Atomistic model for nearly quantitative simulations of Langmuir monolayers

Lung surfactant and a tear film lipid layer are examples of biologically relevant macromolecular structures found at the air–water interface. Because of their complexity, they are often studied in terms of simplified lipid layers, the simplest example being a Langmuir monolayer. Given the profound biological significance of these lipid assemblies, there is a need to understand their structure and dynamics on the nanoscale, yet there are not many techniques able to provide this information. Atomistic molecular dynamics simulations would be a tool fit for this purpose; however, the simulation models suggested until now have been qualitative instead of quantitative. This limitation has mainly stemmed from the challenge to correctly describe the surface tension of water with simulation parameters compatible with other biomolecules. In this work, we show that this limitation can be overcome by using the recently introduced four-point OPC water model, whose surface tension for water is demonstrated to be quantitatively consistent with experimental data and which is also shown to be compatible with the commonly employed lipid models. We further establish that the approach of combining the OPC four-point water model with the CHARMM36 lipid force field provides nearly quantitative agreement with experiments for the surface pressure–area isotherm for POPC and DPPC monolayers, also including the experimentally observed phase coexistence in a DPPC monolayer. The simulation models reported in this work pave the way for nearly quantitative atomistic studies of lipid-rich biological structures at air–water interfaces.

Key steps in unconventional secretion of fibroblast growth factor 2 reconstituted with purified components

FGF2 is secreted from cells by an unconventional secretory pathway. This process is mediated by direct translocation across the plasma membrane. Here, we define the minimal molecular machinery required for FGF2 membrane translocation in a fully reconstituted inside-out vesicle system. FGF2 membrane translocation is thermodynamically driven by PI(4,5)P2-induced membrane insertion of FGF2 oligomers. The latter serve as dynamic translocation intermediates of FGF2 with a subunit number in the range of 8-12 FGF2 molecules. Vectorial translocation of FGF2 across the membrane is governed by sequential and mutually exclusive interactions with PI(4,5)P2 and heparan sulfates on opposing sides of the membrane. Based on atomistic molecular dynamics simulations, we propose a mechanism that drives PI(4,5)P2
dependent oligomerization of FGF2. Our combined findings establish a novel type of self-sustained protein translocation across membranes revealing the molecular basis of the unconventional secretory pathway of FGF2.
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
Authors: Kulig, W., Cwiklik, L., Jurkiewicz, P., Rog, T., Vattulainen, I.
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Scopus rating (2012): SJR 0.803 SNIP 0.974 CiteScore 2.41
Scopus rating (2011): SJR 0.727 SNIP 0.984 CiteScore 2.56
Scopus rating (2010): SJR 0.874 SNIP 0.964
Scopus rating (2009): SJR 0.9 SNIP 0.995
Scopus rating (2008): SJR 1.114 SNIP 1.057
Scopus rating (2007): SJR 1.083 SNIP 1.091
Scopus rating (2006): SJR 0.808 SNIP 0.881
Scopus rating (2005): SJR 1.038 SNIP 1.035
Scopus rating (2004): SJR 0.69 SNIP 0.831
Scopus rating (2003): SJR 0.917 SNIP 0.817
Scopus rating (2002): SJR 1.005 SNIP 0.813
Cis and Trans Unsaturated Phosphatidylcholine Bilayers: A Molecular Dynamics Simulation Study

Trans unsaturated lipids are uncommon in nature. In the human diet, they occur as natural products of ruminal bacteria or from industrial food processing like hydrogenation of vegetable oils. Consumption of trans unsaturated lipids has been shown to have a negative influence on human health; in particular, the risk of cardiovascular disease is higher when the amount of trans unsaturated lipids in the diet is elevated. In this study, we first performed quantum mechanical calculations to specifically and accurately parameterize cis and trans mono-unsaturated lipids and subsequently validated the newly derived parameter set. Then, we carried out molecular dynamics (MD) simulations of lipid bilayers composed of cis or trans unsaturated lipids with and without cholesterol. Our results show that trans mono-unsaturated chains are more flexible than cis mono-unsaturated chains due to lower barriers for rotation around the single bonds next to the trans double bond than those next to the cis double bond. In effect, interactions between cholesterol and trans unsaturated chains are stronger than cis unsaturated chains, which results in a higher ordering effect of cholesterol in trans unsaturated bilayers.
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.

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Organisations: Department of Physics, Research area: Computational Physics, Research group: Biological Physics and Soft Matter, University of Helsinki, University of Southern Denmark
Authors: Pöyry, S., Vattulainen, I.
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Scopus rating (2013): SJR 1.592 SNIP 0.975 CiteScore 3.45
Scopus rating (2012): SJR 1.833 SNIP 1.156 CiteScore 3.99
Scopus rating (2011): SJR 1.644 SNIP 1.227 CiteScore 4.17
Scopus rating (2010): SJR 2.179 SNIP 1.291
Scopus rating (2009): SJR 2.152 SNIP 1.298
Scopus rating (2008): SJR 2.035 SNIP 1.123
Scopus rating (2007): SJR 2.021 SNIP 1.158
Scopus rating (2006): SJR 1.922 SNIP 1.212
Scopus rating (2005): SJR 2.037 SNIP 1.231
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Scopus rating (2003): SJR 1.401 SNIP 1.115
Scopus rating (2002): SJR 1.594 SNIP 1.228
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Scopus rating (2000): SJR 1.089 SNIP 0.907
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ASJC Scopus subject areas: Biochemistry, Cell Biology, Biophysics
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Source-ID: 84961924291
Research output: Scientific - peer-review › Article
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.

What can we learn about cholesterol's transmembrane distribution based on cholesterol-induced changes in membrane potential?
Cholesterol is abundant in the plasma membranes of animal cells and is known to regulate a variety of membrane properties. Despite decades of research, the transmembrane distribution of cholesterol is still a matter of debate. Here we consider this outstanding issue through atomistic simulations of asymmetric lipid membranes, whose composition is largely consistent with eukaryotic plasma membranes. We show that the membrane dipole potential changes in a cholesterol-dependent manner. Remarkably, moving cholesterol from the extracellular to the cytosolic leaflet increases the dipole potential on the cytosolic side, and vice versa. Biologically this implies that by altering the dipole potential, cholesterol can provide a driving force for cholesterol molecules to favor the cytosolic leaflet, in order to compensate for the intramembrane field that arises from the resting potential.

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Organisations: Department of Physics, Research area: Computational Physics, Research group: Biological Physics and Soft Matter, Institute of Macromolecular Compounds, Russian Academy of Sciences, St. Petersburg, Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences, Flemingovo náměstí 542/2, 166 10 Praha 6, Czech Republic, Belozersky Institute of Physico-Chemical Biology, Lomonosov Moscow State University, Leninskie Gory, 1/40, 119991 Moscow, Russia

Authors: Falkovich, S. G., Martinez-Seara, H., Nesterenko, A. M., Vattulainen, I., Gurtovenko, A. A.

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Scopus rating (2014): SJR 3.722 SNIP 1.724 CiteScore 7
Scopus rating (2013): SJR 3.515 SNIP 1.61 CiteScore 6.61
Scopus rating (2012): SJR 3.943 SNIP 1.751 CiteScore 6.3
Scopus rating (2011): SJR 3.244 SNIP 1.602 CiteScore 5.95

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How Well Does BODIPY-Cholesteryl Ester Mimic Unlabeled Cholesteryl Esters in High Density Lipoprotein Particles?

We compare the behavior of unlabeled and BODIPY-labeled cholesteryl ester (CE) in high density lipoprotein by atomistic molecular dynamics simulations. We find through replica exchange umbrella sampling and unbiased molecular dynamics simulations that BODIPY labeling has no significant effect on the partitioning of CE between HDL and the water phase. However, BODIPY-CE was observed to diffuse more slowly and locate itself closer to the HDL-water interface than CE due to the BODIPY probe that is constrained to the surface region, and because the CE body in BODIPY-CE prefers to align itself away from the HDL surface. The implications as to the suitability of BODIPY to explore lipoprotein properties are discussed.

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Authors: Karilainen, T., Vuorela, T., Vattulainen, I.

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Variance-corrected Michaelis-Menten equation predicts transient rates of single-enzyme reactions and response times in bacterial gene-regulation

Many chemical reactions in biological cells occur at very low concentrations of constituent molecules. Thus, transcriptional gene-regulation is often controlled by poorly expressed transcription-factors, such as E.coli lac repressor with few tens of copies. Here we study the effects of inherent concentration fluctuations of substrate-molecules on the seminal Michaelis-Menten scheme of biochemical reactions. We present a universal correction to the Michaelis-Menten equation for the reaction-rates. The relevance and validity of this correction for enzymatic reactions and intracellular gene-regulation is demonstrated. Our analytical theory and simulation results confirm that the proposed variance-corrected Michaelis-Menten equation predicts the rate of reactions with remarkable accuracy even in the presence of large non-equilibrium concentration fluctuations. The major advantage of our approach is that it involves only the mean and variance of the substrate-molecule concentration. Our theory is therefore accessible to experiments and not specific to the exact source of the concentration fluctuations.

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How do Water Solvent and Glutathione Ligands Affect the Structure and Electronic Properties of Au25(SR)18-?

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Authors: Rojas-Cervellera, V., Rovira, C., Akola, J.
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Scopus rating (2013): SJR 3.515 SNIP 1.61 CiteScore 6.61
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Scopus rating (2011): SJR 3.244 SNIP 1.602 CiteScore 5.95
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ASJC Scopus subject areas: Materials Science(all)

PIP2 and Talin Join Forces to Activate Integrin
Integrins are major players in cell adhesion and migration, and malfunctions in controlling their activity are associated with various diseases. Nevertheless, the details of integrin activation are not completely understood, and the role of lipids in the process is largely unknown. Herein, we show using atomistic molecular dynamics simulations that the interplay of phosphatidylinositol 4,5-bisphosphate (PIP2) and talin may directly alter the conformation of integrin αIIbβ3. Our results provide a new perspective on the role of PIP2 in integrin activation and indicate that the charged PIP2 lipid headgroup can perturb a clasp at the cytoplasmic face of the integrin heterodimer.

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Authors: Orłowski, A., Kukkurainen, S., Pöyry, A., Rissanen, S., Vattulainen, I., Hytönen, V. P., Rög, T.
Redox-induced activation of the proton pump in the respiratory complex I

Complex I functions as a redox-linked proton pump in the respiratory chains of mitochondria and bacteria, driven by the reduction of quinone (Q) by NADH. Remarkably, the distance between the Q reduction site and the most distant proton channels extends nearly 200 Å. To elucidate the molecular origin of this long-range coupling, we apply a combination of large-scale molecular simulations and a site-directed mutagenesis experiment of a key residue. In hybrid quantum mechanics/molecular mechanics simulations, we observe that reduction of Q is coupled to its local protonation by the His-38/Asp-139 ion pair and Tyr-87 of subunit Nqo4. Atomic classical molecular dynamics simulations further suggest that formation of quinol (QH2) triggers rapid dissociation of the anionic Asp-139 toward the membrane domain that couples to conformational changes in a network of conserved charged residues. Site-directed mutagenesis data confirm the importance of Asp-139; upon mutation to asparagine the Q reductase activity is inhibited by 75%. The current results, together with earlier biochemical data, suggest that the proton pumping in complex I is activated by a unique combination of electrostatic and conformational transitions.
How large are nonadiabatic effects in atomic and diatomic systems?

With recent developments in simulating nonadiabatic systems to high accuracy, it has become possible to determine how much energy is attributed to nuclear quantum effects beyond zero-point energy. In this work, we calculate the non-relativistic ground-state energies of atomic and molecular systems without the Born-Oppenheimer approximation. For this purpose, we utilize the fixed-node diffusion Monte Carlo method, in which the nodes depend on both the electronic and ionic positions. We report ground-state energies for all systems studied, ionization energies for the first-row atoms and atomization energies for the first-row hydrides. We find the ionization energies of the atoms to be nearly independent of the Born-Oppenheimer approximation, within the accuracy of our results. The atomization energies of molecular systems, however, show small effects of the nonadiabatic coupling between electrons and nuclei.
Building synthetic sterols computationally: unlocking the secrets of evolution?

Cholesterol is vital in regulating the physical properties of animal cell membranes. While it remains unclear what renders cholesterol so unique, it is known that other sterols are less capable in modulating membrane properties, and there are membrane proteins whose function is dependent on cholesterol. Practical applications of cholesterol include its use in liposomes in drug delivery and cosmetics, cholesterol-based detergents in membrane protein crystallography, its fluorescent analogs in studies of cholesterol transport in cells and tissues, etc. Clearly, in spite of their difficult synthesis, producing the synthetic analogs of cholesterol is of great commercial and scientific interest. In this article, we discuss how synthetic sterols non-existent in nature can be used to elucidate the roles of cholesterol’s structural elements. To this end, we discuss recent atomistic molecular dynamics simulation studies that have predicted new synthetic sterols with properties comparable to those of cholesterol. We also discuss more recent experimental studies that have vindicated these predictions. The paper highlights the strength of computational simulations in making predictions for synthetic biology, thereby guiding experiments.
Effect of Phosphatidic Acid on Biomembrane: Experimental and Molecular Dynamics Simulations Study

We consider the impact of phosphatidic acid (namely, 1,2-dioleoyl-sn-glycero-3-phosphate, DOPA) on the properties of a zwitterionic (1,2-dipalmitoyl-sn-glycero-3-phosphocholine, DPPC) bilayer used as a model system for protein-free cell membranes. For this purpose, experimental measurements were performed using differential scanning calorimetry and the Langmuir monolayer technique at physiological pH. Moreover, atomistic-scale molecular dynamics (MD) simulations were performed to gain information on the mixed bilayer's molecular organization. The results of the monolayer studies clearly showed that the DPPC/DOPA mixtures are nonideal and the interactions between lipid species change from attractive, at low contents of DOPA, to repulsive, at higher contents of that component. In accordance with these results, the MD simulations demonstrated that both monoanionic and dianionic forms of DOPA have an ordering and condensing effect on the mixed bilayer at low concentrations. For the DOPA monoanions, this is the result of both (i) strong electrostatic interactions between the negatively charged oxygen of DOPA and the positively charged choline groups of DPPC and (ii) conformational changes of the lipid acyl chains, leading to their tight packing according to the so-called umbrella model, in which large headgroups of DPPC shield the hydrophobic part of DOPA (the conical shape lipid) from contact with water. In the case of the DOPA dianions, cation-mediated clustering was observed. Our results provide a detailed molecular-level description of the lipid organization inside the mixed zwitterionic/PA membranes, which is fully supported by the experimental data.

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Authors: Kwolek, U., Kulig, W., Wydro, P., Nowakowska, M., Róg, T., Kepczynski, M.
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Scopus rating (2013): SJR 1.494 SNIP 1.2 CiteScore 3.53
Scopus rating (2012): SJR 1.92 SNIP 1.251 CiteScore 3.66
Scopus rating (2011): SJR 1.78 SNIP 1.226 CiteScore 3.62
Scopus rating (2010): SJR 1.849 SNIP 1.214
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Scopus rating (2008): SJR 2.543 SNIP 1.381
Scopus rating (2007): SJR 2.346 SNIP 1.282
Scopus rating (2006): SJR 2.369 SNIP 1.415
Scopus rating (2005): SJR 2.275 SNIP 1.474
Scopus rating (2004): SJR 2.148 SNIP 1.511
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Scopus rating (2002): SJR 2.118 SNIP 1.496
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Scopus rating (2000): SJR 2.145 SNIP 1.527
Nonlinear Optical Properties of Fluorescent Dyes Allow for Accurate Determination of Their Molecular Orientations in Phospholipid Membranes

Several methods based on single- and two-photon fluorescence detected linear dichroism have recently been used to determine the orientational distributions of fluorescent dyes in lipid membranes. However, these determinations relied on simplified descriptions of nonlinear anisotropic properties of the dye molecules, using a transition dipole-moment-like vector instead of an absorptivity tensor. To investigate the validity of the vector approximation, we have now carried out a combination of computer simulations and polarization microscopy experiments on two representative fluorescent dyes (DiI and F2N12S) embedded in aqueous phosphatidylcholine bilayers. Our results indicate that a simplified vector-like treatment of the two-photon transition tensor is applicable for molecular geometries sampled in the membrane at ambient conditions. Furthermore, our results allow evaluation of several distinct polarization microscopy techniques. In combination, our results point to a robust and accurate experimental and computational treatment of orientational distributions of DiI, F2N12S, and related dyes (including Cy3, Cy5, and others), with implications to monitoring physiologically relevant processes in cellular membranes in a novel way.
Real sequence effects on the search dynamics of transcription factors on DNA

Recent experiments show that transcription factors (TFs) indeed use the facilitated diffusion mechanism to locate their target sequences on DNA in living bacteria cells: TFs alternate between sliding motion along DNA and relocation events through the cytoplasm. From simulations and theoretical analysis we study the TF-sliding motion for a large section of the DNA-sequence of a common E. coli strain, based on the two-state TF-model with a fast-sliding search state and a recognition state enabling target detection. For the probability to detect the target before dissociating from DNA the TF-search times self-consistently depend heavily on whether or not an auxiliary operator (an accessible sequence similar to the main operator) is present in the genome section. Importantly, within our model the extent to which the interconversion rates between search and recognition states depend on the underlying nucleotide sequence is varied. A moderate dependence maximises the capability to distinguish between the main operator and similar sequences. Moreover, these auxiliary operators serve as starting points for DNA looping with the main operator, yielding a spectrum of target detection times spanning several orders of magnitude. Auxiliary operators are shown to act as funnels facilitating target detection by TFs.

Signal focusing through active transport

The accuracy of molecular signaling in biological cells and novel diagnostic devices is ultimately limited by the counting noise floor imposed by the thermal diffusion. Motivated by the fact that messenger RNA and vesicle-engulfed signaling molecules transiently bind to molecular motors and are actively transported in biological cells, we show here that the
random active delivery of signaling particles to within a typical diffusion distance to the receptor generically reduces the correlation time of the counting noise. Considering a variety of signaling particle sizes from mRNA to vesicles and cell sizes from prokaryotic to eukaryotic cells, we show that the conditions for active focusing - faster and more precise signaling - are indeed compatible with observations in living cells. Our results improve the understanding of molecular cellular signaling and novel diagnostic devices.

**General information**

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- Scopus rating (2014): SJR 1.22 SNIP 1.123 CiteScore 2.05
- Scopus rating (2013): SJR 1.311 SNIP 1.239 CiteScore 2.28
- Scopus rating (2012): SJR 1.42 SNIP 1.226 CiteScore 2.28
- Scopus rating (2011): SJR 1.485 SNIP 1.225 CiteScore 2.28
- Scopus rating (2010): SJR 1.69 SNIP 1.215
- Scopus rating (2009): SJR 1.694 SNIP 1.259
- Scopus rating (2008): SJR 1.96 SNIP 1.314
- Scopus rating (2007): SJR 1.926 SNIP 1.332
- Scopus rating (2006): SJR 1.787 SNIP 1.324
- Scopus rating (2005): SJR 1.71 SNIP 1.302
- Scopus rating (2004): SJR 1.672 SNIP 1.214
- Scopus rating (2003): SJR 1.303 SNIP 1.166
- Scopus rating (2002): SJR 0.936 SNIP 1.241
- Scopus rating (2001): SJR 0.709 SNIP 1.429
- Scopus rating (2000): SJR 0.299 SNIP 1.252
- Scopus rating (1999): SJR 0.381 SNIP 1.232

Original language: English
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**Bioluminescent whole-cell reporter gene assays as screening tools in the identification of antimicrobial natural product extracts**

We describe novel tools, bioluminescent whole-cell reporter gene assays, for facilitating the use of natural products in antimicrobial drug discovery. As proof-of-concept, a plant extract library was screened and follow-up experiments were carried out. Primary results can be obtained in 2-4 h with high sensitivity, leading to significant improvements of the process.

**General information**

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Ministry of Education publication type: A1 Journal article-refereed
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.
How To Minimize Artifacts in Atomistic Simulations of Membrane Proteins, Whose Crystal Structure Is Heavily Engineered: beta(2)-Adrenergic Receptor in the Spotlight

Atomistic molecular dynamics (MD) simulations are used extensively to elucidate membrane protein properties. These simulations are based on three-dimensional protein structures that in turn are often based on crystallography. The protein structures resolved in crystallographic studies typically do not correspond to pristine proteins, however. Instead the crystallized proteins are commonly engineered, including structural modifications (mutations, replacement of protein sequences by antibodies, bound ligands, etc.) whose impact on protein structure and dynamics is largely unknown. Here we explore this issue through atomistic MD simulations (~5 its in total), focusing on the beta(2)-adrenergic receptor (beta(2)AR) that is one of the most studied members of the G-protein coupled receptor superfamily. Starting from an inactive-state crystal structure beta(2)AR, we remove the many modifications in beta(2)AR systematically one at a time, in six consecutive steps. After each step, we equilibrate the system and simulate it quite extensively. The results of this step-by-step approach highlight that the structural modifications used in crystallization can affect ligand and G-protein binding sites, packing at the transmembrane-helix interface region, and the dynamics of connecting loops in beta(2)AR. When the results of the systematic step-by-step approach are compared to an all-at-once technique where all modifications done on beta(2)AR are removed instantaneously at the same time, it turns out that the step-by-step method provides results that are superior in terms of maintaining protein structural stability. The results provide compelling evidence that for membrane proteins whose 3D structure is based on structural engineering, the preparation of protein structure for atomistic MD simulations is a delicate and sensitive process. The results show that most valid results are found when the structural modifications are reverted slowly, one at a time.
Membrane targeting of the yeast exocyst complex

The exocytosis is a process of fusion of secretory vesicles with the plasma membrane, which plays a prominent role in many crucial cellular processes, e.g. secretion of neurotransmitters, cytokinesis or yeast budding. Prior to the SNARE-mediated fusion, the initial contact of secretory vesicle with the target membrane is mediated by an evolutionary conserved vesicle tethering protein complex, the exocyst. In all eukaryotic cells, the exocyst is composed of eight subunits - Sec5, Sec6, Sec8, Sec10, Sec15, Exo84 and two membrane-targeting landmark subunits Sec3 and Exo70, which have been described to directly interact with phosphatidylinositol (4,5)-bisphosphate (PIP2) of the plasma membrane. In this work, we utilized coarse-grained molecular dynamics simulations to elucidate structural details of the interaction of yeast Sec3p and Exo70p with lipid bilayers containing PIP2. We found that PIP2 is coordinated by the positively charged pocket of N-terminal part of Sec3p, which folds into unique Pleckstrin homology domain. Conversely, Exo70p interacts with the lipid bilayer by several binding sites distributed along the structure of this exocyst subunit. Moreover, we observed that the interaction of Exo70p with the membrane causes clustering of PIP2 in the adjacent leaflet. We further revealed that PIP2 is required for the correct positioning of small GTPase Rho1p, a direct Sec3p interactor, prior to the formation of the functional Rho1p-exocyst-membrane assembly. Our results show the critical importance of the plasma membrane pool of PIP2 for the exocyst function and suggest that specific interaction with acidic phospholipids represents an ancestral mechanism for the exocyst regulation. (C) 2015 Elsevier B.V. All rights reserved.
Superdiffusion dominates intracellular particle motion in the supercrowded cytoplasm of pathogenic Acanthamoeba castellanii

Acanthamoebae are free-living protists and human pathogens, whose cellular functions and pathogenicity strongly depend on the transport of intracellular vesicles and granules through the cytosol. Using high-speed live cell imaging in combination with single-particle tracking analysis, we show here that the motion of endogenous intracellular particles in the size range from a few hundred nanometers to several micrometers in Acanthamoeba castellanii is strongly superdiffusive and influenced by cell locomotion, cytoskeletal elements, and myosin II. We demonstrate that cell locomotion significantly contributes to intracellular particle motion, but is clearly not the only origin of superdiffusivity. By analyzing the contribution of microtubules, actin, and myosin II motors we show that myosin II is a major driving force of intracellular motion in A. castellanii. The cytoplasm of A. castellanii is supercrowded with intracellular vesicles and granules, such that significant intracellular motion can only be achieved by actively driven motion, while purely thermally driven diffusion is negligible.

General information

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Organisations: Department of Physics, Institute for Physics and Astronomy, University of Potsdam, Institute for Materials Science, Biocompatible Nanomaterials, Christian-Albrechts-Universität zu Kiel, Zoological Institute, Comparative Immunobiology, Korea Institute for Advanced Study
Authors: Reverey, J. F., Jeon, J., Bao, H., Leippe, M., Metzler, R., Selhuber-Unkel, C.
PEGylated liposomes as carriers of hydrophobic porphyrins

Sterically stabilized liposomes (SSLs) (PEGylated liposomes) are applied as effective drug delivery vehicles. Understanding the interactions between hydrophobic compounds and PEGylated membranes is therefore important to determine the effectiveness of PEGylated liposomes for delivery of drugs or other bioactive substances. In this study, we have combined fluorescence quenching analysis (FQA) experiments and all-atom molecular dynamics (MD) simulations to study the effect of membrane PEGylation on the location and orientation of 5,10,15,20-tetrakis(4-hydroxyphenyl)porphyrin (p-THPP) that has been used in our study as a model hydrophobic compound. First, we consider the properties of p-THPP in the presence of different fluid phosphatidylcholine bilayers that we use as model systems for protein-free cell membranes. Next, we studied the interaction between PEGylated membranes and p-THPP. Our MD simulation results indicated that the arrangement of p-THPP within zwitterionic membranes is dependent on their free volume, and p-THPP solubilized in PEGylated liposomes is localized in two preferred positions: deep within the membrane (close to the center of the bilayer) and in the outer PEG corona (p-THPP molecules being wrapped with the polymer chains). Fluorescence quenching methods confirmed the results of atomistic MD simulations and showed two populations of p-THPP molecules as in MD simulations. Our results provide both an explanation for the experimental observation that PEGylation improves the drug-loading efficiency of membranes and also a more detailed molecular-level description of the interactions between porphyrins and lipid membranes.
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.

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Sec14-nodulin proteins and the patterning of phosphoinositide landmarks for developmental control of membrane morphogenesis

Polarized membrane morphogenesis is a fundamental activity of eukaryotic cells. This process is essential for the biology of cells and tissues, and its execution demands exquisite temporal coordination of functionally diverse membrane signaling reactions with high spatial resolution. Moreover, mechanisms must exist to establish and preserve such organization in the face of randomizing forces that would diffuse it. Here we identify the conserved AtSfh1 Sec14-nodulin protein as a novel effector of phosphoinositide signaling in the extreme polarized membrane growth program exhibited by growing Arabidopsis root hairs. The data are consistent with Sec14-nodulin proteins controlling the lateral organization of phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P<sub>2</sub>) landmarks for polarized membrane morphogenesis in plants. This patterning activity requires both the PtdIns(4,5)P<sub>2</sub> binding and homo-oligomerization activities of the AtSfh1 nodulin domain and is an essential aspect of the polarity signaling program in root hairs. Finally, the data suggest a general principle for how the phosphoinositide signaling landscape is physically bit mapped so that eukaryotic cells are able to convert a membrane surface into a high-definition lipid-signaling screen.
Transbilayer lipid interactions mediate nanoclustering of lipid-anchored proteins

Understanding how functional lipid domains in live cell membranes are generated has posed a challenge. Here, we show that transbilayer interactions are necessary for the generation of cholesterol-dependent nanoclusters of GPI-anchored proteins mediated by membrane-adjacent dynamic actin filaments. We find that long saturated acyl-chains are required for forming GPI-anchor nanoclusters. Simultaneously, at the inner leaflet, long acyl-chain-containing phosphatidylserine (PS) is necessary for transbilayer coupling. All-atom molecular dynamics simulations of asymmetric multicomponent-membrane bilayers in a mixed phase provide evidence that immobilization of long saturated acyl-chain lipids at either leaflet stabilizes cholesterol-dependent transbilayer interactions forming local domains with characteristics similar to a liquid-ordered (lo) phase. This is verified by experiments wherein immobilization of long acyl-chain lipids at one leaflet effects transbilayer interactions of corresponding lipids at the opposite leaflet. This suggests a general mechanism for the generation and stabilization of nanoscale cholesterol-dependent and actin-mediated lipid clusters in live cell membranes.
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 O2 diffusion into the active site. The role of subunit III with its indigenous lipids in the molecular mechanism of CcO is discussed.
Rate constant and thermochemistry for $K + O_2 + N_2 = KO_2 + N_2$

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Oxidation of cholesterol does not alter significantly its uptake into high-density lipoprotein particles

Using replica exchange umbrella sampling we calculated free energy profiles for uptake of cholesterol and one of its oxysterols (7-ketocholesterol) from an aqueous solution into a high-density lipoprotein particle. These atomistic molecular dynamics simulations show that both sterols are readily taken up from the aqueous solution with comparable free energy minima at the surface of the particle of -17 kcal/mol for cholesterol and -14 kcal/mol for 7-ketocholesterol. Moreover, given its preferred position at the particle surface, 7-ketocholesterol is expected to be able to participate directly in biological signaling processes.

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Authors: Karilainen, T., Timr, Š., Vattulainen, I., Jungwirth, P.
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CO oxidation catalyzed by neutral and anionic Cu20 clusters: Relationship between charge and activity

Reactions of CO and O2 on neutral and anionic Cu20 clusters have been investigated by spin-polarized density functional theory. Three reaction mechanisms of CO oxidation are explored: reactions with atomic oxygen (dissociated O2) as well as reactions with molecular oxygen, including Langmuir-Hinshelwood (LH) and Eley-Rideal (ER) mechanisms. The adsorption energies, reaction pathways, and reaction barriers for CO oxidation are calculated systematically. The anionic Cu20- cluster can adsorb CO and O2 more strongly than the neutral counterpart due to the superatomic shell closing of 20 valence electrons which leaves one electron above the band gap. The activation of O2 molecule upon adsorption is crucial to determine the rate of CO oxidation. The CO oxidation proceeds efficiently on both Cu20 and Cu20- clusters, when O2 is pre-adsorbed dissociatively. The ER mechanism has a lower reaction barrier than the LH mechanism on the neutral Cu20. In general, CO oxidation occurs more readily on the anionic Cu20- (effective reaction barriers 0.1-0.3 eV) than on the neutral Cu20 cluster (0.3-0.5 eV). Moreover, Cu20- exhibits enhanced binding for CO2. From the analysis of the reverse direction of CO oxidation, it is observed that the transition of CO2 to CO + O can occur on the Cu20- cluster, which demonstrates that Cu clusters may serve as good catalyst for CO2 chemistry.

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Scopus rating (2012): SJR 1.916 SNIP 1.184 CiteScore 3.67
Scopus rating (2011): SJR 1.697 SNIP 1.203 CiteScore 3.6
Scopus rating (2010): SJR 1.802 SNIP 1.196
New perspectives on proton pumping in cellular respiration

Complexes I, III (cytochrome bc₁), and IV (cytochrome c oxidase) of the respiratory chain employ fundamentally different mechanisms for redox-coupled proton pumping. In the Q-cycle of cytochrome bc₁, charge separation is the result of electron transfer through the membrane, whereas the protons are shuttled across the membrane by a neutral quinol carrier, QH₂. In this Q cycle, the mobile quinols get protonated on the N-side of the membrane and deprotonated on the P-side. Cytochrome bc₁ thus transduces chemical energy into an electrochemical gradient through a redox loop, but is not a true proton pump in the sense of moving protonic charge through the protein directly against a pmf. By contrast, cytochrome c oxidase, the terminal enzyme of the respiratory chain, operates as a true proton pump. In cytochrome c oxidase (CcO), the pathways of chemical electron and proton fluxes intersect in the binuclear center, and the pathway of pumped protons passes close to the BNC as well. This spatial proximity of proton and electron pathways establishes the tight electrostatic interactions one might expect for a redox-coupled proton pump.
Resveratrol interferes with the aggregation of membrane-bound human-IAPP: A molecular dynamics study

Amyloid aggregation of islet amyloid polypeptide (IAPP) in pancreatic tissues is a typical feature of type 2 diabetes mellitus. Resveratrol, a natural product extensively studied for its wide range of biological effects, has been shown to inhibit IAPP aggregation. However, the mechanism by which resveratrol inhibits IAPP aggregation is still far from complete elucidation. Now, an increasing knowledge of the mechanism of amyloid toxicity shifts the target of research towards the development of compounds which can prevent amyloid-mediated membrane damage rather than merely inhibit fiber formation. In this study we used all atom molecular dynamics to investigate the interaction of resveratrol with full-length human IAPP in a negatively charged membrane environment. Our results show that the presence of resveratrol induces the formation of secondary structures (sheets and helices) by inserting in a hydrophobic pocket between the interaction surface of two IAPP molecules in aqueous solution. On the other hand, resveratrol significantly perturbs the interaction of IAPP with negatively charged membranes by anchoring specific hydrophobic regions (23FGA25 and 32VGS34) of the peptide and forming a stable 1:2 IAPP:resveratrol complex at the water/membrane interphase.
Improved bioconversion of crude glycerol to hydrogen by statistical optimization of media components

Bioconversion of crude glycerol to hydrogen has gained importance as it addresses both sustainable energy production and waste disposal issues. Until recently, statistical optimizations of crude glycerol bioconversion to hydrogen have been greatly focused on pure strains. In this study, biohydrogen production from crude glycerol by an enriched microbial culture (predominated with Clostridium species) was improved by statistical optimization of media components. Plackett-Burman design identified MgCl₂·6H₂O and KCl with negative effect on hydrogen production and selected NH₄Cl, K₂HPO₄ and KH₂PO₄ as significant variables. Box-Behnken design indicated the optimal region beyond design area and studies were continued by ridge analysis. Central composite face centered design envisaged a maximal hydrogen yield of 1.41mol-H₂/mol-glycerol consumed at concentrations 4.40g/L and 2.27g/L for NH₄Cl and KH₂PO₄ respectively. Confirmation experiment with the optimized media (NH₄Cl, 4.40g/L; K₂HPO₄, 1.6g/L; KH₂PO₄, 2.27g/L; MgCl₂·6H₂O, 1.0g/L; KCl, 1.0g/L; Na-acetate.H₂O, 1.0g/L and tryptone, 2.0g/L) revealed an excellent correlation between predicted and experimental hydrogen yield. Optimization of media components by design of experiments enhanced hydrogen yield by 29%.

General information

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Organisations: Department of Chemistry and Bioengineering, Research group: Industrial Bioengineering and Applied Organic Chemistry, Tampere University of Technology, Department of Signal Processing, Urban circular bioeconomy (UrCirBio)
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Scopus rating (2013): SJR 2.066 SNIP 2.767 CiteScore 4.63
Scopus rating (2012): SJR 1.852 SNIP 2.745 CiteScore 3.97
Scopus rating (2011): SJR 1.688 SNIP 2.404 CiteScore 3.9
Scopus rating (2010): SJR 1.494 SNIP 2.215
Scopus rating (2009): SJR 1.305 SNIP 1.945
Scopus rating (2008): SJR 1.449 SNIP 1.867
Scopus rating (2007): SJR 1.214 SNIP 1.65
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Kinetics of polymer looping with macromolecular crowding: Effects of volume fraction and crowder size

The looping of polymers such as DNA is a fundamental process in the molecular biology of living cells, whose interior is characterised by a high degree of molecular crowding. We here investigate in detail the looping dynamics of flexible polymer chains in the presence of different degrees of crowding. From the analysis of the looping-unlooping rates and the looping probabilities of the chain ends we show that the presence of small crowders typically slows down the chain dynamics but larger crowders may in fact facilitate the looping. We rationalise these non-trivial and often counterintuitive effects of the crowder size on the looping kinetics in terms of an effective solution viscosity and standard excluded volume. It is shown that for small crowders the effect of an increased viscosity dominates, while for big crowders we argue that confinement effects (caging) prevail. The tradeoff between both trends can thus result in the impediment or facilitation of polymer looping, depending on the crowder size. We also examine how the crowding volume fraction, chain length, and the attraction strength of the contact groups of the polymer chain affect the looping kinetics and hairpin formation dynamics. Our results are relevant for DNA looping in the absence and presence of protein mediation, DNA hairpin formation, RNA folding, and the folding of polypeptide chains under biologically relevant high-crowding conditions.
Non-universal tracer diffusion in crowded media of non-inert obstacles

We study the diffusion of a tracer particle, which moves in continuum space between a lattice of excluded volume, immobile non-inert obstacles. In particular, we analyse how the strength of the tracer-obstacle interactions and the volume occupancy of the crowders alter the diffusive motion of the tracer. From the details of partitioning of the tracer diffusion modes between trapping states when bound to obstacles and bulk diffusion, we examine the degree of localisation of the tracer in the lattice of crowders. We study the properties of the tracer diffusion in terms of the ensemble and time averaged mean squared displacements, the trapping time distributions, the amplitude variation of the time averaged mean squared displacements, and the non-Gaussianity parameter of the diffusing tracer. We conclude that tracer-obstacle adsorption and binding triggers a transient anomalous diffusion. From a very narrow spread of recorded individual time averaged trajectories we exclude continuous type random walk processes as the underlying physical model of the tracer diffusion in our system. For moderate tracer-crowder attraction the motion is found to be fully ergodic, while at stronger attraction strength a transient disparity between ensemble and time averaged mean squared displacements occurs. We also put our results into perspective with findings from experimental single-particle tracking and simulations of the diffusion of tagged tracers in dense crowded suspensions. Our results have implications for the diffusion, transport, and spreading of chemical components in highly crowded environments inside living cells and other structured liquids.
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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Authors: Kulig, W., Jurkiewicz, P., Olzyńska, A., Tynkkynen, J., Javanainen, M., Manna, M., Rog, T., Hof, M., Vattulainen, I., Jungwirth, P.
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Scopus rating (2010): SJR 2.179 SNIP 1.291
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Halogen bonding enhances nonlinear optical response in poled supramolecular polymers
We demonstrate that halogen bonding strongly enhances the nonlinear optical response of poled supramolecular polymer systems. We compare three nonlinear optical chromophores with similar electronic structures but different bond-donating units, and show that both the type and the strength of the noncovalent interaction between the chromophores and the polymer matrix play their own distinctive roles in the optical nonlinearity of the systems.
How endoglucanase enzymes act on cellulose nanofibrils: role of amorphous regions revealed by atomistic simulations

Transformation of cellulose into monosaccharides can be achieved in a chemical process performed by a special group of enzymes known as cellulases. We have used atomistic molecular dynamics simulations to study endoglucanase II (Cel5A) that is one of the proteins in this group. Based on the atomistic simulation results, we discuss how the Cel5A enzyme interacts with cellulose fibrils comprised of both crystalline and amorphous regions. We show that the enzyme’s carbohydrate-binding domain prefers to interact with crystalline regions of cellulose, while the catalytic domain has a high affinity to the amorphous regions of fibrils. In particular, through electrostatic interactions the catalytic domain attracts loose glucose chains to its catalytic cleft. The atomistic details of the enzyme-cellulose interaction are presented and the implications for practical applications are briefly discussed.

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Insights into the behavioral difference of water in the presence of GM1

Studies on the structure and dynamics of interfacial water, emphasizing on the properties of water near the surface of biomolecules, are well reported, but there is a lack of evidence on the behavior of water near a comparatively rough surface containing molecules with a bulky head group like GM1. In this report we comparatively analyze the structure and dynamics of water as a function of distance from the lipid head group in GM1 containing lipid bilayers, with the lipid bilayers where GM1 is not present. This approach effectively demonstrates the behavioral difference and hence delayed convergence from bound water to bulk water in the presence of GM1 compared to a relatively smooth surface.

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Investigating the Function of BEST1 in iPS-RPE Cells Derived from a Family with Autosomal Recessive Bestrophinopathy

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Authors: Nymark, S., Nommiste, B., Vainio, I., Juuti-Uusitalo, K., da Cruz, L., Webster, A., Moore, A. T., Strauss, O., Carr, A.
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Scopus rating (2003): SJR 1.854 SNIP 1.607
Scopus rating (2002): SJR 1.974 SNIP 1.478
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Seasonal and diurnal variations of fluorescent bioaerosol concentration and size distribution in the urban environment

A recently introduced fluorescence based real-time bioaerosol instrument, BioScout, and an ultraviolet aerodynamic particle sizer (UVAPS) were used to study fluorescent bioaerosol particles (FBAP) in the Helsinki metropolitan area, Finland, during winter and summer. Two FBAP modes at 0.5–1.5 µm (fine) and 1.5–5 µm (coarse) were detected during the summer, whereas the fine mode dominated in the winter. The concentration and proportion of the coarse FBAP was high in summer (0.028 #/cm<sup>3</sup>, 23%) and low in winter (0.010 #/cm<sup>3</sup>, 6%). Snow cover and low biological activity were assumed to be the main reasons for the low coarse FBAP concentration in the wintertime. Both the fine and the coarse FBAP fraction typically increased at nighttime during the summer. Correlations between the BioScout and the UVAPS were high with the coarse (R = 0.83) and fine (R = 0.92) FBAP. The BioScout showed 2.6 and 9.7 times higher detection efficiencies for the coarse and fine FBAP, respectively, compared to the UVAPS. A long-range transport episode of particles from Eastern Europe increased the fine FBAP concentration by over two orders of magnitude compared to the clean period in the winter, but these FBAP probably also included fluorescent non-biological particles. Correlation analysis indicates that local combustion sources did not generate fluorescent non-biological particles that can disturb fine FBAP counting. The results provide information that can be used to estimate health risks and climatic relevance of bioaerosols in the urban environment.
atomistic models, and compared simulations with NMR experiments in terms of the highly structurally sensitive C-H bond vector order parameters. Focusing on the glycerol backbone and choline headgroups, we showed that the order parameter comparison can be used to judge the atomistic resolution structural accuracy of the models. Accurate models, in turn, allow molecular dynamics simulations to be used as an interpretation tool that translates these NMR data into a dynamic three-dimensional representation of biomolecules in biologically relevant conditions. In addition to lipid bilayers in fully hydrated conditions, we reviewed previous experimental data for dehydrated bilayers and cholesterol-containing bilayers, and interpreted them with simulations. Although none of the existing models reached experimental accuracy, by critically comparing them we were able to distill relevant chemical information: (1) increase of choline order parameters indicates the P-N vector tilting more parallel to the membrane, and (2) cholesterol induces only minor changes to the PC (glycerol backbone) structure. This work has been done as a fully open collaboration, using nmrlipids.blogspot.fi as a communication platform; all the scientific contributions were made publicly on this blog. During the open research process, the repository holding our simulation trajectories and files (https://zenodo.org/collection/user-nmrlipids) has become the most extensive publicly available collection of molecular dynamics simulation trajectories of lipid bilayers.

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Scopus rating (2010): SJR 1.849 SNIP 1.214
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Ultradon polyamide membrane as potential carrier for subretinal transplantation of human embryonic stem cell derived RPE

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Bioprocessing of enhanced cellulase production from a mutant of Trichoderma asperellum RCK2011 and its application in hydrolysis of cellulose

A mutant strain of Trichoderma asperellum RCK2011 was developed through UV-irradiation for enhanced cellulase production and lower catabolite repression. The production of FPase, CMCase and β-glucosidase was optimized under solid state fermentation; up to 20 mM of glucose did not inhibit cellulase production. The mutant strain T. asperellum SR1-7 produced FPase (2.2 IU/gds), CMCase (13.2 IU/gds), and β-glucosidase (9.2 IU/gds) under optimized conditions, which is, 1.4, 1.3, 1.5-fold higher than the wild type. The wild as well as mutant strain produced the cellulases at pH range, 4.0-10.0. Saccharification of pretreated corn cob, wheat straw, and sugarcane bagasse by cellulase from mutant strain SR1-7 resulted in release of reducing sugar at the rate of 530.0 mg/g, 290.0 mg/g, and 335.0 mg/g of substrate, respectively; this is 1.6-fold higher than the wild type strain. © 2014 Published by Elsevier Ltd.

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Authors: Raghuvanshi, S., Deswal, D., Karp, M., Kuhad, R. C.
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Inhibitory effects of substrate and soluble end products on biohydrogen production of the alkalithermophile Caloramator celer: Kinetic, metabolic and transcription analyses

In this study the tolerance of the alkalithermophile Caloramator celer towards substrate (glucose) and soluble end product (acetate, formate and ethanol) inhibition was assessed employing nonlinear inhibition models. In addition, the effects of subinhibitory concentrations of end products on fermentative metabolism and regulation of 12 key genes involved in pyruvate catabolism were studied. Optimal growth and H2 production were found at 50 mM of glucose and the critical substrate concentration was observed at 290-360 mM. Two inhibition models revealed that ethanol had a higher inhibitory effect on growth rate, whereas H2 production kinetics was more sensitive towards increasing concentrations of acetate and formate. Acetate, the main soluble metabolite of the fermentation, inhibited the H2 production by increasing the ionic strength in the medium. Subinhibitory concentrations of soluble end products induced changes in the metabolite profile of C. celer, specifically exogenous acetate (80 mM) and ethanol (40 mM) slightly increased the H2 yield by 4 and 7%, respectively. However, despite the observed metabolic shifts, gene regulation was minimal and not always in agreement with the measured product yields. Overall, the results suggest that further optimization of the H2 production process from C. celer should focus on methods to evolve adapted osmotolerant strains and/or remove soluble metabolites, especially acetate, from the culture. Copyright © 2014, Hydrogen Energy Publications, LLC. Published by Elsevier Ltd. All rights reserved.
Assessment of metabolic flux distribution in the thermophilic hydrogen producer Caloramator celer as affected by external pH and hydrogen partial pressure

Background: Caloramator celer is a strict anaerobic, alkalitolerant, thermophilic bacterium capable of converting glucose to hydrogen (H₂), carbon dioxide, acetate, ethanol and formate by a mixed acid fermentation. Depending on the growth conditions C. celer can produce H₂ at high yields. For a biotechnological exploitation of this bacterium for H₂ production it is crucial to understand the factors that regulate carbon and electron fluxes and therefore the final distribution of metabolites to channel the metabolic flux towards the desired product. Results: Combining experimental results from batch fermentations with genome analysis, reconstruction of central carbon metabolism and metabolic flux analysis (MFA), this study shed light on glucose catabolism of the thermophilic alkalitolerant bacterium C. celer. Two innate factors pertaining to culture conditions have been identified to significantly affect the metabolic flux distribution: culture pH and partial pressures of H₂ (P₃H₂). Overall, at alkaline to neutral pH the rate of biomass synthesis was maximized, whereas at acidic pH the lower growth rate and the less efficient biomass formation are accompanied with more efficient energy recovery from the substrate indicating high cell maintenance possibly to sustain intracellular pH homeostasis. Higher H₂ yields were associated with fermentation at acidic pH as a consequence of the lower synthesis of other reduced by-products such as...
formate and ethanol. In contrast, $P_{H_2}$ did not affect the growth of C. celer on glucose. At high $P_{H_2}$, the cellular redox state was balanced by rerouting the flow of carbon and electrons to ethanol and formate production allowing unaltered glycolytic flux and growth rate, but resulting in a decreased $H_2$ synthesis. Conclusion: C. celer possesses a flexible fermentative metabolism that allows redistribution of fluxes at key metabolic nodes to simultaneously control redox state and efficiently harvest energy from substrate even under unfavorable conditions (i.e. low pH and high $P_{H_2}$). With the $H_2$ production in mind, acidic pH and low $P_{H_2}$ should be preferred for a high yield-oriented process, while a high productivity-oriented process can be achieved at alkaline pH and high $P_{H_2}$. © 2014 Ciranna et al.; licensee BioMed Central Ltd.

Rewiring the wax ester production pathway of acinetobacter baylyi ADP1
Wax esters are industrially relevant high-value molecules. For sustainable production of wax esters, bacterial cell factories are suggested to replace the chemical processes exploiting expensive starting materials. However, it is well recognized that new sophisticated solutions employing synthetic biology toolbox are required to improve and tune the cellular production platform to meet the product requirements. For example, saturated wax esters with alkanol chain lengths C12 or C14 that are convenient for industrial uses are rare among bacteria. Acinetobacter baylyi ADP1, a natural producer of wax esters, is a convenient model organism for studying the potentiality and modifiability of wax esters in a natural host by means of synthetic biology. In order to establish a controllable production platform exploiting well-characterized biocomponents, and to modify the wax ester synthesis pathway of A. baylyi ADP1 in terms product quality, a fatty acid
reductase complex LuxCDE with an inducible arabinose promoter was employed to replace the natural fatty acyl-CoA reductase acr1 in ADP1. The engineered strain was able to produce wax esters by the introduced synthetic pathway. Moreover, the fatty alkanol chain length profile of wax esters was found to shift toward shorter and more saturated carbon chains, C16:0 accounting for most of the alkanols. The study demonstrates the potentiality of recircuiting a biosynthesis pathway in a natural producer, enabling a regulated production of a customized bioproduct. Furthermore, the LuxCDE complex can be potentially used as a well-characterized biopart in a variety of synthetic biology applications involving the production of long-chain hydrocarbons. © 2014 American Chemical Society.
A structural and functional perspective on the evolution of the heme-copper oxidases

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Scopus rating (2012): SJR 2.259 SNIP 0.914 CiteScore 3.67
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Scopus rating (2010): SJR 2.197 SNIP 0.795
Scopus rating (2009): SJR 2.131 SNIP 0.792
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Biofunctional hybrid materials: bimolecular organosilane monolayers on FeCr alloys

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Scopus rating (2012): SJR 1.846 SNIP 1.306 CiteScore 3.34
Scopus rating (2011): SJR 1.892 SNIP 1.461 CiteScore 3.86
Scopus rating (2010): SJR 1.844 SNIP 1.259
Scopus rating (2009): SJR 1.819 SNIP 1.28
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Scopus rating (2007): SJR 1.91 SNIP 1.36
Scopus rating (2006): SJR 1.934 SNIP 1.378
Scopus rating (2005): SJR 1.925 SNIP 1.445
Scopus rating (2004): SJR 1.849 SNIP 1.477
Scopus rating (2003): SJR 1.427 SNIP 1.371
Scopus rating (2002): SJR 0.962 SNIP 0.993
Scopus rating (2001): SJR 0.901 SNIP 0.94
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Metabolic engineering of Acinetobacter baylyi ADP1 for improved growth on gluconate and glucose

A high growth rate in bacterial cultures is usually achieved by optimizing growth conditions, but metabolism of the bacterium limits the maximal growth rate attainable on the carbon source used. This limitation can be circumvented by engineering the metabolism of the bacterium. Acinetobacter baylyi has become a model organism for studies of bacterial metabolism and metabolic engineering due to its wide substrate spectrum and easy-to-engineer genome. It produces naturally storage lipids, such as wax esters, and has a unique gluconate catabolism as it lacks a gene for pyruvate kinase.

We engineered the central metabolism of A. baylyi ADP1 more favorable for gluconate catabolism by expressing the pyruvate kinase gene (pykF) of Escherichia coli. This modification increased growth rate when cultivated on gluconate or glucose as a sole carbon source in a batch cultivation. The engineered cells reached stationary phase on these carbon sources approximately twice as fast as control cells carrying an empty plasmid and produced similar amount of biomass. Furthermore, when grown on either gluconate or glucose, pykF expression did not lead to significant accumulation of overflow metabolites and consumption of the substrate remained unaltered. Increased growth rate on glucose was not accompanied with decreased wax ester production, and the pykF-expressing cells accumulated significantly more of these storage lipids with respect to cultivation time.
Murein lytic enzyme TgaA of Bifidobacterium bifidum MIMBb75 modulates dendritic cell maturation through its cysteine- and histidine-dependent amidohydrolase/peptidase (CHAP) amidase domain

Bifidobacteria are Gram-positive inhabitants of the human gastrointestinal tract that have evolved close interaction with their host and especially with the host's immune system. The molecular mechanisms underlying such interactions, however, are largely unidentified. In this study, we investigated the immunomodulatory potential of Bifidobacterium bifidum MIMBb75, a bacterium of human intestinal origin commercially used as a probiotic. Particularly, we focused our attention on TgaA, a protein expressed on the outer surface of MIMBb75's cells and homologous to other known bacterial immunoreactive proteins. TgaA is a peptidoglycan lytic enzyme containing two active domains: lytic murein transglycosylase (LT) and cysteine- and histidine-dependent amidohydrolase/peptidase (CHAP). We ran immunological experiments stimulating dendritic cells (DCs) with the B. bifidum MIMBb75 and TgaA, with the result that both the bacterium and the protein activated DCs and triggered interleukin-2 (IL-2) production. In addition, we observed that the heterologous expression of TgaA in Bifidobacterium longum transferred to the bacterium the ability to induce IL-2. Subsequently, immunological experiments performed using two purified recombinant proteins corresponding to the single domains LT and CHAP demonstrated that the CHAP domain is the immune-reactive region of TgaA. Finally, we also showed that TgaA-dependent activation of DCs requires the protein CD14, marginally involves TRIF, and is independent of Toll-like receptor 4 (TLR4) and MyD88. In conclusion, our study suggests that the bacterial CHAP domain is a novel microbe-associated molecular pattern actively participating in the cross talk mechanisms between bifidobacteria and the host's immune system. © 2014, American Society for Microbiology.
Bifidobacterium bifidum MIMBb75 is a human intestinal isolate demonstrated to be interactive with the host and efficacious as a probiotic. However, the molecular biology of this microorganism is yet largely unknown. For this reason, we undertook whole-genome sequencing of B. bifidum MIMBb75 to identify potential genetic factors that would explain the metabolic and probiotic attributes of this bacterium. Comparative genomic analysis revealed a 45-kb chromosomal region that comprises 19 putative genes coding for a potential type IV secretion system (T4SS). Thus, we undertook the initial characterization of this genetic region by studying the putative virB1-like gene, named tgaA. Gene tgaA encodes a peptidoglycan lytic enzyme containing two active domains: lytic murein transglycosylase (LT, cd00254.3) and cysteine- and histidine-dependent amidohydrolase/peptidase (CHAP, pfam05257.4). By means of several in vitro assays, we experimentally confirmed that protein TgaA, consistent with its computationally assigned role, has peptidoglycan lytic activity, which is principally associated to the LT domain. Furthermore, immunofluorescence and immunogold labeling showed that the protein TgaA is abundantly expressed on the cell surface of B. bifidum MIMBb75. According to the literature, the T4SSs, which have not been characterized before in bifidobacteria, can have important implications for bacterial cell-to-cell communication as well as cross talk with host cells, justifying the interest for further studies aimed at the investigation of this genetic region. © 2014, American Society for Microbiology.
Non-sterile process for biohydrogen and 1,3-propanediol production from raw glycerol

Raw glycerol is a tempting substrate for fermentations, but contains impurities that can be inhibitory for organisms. In this study, raw glycerol tolerance and contamination risk of pure bacterial culture at hypersaline process conditions were evaluated. The inhibitory effect of raw glycerol was similar on a halophilic (Halanaerobium saccharolyticum) and a non-halophilic (Clostridium butyricum) bacterium implying the inhibition originating from methanol or other impurities rather than salt. The hypersaline process conditions decreased efficiently contaminations and no growth of contaminants was observed at and above 125 g/l NaCl. Halophilic H$_2$ and 1,3-PD production from raw glycerol were studied separately as 1-stage processes and jointly as 2-stage process in non-sterile conditions. Non-sterile conditions were successfully applied and the highest production yields obtained were 3.0 mol H$_2$/mol glycerol and 0.66 mol 1,3-PD/mol glycerol (1-stage processes), whereas the highest cumulative production was 74 mmol H$_2$/l culture and 31 mmol 1,3-PD/l culture (2-stage process). © 2013, Hydrogen Energy Publications, LLC. Published by Elsevier Ltd. All rights.

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Scopus rating (2013): SJR 1.278 SNIP 1.467 CiteScore 3.38
Scopus rating (2012): SJR 1.515 SNIP 1.729 CiteScore 3.96
Scopus rating (2011): SJR 1.456 SNIP 1.837 CiteScore 4.42
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Prospecting hydrogen production of Escherichia coli by metabolic network modeling

Genome-scale model was applied to analyze the anaerobic metabolism of Escherichia coli. Three different methods were used to find deletions affecting fermentative hydrogen production: flux balance analysis (FBA), algorithm for blocking competing pathways (ABCP), and manual selection. Based on these methods, 81 E. coli mutants possessing one gene deletion were selected and cultivated in batch experiments. Experimental results of H₂ and biomass production were compared against the results of FBA. Several gene deletions enhancing H₂ production were found. Correctness of gene essentiality predictions of FBA for the selected genes was 78% and 77% in glucose and galactose media, respectively. 33% of the mutations that were predicted by FBA to increase H₂ production had a positive effect in experiments. Batch cultivation is a simple and straightforward experimental way to screen improvements in H₂ production. However, the ability of FBA to predict the H₂ production rate cannot be evaluated by batch experiments. Metabolic network models provide a method for gaining broader understanding of the complicated metabolic system of a cell and can aid in prospecting suitable gene deletions for enhancing H₂ production. © 2013, Hydrogen Energy Publications, LLC. Published by Elsevier Ltd. All rights.
Antimicrobial assay optimization and validation for HTS in 384-well format using a bioluminescent E. coli K-12 strain

This report describes the optimization and validation of an antimicrobial assay based on the genetically modified bacterial strain Escherichia coli K-12 (pTetLux1). The use of this particular strain enables an inducible cell-based bioluminescent assay for high-throughput screening (HTS) of antimicrobial agents, which shows a pronounced detection of compounds targeting transcriptional and translational events in protein synthesis. The optimizations in 96-well format led to several improvements in assay conditions, such as reduction of the pre-incubation time before luminescence induction by half. The threshold for DMSO tolerability was concluded to be up to 1%. Assay protocol was further miniaturized into 384-well format and the liquid handling was automated using a robotic workstation. The use of compound pre-plating into 384-well plates as a part of the process was evaluated, and the total assay volume was further downscaled from 50 μl to 30 μl. With this approach, the amount of test compound needed per well was reduced to nanoliter volumes. Using the miniaturized protocol a pilot screen of 2000 known drugs and bioactives was performed. The assay performance was evaluated by calculating known assay quality parameters, the Z' factor having a mean value of 0.8 during the compound library screening indicated an excellent performance. Of the assay positives, 54 compounds showed high inhibitions (60-100%), of which the majority (89%) were known antibacterial agents. Of the actives showing >60% inhibition, 16 compounds were identified as known transcriptional and translational inhibitors. The screening results demonstrated that the miniaturized assay is well suited for identification of antimicrobial compounds in HT screening, and that the assay is specifically sensitive towards bacterial transcription and translation inhibitors. © 2013 Elsevier B.V.
Computational model of Ca2+ wave propagation in human retinal pigment epithelium

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