European UGM & Conference 2021

Wednesday, May 19: Moderator: Markus Kossner **09:00 AM - 10:15 AM**

Antibody Modeling and Protein Engineering

Andrew Henry, Senior Applications Scientist, Chemical Computing Group (UK)

Moderator: Markus Kossner | Morning Session – Virtual Workshops

Andrew Henry
Senior Applications Scientist, Chemical Computing Group (UK)

Protein Engineering / Protein Properties / Developability / Hot Spot Analysis / Antibody Modeling / Humanization / Molecular Surfaces The course covers approaches for structure-based antibody design and includes protein-protein interactions analysis, in silico protein engineering, affinity modeling and antibody homology modeling. The interaction of a co-crystallized antibody-antigen complex will be studied by generating and examining the molecular surfaces and visualizing protein-protein interactions in 3D and 2D. Antibody properties will be evaluated using specialized calculated protein property descriptors and analyzing protein patches. The application of protein engineering tools for homology modeling and conducting property optimization of antibodies in the context ...

Wednesday, May 19: Moderator: Markus Kossner **10:30 AM - 11:45 AM**

Biologics: Protein Alignments, Modeling and Docking

Sarah Witzke, Applications Scientist, Chemical Computing Group (UK)

Moderator: Markus Kossner | Morning Session – Virtual Workshops

Sarah Witzke
Applications Scientist, Chemical Computing Group (UK)

Protein Alignments and Superposition / Loop and Linker Modeling / Homology Modeling / Protein- Protein Docking The course covers methods for aligning protein sequences, superposing structures, homology modeling fusion proteins and conducting protein-protein docking. In particular, an approach for aligning and superposing multiple structures will be described for determining structural and surface protein variations in relation to protein property modulation. A method for grafting and refining antibody CDR loops as well as using a knowledge-based approach to scFv fusion protein modeling using the MOE linker application will be described. An approach to generate homology models of a murine antigen structure ...

Wednesday, May 19 **12:00 PM - 01:00 PM**

Posters & Group Discussions

On the Virtual Portal left-side menu, go to Networking > Groups > Select a Poster

Poster Session

Poster Title / Presenter / Poster AbstractPoster Title / Presenter / Poster AbstractPoster Title / Presenter / Poster Abstract

Wednesday, May 19 **01:15 PM - 01:20 PM**

Opening Remarks

Markus Kossner, Scientific Services Manager, Chemical Computing Group (DE)

Afternoon Session – Scientific Presentations

Wednesday, May 19: Chair: Markus Kossner **01:20 PM - 01:50 PM**

Charting Therapeutically Relevant Protein Conformational Space with Adaptive MD

Silvia Lovera, Senior Scientist, UCB Biopharma SPL (BE)

Chair: Markus Kossner Afternoon Session – Scientific Presentations

Silvia Lovera
Senior Scientist, UCB Biopharma SPL (BE)

GPCRs play a pivotal role in transmitting signals at the cellular level and structural insights can be exploited to support structure-based drug discovery endeavors. Despite advances in GPCR crystallography, it remains challenging to obtain crystal structures particularly of active states. Molecular dynamics (MD) simulations have been used to explore the conformational landscape of GPCRs. Nevertheless, the search for physiologically relevant conformations, allosteric pockets and ligand binding events using classical MD simulations is still impractical. The work I will present shows how by applying adaptive MD it is possible to computationally access, in a rigorous and timely manner, key functional states ...

Wednesday, May 19: Chair: Markus Kossner **01:50 PM - 02:20 PM**

Computational Evolution of Threonine-Rich β Hairpin Peptides Mimicking Specificity and Affinity of Antibodies

Morten Meldal, Professor in Chemistry, University of Copenhagen (DK)

Chair: Markus Kossner Afternoon Session – Scientific Presentations

Morten Meldal
Professor in Chemistry, University of Copenhagen (DK)

A successful approach for design and preparation of peptide based recognition molecules that mimic the activity of antibodies in terms of specificity and affinity is presented. The technology exploits a structurally stabilized β-hairpin scaffold termed a β-body. The scaffold was derived from a combination of observations in crystal structures and NMR-studies on threonine rich mucin glyco-peptides. The structure of the β-body may be further stabilized using the versatile CuAAC click reaction to bridge the C- and N-terminal of the scaffold. The structural stability of the β-body scaffold allows virtual combinatorial chemistry in the design and development. To this end we ...

Wednesday, May 19: Chair: Markus Kossner **02:20 PM - 02:50 PM**

Developability Optimization of Antibodies

Anette Henriksen, Principal Scientist, Novo Nordisk A/S (DK)

Chair: Markus Kossner | Afternoon Session – Scientific Presentations

Anette Henriksen
Principal Scientist, Novo Nordisk A/S (DK)

The development of protein therapeutics can be time consuming and cumbersome and often requires a trade-off between enhancing the biological effect of a protein and its stability and solubility. More specifically, the biophysical properties often highlighted as important for the developability of proteins are aggregation propensity, viscosity, adsorption, stability and solubility. This presentation discusses how in-vitro assay guided optimization of antibody developability correlates with developability indicators obtained using in-silico tools.

Wednesday, May 19: Chair: Markus Kossner **02:50 PM - 03:20 PM**

Developability Assessment and Property Prediction by pH-Dependent Conformational Sampling

Andrew Henry, Principal Scientist, Chemical Computing Group (UK)

Chair: Markus Kossner | Afternoon Session – Scientific Presentations

Andrew Henry
Senior Applications Scientist, Chemical Computing Group (UK)

mAb candidates identified from high-throughput screening or binding affinity optimization often present liabilities for developability, such as aggregation-prone regions or poor solution behavior. In this work, we developed a method for modeling proteins and performing pH-dependent conformational sampling, which can enhance property calculations such as hydrophobic patches, charge and pI. A retrospective data analysis demonstrates that these 3D descriptors, averaged over conformational sampling and stochastic titration, can accurately predict pI values, screen candidates and enrich libraries with favorable developability properties for a range of biotherapeutics. The clinical landscape of antibodies is also analyzed and its property profile and insights thereof ...

Wednesday, May 19: Chair: Nels Thorsteinson **03:20 PM - 03:50 PM**

MOE Showcase: Antibody Structural Analysis, Developability Assessment & More

Chair: Nels Thorsteinson | Afternoon Session – Scientific Presentations

Freya Trasischker
Senior Applications Scientist, Chemical Computing Group (AT)

Building and analysing a model for an IgG4 antibody, calculating properties and identifying aggregation prone regions
Another MOE biological modeling topic, selected from attendees' suggestions

Wednesday, May 19: Chair: Nels Thorsteinson **03:50 PM - 04:20 PM**

Using MOE's "Ensemble Protein Properties" in Early Developability Assessment of Therapeutic Antibodies

Hubert Kettenberger, Senior Principal Scientist Protein Engineering, Roche Diagnostics GmbH (DE)

Chair: Nels Thorsteinson | Afternoon Session – Scientific Presentations

Hubert Kettenberger
Senior Principal Scientist Protein Engineering, Roche Diagnostics GmbH (DE)

During the lead identification and optimization phase, predicting and engineering biophysical properties of therapeutic antibody candidates is an important but challenging task. Properties such as aggregation propensity, folding stability, hydrophobicity, charge distribution, etc. are of particular interest because they may affect manufacturability, storage stability, pharmacokinetics and others. The presentation will focus on a comparison between different in-silico property calculation methods with MOE's molecular dynamics-supported ensemble protein property method in terms of predictivity.

Wednesday, May 19: Chair: Nels Thorsteinson **04:20 PM - 04:50 PM**

Analysis of TCR-pHLA Complex Crystal Structures in MOE Using a Custom SVL Script

Ross Robinson, Associate Director, Protein Engineering, Immunocore Ltd (UK)

Chair: Nels Thorsteinson | Afternoon Session – Scientific Presentations

Ross Robinson
Associate Director, Protein Engineering, Immunocore Ltd (UK)

ImmTAC® molecules are TCR/anti-CD3 bispecific fusion proteins that target specific peptide-human leukocyte antigen complexes (pHLA) to activate a highly potent and specific T cell response against cancer cells. TCR-pHLA crystal structures are used to inform decisions at both TCR discovery and affinity enhancement stages. A custom MOE SVL script is used to assess crystal structures to provide both global features and detailed interface information. Using this approach, we are able to feedback unbiased structural analysis in a fast and efficient manner.

Wednesday, May 19: Chair: Nels Thorsteinson **04:50 PM - 05:20 PM**

Platformization of Multi-Specific Protein Engineering: Leveraging High-Throughput Screening Data for in silico Antibody Design

Norbert Furtmann, Head of Data Lab, High Throughput Biologics, Sanofi Deutschland GmbH (DE)

Chair: Nels Thorsteinson | Afternoon Session – Scientific Presentations

Norbert Furtmann
Head of Data Lab, High Throughput Biologics, Sanofi Deutschland GmbH (DE)

Our novel, automated high-throughput engineering platform enables the fast generation of large panels of multi-specific variants (up to 10.000) giving rise to large data sets (more than 100.000 data points). Here we report on our visualization and data analysis workflows to improve the understanding of our complex molecules and guide the engineering process.

Wednesday, May 19 **05:20 PM - 05:30 PM**

Closing Remarks

TBA

Afternoon Session – Scientific Presentations

Wednesday, May 19 **05:30 PM - 06:00 PM**

Further Discussions | Social Interactions

(Bring Your Own Beverage)

Thursday, May 20: Moderator: Markus Kossner **09:00 AM - 10:15 AM**

Small Molecule Virtual Screening

Barbara Sander, Senior Applications Scientist, Chemical Computing Group (DE)

Moderator: Markus Kossner Morning Session – Virtual Workshops

Barbara Sander
Senior Applications Scientist, Chemical Computing Group (DE)

MOE Databases / Descriptors / Fingerprints / QSPR Modeling / Pharmacophore Modeling / Template-Forced Docking / Scaffold Replacement / MedChem Transformations The course covers the suite of MOE applications which can be applied to small-molecule virtual screening. Topics include the preparation of small molecule databases for virtual screening, filtering databases based on substructure matching and property values, building QSAR/QSPR models and fingerprint similarity models as database filters, pharmacophore query creation and searching, and small-molecule docking. These tools are used in conjunction to present a complete virtual screening workflow. The creation of de novo structures using the MOE Scaffold Replacement and ...

Thursday, May 20: Moderator: Markus Kossner **10:30 AM - 11:45 AM**

Advanced Structure-Based Drug Design

Freya (Klepsch) Trasischker, Senior Applications Scientist, Chemical Computing Group (AT)

Moderator: Markus Kossner Morning Session – Virtual Workshops

Freya Trasischker
Senior Applications Scientist, Chemical Computing Group (AT)

Pharmacophore Modeling / Docking / Fragment-based Design / Scaffold Replacement / R-Group Screening / Project Search / Protein-Ligand Interaction Fingerprints The course describes advanced SBDD workflows in drug discovery projects and encompasses a range of topics from pharmacophore query generation to protein-ligand interaction fingerprints. More specifically, the course will cover the application of pharmacophores in the context of protein-ligand docking, scaffold replacement and R-group screening. A method for querying a 3D project database will also be presented along with the generation and analysis of protein- ligand interaction fingerprints (PLIF).

Thursday, May 20 **12:00 PM - 01:00 PM**

Posters & Group Discussions

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Poster Session

Poster Title / Presenter / Poster AbstractPoster Title / Presenter / Poster AbstractPoster Title / Presenter / Poster Abstract

Thursday, May 20 **01:15 PM - 01:20 PM**

Opening Remarks

Markus Kossner, Scientific Services Manager, Chemical Computing Group (DE)

Afternoon Session – Scientific Presentations

Thursday, May 20: Chair: Markus Kossner **01:20 PM - 01:50 PM**

Exploring FE Calculations in Drug Discovery Programs and Collaborations

Gary Tresadern, Senior Principal Scientist, Janssen R&D (ES)

Chair: Markus Kossner Afternoon Session – Scientific Presentations

Gary Tresadern
Senior Principal Scientist, Janssen R&D (ES)

Free energy perturbation calculations have now become commonplace in industrial drug discovery across programs. At Janssen our efforts started around 6 to 7 years ago and have ventured from tentative and skeptical small scale applications, through use in monthly molecular design cycles, to present day application on large VLs. In general, time has revealed that FEP calculations can be valuable in drug discovery but much remains to be understood. Along the way we have invested to understand the origins of successes and failures, often trying to understand this in terms of the chemistry and physics that is being modeled, rather ...

Thursday, May 20: Chair: Markus Kossner **01:50 PM - 02:20 PM**

Understanding Molecule Conformation in Solution: Refining Conformational Analysis with NMR Data

Iuni Trist, Principal Scientist, Aptuit, an Evotec company (IT)

Chair: Markus Kossner Afternoon Session – Scientific Presentations

Iuni Trist
Principal Scientist, Aptuit, an Evotec company (IT)

Small molecules can adopt diverse conformations in solution according to the combination of conformational energy and interactions with the solvent itself. These conformations might be similar or different from the one needed to bind to the biological target. In the latter case, before binding, the small molecule needs to assume the bioactive conformation, not favoured in solution, causing a loss of activity (entropic penalty). 3D structures are not always available and, even if they are, these “static pictures” are not able to support all aspects of lead optimization as they do not account “how” the ligand reaches the correct conformation. ...

Thursday, May 20: Chair: Markus Kossner **02:20 PM - 02:50 PM**

Almost Square: The Impact of Oxetanes on Compound Design

Anders Johansson, Team Leader Chemistry, AstraZeneca (SE)

Chair: Markus Kossner | Afternoon Session – Scientific Presentations

Anders Johansson
Team Leader Chemistry, AstraZeneca (SE)

Oxetane-containing ring systems have shown great utility in medicinal chemistry to modulate physicochemical properties. There is an increasing number of examples of how incorporation of oxetanes can have a beneficial impact on the pharmacokinetic (PK) properties of compounds. A less explored aspect is how oxetanes affect metabolic pathways. An exaggerated dependence on one specific isoenzyme increases the risk of drug-drug interactions with co-administered drugs. It is not unusual to observe strong dependence of one isoform of cytochrome P450, most notably CYP3A4. This talk will illustrate that mEH-catalyzed (microsomal epoxide hydrolase) hydrolysis is an important metabolic pathway for structurally diverse oxetanes. ...

Thursday, May 20: Moderator: Markus Kossner **02:50 PM - 03:20 PM**

Modeling PROTAC-Mediated Targeted Protein Degradation: Case Studies and Recent Developments

Mike Drummond, Scientific Applications Manager, Chemical Computing Group (US)

Moderator: Markus Kossner | Afternoon Session – Scientific Presentations

Mike Drummond
Scientific Applications Manager, Chemical Computing Group (US)

Targeted protein degradation using bivalent small molecules (such as PROTACs) is a new modality that provides a means to control protein levels in vivo. Despite many clear advantages, numerous challenges exist in PROTAC development, particularly concerning the rational design of efficacious molecules. In this presentation, multiple computational methods that enable the a priori evaluation of putative PROTAC molecules will be discussed. Numerous case studies will be offered, where the application of these computational tools can successfully recommend not only potent PROTAC candidates, but also molecules to avoid. Results from scenarios across different target proteins, E3 ligases, and PROTAC architectures will ...

Thursday, May 20: Chair: Alain Deschenes **03:20 PM - 03:50 PM**

MOE Showcase: Data Mining for Medicinal Chemists, High Throughput Docking & More

Chair: Alain Deschenes | Afternoon Session – Scientific Presentations

Andrew Henry
Senior Applications Scientist, Chemical Computing Group (UK)

Barbara Sander
Senior Applications Scientist, Chemical Computing Group (DE)

Sarah Witzke
Applications Scientist, Chemical Computing Group (UK)

MOEsaic for mining project activity data and guiding development pathways High Throughput Docking for virtual screening Another MOE small molecule modeling topic, selected from attendees' suggestions

Thursday, May 20: Chair: Alain Deschenes **03:50 PM - 04:20 PM**

Molecular Basis and Design of NADH Competitive Inhibitors: The Case of PYCR1

Rafael S. Depetris, Principal Scientist II – Head of Structure Based Drug Design, Kadmon (US)

Chair: Alain Deschenes | Afternoon Session – Scientific Presentations

Rafael S. Depetris
Principal Scientist II – Head of Structure Based Drug Design, Kadmon (US)

Pyrroline 5-carboxylate reductase (PYCR1) is a NADH dependent enzyme that catalyzes the reduction of P5C into proline. Proline metabolism is of critical importance in abnormal cell growth, which is supported by the overexpression of PYCR1 in prostate and breast cancer and in lung fibrosis. Kadmon is interested in developing a new generation of potent, NADH competitive inhibitors of PYCR1 for fibrosis indications. We developed a structure based drug design approach taking our crystal structures of previous PYCR1 inhibitors which were the starting point of our MOE based in silico design of enhanced therapeutic agents. The talk will show the structural ...

Thursday, May 20: Chair: Alain Deschenes **04:20 PM - 04:50 PM**

Preparing Shape-Diverse Relevant Conformer Sets Using Quantum Chemistry and Cheminformatics

Jimmy Kromann, Data Scientist, Novartis (CH)

Chair: Alain Deschenes | Afternoon Session – Scientific Presentations

Jimmy Kromann
Data Scientist, Novartis (CH)

Modelling low-energy conformers of drug-like organic molecules is a long-standing problem in computational chemistry. The quality of molecular conformers is vital to subsequent analysis and calculations, such as ligand docking, pharmacophore searches or quantum chemical properties. Most importantly, relevant conformations of a molecule cannot be described by a single graph, but depend on tautomeric and protomeric forms of the compound, each with their own associated conformational space. We present a flexible and automatic workflow based on cheminformatics tools and quantum chemistry to produce relevant conformers for all our in-house compounds and highlight some of their potential uses.

Thursday, May 20: Chair: Alain Deschenes **04:50 PM - 05:20 PM**

Charting Medicinal Chemistry Design Space for Rapid Ideation

Mahendra Awale, Postdoctoral Research Fellow, F. Hoffman La Roche (CH)

Chair: Alain Deschenes | Afternoon Session – Scientific Presentations

Mahendra Awale
Postdoctoral Research Fellow, F. Hoffman La Roche (CH)

Lead optimization campaigns typically follow an iterative ‘Design-Synthesis-Evaluation-Feedback’ loop until a compound with desired clinical candidate profile is obtained. The key here is to have continuous access to relevant design ideas that can be synthesized and evaluated as fast as possible. Therefore, computational methods that can assist in compound ideation is of high importance in the lead optimization campaign. Among many, Matched Molecular Pair Analysis (MMPA) has particularly received considerable attention and became one of the standard tools for ideas generation. When applied systematically, MMPA can be used to chart the space of medchem design moves. These design moves (MMP ...

Thursday, May 20 **05:20 PM - 05:30 PM**

Closing Remarks

TBA

Afternoon Session – Scientific Presentations

Thursday, May 20 **05:30 PM - 06:00 PM**

Further Discussions | Social Interactions

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