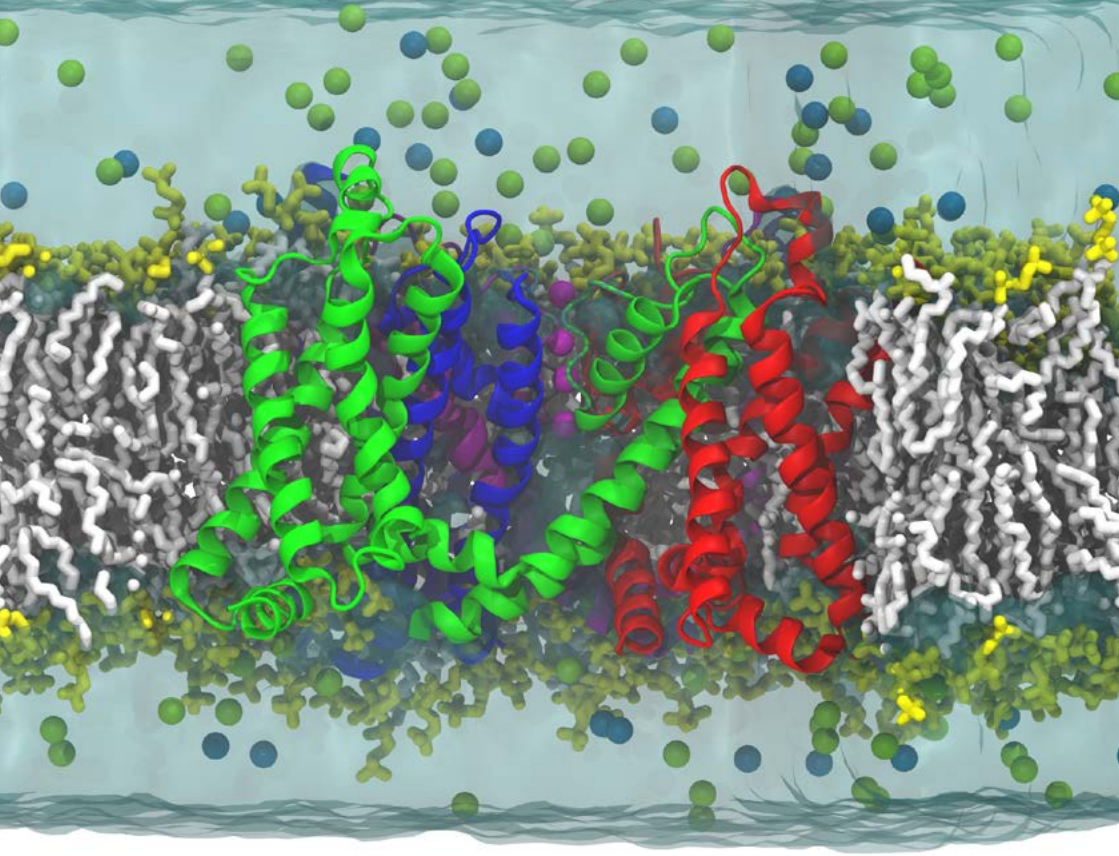

May 21 - 23
2018

PHYSIOLOGICAL ROLE OF IONS IN THE BRAIN

Towards a comprehensive view by molecular simulation

BOOK OF ABSTRACTS

Sala Azzurra
Palazzo della Carovana
Piazza dei Cavalieri, 7
Pisa

INFO
giuseppe.brancato@sns.it
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SCUOLA NORMALE SUPERIORE

JÜLICH FORSCHUNGSZENTRUM

UPEM UNIVERSITÉ PARIS-EST MARNE-LA-VALLÉE

cecam Centre Européen de Calcul Atomique et Moléculaire

bioexcel

MONDAY, 21.05.2018

08:30 Registration

09:10 Welcome & Opening from the Organizers

09:30 **ROSSEN APOSTOLOV,** BioExcel & KTH, Sweden
Introduction to BioExcel

MORNING SESSION *Force fields and coarse-grain modeling*

09:45 **KENNY MERZ**, Michigan State U., USA
Modeling Metal Ions Using Classical Potentials: Approach and Application to Metal Ion Homeostasis

10:15 **THOMAS BECK**, U. of Cincinnati, USA
Why understanding single-ion solvation thermodynamics is important for ion permeation through channels

Discussion and coffee break

11:15 **GIULIA ROSSETTI**, Forschungszentrum Jülich, Germany
Metal Interactions with DNA from drug design prospective

11:45 **RAN FRIEDMAN**, Linnaeus University, Sweden
Simulations of proteins with zinc - challenges and opportunities

12:15 **MERCEDES ALFONSO-PRIETO**, FZ Jülich, Germany
Multiscale simulations of chemosensory receptors

12:45 LUNCH

AFTERNOON SESSION *Transition metal ions-I*

14:30 **LILIANA QUINTANAR**, Mexico City U., Mexico
From trafficking to the brain to a wrestling match for copper ions at the synapse

15:00 **RACHEL NECHUSHTAI**, Hebrew University, Jerusalem, Israel
The Novel Role of the NEET proteins in Controlling the Fe/Fe-S Homeostasis in the Brain; The Genetic Neurological Disease Wolfram Syndrome-2 as an Example

15:30 **MODESTO OROZCO**, IRB, Barcelona, Spain
Ions and DNA

Discussion and coffee break

16:30 **ANNALISA PASTORE**, King's College, UK
Towards a full understanding of iron sulfur cluster biogenesis

17:00 **URSULA ROETHLISBERGER**, EPFL, Switzerland
Computational design of artificial metalloenzymes

17:30 **CLAUDIO FERNANDEZ**, Max Planck Institute, Rosario, Argentina
Reshaping the role of metal ions on αS aggregation

18:00 Poster Session & Welcome Cocktails

TUESDAY, 22.05.2018

MORNING SESSION — *Transition metal ions - II*

09:00 **MARIA J. RAMOS**, University of Porto, Portugal
Metal ions in proteins

09:30 **ALESSANDRA MAGISTRATO**, CNR-IOM at SISSA, Italy
How can phosphorylation regulate estrogen biosynthesis in Human Aromatase enzyme? An answer from multiscale

10:00 **PAVEL JUNGWIRTH**,CAS, Czech Republic
Cell Penetration and Calcium Induced Membrane Fusion: Two Sides of the Same Coin

Discussion and coffee break

11:00 **BIRGIT STRODEL**, Research Centre Jülich, Germany
Bonded and Dummy Models for Modeling Metal Ions in Classical MD Simulations: Applications to Alzheimer's Aβ peptide

11:30 **GIULIA PALERMO**, University of California San Diego, USA
An allosteric cross-talk in chromatin can mediate a ruthenium-gold/ drug-drug synergy

12:00 **ROBERTO LINGUERRI**, U. Paris-Est Marne-La-Vallée, France
Accurate ab initio characterization of molecular properties of copper-based organometallic compounds

12:30 LUNCH

AFTERNOON SESSION — *Ion Channels and membranes*

14:00 **ALI HASSANALI**, ICTP, Italy
Proton Transfer in the Brain: The Importance of Hydrogen Bonds

14:30 **BERT DE GROOT**, Max Planck Institute for Biophysical Chemistry
The molecular dynamics of potassium channel permeation, selectivity and gating

15:00 **SUSAN REMPE**, Sandia National Laboratories, USA
Hydration Mimicry for Ion Permeation

Discussion and coffee break

16:00 **CHRISTOPH FAHLKE**, Universitat Dusseldorf, Germany
Molecular mechanisms of the anion channel function of secondary active glutamate transporters

16:30 **ARMAGAN KOCER**, U. of Groningen, The Netherlands
Structure-function studies on Voltage-gated potassium channel Kv4.3

17:00 **ANDREA CATTE**, Scuola Normale Superiore, Italy
Modeling inherited and de novo mutations in a voltage-gated potassium channel

17:30 **SIMON BERNÈCHE**, Biozentrum, U. of Basel, Switzerland
Ion transport: from kinetic models to high resolution structures and back

20:00 Social Dinner, Restaurant La Clessidra

WEDNESDAY, 23.05.2018

MORNING SESSION

Nucleic acids/ions interactions

09:00 **PAOLA TURANO**, niversità di Firenze, Italy
Ferritin: learning about iron uptake, biomineralization and release

09:30 **CHAO ZHANG**, University of Cambridge, UK
Finite field methods for modelling liquid water and electric double layer

Discussion and coffee break

10:30 **WALTER ROCCHIA**, Italian Institute of Technology, Italy
Addressing the study of ions from complementary perspectives: methods for force field parametrization and continuum description

BioExcel Special Session

11:00 **ADAM CARTER**, BioExcel & EPCC, UK
BioExcel Session

12:00 Concluding remarks and discussions

12:30 LUNCH

Modeling Metal Ions Using Classical Potentials: Approach and Application to Metal Ion Homeostasis

Kenneth M. Merz Jr.
Director, Institute for Cyber Enabled Research (iCER)
Joseph Zichis Chair in Chemistry
Department of Chemistry
Department of Biochemistry and Molecular Biology
Michigan State University
578 S. Shaw Lane
East Lansing, MI 48824-1322
kmerz1@gmail.com

Though transition metal ions play an essential role in many cellular processes, they are extremely toxic at high concentrations. Biological metal ion homeostasis maintains the intracellular concentrations of these metal ions through a number of metal sensor proteins that regulate the expression of genes that encode specific transition metal efflux and sequestration proteins. To tackle this class of problem we have had to develop novel computational tools and approaches. In particular, we will briefly discuss the history of classical model of TM ions with a highlight on the novel 12-6-4 modification to the classic Lennard-Jones (12-6) potential that allows us to model TM ions accurately. Using our computational tools, we will describe and discuss how prototypical transition metal ion transcriptional repressors of the ArsR family of transcriptional repressor proteins carry out their function. In particular, the role of protein dynamics and the function of a key hydrogen bond connecting the metal binding domain with the DNA recognition domain will be discussed. The second half of the talk will focus on the novel Cu(I) transporting protein CusF, which has at its metal binding site a biologically novel □-complex between the metal ion and an indole side chain from Trp44. The mechanism by which CusF delivers the Cu(I) ion to its biological target, the CusABC transporter, will be discussed. Finally, we will describe a novel antibiotic strategy that involves the alteration of the transition metal ion balance in a cell via the disruption of the transition metal homeostatic machinery.

Why understanding single-ion solvation thermodynamics is important for ion permeation through channels

T. L. Beck

Univ. of Cincinnati, Cincinnati, OH USA

The passage of ions through narrow pores in proteins embedded in membranes involves a wide range of basic physical steps. These steps include the initial approach, (perhaps partial) desolvation, interactions with specific groups on the protein, temporary ion binding in particular locations, gating motions, etc. Each process requires a delicate balance of forces that affects the selectivity and dynamics without producing too-strong repulsive or attractive interactions that could kill the transport. Thus interaction energy variations of a few kcal/mol can change the predicted behavior of a channel. We have performed computational studies of the thermodynamics of ion binding in the EcCLC bacterial chloride channel. These studies will be briefly reviewed, but the main focus will be on fundamental theoretical/computational studies of ion solvation structure and thermodynamics in water and organic solvents. We suggest that these studies, along with careful experimental measurements, are necessary to move forward in developing more accurate models of ion channels.

Metal Interactions with DNA from drug design prospective

Giulia Rossetti
Forschungszentrum Jülich, Germany

Metal-based drugs targeting DNA, like Cisplatin, are important therapeutic tools in the struggle against different tumors, yet they are plagued with the emergence of resistance mechanisms after repeated administrations. This hampers greatly its efficacy. Overcoming resistance problems requires first and foremost an integrated and systematic understanding of the molecular recognition processes involving the drug. Coupling hybrid Quantum Mechanics/Molecular Mechanics (QM/MM) simulations with classical Molecular Dynamics (MD) and free energy calculations, based on force field parameters refined by the so-called “Force Matching” procedure, we have characterized the structural modifications and the free energy landscape associated with the recognition between platinated DNA and the in vivo post-translationally modified forms of HMGB1 protein, belonging to the chromosomal high-mobility group proteins HMGB that inhibit the repair of platinated DNA. This may alleviate issues relative to on-target resistance process. The elucidation of the mechanisms by which tumors are sensitive or refractory to cisplatin may lead to the discovery of prognostic biomarkers. The approach reviewed here could be straightforwardly extended to other metal-based drugs.

Simulations of proteins with zinc - challenges and opportunities

Ran Friedman
Linnaeus University
Department of Chemistry and Biomedical Sciences
391 82 Kalmar, Sweden

The zinc ion is a common co-factor of proteins. This ion is important for the correct folding of proteins, as a catalyst and as a second messenger. On the other hand, too much zinc can be toxic, and the ion appears to be involved in pathologies such as Alzheimer's disease. In spite of its relative simple electronic structure (filled d-shell), simulations of proteins with zinc are not straightforward. Whereas schemes were developed to model Zn inside proteins where its coordination is constant, changes of the coordination shell are difficult to study.
We have studied the interactions between Zn and biologically relevant ligands using post-HF methods and DFT. High level QM interaction energies were used as reference to force-field based calculations, in order to test whether the force-fields can be improved. Furthermore, energy decomposition analysis was used to understand the limitations of DFT calculations for systems that include Zn. Finally, we carried out similar calculations with a polarisable force-field. Our results indicated that the current sets of classical force-fields were not adequate to study Zn-containing proteins. Modifications of the LJ parameters or rescaling of the interaction energies are not expected to improve the agreement with high level QM calculations. Charge transfer appears to be considerable for some ligands, but less so for others. On the other hand, the use of a polarisable force-field, even without charge-transfer, has shown some encouraging results.

Multiscale simulations of chemosensory receptors

Mercedes Alfonso-Prieto[1,2], Fabrizio Fierro[1], Eda Suku[3], Juan Zeng[1], Alejandro Giorgetti[1,3] and Paolo Carloni[1,4]

[1] Institute for Neuroscience and Medicine (INM-9) & Institute for Advanced Simulations (IAS-5), Forschungszentrum Jülich (Germany).
[2] Cécile and Oskar Vogt Institute for Brain Research, Medical Faculty, Heinrich Heine University Düsseldorf (Germany).
[3] Department of Biotechnology, University of Verona (Italy).
[4] Department of Physics, RTWH Aachen University (Germany).

Bitter taste (TAS2R) and olfactory (OR) receptors are chemosensory receptors responsible for the perception of bitter taste and smell. Besides chemical senses in the tongue and the nose, they also participate in other physiological and pathological processes. In particular, chemosensory receptors are also expressed in the brain, and hence they may be involved in neurological diseases.

Bitter taste and olfactory receptors contain half of the members of the G-protein coupled receptor (GPCR) superfamily, in turn the largest group of membrane proteins in the human genome. Compared to other GPCRs, chemosensory receptors are particularly promiscuous, so that one receptor can recognize multiple ligands. Moreover, the same ligand can be detected by different receptors. Therefore, their combinatorial coding is particularly complex, which hampers its characterization at the molecular level.

In addition, ions have been shown to be modulate bitterness perception and olfaction. On one hand, sodium has a suppressive effect on bitterness (even though bitter taste receptors lack the allosteric sodium binding site present in other class A GPCRs), whereas magnesium can activate some bitter taste receptors. On the other, copper enhances the response of some olfactory receptors to sulfur-containing compounds.

In this work, a systematic bioinformatics study was carried out for all the human chemosensory receptors for which experimental data is available. Our results show that, while bioinformatics can provide a starting point to study ligand binding to chemosensory receptors, subsequent refinement by multiscale simulations is essential to improve the agreement with experiments and to make successful predictions. In addition, multiscale simulations for the human TAS2R16 (a bitter taste receptor that detects both toxic cyanogenic glucosides and health-promoting glucosides present in food) indicate the presence of a dual binding mode for glucosides. This could potentially help to increase the spectrum of aglycons recognized by TAS2R16.

From trafficking to the brain to a wrestling match for copper ions at the synapse

Liliana Quintanar
Department of Chemistry,
Centro de Investigación y de Estudios Avanzados (Cinvestav), Mexico City

Transition metals such as copper, iron, zinc and manganese are essential for brain function, as cofactors of a wide range of metalloproteins. While metal ion trafficking to the brain is highly regulated, alterations in metal ion homeostasis have been associated to neurodegenerative disorders, such as Alzheimer´s disease (AD).[1] In this presentation, a brief overview on how copper ions are trafficked to the brain will be provided, with an emphasis on copper trafficking at the synapse and the role of Cu ions in neuromodulation. A discussion of Cu-protein interactions that are key players in neuroprotective mechanisms and how they might be affected in AD will be provided. Recently, it has been proposed that the amyloid-beta peptide (Aβ) acts as a chelating agent disrupting the function of other Cu-binding proteins, such as the cellular prion protein (PrP^C).[2,3] Specifically, the Cu coordination properties of PrP^C and Aβ will be discussed;[4-6] while a recent spectroscopic study on the competition for Cu ions between these two players will be presented. Our work reveals the formation of a key ternary Aβ-Cu-PrP complex, providing further insights into how Aβ might alter the Cu-dependent neuroprotective role of PrP^C. This research has been supported by the National Council for Science and Technology in Mexico (CONACyT grant #221134).

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[2] You, H., Tsutsui, S., Hameed, S., Kannanayakal, T. J., Chen, L., Xia, P., Engbers, J. D., Lipton, S. A., Stys, P. K., and Zamponi, G. W. (2012) Abeta neurotoxicity depends on interactions between copper ions, prion protein, and N-methyl-D-aspartate receptors, *Proc Natl Acad Sci U S A 109*, 1737-1742.
[3] Gasperini, L., Meneghetti, E., Pastore, B., Benetti, F., and Legname, G. (2015) Prion protein and copper cooperatively protect neurons by modulating NMDA receptor through S-nitrosylation, *Antioxid Redox Signal 22*, 772-784.
[4] Faller, P., and Hureau, C. (2009) Bioinorganic chemistry of copper and zinc ions coordinated to amyloid-beta peptide, *Dalton Trans*, 1080-1094.
[5] Quintanar, L., Rivillas-Acevedo, L., Grande-Aztatzi, R., Gómez-Castro, C. Z., Arcos-López, T., and Vela, A. (2013) Copper coordination to the prion protein: Insights from theoretical studies, *Coord Chem Rev 257*, 429-444.
[6] Sánchez-López, C., Fernández, C. O., and Quintanar, L. (2018) Neuroprotective alpha-cleavage of the human prion protein significantly impacts Cu(II) coordination at its His111 site, *Dalton Trans*, Advance Article DOI: 10.1039/C1037DT03400H.

The Novel Role of the NEET proteins in Controlling the Fe/Fe-S Homeostasis in the Brain; The Genetic Neurological Disease Wolfram Syndrome-2 as an Example

Ola Karmi[1], Henri-Baptist Marjault[1], Yang-sung Sohn[1], Luca Pesce[2], U. Najwa Abdulhaq[3], Gil Leibowitz[4], Ioav Cabantchik[1], David H. Zangen[3], Paolo Carloni[2], **Rachel Nechushtai[1]**

Alexander Silberman Institute of Life Sciences[1], *Computational Biomedicine Section, Institute of Advanced Simulation (IAS-5) and Institute of Neuroscience and Medicine (INM-9), Forschungszentrum Jülich GmbH*[2], Hadassah Medical Center at Mt Scopus[3] and Ein Kerem[4], The Hebrew University of Jerusalem, Israel.

The human NEET proteins mitoNEET (mNT) and NAF-1 (encoded by *CISD1* and *CISD2* genes, respectively) were shown to be important players in the key cellular processes of apoptosis, autophagy, Fe/2Fe-2S and ROS homeostasis. These proteins shown to be important in neurological disorders (e.g. Parkinson and Alzheimer), have a novel 'NEET fold' and a unique 3Cyst:1His coordinating structure of their [2Fe-2S] clusters[1]. In a recent simulation study, we have shown the key role of the cluster coordinating histidine (H87 in mNT and H114 in NAF-1) and the importance of its deprotonated state in the stabilization of the [2Fe-2S] cluster of the NEET proteins; The latters ensure the NEET proteins' proper fold and prevent the release of the clusters[2]. Controlling the stabilization of the cluster is highly important to prevent Fe/2Fe-2S accumulation which leads to development of reactive oxygen species (ROS) that cause severe damage in cells and organs, e.g. brain. In our regional population the neurological Wolfram Syndrome type 2 (WFS-2) disease, a monogenic autosomal recessive disorder[1], is highly abundant. Point mutation in *CISD2* gene (G109C), leads to exon skipping, frameshift and premature stop codon[3] causing NAF-1 absence in WFS-2 patients. The main pathophysiological neurological disorders in these patients are; optical nerve atrophy, sensorineural hearing loss and Physiological episodes. In cellular systems we showed that reduced/no expression of NAF-1 results in misdistribution of cellular iron, mitochondrial iron accumulation and oxidative damage with ensuing autophagy and apoptosis. These disorders can partially be repaired by conservative iron chelator treatment. Similar phenotype observed in WFS-2 patients were also partly repaired by similar treatment approach that will be described in the talk and suggests a potential pharmacological target[4]

Acknowledgements: RN to BSF grant - 2015831

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Ions and DNA

Modesto Orozco
IRB, Barcelona, Spain

The standard view of nucleic acids, derived from early Manning's theory presents the ions as mere generators of an ionic atmosphere damping phosphate-phosphate repulsion and stabilizing the three-dimensional structure of the nucleic acid. In reality, ions are co-solutes that plays a major role in determining nucleic acids structures. I will summarize recent theoretical studies, supported by experimental measures showing the importance of ions in nucleic acids, to determine a myriad of properties: from structure, to sequence-dependent stability, catalytic power and aggregation properties.

Towards a full understanding of iron sulfur cluster biogenesis

Annalisa Pastore
The Wohl Institute, King's College London, 5 Cutcombe Rd London (UK)
Department of Molecular Medicine, University of Pavia, Pavia (Italy)

Iron sulfur cluster formation is an essential and yet poorly understood molecular machine common to all living organisms and involved in several different pathways. They are formed by a complex network of weak interactions which involve evolutionary conserved proteins which in bacteria are grouped in operons. Frataxin, an essential and highly conserved mitochondrial protein whose reduced expression causes Friedreich's ataxia (FRDA) in humans, is an active part of this assembly: using a bacterial model and different biochemical and molecular biology techniques, we have proven that frataxin acts as an iron concentration dependent inhibitor of cluster formation. This suggests that frataxin is an iron sensor which acts as the gate keeper for Fe-S cluster formation and fine tunes the quantity of Fe-S clusters to the concentration and/or possibly the distribution of the available acceptors. I will review our work and the more recent advancements of our research. Our observations provide a new perspective for understanding iron sulfur cluster biogenesis and a mechanistic model which rationalizes the available knowledge.

Computational design of artificial metalloenzymes

Ursula Roethlisberger
EPFL, Switzerland

Reshaping the role of metal ions on αS aggregation

Claudio O. Fernández [1,2]

[1]*Max Planck Laboratory of Structural Biology, Chemistry and Molecular Biophysics of Rosario (MPLbioR, UNR-MPIbpC), Rosario, Argentina;* [2]*Instituto de Investigaciones para el Descubrimiento de Fármacos de Rosario (IIDEFAR, UNR-CONICET), Rosario, Argentina*

Transition-metal ion homeostasis (copper, iron, zinc) plays a key role in neurodegenerative disorders, as these ions are considered one of the possible factors leading to protein aggregation. Indeed, metal-protein interactions can have an important impact on the kinetics of amyloid aggregation and the neurotoxicity of protein aggregates; particularly, this has been demonstrated for the case of copper and zinc interactions with the amyloid beta peptide, associated with Alzheimer's disease.

An unresolved question in the neuropathology of Parkinson disease relates to the role of metal ions in α-Synuclein (αS) fibril formation and neurodegeneration. Protein-metal interactions have been demonstrated to play an important role in αS aggregation and might represent the link between the pathological processes of protein aggregation, oxidative damage, and neuronal cell loss. Particularly, the structural and affinity features for the interaction between αS and the Cu(II)/Cu(I) couple became recently the focus of numerous investigations. Added to the abundant evidence revealing that αS undergoes N-terminal acetylation in vivo (AcαS), it was reported recently that this modification of αS abolishes Cu(II) binding at the high-affinity binding site. Since copper ions are predominantly found in their Cu(I) state in the reducing environment of living cells, characterization of the physiologically relevant AcαS–Cu(I) complexes is particularly important. These studies revealed that the Cu(I) binding sites were preserved in the acetylated form of the protein. From the structural residue-specific characterization of Cu(I) binding to AcαS, it was demonstrated that the protein is able to bind Cu(I) in a coordination environment that involves the participation of Met1 and Met5 as the main anchoring residues. The formation of an AcαS–Cu(I) complex at the N-terminal region induced a dramatic impact on protein conformation, leading to stabilized local conformations with α- helical secondary structure and restricted motility.

Considering that copper concentrations can reach up to 300 μM in synaptic vesicles and that AcαS is highly abundant (~50 μM) in brain synaptosomes, our works suggest that an AcαS-Cu(I) complex with stabilized helically folded conformations might exist *in vivo*. Linked to the fact that the Met-X3-Met motif at the N-terminus of AcαS resemble those found in helical copper transport proteins, the formation of the AcαS-Cu(I) complex(es) might have physiologically relevant implications in processes related to metal-transport, membrane binding or protein aggregation, which are enhanced by increased α-helical content at the N-terminus of the protein. Overall, our findings open new avenues of investigations into the metallobiology of PD, reshaping the consideration of copper mediated pathology *in vivo*.

Ref.: 1. Rasia, RM et *al* (2005) *Proc Natl Acad Sci U S A* 102: 4294-4299. 2. Binolfi A, et *al* (2006) *J Am Chem Soc*. 128:9893-9901. 3. Binolfi, A, et *al* (2008) *J Am Chem Soc*. 130: 11801-11812. 4. Binolfi A, et *al* (2011) *J Am Chem Soc*. 133:194-196.5. Miotto MC, et *al* (2015) *J Am Chem Soc*, 137: 6444-6447. 6. Villar-Piqué A, et *al* (2016) *Proc Natl Acad Sci U S A*. 113:E6506-E6515.

Metal ions in proteins

Maria João Ramos

[a] *UCIBIO@REQUIMTE, Departamento de Química e Bioquímica, Faculdade de Ciências, Universidade do Porto, Rua do Campo Alegre s/n, 4169-007 Porto, Portugal*

This talk is concerned with metals in proteins. We begin by looking at the pdf with its many biological systems that contain ions and carry on to study in more detail some of those that are meaningful to life. Calculations devised to study protein interactions and circumvent problems in some relevant systems will be reported as well as recent developments in the establishment of some catalytic mechanisms. We have resorted to QM/MM as well as other calculations[1-3], in order to analyse the energetics of processes related to the systems under study and evaluate their feasibility according to the available experimental data.

1. AJM Ribeiro, MJ Ramos, PA Fernandes, JACS, 134, 13436, 2012.
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How can phosphorylation regulate estrogen biosynthesis in Human Aromatase enzyme? An answer from multiscale simulations

Alessandra Magistrato
CNR-IOM@SISSA, Italy

Human Aromatase (HA) is a heme-protein belonging to the cytochrome P450 family. This catalyzes the conversion of androgens to estrogens through reactions requiring oxygen and electrons provided by NADPH cytochrome reductase (CPR) [1]. However, high levels of estrogens, resulting from enhanced HA activity, are related to abnormal cellular proliferation, which leads to several diseases among which breast cancer (BC). Besides, being a major oncological target, brain HA is also involved in diverse neurophysiological and behavioral functions including sexual behavior, aggression, cognition, and neuroprotection. Estrogens may induce a non-genomic regulation of neuronal physiology in a manner akin to the action of a neuropeptide/neurotransmitter. Recently, it has been shown that post-translational regulation of HA by the tyrosine 361 (Y361) phosphorylation up-regulates HA activity [2]. It is hypothesized that phosphorylated Y361 accelerates the electronic transfer (ET) from the CPR to the heme of the HA, enhancing estrogen biosynthesis. Aim of this work was to rationalize both the mechanism of post-translation regulation and the interaction mechanism of HA with CPR combining different computational techniques, e.g. protein-protein docking, molecular dynamics (MD) simulations and hybrid quantum-classical (QM/MM) MD simulations. Our simulations reveal that phosphorylation only slightly affects the ET rate between the FMN domain of the CPR and HA, while having the largest impact on the stabilization of the CPR/HA adduct.

[1] E. R. Simpson et al., Endocr. Rev. 1994, 15, 342;
[2] S. Catalano et al., Mol. Endodrinol. 2009, 23, 1634.

Cell Penetration and Calcium Induced Membrane Fusion: Two Sides of the Same Coin

Pavel Jungwirth

Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences, Flemingovo nám. 2, 16610 Prague 6, Czech Republic
E-mail: pavel.jungwirth@uochb.cas.cz

Cell penetrating peptides have a unique potential for targeted drug delivery, therefore, mechanistic understanding of their membrane action has been sought since their discovery over 20 years ago. While ATP-driven endocytosis is known to play a major role in their internalization, there has been also ample evidence for the importance of passive translocation for which the direct mechanism, where the peptide is thought to directly pass through the membrane via a temporary pore, has been widely advocated. In this talk, I will question this view and demonstrate that arginine-rich cell penetrating peptides instead enter vesicles by inducing multilamellarity and fusion, analogously to the action of calcium ions. The molecular picture of this penetration mode, which differs qualitatively from the previously proposed direct mechanism, is provided by molecular dynamics simulations. In addition, the kinetics of vesicle agglomeration and fusion by nonaarginine, nonalysine, and calcium ions are documented in real time by fluorescence techniques and the induction of multilamellar phases is revealed both via electron microscopy and fluorescence spectroscopy. We thus show that the newly identified passive cell penetration mechanism is analoguous to vesicle fusion induced by calcium ions, demonstrating that the two processes are of a common mechanistic origin.

Bonded and Dummy Models for Modeling Metal Ions in Classical MD Simulations: Applications to Alzheimer's Aβ peptide

Qinghua Liao,[1,2] S. C. Lynn Kamerlin,[2] Birgit Strodel[1,3]
[1] Institute of Complex Systems: Structural Biochemistry, FZ Jülich, 52425 Jülich, Germany
[2] Department of Cell and Molecular Biology, Uppsala University, Sweden
[3] Heinrich Heine University Düsseldorf, Germany

In classical simulations, metal ions are typically described as simple van der Waals spheres, which is often insufficient for ions other than alkali ions. Alternatives are given by bonded and nonbonded dummy models. The bonded plus electrostatics model defines charges as well as bonds and angles between the metal ion and its ligands, thus maintaining the geometry of the metal coordination configuration in longtime simulations. However, a disadvantage of this approach is that it does not allow the description of the interconversion between different coordination configurations. The dummy model approach aims at resolving this problem by providing a nonbonded description that captures both structural and electrostatic effects via the introduction of dummy atoms surrounding the metal ion. While such dummy models already existed for other metal ions, none was available yet for Cu^{2+} because of the challenge to reproduce the Jahn–Teller distortion, which we successfully addressed.[1] Another shortcoming of current dummy models is the neglect of ion-induced dipole interactions, which we resolved by taking advantage of the recently introduced 12–6–4 type Lennard-Jones potential. Using this approach, we developed dummy models for Al^{3+}, Fe^{3+}, and Cr^{3+}, where ion-induced dipole interactions become particularly important due to their high charge.[2] The effectiveness of our new models is demonstrated in MD simulations of several diverse (and highly challenging to simulate) metalloproteins, including the Aβ peptide whose aggregation is strongly correlated with the development of Alzheimer's disease. The binding of copper to Aβ increases its neurotoxicity, as Cu^{2+} causes Aβ to become redox active and decreases the lag time associated with Aβ aggregation. Using bonded Cu^{2+} models we elucidated the effects of neurotoxic Cu^{2+} binding on the conformational ensemble of the Aβ monomer and dimer, and compare them to the effects of a pH reduction representing acidic conditions linked to brain inflammation and oxidized Aβ resulting from oxidative stress.[3,4]

[1] Q. Liao, S.C.L. Kamerlin, B. Strodel. Development and Application of a Nonbonded Cu^{2+} Model That Includes the Jahn–Teller Effect. *J. Phys. Chem. Lett.* 6: 2657–2662 (2015)

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An allosteric cross-talk in chromatin can mediate a ruthenium-gold/drug-drug synergy

Giulia Palermo[1+], Zenita Adhireksan[2], Tina Riedel[1], Zhujun Ma[2], Reyhan Muhammad[2], Paul J. Dyson[1], Curt A. Davey[2] & Ursula Rothlisberger[1]

1 Institut des Sciences et Ingenierie Chimiques, Ecole Polytechnique Federale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland.
2 School of Biological Sciences, Nanyang Technological University, 60 Nanyang Drive, Singapore 637551, Singapore.

Over the years, chromatin drug targeting has become an effective strategy for cancer treatment. In particular, emerging transition metal agents have been shown to act at both nucleosomal DNA and histones levels with high efficiency. The class of ruthenium-based RAPTA (Ru(II), Arene, PTA = 1,3,5-triaza-7-phosphatricyclo[3.3.1.1]decane) compounds interfere with transcription resulting in apoptosis, while gold-based compounds, such as the clinically approved antiarthritic drug Auranofin, have significant antiproliferative properties in vivo and in vitro. Although the anticancer activity can be referred to the ability of these compounds to interfere at the chromatin level, their mechanistic action remains poorly understood. Here, by integrating X-ray crystallography, biochemical assay and extensive molecular dyamics simulations, we reveal a cooperative mechanism of action of Rapta-T (T = Toluene) and Auranofin at the chromatin level. High-resolution crystal structures of the nucleosome core particle (NCP) in complex with the two compounds reveal that the binding occurs at two distal sites on the NCP histone core that are ~35 Å apart. In parallel, biochemical and quantitative ICP/MS experiments show a ~3 fold increased binding of Auranofin when in combination with RAPTA-T, indicating a synergistic effect of the two compounds. By employing microsecond lengths molecular simulations, we clarify at the atomistic level the cooperative binding mechanism, revealing a mechanism of allosteric communication between the ruthenium and gold sites, which occur through a series of subtle conformational changes within the protein framework, transmitted via coupled motions of the histone components. By clarifying the allosteric determinants at molecular level, molecular simulations are key in providing an explanation for an intriguing synergy at cellular level. This opens up new possibilities for epigenetic targeting and suggests that allosteric modulation in nucleosomes may have biological relevance and potential for therapeutic interventions.

Accurate ab initio characterization of molecular properties of copper-based organometallic compounds

K. Mahjoubi, T. Trabelsi, **R. Linguerri**, M. Hochlaf, H. Mouhib
Theoretical Chemistry Laboratory, University of Paris-Est Marne-la-Vallée, France
roberto.linguerri@u-pem.fr

Copper-organo complexes are involved in the pathogenesis of neurodegenerative diseases and in molecular recognition processes. Here, structural and electronic, features of simple model sulphur-copper compounds are described by means of advanced correlated ab initio methods. These methodologies provide reliable tools to predict accurate anharmonic force fields for this class of compounds to be used in conjunction with large-scale molecular dynamics simulations. The accurate characterization of small copper-sulfur molecular entities provides the first step towards a better understanding of the role of copper in molecular recognition.

Proton transfer in the brain: The importance of hydrogen bonds

Ali Hassanali
ICTP Italy

Textbook biophysical chemistry tells us that optical absorption and fluorescence in biological systems is associated with aromatic amino acids. Recent experiments have shown however, that amyloid proteins implicated in neurodegenerative diseases such as Alzheimers and Parkinsons, are able to fluoresce in the absence of aromatic amino acids. In this talk, I will discuss our attempts to shed theoretical insights into these experimental findings. Using a combination of ab initio molecular dynamics and time-dependent density functional theory to show that protons in the amyloid fibrils are delocalised and that this can couple with low energy excitations and subsequently fluorescence. We also demonstrate that absorption spectra are highly sensitive to nuclear quantum effects. More recent results showing fluorescence in single amino acids will also be briefly touched on.

The molecular dynamics of potassium channel permeation, selectivity and gating

Bert de Groot

Max Planck Institute for Biophysical Chemistry
http://www.mpibpc.mpg.de/groups/de_groot

Ion channels facilitate the passive, selective permeation of ions such as sodium, potassium and chloride across biological membranes and as such are essential for cellular electrical signalling. Molecular dynamics simulations based on the computational electrophysiology scheme will be presented to study ion permeation across potassium channels. Together with crystallographic analyses and electrophysiology experiments these provide insight into the mechanisms of permeation, selectivity and gating in potassium channels.

Hydration Mimicry for Ion Permeation

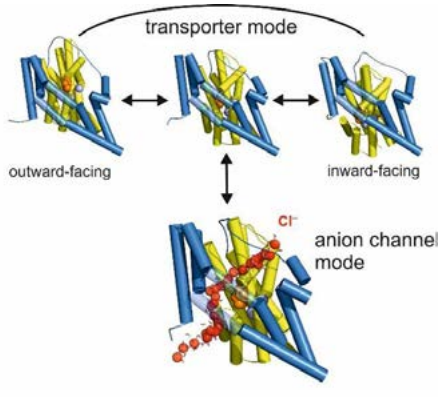
Susan Rempe, Mangesh Chaudhari, and Juan Vanegas
Sandia National Laboratories, Albuquerque, NM 87123

Water is important biologically as a reference environment for ion transport across cellular membranes in all parts of the body, including the brain. An interesting idea is that ions pass through specific ion channels when channel-lining amino acid residues provide an environment similar to local ion hydration environments. To test that idea, we compare the local solvent structure and solvation free energy of ions in bulk water with ions at the binding sites of ion channels. We combine ab initio molecular dynamics (AIMD), statistical mechanical theory, and electronic structure calculations to interrogate those properties. The cations studied include Mg^{2+}, Ca^{2+}, $Sr^{2+}$and Ba^{2+}. $Ca^{2+}$and $Mg^{2+}$are biologically important ions and $Ba^{2+}$and $Sr^{2+}$are blockers of potassium ion channels. We find that hydration mimicry is valid for ions that block biological ion channels, but not necessarily for fast ion permeation.
Sandia National Laboratories (SNL) is a multi-mission laboratory managed and operated by National Technology and Engineering Solutions of Sandia, LLC., a wholly owned subsidiary of Honeywell International, Inc., for the U.S. Department of Energy's National Nuclear Security Administration under contract DE-NA-0003525.

Molecular mechanisms of the anion channel function of secondary active glutamate transporters

Christoph Fahlke, Institute of Complex Systems, Zelluläre Biophysik (ICS-4), Forschungszentrum Jülich, German, E-mail: c.fahlke@fz-juelich.de

EAAT glutamate transporters terminate glutamatergic synaptic transmission via rapid and effective re-uptake of glutamate into surrounding cells. However, EAATs are not only glutamate transporters, but also anion channels. Whereas EAAT glutamate transport is well understood, mechanisms and cellular roles of EAAT anion conduction have remained elusive for many years. We described the mechanistic basis of EAAT anion channel function using a combination of computational and experimental approaches (Machtens *et al*. (2015) *Cell* **160**, 542-553). In all-atom MD simulations with the archeal transporter Glt_{Ph}, the lateral movement of the transport domain starting from transport intermediates opens a perfectly anion-selective conduction pathway at the interface between trimerization and transport domains. Anion selectivity is ensured by a single positively charged residue (Arg 276), and neutralization of this residue permits the additional permeation of cations. We identified mutations in pore-forming residues that modified the selectivity or unitary conductance of Glt_{Ph} anion channels *in silico*. Subsequent patch-clamp recordings of homologous mutations in EAAT2 and EAAT4 revealed perfect agreement between functional effects of *in silico* and *in vitro* mutagenesis, indicating that the novel conformation is responsible for EAAT anion channel function.



Structure-function studies on Voltage-gated potassium channel Kv4.3

Claudio Tiecher1, Giuseppe Brancato2, Dineke Verbeek3, Armagan Kocer1,*
1 Department of Neuroscience, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands,
2 Scuola Normale Superiore, Pisa, Italy,
3 Department of Genetics, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

The voltage-gated potassium channel (Kv4.3) is involved in the electrical communication of Purkinje neurons, for governing of the fine-tuned motor coordination of the body. Patients carrying mutated forms of Kv4.3 lose their Purkinje cells and cerebellar tissue, in time. Based on large patient cohorts, two groups independently reported that nine mutations on Kv4.3 in Purkinje neurons individually cause the movement disorder Spinocerebellar ataxia type 19/22 (SCA19/22)1,2. In Purkinje neurons, Kv4.3 generates a so-called A-type current together with its modulatory proteins. This fast, transient current activates at voltages near the spiking threshold and determines the interval between consecutive action potentials during repetitive firing. However, how mutated Kv4.3 channels affect A-type current at the molecular level and can generate such dramatic effects is not yet known3. We will present our experimental findings on the wild-type and two pathogenic mutants of Kv4.3 at the wholecell and single-channel levels. Next, we will present a bottom-up approach to studying this channel and its interaction partners in well-defined, synthetic lipid environments.

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72, 870–880 (2012).
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33, 1324–1332 (2012).

Modeling inherited and de novo mutations in a voltage-gated potassium channel

Andrea Catte,[1] Nicholus Bhattacharjee,[1] Muhammad Jan Akhunzada,[1] Dineke S. Verbeek,[2] Armagan Kocer[3] and Giuseppe Brancato[1,*]
[1] Scuola Normale Superiore and Istituto Nazionale di Fisica Nucleare (INFN), Pisa, Italy.
[2] Department of Genetics, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.
[3] Department of Neuroscience, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.

Mutations in the gene KCND3 encoding the voltage-gated potassium channel K_v4.3 have been reported to be associated with heart disorders, such as atrial fibrillation and Brugada syndrome,[1] as well as brain disorders, such as spinocerebellar ataxia, intellectual disability and epilepsy.[2] In particular, such disease-causing K_v4.3 variants may have negative effects on the trafficking and membrane localization of the protein or they may alter the gating and current amplitude of the channel. Recently, a few inherited mutations, among which there are the M373I and S390N single mutations, have been suggested to cause the onset of spinocerebellar ataxia type 19/22 (SCA19/22) through Purkinje cell loss and progressive neurodegeneration.[3,4] In this study, we investigate the molecular basis of K_v4.3 dysfunction upon specific point mutation by taking into consideration the above-mentioned variants, namely M373I and S390N, as compared to the wild-type (WT) channel. Our investigation aims at elucidating in some detail the effects of these mutations on the structural stability and ion conduction properties of K_v4.3 and is based on atomistic molecular dynamics (MD) simulations of a K_v4.3 channel model embedded into a lipid bilayer under applied voltage. Overall, our results nicely complement the clinical, genetic and biophysical information collected so far on these pathological mutants. From microsecond-long simulations, we observe that both M373I and S390N variants show a reduction in ion conductance as compared to WT, in good agreement with electrophysiological measurements at single-channel level (see poster Tiecher et al. for further details). Thanks to our model, we provide a mechanistic picture of the specific effects the mutated residues brought about in the K_v4.3 channel, thus allowing us to interpret the molecular origin of the protein dysfunction caused by these mutations. Besides, we expect the present model to be well suited for further investigations of other inherited or de novo mutations impairing K_v4.3 function.

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2. Lee Y-C., et al. (2012) Mutations in KCND3 Cause Spinocerebellar Ataxia Type 22. *Ann Neurol* 72:859–869.
3. Duarri A., et al. (2015) Spinocerebellar ataxia type 19/22 mutations alter heterocomplex Kv4.3 channel function and gating in a dominant manner. *Cell Mol Life Sci* 72(17):3387–3399.
4. Duarri A, et al. (2012) Mutations in Potassium Channel KCND3 Cause Spinocerebellar Ataxia Type 19. *Ann Neurol* 72:870–880.

Ion transport: from kinetic models to high resolution structures and back

Simon Berneche
Biozentrum, University of Basel, Klingelbergstrasse 50 / 70, CH - 4056 Basel

High resolution structures have changed our way of looking at the function of ion channels and transporters. These molecular structures constitute an invaluable source of information and a prerequisite to any detailed calculation. Unfortunately, they have also overshadowed decades of findings that were well described by kinetic models. Kinetic models remain an efficient way to link the structure and function of ion channels and to allow integration of our molecular and mechanistic knowledge into cellular models. I will discuss our learnings from different studies of ion channels and transporters, and from our implication in the Human Brain Projects, a flagship project of the European Union.

Ferritin: learning about iron uptake, biomineralization and release

Paola Turano
CERM & Department of Chemistry, University of Florence

Mammalian ferritins are generally heteropolymeric nanocages composed by variable amounts of two types of subunits, namely H subunits, with ferroxidase catalytic activity, and L subunits, which lack catalytic activity. The H/L is tissue-dependent. Fast iron metabolism is associated to cages rich in H-subunits. On the contrary, ferritins in iron storage organs are rich in L-subunits, proposed to facilitate iron biomineral formation via nucleation sites.
Here we report the structural and functional characterization on ferritin variants obtained by mutating key residues along the iron pathways in the ferritin cage. These data draw distinct mechanism of action for the two types of subunits. The results are relevant for a better understanding of iron metabolism in the brain, where different types of cells express different amount of H and L subunits, giving rise to holigomeric ferritin nanocages with different composition.

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Bernacchioni C, Pozzi C, Di Pisa F, Mangani S, Turano P. *Chemistry*. 2016, 22:16213-16219.
Chandramouli B, Bernacchioni C, Di Maio D, Turano P, Brancato G. *J Biol Chem*. 2016,291:25617-25628.
Pozzi C, Di Pisa F, Bernacchioni C, Ciambellotti S, Turano P, Mangani S. *Acta Crystallogr D Biol Crystallogr*. 2015, 71:1909-20.

Finite field methods for modelling liquid water and electric double layer

Chao Zhang

Department of Chemistry-Ångström Laboratory, Uppsala University

Oxide-electrolyte interfaces are universally present in energy storage device, nanofluidic chemical processor, drug delivery nanoparticles and containments treatment in ground water. The surface charge of all these interfaces is controlled by the pH of the electrolyte solution and this leads to the formation of the electric double layer (EDL) by deprotonation of adsorbed water molecules or protonation of the oxide surfaces. Despite of the rapid development of experimental techniques, the missing of microscopic understanding imposes a knowledge gap. In this regard, modelling and simulation of EDL can provide complementary information of the structure, dynamics and energetics of charged interfaces. Here, I will report our recent methodological progress on the atomistic modelling of dielectric properties of liquid water and charged oxide-electrolyte interfaces. Its implication for modeling membrane potential will also be mentioned.

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[3] Zhang C. and Sprik M. *Phys. Rev. B*, **2016**, 94: 245309 (Editors' Suggestion).
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Addressing the study of ions from complementary perspectives: methods for force field parametrization and continuum description

Walter Rocchia
CONCEPT Lab, Istituto Italiano di Tecnologia,
Genoa Italy

In the first part of the talk I will describe a novel statistical procedure that has been developed to optimize the parameters of nonbonded force fields for metal ions in soft matter. The criterion for the optimization is the minimization of the deviations from ab initio forces and energies calculated for model systems. The method exploits the combination of the linear ridge regression and the cross-validation techniques with a differential evolution algorithm. Wide freedom in the choice of the functional form of the force fields is allowed since both linear and nonlinear parameters can be optimized. In order to maximize the information content of the data employed in the fitting procedure, the composition of the training set is entrusted to a combinatorial optimization algorithm which maximizes the dissimilarity of the included instances. The methodology has been validated using the force field parametrization of five metal ions (Zn^{++}, Ni^{++}, Mg^{++}, Ca^{++}, and Na^{+}) in water as test cases.

In the second part, I will show how the concept of Molecular Surface, widely used for molecular visualization and for separating high- from low-dielectric regions for continuum-electrostatics calculations, can be exploited to define and identify pockets on the protein surface and also the lumen in molecular ion channels. The tool used to do this, NanoShaper, has recently been integrated with the widely used VMD software [2]. Development and potential application for processing of molecular dynamics trajectories will be discussed.

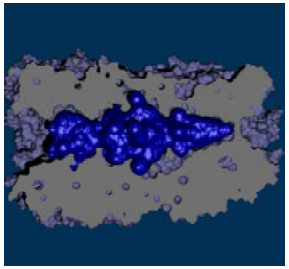

Figure Pictorial representation of the channel in the human gamma-aminobutyric acid receptor

[1] Fracchia F., Del Frate G., Mancini, G., Rocchia, W., and Barone, V., "*Force Field Parametrization of Metal Ions from Statistical Learning Techniques*", J. Chem. Theory Comput. 2018, 14, 255–273
[2] Decherchi, S., Spitaleri, A., Stone, J., and Rocchia, W., "*NanoShaper-VMD interface: computing and visualizing surfaces, pockets, and channels in molecular systems*", submitted

About BioExcel CoE

Adam Carter
BioExcel & KTH, Sweden

BioExcel is the European Center of Excellence for Computational Biomolecular Research (www.bioexcel.eu). The centre was established in 2015 with main goals to 1) improve the performance and scalability of major applications for biomolecular simulations – CPMD, GROMACS and HADDOCK; 2) develop user-friendly and automated workflow solutions for computation and data handling based on platforms such as CWL, Galaxy, KNIME, OpenPHACTS, Taverna and COMPSs, 3) provide advanced support to the user communities and 4) strengthen the links between stakeholders in the computational life science domain. The centre offers a number of services including hands-on training, tailored customization of code and personalized consultancy support.

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SILVANADE LILLO	Università di Perugia & INFN
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Organizers

GIUSEPPE BRANCATO
Scuola Normale Superiore, Italy

THOMAS BECK
Department of chemistry, University of Cincinnati, USA

PAOLO CARLONI
Forschungszentrum Jülich and RWTH Aachen University, Germany

HALIMA MOUHIB
Laboratoire de Modélisation et Simulation Multi Echelle, Université Paris-Est-Marne-la-Vallée, France