject areas: Structural Biology, Biochemistry
Keywords: Biotin, Chimeric avidin, Ligand binding, NMR, Thermostability
DOIs:

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Source: Scopus
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Research output: Contribution to journal › Article › Scientific › peer-review

How the amyloid-β peptide and membranes affect each other: An extensive simulation study

The etiology of Alzheimer's disease is thought to be linked to interactions between amyloid-β (Aβ) and neural cell membranes, causing membrane disruption and increased ion conductance. The effects of Aβ on lipid behavior have been characterized experimentally, but structural and causal details are lacking. We used atomistic molecular dynamics simulations totaling over 6 μs in simulation time to investigate the behavior of $A\beta_{42}$ in zwitterionic and anionic lipid bilayers. We simulated transmembrane β-sheets (monomer and tetramer) resulting from a global optimization study and a helical structure obtained from an NMR study. In all simulations $A\beta_{42}$ remained embedded in the bilayer. It was found that the surface charge and the lipid tail type are determinants for transmembrane stability of $A\beta_{42}$ with zwitterionic surfaces and unsaturated lipids promoting stability. From the considered structures, the β-sheet tetramer is most stable as a result of interpeptide interactions. We performed an in-depth analysis of the translocation of water in the $A\beta_{42}$-bilayer systems. We observed that this process is generally fast (within a few nanoseconds) yet generally slower than in the peptide-free bilayers. It is mainly governed by the lipid type, simulation temperature and $A\beta_{42}$ conformation. The rate limiting step is the permeation through the hydrophobic core, where interactions between $A\beta_{42}$ and permeating H_2O molecules slow the translocation process. The β-sheet tetramer allows more water molecules to pass through the bilayer compared to monomeric Aβ, allowing us to conclude that the experimentally observed permeabilization of membranes must be due to membrane-bound Aβ oligomers, and not monomers.

General information

Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Computational Science X (CompX), Forschungszentrum Jülich (FZJ), University of Hertfordshire, Heinrich Heine University Düsseldorf
Contributors: Poojari, C., Kukol, A., Strodel, B.
Number of pages: 13
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Peer-reviewed: Yes

Publication information

Journal: Biochimica et Biophysica Acta: Biomembranes

Volume: 1828
Issue number: 2
ISSN (Print): 0005-2736
Ratings:

Scopus rating (2013): CiteScore 3.45 SJR 1.632 SNIP 0.992
Original language: English
ASJC Scopus subject areas: Biochemistry, Cell Biology, Biophysics
Keywords: Alzheimer's disease, Amyloid-beta peptide, Molecular simulations, Phospholipid membranes, Water permeation
DOIs:

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Source: Scopus
Source ID: 84869868315
Research output: Contribution to journal › Article › Scientific › peer-review

Visualizing functional motions of membrane transporters with molecular dynamics simulations

Computational modeling and molecular simulation techniques have become an integral part of modern molecular research. Various areas of molecular sciences continue to benefit from, indeed rely on, the unparalleled spatial and temporal resolutions offered by these technologies, to provide a more complete picture of the molecular problems at hand. Because of the continuous development of more efficient algorithms harvesting ever-expanding computational resources, and the emergence of more advanced and novel theories and methodologies, the scope of computational studies has expanded significantly over the past decade, now including much larger molecular systems and far more complex molecular phenomena. Among the various computer modeling techniques, the application of molecular dynamics (MD) simulation and related techniques has particularly drawn attention in biomolecular research, because of the ability of the method to describe the dynamical nature of the molecular systems and thereby to provide a more realistic representation, which is often needed for understanding fundamental molecular properties. The method has proven to be remarkably successful in capturing molecular events and structural transitions highly relevant to the function and/or physicochemical properties of biomolecular systems. Herein, after a brief introduction to the method of MD, we use a number of membrane transport proteins studied in our laboratory as examples to showcase the scope and applicability of the method and its power in characterizing molecular motions of various magnitudes and time scales that are involved in the function of this important class of membrane proteins.

General information

Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Computational Science X (CompX), Univ Illinois, University of Illinois System, University of Illinois Urbana-Champaign, Frederick Seitz Mat Res Lab, Dept Mat Sci & Engn, Department of Biochemistry
Contributors: Shaikh, S. A., Li, J., Enkavi, G., Wen, P. C., Huang, Z., Tajkhorshid, E.
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ISSN (Print): 0006-2960
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Scopus rating (2013): CiteScore 3.28 SJR 2.154 SNIP 0.971
Original language: English
ASJC Scopus subject areas: Biochemistry
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Source: Scopus
Source ID: 84873845174
Research output: Contribution to journal › Article › Scientific › peer-review

Hollow fibers of poly(lactide-co-glycolide) and poly(ε-caprolactone) blends for vascular tissue engineering applications

At present the manufacture of small-diameter blood vessels is one of the main challenges in the field of vascular tissue engineering. Currently available vascular grafts rapidly fail due to development of intimal hyperplasia and thrombus formation. Poly(lactic-co-glycolic acid) (PLGA) hollow fiber (HF) membranes have previously been proposed for this application, but as we show in the present work, they have an inhibiting effect on cell proliferation and rather poor mechanical properties. To overcome this we prepared HF membranes via phase inversion using blends of PLGA with poly(ε-caprolactone) (PCL). The influence of polymer composition on the HF physicochemical properties (topography, water transport and mechanical properties) and cell attachment and proliferation were studied. Our results show that only the ratio PCL/PLGA of 85/15 (PCL/PLGA85/15) yielded a miscible blend after processing. A higher PLGA concentration in the blend led to immiscible PCL/PLGA phase-separated HFs with an inhomogeneous morphology and variation in the cell culture results. In fact, the PCL/PLGA85/15 blend, which had the most homogeneous morphology and suitable pore structure, showed better human adipose stem cell (hASC) attachment and proliferation compared with the homopolymers. This, combined with the good mechanical and transport properties, makes them potentially useful for the development of small-caliber vascular grafts.

General information

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Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), University of Cantabria, University of Twente, BioMediTech, University of Groningen
Contributors: Diban, N., Haimi, S., Bolhuis-Versteeg, L., Teixeira, S., Miettinen, S., Poot, A., Grijpma, D., Stamatialis, D.
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Publication information

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Volume: 9
Issue number: 5
ISSN (Print): 1742-7061
Ratings:

Scopus rating (2013): CiteScore 6.41 SJR 1.988 SNIP 2.225
Original language: English
ASJC Scopus subject areas: Biomaterials, Biomedical Engineering, Biotechnology, Biochemistry, Molecular Biology
Keywords: Blends, Hollow fibers, Poly(ε-caprolactone), Poly(lactide-co-glycolide), Vascular tissue engineering
DOIs:

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URLs:

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Source ID: 84879884261
Research output: Contribution to journal › Article › Scientific › peer-review

Molecular mechanism of T-cell protein tyrosine phosphatase (TCPTP) activation by mitoxantrone

T-cell protein tyrosine phosphatase (TCPTP) is a ubiquitously expressed non-receptor protein tyrosine phosphatase. It is involved in the negative regulation of many cellular signaling pathways. Thus, activation of TCPTP could have important therapeutic applications in diseases such as cancer and inflammation. We have previously shown that the α-cytoplasmic tail of integrin $\alpha_1\beta_1$ directly binds and activates TCPTP. In addition, we have identified in a large-scale high-throughput screen six small molecules that activate TCPTP. These small molecule activators include mitoxantrone and spermidine. In this study, we have investigated the molecular mechanism behind agonist-induced TCPTP activation. By combining several molecular modeling and biochemical techniques, we demonstrate that α_1-peptide and mitoxantrone activate TCPTP via direct binding to the catalytic domain, whereas spermidine does not interact with the catalytic domain of TCPTP in vitro. Furthermore, we have identified a hydrophobic groove surrounded by negatively charged residues on the surface of TCPTP as a putative binding site for the α_1-peptide and mitoxantrone. Importantly, these data have allowed us to identify a new molecule that binds to TCPTP, but interestingly cannot activate its phosphatase activity. Accordingly, we describe here mechanism of TCPTP activation by mitoxantrone, the cytoplasmic tail of α_1-integrin, and a mitoxantrone-like molecule at the atomic level. These data provide invaluable insight into the development of novel TCPTP activators, and may facilitate the rational discovery of small-molecule cancer therapeutics.

General information

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MoE publication type: A1 Journal article-refereed
Organisations: Multi-scaled biodata analysis and modelling (MultiBAM), Jyväskylän yliopisto, Turku Centre for Biotechnology, Turun Yliopisto/Turun Biomateriaalikeskus, School of Management (JKK)

Contributors: Ylilauri, M., Mattila, E., Nurminen, E. M., Käpylä, J., Niinivehmas, S. P., Määttä, J. A., Pentikäinen, U., Ivaska, J., Pentikäinen, O. T.
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Keywords: Differential scanning fluorimetry, Integrin, Isothermal titration calorimetry, Mitoxantrone, Molecular dynamics simulation, T-cell protein tyrosine phosphatase
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Gene set analysis for self-contained tests: Complex null and specific alternative hypotheses
Motivation: The analysis of differentially expressed gene sets became a routine in the analyses of gene expression data. There is a multitude of tests available, ranging from aggregation tests that summarize gene-level statistics for a gene set to true multivariate tests, accounting for intergene correlations. Most of them detect complex departures from the null hypothesis but when the null hypothesis is rejected the specific alternative leading to the rejection is not easily identifiable. Results: In this article we compare the power and Type I error rates of minimum-spanning tree (MST)-based non-parametric multivariate tests with several multivariate and aggregation tests, which are frequently used for pathway analyses. In our simulation study, we demonstrate that MST-based tests have power that is for many settings comparable with the power of conventional approaches, but outperform them in specific regions of the parameter space corresponding to biologically relevant configurations. Further, we find for simulated and for gene expression data that MST-based tests discriminate well against shift and scale alternatives. As a general result, we suggest a two-step practical analysis strategy that may increase the interpretability of experimental data: first, apply the most powerful multivariate test to find the subset of pathways for which the null hypothesis is rejected and second, apply MST-based tests to these pathways to select those that support specific alternative hypotheses.

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Organisations: Prostate cancer research center (PCRC), University of Arkansas for Medical Sciences, Computational Biology and Machine Learning, Queen's University, Belfast, Northern Ireland
Contributors: Rahmatallah, Y., Emmert-Streib, F., Glazko, G.
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Research output: Contribution to journal › Article › Scientific › peer-review

Biophysics of lipid bilayers containing oxidatively modified phospholipids: Insights from fluorescence and EPR experiments and from MD simulations

This review focuses on the influence of oxidized phosphatidylcholines (oxPCs) on the biophysical properties of model membranes and is limited to fluorescence, EPR, and MD studies. OxPCs are divided into two classes: A) hydroxy- or hydroperoxy-dieonyl phospatidylcholines, B) phospatidylcholines with oxidized and truncated chains with either aldehyde or carboxylic group. It was shown that the presence of the investigated oxPCs in phospholipid model membranes may have the following consequences: 1) decrease of the lipid order, 2) lowering of phase transition temperatures, 3) lateral expansion and thinning of the bilayer, 4) alterations of bilayer hydration profiles, 5) increased lipid mobility, 6) augmented flip-flop, 7) influence on the lateral phase organisation, and 8) promotion of water defects and, under extreme conditions (i.e. high concentrations of class B oxPCs), disintegration of the bilayer. The effects of class A oxPCs appear to be more moderate than those observed or predicted for class B. Many of the abovementioned findings are related to the ability of the oxidized chains of certain oxPCs to reorient toward the water phase. Some of the effects appear to be moderated by the presence of cholesterol. Although those biophysical alternations are found at oxPC concentrations higher than the total oxPC concentrations found under physiological conditions, certain organelles may reach such elevated oxPC concentrations locally. It is a challenge for the future to correlate the biophysics of oxidized phospholipids to metabolic studies in order to define the significance of the findings presented herein for pathophysiology. This article is part of a Special Issue entitled: Oxidized phospholipids - their properties and interactions with proteins.

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Organisations: Computational Science X (CompX), J. Heyrovský Institute of Physical Chemistry, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Universita degli Studi di Bari
Contributors: Jurkiewicz, P., Olzyńska, A., Cwiklik, L., Conte, E., Jungwirth, P., Megli, F. M., Hof, M.
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Research output: Contribution to journal › Review Article › Scientific › peer-review

Endocrine prevention and treatment of prostate cancer

The major androgen within the prostate is dihydrotestosterone (DHT). DHT and 5α-reductase are highly associated with prostate cancer. It has been hypothesised that inhibition of 5α-reductase activity might reduce the risk of prostate cancer development, slow tumour progression and even treat the existing disease. The basis for endocrine treatment of prostate cancer is to deprive the cancer cells of androgens. Every type of endocrine treatment carries adverse events which influence quality of life in different ways.5α-Reductase inhibitors (5-ARI) reduce risk of being diagnosed with prostate cancer but they do not eliminate it. By suppressing PSA from BPH and indolent prostate cancers 5-ARI enhances the ability of a rising PSA to define a group of men at increased risk of clinically significant prostate cancer. Also fewer high-grade cancers are missed because biopsy is more accurate in smaller prostates.Androgen deprivation is an effective treatment for patients with advanced prostate cancer. However, it is not curative, and creates a spectrum of unwanted effects that influence quality of life. Castration remains the frontline treatment for metastatic prostate cancer, where orchiectomy, oestrogen agonists, GnRH agonists and antagonists produce equivalent clinical responses. MAB is not

significantly more effective than single agent GnRH agonist or orchiectomy. Nonsteroidal antiandrogen monotherapy is as effective as castration in treatment of locally advanced prostate cancer offering quality of life benefits. Neoadjuvant endocrine treatment has its place mainly in the external beam radiotherapy setting. Increasing data suggest IAD is as effective as continuous ADT. The decision regarding the type of androgen deprivation should be made individually after informing the patient of all available treatment options, including watchful waiting, and on the basis of potential benefits and adverse effects. There are new promising secondary or tertiary forms of endocrine therapies under evaluation, like CTP17A1 inhibitors and more potent antiandrogens including MDV3100, which give new hope for patients developing castration resistant prostate cancer.

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Contributors: Tammela, T. L. J.
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Molecular mechanisms of ion-specific effects on proteins
The specific binding sites of Hofmeister ions with an uncharged 600-residue elastin-like polypeptide, $(VPGVG)_{120}$, were elucidated using a combination of NMR and thermodynamic measurements along with molecular dynamics simulations. It was found that the large soft anions such as SCN^- and I^- interact with the polypeptide backbone via a hybrid binding site that consists of the amide nitrogen and the adjacent α-carbon. The hydrocarbon groups at these sites bear a slight positive charge, which enhances anion binding without disrupting specific hydrogen bonds to water molecules. The hydrophobic side chains do not contribute significantly to anion binding or the corresponding salting-in behavior of the biopolymer. Cl^- binds far more weakly to the amide nitrogen/α-carbon binding site, while SO_4^{2-} is repelled from both the backbone and hydrophobic side chains of the polypeptide. The Na^+ counterions are also repelled from the polypeptide. The identification of these molecular-level binding sites provides new insights into the mechanism of peptide-anion interactions.

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MoE publication type: A1 Journal article-refereed
Organisations: Computational Science X (CompX), Texas A and M University, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic
Contributors: Rembert, K. B., Paterová, J., Heyda, J., Hilty, C., Jungwirth, P., Cremer, P. S.
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Research output: Contribution to journal › Article › Scientific › peer-review

Neuroprotective effect of RO-20-1724-a phosphodiesterase4 inhibitor against intracerebroventricular streptozotocin induced cognitive deficit and oxidative stress in rats

Cyclic nucleotides viz cGMP and cAMP are known to play an important role in learning and memory processes. Enhancement of cyclic nucleotide signalling through inhibition of phosphodiesterases (PDEs) has been reported to be beneficial in several neurodegenerative disorders associated with cognitive decline. The present study was undertaken to investigate the effect of RO-20-1724-a PDE4 inhibitor on streptozotocin (STZ) induced experimental sporadic dementia of Alzheimer's type. The STZ was injected twice intracerebroventrically (3 mg/kg i.c.v.) on alternate days (day 1 and day 3) in rats. The STZ injected rats were treated with RO-20-1724 (125, 250 and 500 μg/kg i.p.) for 21 days following first i.c.v. STZ administration. Learning and memory in rats were assessed by passive avoidance [PA (days 14 and 15)] and Morris water maze [MWM (days 17, 18, 19, 20 and 21)] following first i.c.v. STZ administration. On day 22 rat cerebral homogenate was used for all the biochemical estimations. The pharmacological inhibition of PDE4 by RO-20-1724 significantly attenuated STZ induced cognitive deficit and oxidative stress. RO-20-1724 was found to not only improve learning and memory in MWM and PA paradigms but also restore STZ induced elevation in cholinesterase activity. Further, RO-20-1724 significantly reduced malondialdehyde and nitrite levels, and restored the glutathione levels indicating attenuation of oxidative stress. Current data complement previous studies by providing evidence for a subset of cognition enhancing effects after PDE4 inhibition. The observed beneficial effects of RO-20-1724 in spatial memory may be due to its ability to restore cholinergic functions and possibly through its antioxidant mechanisms.

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Organisations: Computational Science X (CompX), Neuropharmacology Div., ISF College of Pharmacy
Contributors: Sharma, V., Bala, A., Deshmukh, R., Bedi, K. L., Sharma, P. L.
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Histone H2B ubiquitin ligases RNF20 and RNF40 in androgen signaling and prostate cancer cell growth

Since data-mining from the Oncomine database revealed that expression of histone H2B K120 monoubiquitin (H2Bub1) ligase RNF20 is decreased in metastatic prostate cancer, we elucidated the effect of RNF20 and its homolog RNF40 on androgen receptor (AR)-dependent transcription and prostate cancer cell growth. Both RNF20 and RNF40 were able to

functionally and physically interact with the AR and modulate its transcriptional activity in intact cells. Chromatin immunoprecipitation analyses showed that the androgen induction of FKBP51 and PSA in LNCaP prostate cancer cells is accompanied with a dynamic increase in the H2Bub1 within the transcribed regions of these loci. Interestingly, depletion of RNF20 or RNF40 strongly retarded the growth of LNCaP cells, which was however unlikely to be due to altered androgen signaling, but due to decreased expression of several cell cycle promoters. Collectively, our results suggest that RNF20 and RNF40, either via ubiquitylation of H2B or other targets, are coupled to the proliferation of prostate cancer cells.

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Organisations: Prostate cancer research center (PCRC), Ita-Suomen yliopisto, Tampere University Hospital, The Rockefeller University, University Central Hospital Kuopio
Contributors: Jääskeläinen, T., Makkonen, H., Visakorpi, T., Kim, J., Roeder, R. G., Palvimo, J. J.
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Research output: Contribution to journal › Article › Scientific › peer-review

Counterion condensation in short cationic peptides: Limiting mobilities beyond the Onsager-Fuoss theory
We investigated the effect of the background electrolyte (BGE) anions on the electrophoretic mobilities of the cationic amino acids arginine and lysine and the polycationic peptides tetraarginine, tetralysine, nonaarginine, and nonalysine. BGEs composed of sodium chloride, sodium propane-1,3-disulfonate, and sodium sulfate were used. For the amino acids, determination of the limiting mobility by extrapolation, using the Onsager-Fuoss (OF) theory expression, yielded consistent estimates. For the peptides, however, the estimates of the limiting mobilities were found to spuriously depend on the BGE salt. This paradox was resolved using molecular modeling. Simulations, on all-atom as well as coarse-grained levels, show that significant counterion condensation, an effect not accounted for in OF theory, occurs for the tetra- and nonapeptides, even for low BGE concentrations. Including this effect in the quantitative estimation of the BGE effect on mobility removed the discrepancy between the estimated limiting mobilities in different salts. The counterion condensation was found to be mainly due to electrostatic interactions, with specific ion effects playing a secondary role. Therefore, the conclusions are likely to be generalizable to other analytes with a similar density of charged groups and OF theory is expected to fail in a predictable way for such analytes.

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Organisations: Computational Science X (CompX), Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Charles University in Prague
Contributors: Wernersson, E., Heyda, J., Kubíčková, A., Křížek, T., Coufal, P., Jungwirth, P.
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ASJC Scopus subject areas: Biochemistry, Clinical Biochemistry
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Production of l-xylose from l-xylulose using Escherichia coli l-fucose isomerase

l-Xylulose was used as a raw material for the production of l-xylose with a recombinantly produced Escherichia coli l-fucose isomerase as the catalyst. The enzyme had a very alkaline pH optimum (over 10.5) and displayed Michaelis-Menten kinetics for l-xylulose with a K_m of 41mM and a V_{max} of 0.23μmol/(mgmin). The half-lives determined for the enzyme at 35°C and at 45°C were 6h 50min and 1h 31min, respectively. The reaction equilibrium between l-xylulose and l-xylose was 15:85 at 35°C and thus favored the formation of l-xylose. Contrary to the l-rhamnose isomerase catalyzed reaction described previously [14] l-lyxose was not detected in the reaction mixture with l-fucose isomerase. Although xylitol acted as an inhibitor of the reaction, even at a high ratio of xylitol to l-xylulose the inhibition did not reach 50%.

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Contributors: Usvalampi, A., Turunen, O., Valjakka, J., Pastinen, O., Leisola, M., Nyyssölä, A.
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Source ID: 82455188020
Research output: Contribution to journal › Article › Scientific › peer-review

Human adipose tissue extract induces angiogenesis and adipogenesis in vitro

The induction of adequate vascularization, a major challenge in tissue engineering, has been tried with numerous methods but with unsatisfactory results. Adipose tissue, an active endocrine organ with dense vasculature, secretes a wide number of angiogenic and adipogenic factors and seems an attractive source for these bioactive factors. We produced a novel cell-free extract from mature human adipose tissue (adipose tissue extract [ATE]) and analyzed the ability of this extract to induce angiogenesis and adipogenesis in vitro and studied the cytokine and growth factor composition of ATE with ELISA and cytokine array. We demonstrate that ATE, when added as cell culture supplement, effectively induced triglyceride accumulation in human adipose stem cells at concentrations from 200 μg/mL upward in less than a week and caused elevated levels of adipocyte differentiation markers (proliferator-activated receptor gamma and acyl-CoA-binding protein) when treated with at least 350 μg/mL of ATE. ATE induced angiogenesis from 450 μg/mL upward after a week in vitro. ATE contained numerous angiogenic and adipogenic factors, for example, vascular endothelial growth factor, basic

fibroblast growth factor, interleukin-6, adiponectin, angiogenin, leptin, and insulin-like growth factor-I, as well as lower levels of a wide variety of other cytokines. We here present a novel cell-free angiogenesis-and adipogenesis-inducing agent that is cell-free and easy to produce, and its effect is dose dependent and its composition can be easily modified. Therefore, ATE is a promising novel agent to be used for angiogenesis induction to overcome the challenge of vascularization and for adipogenesis induction in a wide variety of tissue engineering applications in vitro and in vivo. ATE is also efficient for reproduction and modeling of natural adipogenesis in vitro for, for example, obesity and diabetes studies.

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Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Tampere University Hospital, University of Tampere, Medical School, BioMediTech
Contributors: Sarkanen, J. R., Kaila, V., Mannerström, B., Räty, S., Kuokkanen, H., Miettinen, S., Ylikomi, T.
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ASJC Scopus subject areas: Bioengineering, Biochemistry, Biomedical Engineering, Biomaterials, Medicine(all)
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Source ID: 84855405319
Research output: Contribution to journal › Article › Scientific › peer-review

Lipid hydration and mobility: An interplay between fluorescence solvent relaxation experiments and molecular dynamics simulations

Fluorescence solvent relaxation experiments are based on the characterization of time-dependent shifts in the fluorescence emission of a chromophore, yielding polarity and viscosity information about the chromophore's immediate environment. A chromophore applied to a phospholipid bilayer at a well-defined location (with respect to the z-axis of the bilayer) allows monitoring of the hydration and mobility of the probed segment of the lipid molecules. Specifically, time-resolved fluorescence experiments, fluorescence quenching data and molecular dynamic (MD) simulations show that 6-lauroyl-2-dimethylaminonaphthalene (Laurdan) probes the hydration and mobility of the sn-1 acyl groups in a phosphatidylcholine bilayer. The time-dependent fluorescence shift (TDFS) of Laurdan provides information on headgroup compression and expansion induced by the addition of different amounts of cationic lipids to phosphatidylcholine bilayers. Those changes were predicted by previous MD simulations. Addition of truncated oxidized phospholipids leads to increased mobility and hydration at the sn-1 acyl level. This experimental finding can be explained by MD simulations, which indicate that the truncated chains of the oxidized lipid molecules are looping back into aqueous phase, hence creating voids below the glycerol level. Fluorescence solvent relaxation experiments are also useful in understanding salt effects on the structure and dynamics of lipid bilayers. For example, such experiments demonstrate that large anions increase hydration and mobility at the sn-1 acyl level of phosphatidylcholine bilayers, an observation which could not be explained by standard MD simulations. If polarizability is introduced into the applied force field, however, MD simulations show that big soft polarizable anions are able to interact with the hydrophilic/hydrophobic interface of the lipid bilayer, penetrating to the level probed by Laurdan, and that they expand and destabilize the bilayer making it more hydrated and mobile.

General information

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Organisations: Computational Science X (CompX), J. Heyrovský Institute of Physical Chemistry, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic
Contributors: Jurkiewicz, P., Cwiklik, L., Jungwirth, P., Hof, M.
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Osteogenic medium is superior to growth factors in differentiation of human adipose stem cells towards boneforming cells in 3D culture

Human adipose stem cells (hASCs) have been recently used to treat bone defects in clinical practice. Yet there is a need for more optimal scaffolds and cost-effective approaches to induce osteogenic differentiation of hASCs. Therefore, we compared the efficiency of bone morphogenetic proteins (BMP-2 and BMP-7), vascular endothelial growth factor (VEGF), and osteogenic medium (OM) for the osteo-induction of hASCs in 3D culture. In addition, growth factors were tested in combination with OM. Commercially available bioactive glass scaffolds (BioRestore) and biphasic calcium phosphate granules (BoneCeramic) were evaluated as prospective carriers for hASCs. Both biomaterials supported hASC-viability, but BioRestore resulted in higher cell number than BoneCeramic, whereas BoneCeramic supported more significant collagen production. The most efficient osteo-induction was achieved with plain OM, promoting higher alkaline phosphatase activity and collagen production than growth factors. In fact, treatment with BMP-2 or VEGF did not increase osteogenic differentiation or cell number significantly more than maintenance medium with either biomaterial. Moreover, BMP-7 treatment consistently inhibited proliferation and osteogenic differentiation of hASCs. Interestingly, there was no benefit from growth factors added to OM. This is the first study to demonstrate that OM enhances hASC-differentiation towards bone-forming cells significantly more than growth factors in 3D culture.

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Contributors: Tirkkonen, L., Haimi, S., Huttunen, S., Wolff, J., Pirhonen, E., Sándor, G. K., Miettinen, S.
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Keywords: 3D scaffolds, Adipose stem cells, Bioactive glass, Biphasic calcium phosphate, Bone tissue engineering, Growth factors, In vitro culture, Mesenchymal stem cells, Osteogenic differentiation
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Source: Scopus
Source ID: 84878388600
Research output: Contribution to journal › Article › Scientific › peer-review

Structure-function analysis indicates that sumoylation modulates DNA-binding activity of STAT1

Background: STAT1 is an essential transcription factor for interferon-γ-mediated gene responses. A distinct sumoylation consensus site (ψKxE) ^{702}IKTE^{705} is localized in the C-terminal region of STAT1, where Lys703 is a target for PIAS-induced SUMO modification. Several studies indicate that sumoylation has an inhibitory role on STAT1-mediated gene expression but the molecular mechanisms are not fully understood. Results: Here, we have performed a structural and functional analysis of sumoylation in STAT1. We show that deconjugation of SUMO by SENP1 enhances the transcriptional activity of STAT1, confirming a negative regulatory effect of sumoylation on STAT1 activity. Inspection of molecular model indicated that consensus site is well exposed to SUMO-conjugation in STAT1 homodimer and that the conjugated SUMO moiety is directed towards DNA, thus able to form a sterical hindrance affecting promoter binding of dimeric STAT1. In addition, oligoprecipitation experiments indicated that sumoylation deficient STAT1 E705Q mutant has higher DNA-binding activity on STAT1 responsive gene promoters than wild-type STAT1. Furthermore, sumoylation deficient STAT1 E705Q mutant displayed enhanced histone H4 acetylation on interferon-γ- responsive promoter compared to wild-type STAT1. Conclusions: Our results suggest that sumoylation participates in regulation of STAT1 responses by modulating DNA-binding properties of STAT1.

General information

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Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Multi-scaled biodata analysis and modelling (MultiBAM), Ita-Suomen yliopisto, Tampere University Hospital
Contributors: Grönholm, J., Vanhatupa, S., Ungureanu, D., Väliaho, J., Laitinen, T., Valjakka, J., Silvennoinen, O.
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ASJC Scopus subject areas: Biochemistry, Molecular Biology
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http://www.scopus.com/inward/record.url?scp=84871785836&partnerID=8YFLogxK (Link to publication in Scopus)
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Source ID: 84871785836
Research output: Contribution to journal › Article › Scientific › peer-review

Structural Measures for Network Biology Using QuACN

Background: Structural measures for networks have been extensively developed, but many of them have not yet demonstrated their sustainably. That means, it remains often unclear whether a particular measure is useful and feasible to solve a particular problem in network biology. Exemplarily, the classification of complex biological networks can be named, for which structural measures are used leading to a minimal classification error. Hence, there is a strong need to provide freely available software packages to calculate and demonstrate the appropriate usage of structural graph measures in network biology.Results: Here, we discuss topological network descriptors that are implemented in the R-package QuACN and demonstrate their behavior and characteristics by applying them to a set of example graphs. Moreover, we show a representative application to illustrate their capabilities for classifying biological networks. In particular, we infer gene regulatory networks from microarray data and classify them by methods provided by QuACN. Note that QuACN is the first freely available software written in R containing a large number of structural graph measures.Conclusion: The R package QuACN is under ongoing development and we add promising groups of topological network descriptors continuously. The package can be used to answer intriguing research questions in network biology, e.g., classifying biological data or identifying meaningful biological features, by analyzing the topology of biological networks.

General information

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MoE publication type: A1 Journal article-refereed
Organisations: Research Community on Data-to-Decision (D2D), Institute for Bioinformatics and Translational Research, Computational Biology and Machine Learning Lab., Faculty of Medicine, Health and Life Sciences, Queen's University, Belfast, Northern Ireland

Contributors: Mueller, L. A. J., Kugler, K. G., Graber, A., Emmert-Streib, F., Dehmer, M.
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Article number: 492
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Original language: English
ASJC Scopus subject areas: Biochemistry, Molecular Biology, Computer Science Applications, Applied Mathematics, Structural Biology
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Modification of olivomycin A at the side chain of the aglycon yields the derivative with perspective antitumor characteristics
A novel way of chemical modification of the antibiotic olivomycin A (1) at the side chain of the aglycon moiety was developed. Interaction of olivomycin A with the sodium periodate produced the key acid derivative olivomycin SA (2) in 86% yield. This acid was used in the reactions with different amines in the presence of benzotriazol-1-yl-oxy-trispyrrolidino-phosphonium hexafluorophosphate (PyBOP) or diphenylphosphoryl azide (DPPA) to give corresponding amides. Whereas olivomycin SA was two orders of magnitude less cytotoxic than the parent antibiotic, the amides of 2 demonstrated a higher cytotoxicity. In particular, N,N-dimethylaminoethylamide of olivomycin SA showed a pronounced antitumor effect against transplanted experimental lymphoma and melanoma and a remarkably high binding constant to double stranded DNA. The therapeutic effects of this derivative were achievable at tolerable concentrations, suggesting that modifications of the aglycon's side chain, namely, its shortening to methoxyacetic residue and blocking of free carboxyl group, are straightforward for the design of therapeutically applicable derivatives of olivomycin A.

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MoE publication type: A2 Review article in a scientific journal
Organisations: Frontier Photonics, Russian Academy of Medical Sciences, N.N. Blokhin Russian Cancer Research Center, Russian Academy of Medical Sciences, Emanuel' Institute of Biochemical Physics, Russian Academy of Sciences
Contributors: Tevyashova, A. N., Shtil, A. A., Olsufyeva, E. N., Luzikov, Y. N., Reznikova, M. I., Dezhenkova, L. G., Isakova, E. B., Bukhman, V. M., Durandin, N. A., Vinogradov, A. M., Kuzmin, V. A., Preobrazhenskaya, M. N.
Number of pages: 7
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Original language: English
ASJC Scopus subject areas: Biochemistry, Molecular Medicine, Molecular Biology, Pharmaceutical Science, Drug Discovery, Clinical Biochemistry, Organic Chemistry
Keywords: Antibiotics, Antitumor activity, Aureolic acid, Chemical modifications, Drug-DNA complexes, Olivomycin A, Olivomycin SA
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Source ID: 82255193979
Research output: Contribution to journal › Review Article › Scientific › peer-review

Laser-induced primary and secondary hemostasis dynamics and mechanisms in relation to selective photothermolysis of port wine stains

Background: Superficial vascular anomalies such as port wine stains are commonly treated by selective photothermolysis (SP). The endovascular laser-tissue interactions underlying SP are governed by a photothermal response (thermocoagulation of blood) and a hemodynamic response (thrombosis). Currently it is not known whether the hemodynamic response encompasses both primary and secondary hemostasis, which platelet receptors are involved, and what the SP-induced thrombosis kinetics are in low-flow venules. Objectives: To (1) define the role and kinetics of primary and secondary hemostasis in laser-induced thrombus formation and (2) determine which key platelet surface receptors are involved in the hemodynamic response. Methods: 532-nm laser-irradiated hamster dorsal skin fold venules were studied by intravital fluorescence microscopy following fluorescent labeling of platelets with 5(6)-carboxyfluorescein. Heparin and fluorescently labeled anti-glycoprotein Ib-α (GPIbα) and anti-P-selectin antibodies were administered to investigate the role of coagulation and platelet receptors, respectively. Lesional sizes were quantified by software. Results: Laser irradiation consistently produced sub-occlusive thermal coagula. Thrombosis was triggered in all irradiated venules in a thermal coagulum-independent manner and peaked at 6.25. min post-irradiation. Heparin decreased the maximum thrombus size and caused thrombosis to reach a maximum at 1.25. min. Immunoblocking of GPIbα abated the extent of thrombosis, whereas immunoblocking of P-selectin had no effect. Conclusions: The hemodynamic response ensues the photothermal response in a thermal coagulum-independent manner and involves primary and secondary hemostasis. Primary hemostasis is mediated by constitutively expressed GPIbα but not by activation-dependent P-selectin.

General information

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MoE publication type: A1 Journal article-refereed
Organisations: Frontier Photonics, University of Amsterdam, KU Leuven, Lille University Hospital - CHRU, University of Montpellier
Contributors: Heger, M., Salles, I. I., Bezemer, R., Cloos, M. A., Mordon, S. R., Bégu, S., Deckmyn, H., Beek, J. F.
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Keywords: Glycoprotein Ib-alpha, Hamster dorsal skinfold model, P-selectin, Port wine stains, Site-specific pharmaco-laser therapy, Thermosensitive liposomes
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Research output: Contribution to journal › Article › Scientific › peer-review

Stabilization of the peroxy intermediate in the oxygen splitting reaction of cytochrome cbb_3

The proton-pumping cbb_3-type cytochrome c oxidases catalyze cell respiration in many pathogenic bacteria. For reasons not yet understood, the apparent dioxygen (O_2) affinity in these enzymes is very high relative to other members of the heme-copper oxidase (HCO) superfamily. Based on density functional theory (DFT) calculations on intermediates of the oxygen scission reaction in active-site models of cbb_3- and aa_3-type oxidases, we find that a transient peroxy intermediate (I_P, Fe[III]-OOH^-) is ~ 6 kcal/mol more stable in the former case, resulting in more efficient kinetic trapping of dioxygen and hence in a higher apparent oxygen affinity. The major molecular basis for this stabilization is a glutamate residue, polarizing the proximal histidine ligand of heme b_3 in the active site.

General information

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Organisations: Computational Science X (CompX), Programme for Structural Biology and Biophysics, University of Helsinki Institute of Biotechnology, National Institute of Diabetes and Digestive and Kidney Diseases
Contributors: Sharma, V., Wikström, M., Kaila, V. R. I.
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Source ID: 79956091140
Research output: Contribution to journal › Article › Scientific › peer-review

BACOM: In silico detection of genomic deletion types and correction of normal cell contamination in copy number data
Motivation: Identification of somatic DNA copy number alterations (CNAs) and significant consensus events (SCEs) in cancer genomes is a main task in discovering potential cancer-driving genes such as oncogenes and tumor suppressors. The recent development of SNP array technology has facilitated studies on copy number changes at a genome-wide scale with high resolution. However, existing copy number analysis methods are oblivious to normal cell contamination and cannot distinguish between contributions of cancerous and normal cells to the measured copy number signals. This contamination could significantly confound downstream analysis of CNAs and affect the power to detect SCEs in clinical samples. Results: We report here a statistically principled in silico approach, Bayesian Analysis of COpy number Mixtures (BACOM), to accurately estimate genomic deletion type and normal tissue contamination, and accordingly recover the true copy number profile in cancer cells. We tested the proposed method on two simulated datasets, two prostate cancer datasets and The Cancer Genome Atlas high-grade ovarian dataset, and obtained very promising results supported by the ground truth and biological plausibility. Moreover, based on a large number of comparative simulation studies, the proposed method gives significantly improved power to detect SCEs after in silico correction of normal tissue contamination. We develop a cross-platform open-source Java application that implements the whole pipeline of copy number analysis of heterogeneous cancer tissues including relevant processing steps. We also provide an R interface, bacomR, for running BACOM within the R environment, making it straightforward to include in existing data pipelines.

General information
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MoE publication type: A1 Journal article-refereed
Organisations: Prostate cancer research center (PCRC), Virginia Tech, Johns Hopkins School of Medicine, Wake Forest University School of Medicine
Contributors: Yu, G., Zhang, B., Bova, G. S., Xu, J., Shih, I. M., Wang, Y.
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Source ID: 79957859881
Research output: Contribution to journal › Article › Scientific › peer-review

Trans-interaction of nephrin and Neph1/Neph3 induces cell adhesion that associates with decreased tyrosine phosphorylation of nephrin

Slit diaphragms are specialized junctions between glomerular epithelial cells (podocytes) that are crucial for glomerular ultrafiltration. The Ig superfamily members nephrin and Neph1 are essential components of the slit diaphragm, whereas the role of Neph1 homologue Neph3 in the slit diaphragm is unknown. In the present paper we show that Neph3 homodimerizes and heterodimerizes with nephrin and Neph1.We further investigated whether these interactions play a role in cell adhesion by using mouse L fibroblasts that lack endogenous cell-adhesion activity and found that Neph1 and Neph3 are able to induce cell adhesion alone, whereas nephrin needs to trans-interact with Neph1 or Neph3 in order to promote formation of cell - cell contacts. Tyrosine phosphorylation of nephrin was down-regulated after nephrin trans-interacted with either Neph1 or Neph3 leading to formation of cell - cell contacts. We further found that the expression of Neph3 was increased in nephrin-deficient mouse podocytes. The findings of the present paper show that nephrin and Neph1 or Neph3 trans-interactions promote cell-contact formation, suggesting that they may also function together in slit diaphragm assembly.

General information

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MoE publication type: A1 Journal article-refereed
Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Haartman Institute, University of Guelph , Dublin City University
Contributors: Heikkilä, E., Ristola, M., Havana, M., Jones, N., Holthöfer, H., Lehtonen, S.
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ASJC Scopus subject areas: Biochemistry, Cell Biology, Molecular Biology
Keywords: Cell - cell contact, Neph family, Nephrin, Podocyte, Slit diaphragm
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http://www.scopus.com/inward/record.url?scp=79954471298&partnerID=8YFLogxK (Link to publication in Scopus)
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Source ID: 79954471298
Research output: Contribution to journal › Article › Scientific › peer-review

Detection of DNA hybridisation in a diluted serum matrix by surface plasmon resonance and film bulk acoustic resonators

Nanomolar quantities of single-stranded DNA products ~ 100 nucleotides long can be detected in diluted 1% serum by surface plasmon resonance (SPR) and film bulk acoustic resonators (FBARs). We have used a novel FBAR sensor in parallel with SPR and obtained promising results with both the acoustic and the optical device. Oligonucleotides and a repellent lipoamide, Lipa-DEA, were allowed to assemble on the sensor chip surfaces for only 15 min by dispensing. Lipa-DEA surrounds the analyte-binding probes on the surface and effectively reduces the non-specific binding of bovine serum albumin and non-complementary strands. In a highly diluted serum matrix, the non-specific binding is, however, a hindrance, and the background response must be reduced. Nanomolar concentrations of short complementary oligos could be detected in buffer, whereas the response was too low to be measured in serum. DNA strands that are approximately 100 base pairs long at concentrations as low as 1-nM could be detected both in buffer and in 1% serum by both SPR and the FBAR resonator.

General information

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Organisations: Multi-scaled biodata analysis and modelling (MultiBAM), VTT Technical Research Centre of Finland, HCI e 486.1, Siemens AG
Contributors: Auer, S., Nirschl, M., Schreiter, M., Vikholm-Lundin, I.
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Keywords: DNA hybridisation detection, DNA sensor, Film bulk acoustic resonator, Self-assembled monolayer, Serum, Surface plasmon resonance
DOIs:

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The identity of the transient proton loading site of the proton-pumping mechanism of cytochrome c oxidase
Cellular respiration is driven by cytochrome c oxidase (CcO), which reduces oxygen to water and couples the released energy to proton pumping across the mitochondrial or bacterial membrane. Proton pumping in CcO involves proton transfer from the negatively charged side of the membrane to a transient proton-loading or pump site (PLS), before it is ejected to the opposite side. Although many details of the reaction mechanism are known, the exact location of the PLS has remained elusive. We report here results from combined classical molecular dynamics simulations and continuum electrostatic calculations, which show that the hydrogen-bonded system around the A-propionate of heme a_3 dissociates reversibly upon reduction of heme a. The dissociation increases the pK_a value of the propionate to a value above ~9, making it accessible for redox-state dependent protonation. The redox state of heme a is of key importance in controlling proton leaks by polarizing the PLS both statically and dynamically. These findings suggest that the propionate region of heme a_3 fulfills the criteria of the pump site in the proton translocation mechanism of CcO.

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MoE publication type: A1 Journal article-refereed
Organisations: Computational Science X (CompX), National Institute of Diabetes and Digestive and Kidney Diseases, Programme for Structural Biology and Biophysics, University of Helsinki Institute of Biotechnology
Contributors: Kaila, V. R. I., Sharma, V., Wikström, M.
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Original language: English
ASJC Scopus subject areas: Biophysics, Biochemistry, Cell Biology
Keywords: Continuum electrostatics, Heme-copper oxidase, MD simulation, Proton pump, Proton-coupled electron transfer
DOIs:

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Source ID: 78249242740
Research output: Contribution to journal › Article › Scientific › peer-review

Efficient production of NV colour centres in nanodiamonds using high-energy electron irradiation

Nanodiamond powders with an average size of 50 nm have been irradiated using high-energy electron beam. After annealing and chemical treatment, nanodiamond colloidal solutions were obtained and deposited on silica coverslips by spin-coating. The fluorescence of nanodiamonds was studied by confocal microscopy together with atomic force microscopy. We evaluated the proportion of luminescent nanodiamonds as a function of the irradiation duration and showed that large quantities, exceeding hundreds of mg, of luminescent nanodiamonds can be produced within 1 h of electron irradiation.

General information

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Organisations: Laboratoire de Physique Quantique et Moléculaire
Contributors: Dantelle, G., Slablab, A., Rondin, L., Lainé, F., Carrel, F., Bergonzo, P., Perruchas, S., Gacoin, T., Treussart, F., Roch, J. F.
Number of pages: 4
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Original language: English
ASJC Scopus subject areas: Atomic and Molecular Physics, and Optics, Condensed Matter Physics, Chemistry(all), Biochemistry, Biophysics
Keywords: Diamond, Luminescence, NV centre
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Revealing differences in gene network inference algorithms on the network level by ensemble methods

Motivation: The inference of regulatory networks from large-scale expression data holds great promise because of the potentially causal interpretation of these networks. However, due to the difficulty to establish reliable methods based on observational data there is so far only incomplete knowledge about possibilities and limitations of such inference methods in this context. Results: In this article, we conduct a statistical analysis investigating differences and similarities of four network inference algorithms, ARACNE, CLR, MRNET and RN, with respect to local network-based measures. We employ ensemble methods allowing to assess the inferability down to the level of individual edges. Our analysis reveals the bias of these inference methods with respect to the inference of various network components and, hence, provides guidance in the interpretation of inferred regulatory networks from expression data. Further, as application we predict the total number of regulatory interactions in human B cells and hypothesize about the role of Myc and its targets regarding molecular information processing.

General information

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Organisations: School of Medicine, Computational Biology and Machine Learning
Contributors: Altay, G., Emmert-Streib, F.
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Article number: btq259
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Scopus rating (2010): SJR 3.661 SNIP 1.884
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Surface science analysis and surface modification methods for biomaterials research

General information
Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: Research group: Surface Science, Department of Physics, Department of Biomedical Engineering, University of Tampere Institute of Medical Technology, Department of Biomedical Engineering
Contributors: Kanninen, L., Jokinen, N., Lahtonen, K., Jussila, P., Ali-Löytty, H., Hirsimäki, M., Leppiniemi, J., Hytönen, V., Kulomaa, M., Ahola, N., Paakinaho, K., Kellomäki, M., Valden, M.
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ASJC Scopus subject areas: Bioengineering, Biochemistry, Biomaterials, Biomedical Engineering, Cell Biology
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Source: Scopus
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Research output: Contribution to journal › Article › Scientific › peer-review

Unite and conquer: Univariate and multivariate approaches for finding differentially expressed gene sets
Motivation: Recently, many univariate and several multivariate approaches have been suggested for testing differential expression of gene sets between different phenotypes. However, despite a wealth of literature studying their performance on simulated and real biological data, still there is a need to quantify their relative performance when they are testing different null hypotheses. Results: In this article, we compare the performance of univariate and multivariate tests on both simulated and biological data. In the simulation study we demonstrate that high correlations equally affect the power of both, univariate as well as multivariate tests. In addition, for most of them the power is similarly affected by the dimensionality of the gene set and by the percentage of genes in the set, for which expression is changing between two phenotypes. The application of different test statistics to biological data reveals that three statistics (sum of squared t-tests, Hotelling's T^2, N-statistic), testing different null hypotheses, find some common but also some complementing differentially expressed gene sets under specific settings. This demonstrates that due to complementing null hypotheses each test projects on different aspects of the data and for the analysis of biological data it is beneficial to use all three tests simultaneously instead of focusing exclusively on just one.

General information
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Organisations: University of Rochester Medical Center, Computational Biology and Machine Learning, Queen's University, Belfast, Northern Ireland
Contributors: Glazko, G. V., Emmert-Streib, F.
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ISSN (Print): 1367-4803
Ratings:

Scopus rating (2009): SJR 3.111 SNIP 1.834
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ASJC Scopus subject areas: Biochemistry, Molecular Biology, Computational Theory and Mathematics, Computer Science Applications, Computational Mathematics, Statistics and Probability
DOIs:

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Source: Scopus
Source ID: 69849105388
Research output: Contribution to journal › Article › Scientific › peer-review

Structural information content of networks: Graph entropy based on local vertex functionals
In this paper we define the structural information content of graphs as their corresponding graph entropy. This definition is based on local vertex functionals obtained by calculating j-spheres via the algorithm of Dijkstra. We prove that the graph entropy and, hence, the local vertex functionals can be computed with polynomial time complexity enabling the application of our measure for large graphs. In this paper we present numerical results for the graph entropy of chemical graphs and discuss resulting properties.

General information
Publication status: Published
MoE publication type: A1 Journal article-refereed
Organisations: TU Vienna, Department of Biostatistics, Visiting Graduate Student in Department of Urban Design and Planning, University of Washington, Seattle, USA 1.1.2012-15.6.2012 (12.9.2011 alkaen), Department of Genome Sciences
Contributors: Dehmer, M., Emmert-Streib, F.
Number of pages: 8
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Scopus rating (2008): SJR 0.795 SNIP 0.687
Original language: English
ASJC Scopus subject areas: Biochemistry, Structural Biology, Analytical Chemistry, Physical and Theoretical Chemistry
Keywords: Chemical graph theory, Gene networks, Graph entropy, Information theory, Structural information content
DOIs:

10.1016/j.compbiolchem.2007.09.007
Source: Scopus
Source ID: 40049085450
Research output: Contribution to journal › Article › Scientific › peer-review

Responses of methane oxidation to temperature and water content in cover soil of a boreal landfill
Methane oxidation in a cover soil of a landfill located in a boreal climate was studied at temperatures ranging from 1-19 °C and with water content of 7-34% of dry weight (dw), corresponding to 17-81% of water-holding capacity (WHC) in order to

better understand the factors regulating CH_4 oxidation at low temperatures. CH_4 consumption was detected at all the temperatures studied (1-19 °C) and an increase in CH_4 consumption rate in consecutive incubations was obtained even at 1 °C, indicating activation or increase in enzymes and/or microorganisms responsible for CH_4 oxidation. CH_4 consumption was reduced with low water content (17%WHC) at all temperatures. The response of CH_4 consumption to temperature was high with Q_{10} values from 6.5 to 8.4 and dependent on water content: at 33%WHC or more an increase in water content was accompanied by a decrease in Q_{10} values. The responses of CH_4 consumption to water content varied at different temperatures so that at 1-6 °C, CH_4 consumption increased along with water content (33-67%WHC) while at 12-19 °C the response was curvilinear, peaking at 50%WHC. CH_4 consumption was less tolerant (higher Q_{10} values; 6.5-8.4) of low temperatures compared to basal respiration (Q_{10} values for CO_2 production and O_2 consumption 3.2-4.0). Overall, the present results demonstrate the presence of CH_4-oxidizing microorganisms, which are able to consume CH_4 and to be activated or grow at low temperatures, suggesting that CH_4 oxidation can reduce atmospheric CH_4 emissions from methanogenic environments even in cold climates.

General information
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MoE publication type: A1 Journal article-refereed
Organisations: Jyväskylän yliopisto, University of Jyväskylä, Tritonet Ltd.
Contributors: Einola, J. K. M., Kettunen, R. H., Rintala, J. A.
Number of pages: 9
Pages: 1156-1164
Publication date: May 2007
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Journal: Soil Biology and Biochemistry
Volume: 39
Issue number: 5
ISSN (Print): 0038-0717
Ratings:
Scopus rating (2007): SJR 1.626 SNIP 1.557
Original language: English
ASJC Scopus subject areas: Soil Science, Biochemistry, Ecology
Keywords: Carbon dioxide, Greenhouse gases, Landfill cover soil, Low temperature, Methane oxidation, Methanotroph, Moisture, Oxygen, Soil respiration, Water content
DOIs:
10.1016/j.soilbio.2006.12.022
Source: Scopus
Source ID: 33847395396
Research output: Contribution to journal › Article › Scientific › peer-review

Modeling of anaerobic degradation of solid slaughterhouse waste: Inhibition effects of long-chain fatty acids or ammonia
The anaerobic bioconversion of solid poultry slaughterhouse wastes was kinetically investigated. The modified version of <METHANE> simulation model was applied for description of experimental data in mesophilic laboratory digester and assays. Additionally, stages of formation and consumption of long chain fatty acids (LCFA) were included in the model. Batch data on volatile solids, ammonium, acetate, butyrate, propionate, LCFA concentrations, pH level, cumulative volume, and methane partial pressure were used for model calibration. As a reference, the model was used to describe digestion of solid sorted household waste. Simulation results showed that an inhibition of polymer hydrolysis by volatile fatty acids and acetogenesis by NH_3 or LCFA could be responsible for the complex system dynamics during degradation of lipid- and protein-rich wastes.

General information
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MoE publication type: A1 Journal article-refereed
Organisations: Russian Academy of Sciences, University of Jyväskylä, Jyväskylän yliopisto
Contributors: Lokshina, L. Y., Vavilin, V. A., Salminen, E., Rintala, J.
Number of pages: 18
Pages: 15-32
Publication date: Apr 2003
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Journal: Applied Biochemistry and Biotechnology
Volume: 109
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ISSN (Print): 0273-2289

Ratings:

Scopus rating (2003): SJR 0.444 SNIP 0.694
Original language: English
ASJC Scopus subject areas: Biochemistry, Genetics and Molecular Biology(all), Biochemistry, Biotechnology, Bioengineering
Keywords: Ammonia, Anaerobic digestion, Inhibition, Long-chain fatty acids, Model, Poultry slaughterhouse waste, Sorted solid household waste
DOIs:

10.1385/ABAB:109:1-3:15
Source: Scopus
Source ID: 0038459271
Research output: Contribution to journal › Article › Scientific › peer-review

Preparation of 5-substituted 2-carboxyindoles on solid support

The preparation of 5-substituted 2-carboxyindoles on solid support is reported. In the approach, the indole moiety is synthesized in solution phase, followed by nitro-group reduction, reductive amination and alkylation on solid support. The method provides a simple and convenient route for the preparation of 5-substituted 2-carboxyindoles with high purity and good yield. (C) 2000 Elsevier Science Ltd.

General information

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MoE publication type: A1 Journal article-refereed
Organisations: Div. Pharmaceutical Chem., Dept. P., University of Helsinki, Helsinki University
Contributors: Tois, J., Franzén, R., Aitio, O., Huikko, K., Taskinen, J.
Number of pages: 4
Pages: 2443-2446
Publication date: 1 Apr 2000
Peer-reviewed: Yes

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Journal: Tetrahedron Letters
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Issue number: 14
ISSN (Print): 0040-4039
Ratings:

Scopus rating (2000): SJR 1.626 SNIP 0.962
Original language: English
ASJC Scopus subject areas: Biochemistry, Organic Chemistry, Drug Discovery
DOIs:

10.1016/S0040-4039(00)00151-9
URLs:

http://www.scopus.com/inward/record.url?scp=0034175579&partnerID=8YFLogxK (Link to publication in Scopus)
Source: Scopus
Source ID: 0034175579
Research output: Contribution to journal › Article › Scientific › peer-review

Utilization of Grignard reagents in solid-phase synthesis: A review of the literature

General information

Publication status: Published
MoE publication type: A2 Review article in a scientific journal
Organisations: University of Helsinki
Contributors: Franzén, R. G.
Number of pages: 7
Pages: 685-691
Publication date: 28 Jan 2000
Peer-reviewed: Yes

Publication information

Journal: Tetrahedron
Volume: 56
Issue number: 5
ISSN (Print): 0040-4020
Ratings:

Scopus rating (2000): SJR 1.536 SNIP 1.113
Original language: English
ASJC Scopus subject areas: Biochemistry, Organic Chemistry, Drug Discovery
DOIs:
10.1016/S0040-4020(99)00963-1
URLs:
http://www.scopus.com/inward/record.url?scp=0034723167&partnerID=8YFLogxK (Link to publication in Scopus)
Source: Scopus
Source ID: 0034723167
Research output: Contribution to journal › Review Article › Scientific › peer-review

Solution structure of nodularin: An inhibitor of serine/threonine- specific protein phosphatases

The three-dimensional solution structure of nodularin was studied by NMR and molecular dynamics simulations. The conformation in water was determined from the distance and dihedral data by distance geometry and refined by iterative relaxation matrix analysis. The cyclic backbone adopts a well defined conformation but the remote parts of the side chains of arginine as well as the amino acid derivative Adda have a large spatial dispersion. For the unusual amino acids the partial charges were calculated and nodularin was subjected to molecular dynamic simulations in water. A good agreement was found between experimental and computational data with hydrogen bonds, solvent accessibility, molecular motion, and conformational exchange. The three-dimensional structure resembles very closely that of microcystin-LR in the chemically equivalent segment. Therefore, it is expected that the binding of both microcystins and nodularins to serine/threonine-specific protein phosphatases is similar on an atomic level.

General information

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Organisations: VTT Technical Research Centre of Finland, University of Helsinki, University of Oulu, Turku Centre for Biotechnology, Department of Physical Sciences
Contributors: Annila, A., Lehtimäki, J., Mattila, K., Eriksson, J. E., Sivonen, K., Rantala, T. T., Drakenberg, T.
Number of pages: 8
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ISSN (Print): 0021-9258
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ASJC Scopus subject areas: Biochemistry
DOIs:
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Source: Scopus
Source ID: 0029941728
Research output: Contribution to journal › Article › Scientific › peer-review

Synthesis of chlorinated 5-hydroxy 4-methyl-2(5H)-furanones and mucochloric acid

An improved procedure for the synthesis of chlorinated 5-hydroxy-4-methyl-2(5H)-furanones is described. By this method also carbon-labelled (^{13}C and ^{14}C at C-3) hydroxyfuranones, including mucochioric acid, can be prepared. Each step of the method was examined in an effort to optimize both the yield and the purity of the compounds.

General information

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Organisations: Abo Akademi University
Contributors: Franzén, R., Kronberg, L.
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Peer-reviewed: Yes

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ASJC Scopus subject areas: Biochemistry, Organic Chemistry, Drug Discovery
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URLs:
http://www.scopus.com/inward/record.url?scp=0029012567&partnerID=8YFLogxK (Link to publication in Scopus)
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Source ID: 0029012567
Research output: Contribution to journal › Article › Scientific › peer-review