7th Christmas Biophysics Workshop

(XBW 2012)

17. – 18. 12. 2012, Genusshotel Riegersburg

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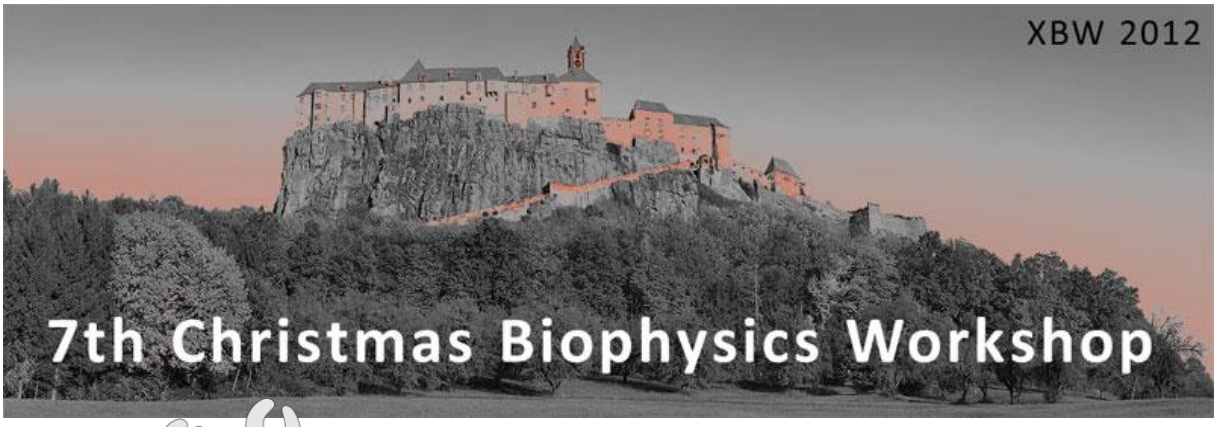

Book of Abstracts

Organizing Committee:

Georg Pabst (Chair), Peter Heftberger, and Benjamin Kollmitzer

University of Graz, Institute of Molecular Biosciences, Biophysics Division

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BIOPHYSICS AUSTRIA

THE CROATIAN BIOPHYSICAL SOCIETY

Program:

Monday, December 17, 2012

10:00 – 10:10		Welcome
10:10 – 11:50		**SESSION I: COLLOIDAL PHYSICS** Chair: Rudolf Podgornik
	10:10 – 10:30	**Many-body contact repulsion of deformable disks** A. Šiber (Institute of Physics, Croatia and Jožef Stefan Institute, Slovenia)
	10:35 – 10:55	**Poisson-Boltzmann approach for sterically asymmetric electrolytes** M. Popović (Insitute Ruđer Bošković, Croatia)
	11:00 – 11:20	**Multiscale modeling & simulation of soft matter** J. Zavadlav (National Institute of Chemistry, Slovenia)
	11:25 – 11:45	**Inverse patchy colloids – a novel colloidal model** G. Kahl (Vienna University of Technology, Austria)
12:00 – 13:00		*Lunch*
13:00 – 15:30		**SESSION II: MEMBRANE BIOPHYSICS 1** Chair: Georg Pabst
	13:00 – 13:20	**Confinement-induced compartmentalization of vesicles** P. Ziherl (University of Ljubljana, Slovenia and Jožef Stefan Institute, Slovenia)
	13:25 – 13:45	**Ground states of model single-layer epithelial tissue** N. Štorgel, M. Krajnc (University of Ljubljana, Slovenia and Jožef Stefan Institute, Slovenia)
	13:50 – 14:10	**Periodic linear membrane structures** U. Jelerčič (Jozef Stefan Institute, Slovenia)
	14:15 – 14:35	**About why fission yeast nucleus divides in a symmetric manner** S. Svetina (University of Ljubljana Slovenia and Jožef Stefan Institute, Slovenia)
	14:40 – 15:00	**Helical properties of an amphiphilic designer-peptide** K. Kornmueller (Medical University of Graz, Austria)
	15:05 – 15:25	**Mode of action of OP-145, a synthetic antimicrobial peptide derived from the human cathelicidin LL-37, triggers specific interaction with lipid membranes** N. Malanovic (University of Graz, Austria and Austrian Academy of Sciences, Austria)

15:30 – 16:00		*Coffee Break*
16:00 – 18:05		**SESSION III: MEMBRANE BIOPHYISCS 2** Chair: Karl Lohner
	16:00 – 16:20	**Fluorescence microspectroscopy – a promising tool for membrane domain characterization** I. Urbančič (Jožef Stefan Institute, Slovenia)
	16:25 – 16:45	**Monitoring receptor-mediated dendritic cell internalization by PH-sensitive fluorescent probe** Z. Arsov (Jozef Stefan Institute, Slovenia and Center of Excellence NAMASTE, Slovenia)
	16:50 – 17:10	**Spontaneous curvature of liquid ordered lipid domains** B. Kollmitzer (University of Graz, Graz, Austria)
	17:15 – 17:35	**Advancing global SAXS data analysis** P. Heftberger (University of Graz, Austria)
	17:40 – 18:00	**Perifosine containing liposomal nanocarriers – yet another drug delivery system across barrier forming cells** T. Koklic (Jožef Stefan Institute, Slovenia and Center of Excellence NAMASTE, Slovenia)
18:05 – 19:30		*Dinner*
20:00 – 24:00		*Social Evening* *(Hike with torches / Hot wine punch reception)*

Tuesday, December 18, 2012

07:30 – 09:00		*Breakfast*
09:00 – 10:40		**SESSION IV: POLYELECTROLYTES 1** Chair: Benjamin Kollmitzer
	09:00 – 09:20	**DNA knotting inside viral capsids: a computational approach** C. Micheletti (SISSA, Italy)
	09:25 – 09:45	**Knots and mulstiscale entanglement in biopolymers** L. Tubiana (Jožef Stefan Institute, Slovenia)
	09:50 – 10:10	**Low frequency impedance spectroscopy: charge transport in aqueous gelatin** S. Marion (University of Zagreb, Croatia)
	10:15 – 10:35	**The complex architecture of bioinorganic aragonite produced by marine invertebrates: nano-scale organization of the cuttlebone** V. Čadež (Ruđer Bošković Institute, Croatia**)**
10:40 – 11:10		*Coffee Break*
11:10 – 12:25		**SESSION V: POLYELECTROLYTES 2** Chair: Peter Heftberger
	11:10 – 11:30	**Conformation of DNA in low added salt solutions** D. Grgičin (Institut za fiziku, Croatia)
	11:35 – 11:55	**Entropy and manning condensation in dilute polyelectrolytes** D. Vurnek (Institut za fiziku, Croatia)
	12:00 – 12:20	**Confinement effects on the structure and dynamics of polymer melts with broadband dielectric spectroscopy** I. Nikić (University of Zagreb, Croatia)
12:25 – 14:00		*Lunch*
14:00		*Departure*

COLLOIDAL PHYSICS

Chair: Rudolf Podgornik 10:10 – 11:50

MANY-BODY CONTACT REPULSION OF DEFORMABLE DISKS

Antonio Šiber[1,2] and Primož Ziherl[2,3]

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[3]*Faculty of Mathematics and Physics, University of Ljubljana, Jadranska 19, SI-1000 Ljubljana, Slovenia*

We use a spring-and-plaquette network model to analyze the repulsion between elastic disks in contact. By studying various 2D geometries, we find that as disks approach the incompressibility limit the many-body effects become dominant and the disk-disk interaction is not pairwise additive. Upon compression, the disks undergo a transition from the localized to the distributed deformation regime accompanied by a steep increase of energy consistent with the onset of a hard core. These results shed new light on the structures formed by deformable objects such as soft nanocolloids.

POISSON-BOLTZMANN APPROACH FOR STERICALLY ASYMMETRIC ELECTROLYTES

M. Popović[1], A. Šiber[2]

[1]*Insitute Ruđer Bošković, Zagreb, Croatia*

[2]*Insitute of physics, Zagreb, Croatia*

We derive a modification of the Poisson-Boltzmann equation considering steric effects of different size ions. Our equation represents a generalization of previous work for equal size ions [I. Borukhov, D. Andelman and H. Orland, Phys. Rev. Lett. 79, 435 (1997)] and allows more general calculations. We show that proposed modification predicts asymmetry of the double-layer differential capacitance. Our derivation provides analytical framework for previously proposed heuristic modification of the Poisson-Boltzmann equation, which also predicts the same effect [A.A. Kornyshev, J. Phys. Chem. B 111, 5545 (2007)].

MULTISCALE MODELING & SIMULATION OF SOFT MATTER

J. Zavadlav[1], S. Bevc[1], J. Sablić[1], M. Praprotnik[1,2]

[1]*Laboratory for Molecular Modeling, National Institute of Chemistry, Hajdrihova 19, SI-1001 Ljubljana, Slovenia.*

[2]*Department of Physics, Faculty of Mathematics and Physics, University of Ljubljana, SI-1000 Ljubljana, Slovenia.*

Soft matter and molecular liquids are characterized by a wide range of length and time scales that are intrinsically interconnected. Multiscale modeling approaches that combine various simulation models represent the most efficient way to bridge many orders of magnitude in the spatial and temporal scales involved in these systems. Here, we present recent results of our multiscale simulations of soft matter systems, e.g., saline solution, DNA liquid crystal, and star polymer melt.

INVERSE PATCHY COLLOIDS - A NOVEL COLLOIDAL MODEL

Emanuela Bianchi[1], Christos N. Likos[2], and Gerhard Kahl[1]

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[2]*Fakultät für Physik, Universität Wien, Wien, Austria.*

We consider a novel type of particles with patterned surfaces, where - in contrast to conventional patchy colloids - patches repel each other. To be more specific we consider a spherical, negatively charged colloid whose surface is decorated by two positively charged patches, located at the poles of the colloid; consequently, the patches as well as the equatorial regions repel each other, while patches are attracted by the equatorial region. Based on Debye-Hückel theory for dilute electrolytes, it is possible to derive for this particular model an effective interaction potential between two inverse patchy colloids. The resulting complex interaction potential can be mapped via a suitable coarse-graining procedure to a simple, analytic pair potential. Based on this model we investigate with computer simulations and theoretical approaches the self-assembly scenarios of such particles into ordered and disordered structures in two and three dimensions.

MEMBRANE BIOPHYSICS 1

Chair: Georg Pabst 13:00 – 15:30

CONFINEMENT-INDUCED COMPARTMENTALIZATION OF VESICLES

A. Sakashita[1,2], P. Ziherl[3,4], M. Imai[5], and H. Noguchi[2]

[1]*Department of Physics, Division of Advanced Sciences, Ochanomizu University, Tokyo, Japan.*

[2]*Institute of Solid State Physics, University of Tokyo, Tokyo, Japan.*

[3]*Faculty of Mathematics and Physics, University of Ljubljana, Ljubljana, Slovenia.*

[4]*Jožef Stefan Institute, Ljubljana, Slovenia.*

[5]*Department of Physics, Faculty of Science, Tohoku University, Sendai, Japan.*

The shape of a vesicle captured by another vesicle of similar volume may be affected considerably by confinement, the effect being most prominent if vesicle volumes are almost identical and the membrane area of the inner vesicle is sufficiently larger than that of the outer vesicle. We use the area-difference-elasticity model to theoretically study the morphologies of vesicles contained within a spherical cavity mimicking a taut outer vesicle. We explore the phase diagram by varying the vesicle reduced volume and reduced monolayer area difference, and we find many shapes not observed in isolated vesicles including a double stomatocyte, a cap-cap vesicle derived from a confined budded shape, shapes consisting of three or more wedges, and several combined shapes. Our results suggest that confinement may lead to compartmentalization of vesicles.

GROUND STATES OF MODEL SINGLE-LAYER EPITHELIAL TISSUE

N. Štorgel[1,3], M. Krajnc[1,3], A. Hočevar Brezavšček[2,3] and P. Ziherl[1,3]

[1]*Faculty of Mathematics and Physics, University of Ljubljana, Ljubljana, Slovenia.*

[2]*The Rockefeller University, New York, USA.*

[3]*Jožef Stefan Institute, Ljubljana, Slovenia.*

In a simple mechanical model, cells of the one-cell-thick epithelium carry a surface energy associated with cortex and interfacial tension as well as cell-cell adhesion. The basal, the lateral, and the apical cell faces are each characterized by a specific effective surface tension. Within this theoretical framework, we explore the periodic minimal-energy configurations of an infinite 2D epithelium, finding that they include both flat and distorted states. As the differential apical-basal tension is increased, the epithelium undergoes a transition from a thin flat state to an expanded corrugated state which is then compactified and transformed into a collapsed corrugated state and eventually replaced by the thick flat state. Apart from outlining the phase diagram, we also study the elastic properties of these states, especially their stretching and bending moduli. Finally we present the continuum version of the discrete model which explains certain morphological features of the corrugated states such as the coupling between epithelial curvature and thickness.

PERIODIC LINEAR MEMBRANE STRUCTURES

U. Jelerčič[1], S. Svetina[1, 2] and P. Ziherl[1, 3]

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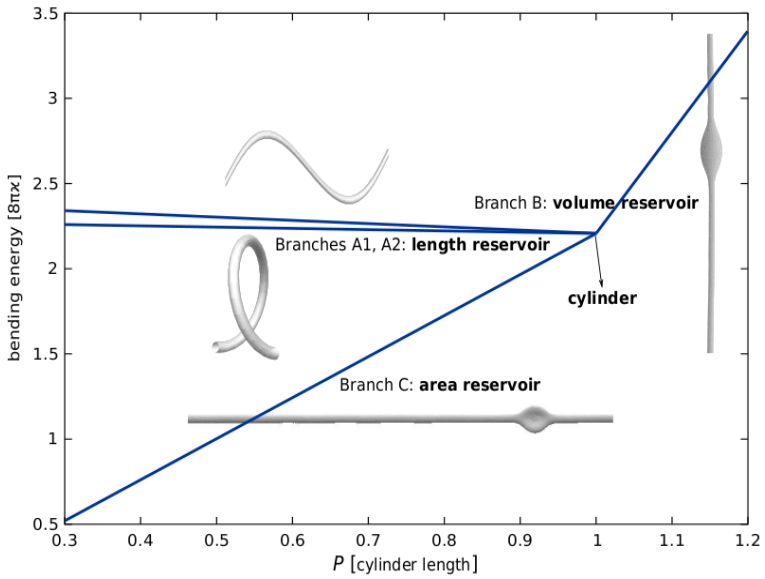
[2]*Institute of Biophysics, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia*

[3]*Department of Physics, Faculty of Mathematics and Physics, University of Ljubljana, Ljubljana, Slovenia*

Linear membrane structures often occur in lipid vesicles with large surface-to-volume ratio and are a common building block of cellular organelles, such as Golgi apparatus and endoplasmic reticulum. In certain conditions these linear structures assume lengthwise periodicity which results in a formation of vesicular structures of different shapes and sizes. We theoretically analyse and classify the three-dimensional shapes of periodic linear membrane structures free of any approximations or restrictions imposed, e.g., symmetry. We use a numerical approach based on the minimization of Helfrich membrane bending energy. Phase diagram includes axisymmetric shapes such as unduloid-like and spiraling tubular shapes, racket-like flattened shapes, and several hybrids. We discuss the relevance of these results for the various intra-cellular structures such as the cis- and the trans-Golgi network.



ABOUT WHY FISSION YEAST NUCLEUS DIVIDES IN A SYMMETRIC MANNER

S. Svetina[1, 2], B. Božič[1], S. Castagnetti[3]

[1]Institute of Biophysics, Faculty of Medicine, University of Ljubljana, [2]Jožef Stefan Institute, Ljubljana, Slovenia, [3]Biosciences, University of Exeter, Exeter, UK.

Fission yeast nucleus divides within an intact nuclear envelope (NE), undergoing in this way closed mitosis. The process of corresponding NE shape transformation is governed by spindle microtubules pushing apart the opposing spindle pole bodies (SPBs). Consequent NE shapes are mirror symmetric and change from sphere to dumbbell to the final two spherical daughter nuclei connected by a thin tether. NE is a double membrane bilayer in a continuum with the endoplasmic reticulum and its shape should thus correspond to the minimum of its bending energy at a fixed value of the membrane lateral tension. However, the corresponding calculations predict the minimum energy shape to be asymmetrical, composed of a lemon-like main body and an axial protrusion. Following the observation of the appearance of asymmetrical NE shapes in fission yeast mutants which undergo spindle elongation prior to chromosome segregation to SPBs, we looked for the explanation of the mirror symmetric nuclear shapes on the basis of the chromosome – SPB associations. We show theoretically that the stability of such shapes can result from the steric effect of chromosomes on the position of the surrounding NE which is significant only if they are bound to SPBs.

HELICAL PROPERTIES OF AN AMPHIPHILIC DESIGNER-PEPTIDE

K. Kornmueller[1], C. Vonach[1], F. Cacho-Nerin[2], K. Gradauer[1], G. Leitinger[3], H. Amenitsch[2], R. Prassl[1]

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[2]*Institute of Inorganic Chemistry, University of Technology, Graz, Austria.*

[3]*Institute of Cell Biology, Histology and Embryology, Medical University of Graz, Graz, Austria.*

Since few years amphiphilic designer-peptides are used as building blocks for materials with exciting new properties. Their ability to self-assemble into supramolecular structures is exploited in order to create these materials in a bottom-up approach. Applications are manifold and cover a wide range from 3D-cell culture systems, tissue engineering, gene and drug delivery systems to templates for nanowires.

In this study we investigated the self-assembly of the 8-residue peptide GAAVILRR. Synchrotron small angle x-ray scattering (SAXS), as well as transmission electron microscopy (TEM) and circular dichroism (CD) spectroscopy were applied to shed light on the process of structure formation as a function of peptide concentration. With all different techniques we were able to follow the transition from a dilute, non-interacting colloidal solution to a system with increasing interparticle interactions that promote the formation of elongated structures. At higher concentrations the formation of a stable hydrogel consisting of a network of helically twisted ribbons was observed.

This work is supported by the Austrian Science Fund (FWF Project No. P20455-B12).

MODE OF ACTION OF OP-145, A SYNTHETIC ANTIMICROBIAL PEPTIDE DERIVED FROM THE HUMAN CATHELICIDIN LL-37, TRIGGERS SPECIFIC INTERACTION WITH LIPID MEMBRANES

N. Malanovic[1,2], M. Schmuck[2], M. Kriechbaum[2], J.W. Drijfhout [3]and K. Lohner[1,2]

[1]*Institute of Molecular Biosciences, University of Graz, Graz, Austria*

[2]*Institute of Biophysics and Nanosystems Research, Austrian Academy of Sciences, Graz, Austria*

[3]*Leiden University Medical Center, Leiden, The Netherlands*

OP-145, termed previously as P60.4[1] is a synthetic 24-amino acid derivative of the human cathelicidin LL-37 and has antimicrobial and antibiofilm activity, but low chemotactic activity as compared to its parent peptide LL-37. In order to gain insight into the mode of action biophysical studies on liposomes composed of phosphatidylglycerol (PG) and phosphatidylcholine (PC) mimicking bacterial and mammalian cell membranes were performed. Similarly to earlier findings on LL-37[2] the peptide interacted with both lipid systems inducing however different extent of perturbation. Leakage experiments revealed that OP-145 induced complete release of entrapped fluorescence marker molecules from PG liposomes, while in case of PC liposomes only about one third was set free under the same experimental condition. Microcalorimetry showed that increasing peptide concentration led to a decrease of the pre- and main transition enthalpy of PC with a concomitant appearance of a low enthalpic, broad transition underlying the main transition of pure PC. These characteristics are indicative for a detergent-like action of OP-145 leading to disintegration of the multilamellar PC liposomes into disk-like aggregates as confirmed by small-angle X-ray scattering experiments. The perturbation of PG liposomes was more clearly detected in cooling scans showing a phase separation into peptide-enriched and -poor lipid domains that is in accordance with the degree of membrane thinning determined by X-ray scattering upon cooling. This suggests that OP-145 induces a quasi-interdigitated structure like LL-37. The different mode of membrane perturbation for zwitterionic and anionic model membranes cannot be explained by different peptide conformations, as CD spectroscopy yield alpha-helical secondary structures for both systems under investigation, but rather by different incorporation of the peptide into the bilayers.

Acknowledgement: This work was supported by FP7-HEALTH-2011, BALI – Biofilm Alliance.

1. Nell J.M.; Tjabringa G.S.; Wafelmann A.R.; Vereijk R.; Hiemstra P.S.; Drijfhout J.W.; Grote J.J. *Peptides* **2006**, 27(4):649.
2. Sevcsik, E.; Pabst, G.; Jilek, A.; Lohner, K. *Biochim. Biophys. Acta* **2007**, *1768*, 2586.

MEMBRANE BIOPHYISCS 2

Chair: Karl Lohner 16:00 – 18:05

FLUORESCENCE MICROSPECTROSCOPY – A PROMISING TOOL FOR MEMBRANE DOMAIN CHARACTERIZATION

Iztok Urbančič[1], Ajasja Ljubetič[1], Zoran Arsov[1,2], Janez Štrancar[1,2]

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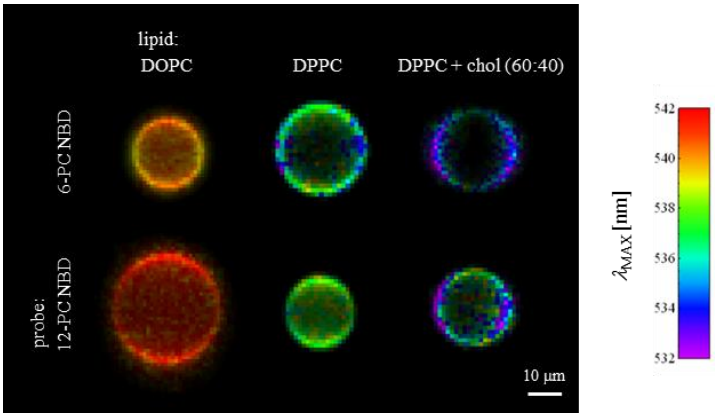
[2] *Centre of Excellence NAMASTE, Ljubljana, Slovenia.*

Recent research in membrane biophysics has provided ample evidence that transport and signalling across cell membranes strongly depend on local membrane properties, e.g. chemical composition, ordering, and viscosity. However, due to contradicting reports from different experimental methods description of membrane domains and lipid rafts remains underdetermined and their functions and regulation mechanisms uncertain. Therefore new techniques are being developed to target the right spatial and temporal scale.
Fluorescence microspectroscopy combines the ultimate sensitivity of fluorescence methods, spatial resolution of optical microscopy and a wealth of information by spectroscopic techniques. Having optimized acquisition and analysis for artefacts due to photobleaching, spectral resolution of 1 nm is achievable and choice of probes is largely expanded.
In the presentation, some examples of lipid phase tracking in model membranes will be shown. Using NBD-based fatty-acid and lipid probes, one can clearly distinguish liposomes in gel, liquid ordered and liquid disordered state or observe phase transitions of single liposomes, even when fluorescence spectra shift for as little as 1–2 nm. Furthermore, fluorescence spectra can reveal specific motional patterns of certain probe molecules in different environments.



MONITORING RECEPTOR-MEDIATED DENDRITIC CELL INTERNALIZATION BY PH-SENSITIVE FLUORESCENT PROBE

Z. Arsov[1,2], U. Svajger[3], J. Mravljak[4], S. Pajk[4], T. Koklic[1,2], J. Strancar[1,2], M. Anderluh[4]

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[2]*Center of Excellence NAMASTE, Ljubljana, Slovenia*

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[4]*Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia*

Dendritic cells (DC) are a type of white blood cells and are the most potent antigen-presenting cells. The antigen presentation goes through antigen-uptake receptor, e.g. DC-SIGN [1], followed by internalization to lysosomes.

The interior of the lysosomes is acidic compared to mainly neutral pH of cytosol. Therefore, monitoring local pH inside living cells is important for studying cellular internalization pathways, such as phagocytosis, endocytosis, and receptor ligand internalization [2].

In order to study possible antigen-uptake mechanisms, a fluorescent probe that combines a DC-SIGN ligand and a pH-sensitive dye has been designed. Control fluorescence spectroscopy measurements in buffers with pH values from neutral to acidic have shown that with lower pH the fluorescence intensity of the probe strongly increases. At the same time the spectrum maximum shifts to higher wavelengths. Subsequently, fluorescence microspectroscopy (FMS) [3] has been used to track the probe internalization efficiency of DC. Assessment of spatial dependence of the spectral shape confirmed presumable probe targeting to lysosomes. The internalization efficiency of monocytes, which are precursors of DC with no DC-SIGN expressed, was much lower. Results support the notion that the internalization is DC-SIGN-mediated.

[1] U. Svajger, M. Anderluh, M. Jeras, and N. Obermajer, Cell. Signal. 22, 1397–1405 (2010)

[2] J. Han and K. Burgess, Chem. Rev. 110, 2709–2728 (2010)

[3] Z. Arsov, I. Urbancic, M. Garvas, D. Biglino, A. Ljubetic, T. Koklic, and J. Strancar, Biomed. Opt. Express 2, 2083–2095 (2011)

SPONTANEOUS CURVATURE OF LIQUID ORDERED LIPID DOMAINS

B. Kollmitzer[1], P. Heftberger[1], M. Rappolt[2], G. Pabst[1]

[1]*Institute of Molecular Biosciences, University of Graz, Graz, Austria.*

[2]*Institute of Inorganic Chemistry, Graz University of Technology, Graz, Austria.*

Diverse biophysical techniques on ternary mixtures of low-melting and high-melting phospholipids and cholesterol have established phase separation into liquid-ordered (Lo) and liquid-disordered (Ld) domains. Lo domains show several features of membrane rafts, such as, e.g. increased cholesterol content, enrichment of the high-melting lipid (sphingomyelin), and partitioning of GPI-anchored proteins. Lo domains are therefore frequently discussed as membrane raft mimetics.

We have performed Small-Angle X-ray diffraction (SAXS) experiments on well-defined lipid mixtures in the inverted hexagonal (H_{II}) phase to determine monolayer spontaneous curvatures J_0 for several lipids (Cholesterol, DOPC, DOPE, DPPC, DSPC, POPC, SOPC, and Sphingomyelin; Fig. 1). These results were applied to estimate J_0 for coexisting Lo/Ld phases, a parameter which supposedly plays a major role in membrane deformation processes (lipid-droplet formation, membrane fusion etc.) and protein-membrane partitioning.

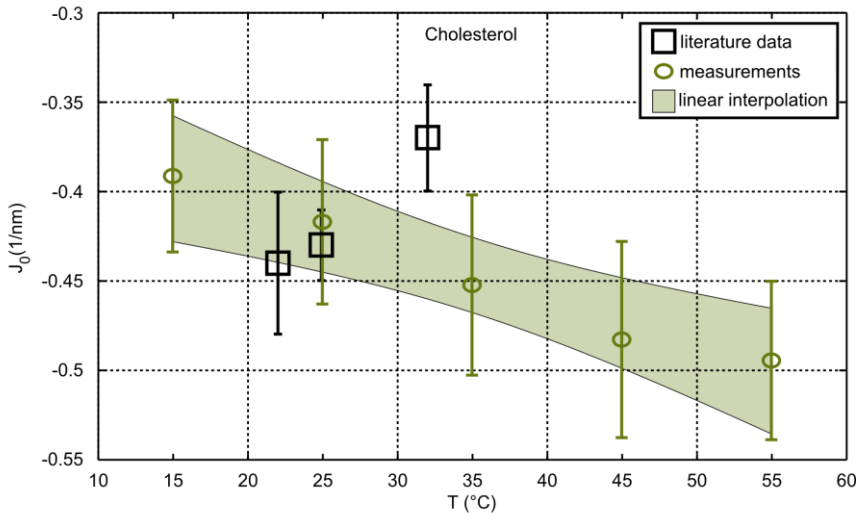

Figure 1: Comparison of new spontaneous curvature data (ellipses) for cholesterol with literature values (squares) as a function of temperature T.

This work is supported by the Austrian Science Funds FWF, Project No. P24459.

ADVANCING GLOBAL SAXS DATA ANALYSIS

P. Heftberger[1], B. Kollmitzer[1], G. Pabst[1]

[1]*Insitute of Molecular Biosciencies, University of Graz, Austria.*

We enhanced an existing global analysis program (GAP) [1] for small angle x-ray scattering data of multilamellar phospholipid bilayer systems at full hydration. The basis for the analysis is a model for volume probability distributions of the individual molecular groups of a given phospholipid, called the SDP (Scattering Density Profile) model [2]. The old method employed two Gaussians, one for the headgroup and one for the tail, modeling the electron density profile and is not very specific concerning structural details of the bilayer [1].
The implementation of the SDP model allows us to retrieve detailed information about spatial positions of the single molecular groups, and yields additional parameters such as the area per lipid, length of lipid chain and Luzzati thickness of the lipid bilayer.
Presently we parse phospholipids (primarily phosphatidylcholine lipids) into five molecular groups (CH3, CH2, CG, PCN, CholCH3, see Fig.1) using a set of Gaussians and error functions to describe their volume distributions. Further we apply a genetic algorithm to optimize the model against data. Our first results of analyzing different lipid vesicles with the SDP model show good accordance with those of Kucerka et al. [3], who combined x-ray and neutron data at various contrasts to obtain high structural resolution. In contrast, we used synchrotron x-ray data for the analysis only. So the experimental effort in our case is lower, at the expense of computational efforts. Results are encouraging to apply the technique to phase separated systems.

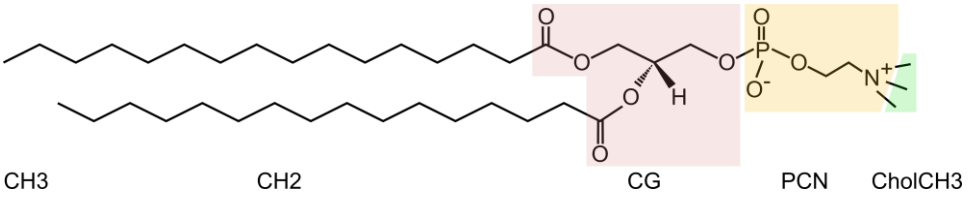

Fig.1: Parsing scheme of dipalmitoylphosphatidylcholine (DPPC)

This work is supported by the Austrian Science Funds FWF, Project No. P24459.

References:

[1] G. Pabst et al., Physical Review E 62, 4000 (2000)

[2] N. Kucerka et al., Biophysical Journal 95, 2356 (2008)

[3] N. Kucerka et al., Biochimica et Biophysica Acta 1808, 2761 (2011)

PERIFOSINE CONTAINING LIPOSOMAL NANOCARRIERS

– YET ANOTHER DRUG DELIVERY SYSTEM ACROSS BARRIER FORMING CELLS

Tilen Koklic[1,2], Rok Podlipec[1,2], Maja Garvas[1], Andrea Orthmann[3], Marjeta Šentjurc[1], Reiner Zeisig[4], Janez Štrancar[1,2]

[1]*Jožef Stefan Institute, Ljubljana, Slovenia*

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[3]*Experimental Pharmakology, Max Delbrück Center for Molecular Medicine, Berlin-Buch, Germany*

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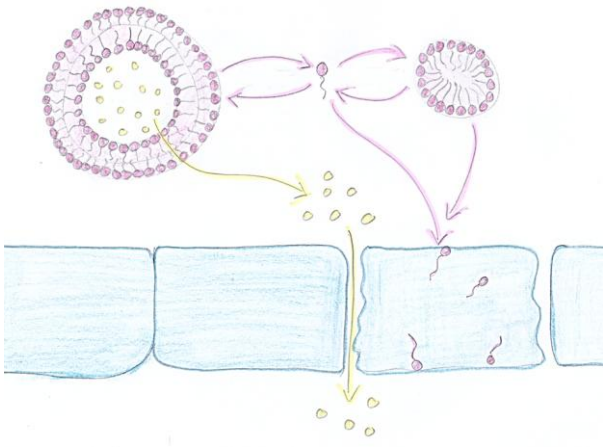
Discovery of efficient drug delivery systems to deliver therapeutics to a disease affected brain tissue in a controlled and non-invasive manner remains one of the key goals of drug development[1]. We hypothesized[2] that liposomes composed of lysolipids might efficiently deliver liposome encapsulated hydrophilic content across barrier forming cells via paracellular route, thus avoiding efflux transporters.



As a proof of principle we show that liposomal nanocarriers containing alkylphospholipid perifosine deliver about 25% of entrapped hydrophilic content, due to the influence of perifosine on lipid membrane properties. At concentrations of perifosine to cholesterol greater than approximately 1, perifosine increases liposome membrane fluidity and leakage of liposome encapsulated content, promotes formation of micelles in liposome formulations, and it is transferred as a part of a micellar phase of liposomal formulations or as a free molecule into cells. How perifosine induces permeability of a tight cellular monolayer remains to be answered, however the possibility of using lysolipid containing liposomes as a drug delivery system for trans cell-barrier transport of hydrophilic drugs into a disease affected tissue is possible.

References:

1. Karkan, D.; Pfeifer, C.; Vitalis, T. Z.; Arthur, G.; Ujiie, M.; Chen, Q.; Tsai, S.; Koliatis, G.; Gabathuler, R.; Jefferies, W. a A Unique Carrier for Delivery of Therapeutic Compounds Beyond the Blood-brain Barrier. *PloS One* **2008**, *3*, e2469.
2. Koklic, T.; Štrancar, J. Lysolipid Containing Liposomes for Transendothelial Drug Delivery. *BMC research notes* **2012**, *5*, 179.

POLYELECTROLYTES 1

Chair: Benjamin Kollmitzer 09:00 – 10:40

DNA KNOTTING INSIDE VIRAL CAPSIDS: A COMPUTATIONAL APPROACH

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The packing of DNA inside bacteriophages arguably yields the simplest example of genome organisation in living organisms. An indirect indication of how DNA is packaged is provided by the detected spectrum of knots formed by DNA that is circularised inside the P4 viral capsid. The experimental results on the knot spectrum of the P4 DNA are here compared to results of coarse-grained simulation of DNA knotting in confined volumes. We start by considering a standard coarse-grained model for DNA which is known to be capable of reproducing the salient physical aspects of free, unconstrained DNA. Specifically the model accounts for DNA bending rigidity and excluded volume interactions. By subjecting the model DNA molecules to spatial confinement it is found that confinement favours chiral knots over achiral ones, in agreement with P4 experiments. However, no significant bias of torus over twist knots is found, contrary to what found in P4 experiments. A good agreement with experiment is found, instead, upon introducing an additional interaction potential that accounts for tendency of contacting DNA portions to order as in cholesteric liquid crystals. Accounting for this local potential allows us to reproduce the main experimental data on DNA organisation in phages, including the cryo-EM observations and detailed features of the spectrum of DNA knots formed inside viral capsids. The DNA knots we observe are strongly delocalized and, intriguingly, this is shown not to interfere with genome ejection out of the phage

KNOTS AND MULSTISCALE ENTANGLEMENT IN BIOPOLYMERS

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It is known that the presence of knots on polymers affects their salient physical properties, like polymers' size, gel-electrophoretic mobility, resistance to mechanical stretching and velocity of translocation through a pore. While a comprehensive understanding of this phenomenon is still lacking, it is often acknowledged that topology-dependent physical properties arise because of a sophisticated interplay of polymer geometry and topology. One of the most important player in this relationship is arguably the degree of localization of the knot on the polymer, that is, whether the knot is tight or loose. Here we show that the two standard algorithms used in literature to locate a knot on a polymer are not equivalent and in general measure different lengths for the same knot . We apply these knot location algorithms to investigate the interplay of geometrical and topological entanglement in knotted polymer rings confined inside a spherical cavity, and show that with increasing confinement the entanglement acquires a multiscale character. We further show that the complex interplay between the length of the knotted portion(s) of polymer, the contour length of the polymer ring, and the radius of the enclosing sphere can be encompassed by a simple scaling argument based on deflection theory.

LOW FREQUENCY IMPEDANCE SPECTROSCOPY: CHARGE TRANSPORT IN AQUEOUS GELATIN

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Our improved approach to low frequency impedance spectroscopy is discussed with implications for conductive liquid samples [*D. Pelc, S. Marion, and M. Basletic, Rev. Sci. Instrum.* ***82****, 073907 (2011)*]. This method enables measurements of the intrinsic sample conductivity at low frequencies (down to sub-Hertz frequencies), avoiding artefacts due to electrode polarization effects. The application of this technique to dilute and semi-dilute aqueous gelatin solutions combined with Pulsed Field Gradient NMR and circular dichroism reveals a gelatin macromolecule self-diffusion contribution to the conductivity via a relaxation process. Scaling relations obtained by combining diffusion and conductivity data show that we have a microscopic phase separation distinct from spinodal decomposition. After the formation of (triple-helix) junction sites in and the onset of gelation, these hydrophobic triple-helix junctions aggregate due to attractive interactions. This leads to the formation of microphase separation between gelatin molecules which are part of the gel macrostructure (gel phase) and those which are free (sol phase).

THE COMPLEX ARCHITECTURE OF BIOINORGANIC ARAGONITE PRODUCED BY MARINE INVERTEBRATES: NANO-SCALE ORGANIZATION OF THE CUTTLEBONE

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Biominerals in marine invertebrates like corals or bivalves mainly serve as a mechanical protection. The cuttlebone in cuttlefish provides a physical shield but owing to the complex structure, its purpose is regulation of buoyancy. This is achieved with the creation of highly porous lamellar chambers build up from aragonitic pillars that are surrounded with an organic sheet and divided by a septal wall (Figure 1A). The process of biomineral formation is governed by the organic matrix that provides a template for mineral nucleation and growth, determines the type of carbonate polymorphs and tunes biomineral properties like stiffness and porosity.

In order to define the nano-architecture of the *Sepia officinalis* cuttlebone, techniques like field emission scanning electron microscopy (FESEM), atomic force microscopy (AFM), X-ray diffraction (XRD) and protein analysis (SDS-PAGE) were used. The comparison of this nano-architecture with biominerals from other mollusks and corals (1-4) confirms the importance of nano-scale aggregation processes in the formation of hierarchically structured biomaterials (Figure 1B).

References:

[1] I. Sondi, B. Salopek – Sondi, S. D. Škapin, S. Šegota, I. Jurina and B. Vukelić, Journal of Colloid and Interface Science 354, (2011), p. 181

[2] I. Sondi, S.D. Škapin, I. Jurina and D. Slovenec, Geologia Croatica 64/1 (2011), p. 61.

[3] I. Sondi and S. D. Škapin in “Biomimetics, Learning from Nature”, ed. Amitava Mukherjee (InTech, Viena) (2010), p. 241.

[4] F. Marin, N. Le Roy and B. Marie, Frontiers in Bioscience S4/1(2012), p. 1099.

A **B**

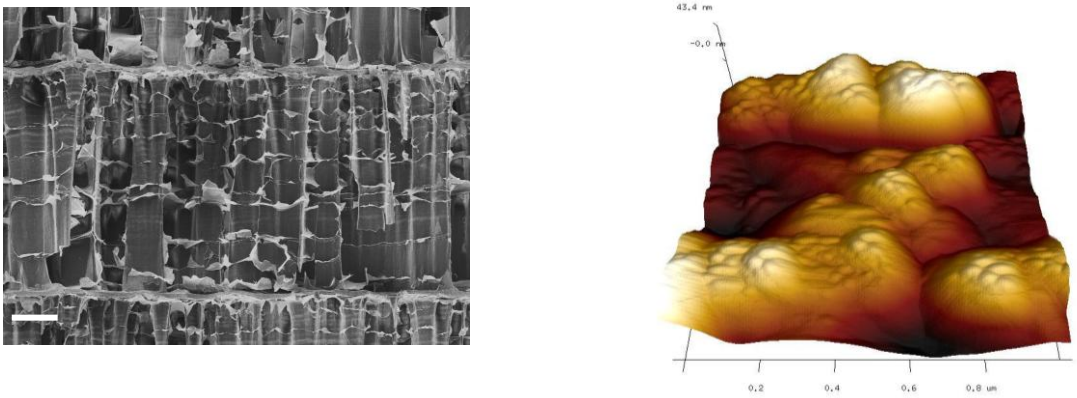

Figure 1: Cuttlebone from common cuttlefish *Sepia officinalis:* FESEM microphotograph of cuttlebone in cross section (A) and AFM 3 D surface plot from the height data of cuttlebone septal wall (B). The aggregations of newly emerged submicrometer sized aragonitic particles are visible on the surface plot image.

POLYELECTROLYTES 2

Chair: Peter Heftberger 11:10 – 12:25

CONFORMATION OF DNA IN LOW ADDED SALT SOLUTIONS

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Function of DNA *in vivo* is determined by its conformation, e.g. the transcription of DNA cannot start if DNA is not in the single stranded (ss) form. We study influence of intrinsic DNA ions on conformation in experimentally accessible low added salt limit (<0.02 mM). Despite this limit does not correspond to *in vivo* conditions its study is a necessary step in understanding the DNA conformation *in vivo*. We use dielectric spectroscopy (DS) and UV spectrophotometry to study DNA semidilute solutions in the concentration range 0.01-5 g/L before and after the controlled denaturation. Denaturation was accomplished by heating the samples for 20 min at a temperature of 97°C, followed by quenching to 4°C. Measurements were subsequently made at 25°C. We focus on the question of minimal intrinsic concentration which keeps Mg-DNA in the native double stranded (ds) conformation. It appears that Mg-DNA remains in ds conformation even down to the concentration c=0.01 g/L. Previously, we found that Na-DNA is also in ds conformation in such conditions, but below concentration c=0.5 g/L it shows locally exposed hydrophobic core in a dynamic sense [1].

[1] S.Tomić, S. Dolanski Babić, T. Vuletić, S. Krča, D.Ivanković, L. Griparić i R. Podgornik, Phys. Rev. E **75,** 021905 (2007).

ENTROPY AND MANNING CONDENSATION IN DILUTE POLYELECTROLYTES

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We obtained the Manning free (uncondensed) counterions fraction θ for dilute aqueous solutions of rodlike polyions: 150 bp DNA fragments, across a range of concentrations, c(monomer) = 0.03 - 8 mM. Conductometry was performed on Na^+-DNA and Mg^{++}-DNA, in 1mM added salt (NaCl and $MgCl_2$, respectively), as well as in pure water conditions. The high linear charge of DNA polyions Manning condenses a fraction of counterions close to the polyion. This partly neutralizes polyion charge, and reduces the effective solution conductivity. Our conductivity study of DNA in added salt confirms theoretical values θ=0.24 and 0.12 for Na^+-DNA and Mg^{++}-DNA, respectively. However, in pure water conditions, towards lower DNA concentrations the effective θ increases well above the Manning values. UV-absorbance measurements showed that this is not due to DNA denaturation (denaturation may occur in pure water conditions due to a reduction in the electrostatic screening; as single stranded DNA has a lower linear charge it also has a correspondingly higher θ fraction.) We presume that in dilute solutions more counterions must become decondensed as the entropy gain overcomes the electrostatic cost, as Deshkovski et al. (Phys.Rev.Lett. 2001) have discussed.

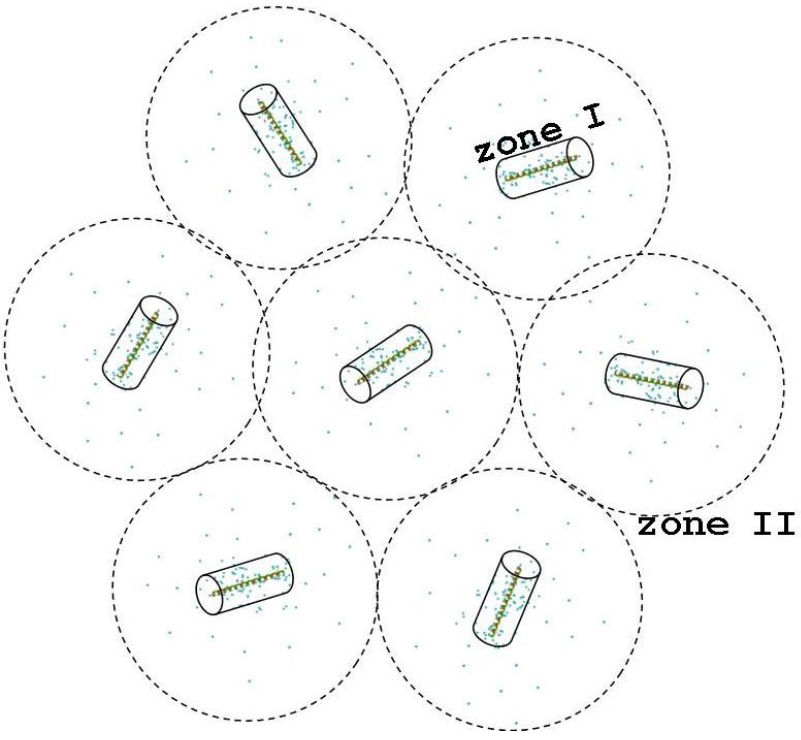

Fig.1. Polyions (DNA) move along with the Manning condensed fraction of counterions (green dots), found in the zone I. In the dilute regime, while DNA concentration is reduced and in absence of added salt, more and more counterions de-condense and enter the zone II.

CONFINEMENT EFFECTS ON THE STRUCTURE AND DYNAMICS OF POLYMER MELTS WITH BROADBAND DIELECTRIC SPECTROSCOPY

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Understanding the structure and dynamics of polymers in presence of confining solid surface is important for applications in nanotechnology such as coatings for electrical devices, lubricants, and polymer nanocomposite materials. Neutron scattering methods allow exploring of the dynamical properties of polymers on different time and length scales. It makes possible, in particular, to investigate an influence of an interaction of polymers with the solid wall, and also geometrical restrictions on the polymer dynamics [1]. In this work we explored the confinement effects using a complementary method, broadband Dielectric Relaxation Spectroscopy (BDRS), due to overlapping of the frequency scale covering by neutron scattering methods. The systems we measured were polyisoprene (PI) (M_w=6 kg/mol and M_w=130 kg/mol) and polybutadiene (PB) (M_w=23,4 kg/mol) that were infiltrated in anodic aluminum oxide (AAO) with well-defined matrix of cylindrical nanopores of different diameter (20 or 60 nm). The bulk polymers were measured as a reference. Measurements were performed on the frequency scale from 10^{-2} to 10^{6} Hz, in the temperature interval from 198K to 338K. The relaxation processes in each case (PI and PB) were found to be different for the bulk and confined polymer, demonstrating changes in the dynamic of polymers due to the confinement effect. In particular normal mode relaxation of PI assigned to the global chain motion have been slowed in the confined samples in comparison to the bulk behavior and the α-relaxation responsible for the glass transition changed its temperature dependence from a Vogel-Fulcher-Tamman law (VFT) in the bulk to an Arrhenius behavior in confinement samples. As for PB in confinement, we observe a slow relaxation process at high temperatures that also has temperature dependence described by VFT law.

[1] M.Krutyeva et al., J.Chem.Phys. 131 174901, (2009)

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Puzzling during talks
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