AARHUS UNIVERSITY

AUSBI Lectures

Hosted by Rune Kidmose and the "Biomolecular Design and Prediction" Interest Group

Time: Friday 8 November 2024 from 13:00-14:45
Venue: Faculty club (1870-816), Dept. MBG, Universitetsbyen 81, 8000 Aarhus

Martin Pačesa, Laboratory of Protein Design and Immunoengineering, EPFL

Engineering complexity and function using computational protein design

***Online lecture streamed in the Faculty club** (https://aarhusuniversity.zoom.us/j/65138438153)*

Martin Pačesa is a postdoctoral researcher at the Institute of Bioengineering, EPFL, in Bruno E. Correia's lab, specializing in protein design and computational methods. Recently he co-developed the BindCraft protein design pipeline, which earned him and Lennart Nickel first place in a recent protein design competition hosted by Adaptyv Bios Lab. Over 700 designs targeting EGFR were submitted, with 200 tested in the lab.

Martin will discuss BindCraft's development, its role in designing functional protein binders, and his contributions to creating functional soluble membrane protein analogues.

Computational protein design is emerging as a powerful tool to create enzymes with novel or enhanced functionalities that cannot be achieved using traditional methods, such as rational engineering and directed evolution. However, most designed proteins to date are composed of structurally simple topologies, far from the complexity sampled in nature. To overcome this limitation, we developed a deep learning-based pipeline leveraging the incredible accuracy of AlphaFold2 for the design of proteins with complex natural protein topologies and high experimental success rates. We applied our approach to the design of soluble analogues of membrane proteins, such as GPCRs and claudins. We demonstrate that our soluble analogues are highly stable, structurally accurate, and are able to support native epitopes for antibody or G-protein binding in solution. We then extended the capabilities of our pipeline to the design of highly specific protein binders. We are now able to design binders with unprecedented experimental success rates against therapeutically relevant targets, such as PD-L1 or CD45, as well as much more challenging targets, such as CRISPR-Cas nucleases, Argonautes, and common allergens. These advancements pave the way for the accurate design of proteins with complex functions and potential applications in research, biotechnology, and therapies.

Joe Rogers, Department of Drug Design and Pharmacology, University of Copenhagen

Targeting protein disorder using protein design and cyclic peptide screening

In-person lecture

Joe Rogers is a group leader at the Dept. Drug Design and Pharmacology, University of Copenhagen. Since 2020, working on discovery methods for new drug modalities, namely cyclic peptides, and exploring new drug mechanisms of actions around protein folding, binding and disorder. Prior to Denmark, Joe was in the USA as a researcher with the company Vertex Pharmaceuticals, best known for bringing drugs to the market that "correct" protein folding. Post-doc was with Hiroaki Suga in Japan, working on the "RaPID system", an experimental method to screen trillions of unique cyclic peptides for drug-like hits, a technology he has since established in Denmark. PhD in the UK with Jane Clarke, studying experimentally the biophysics of peptide-protein interactions, and their mechanisms of folding upon binding.

Protein disorder is abundant in biology. Many of these disordered regions are essential for cellular function, and many of these are linked to human disease. Molecules able to bind to, and modulate, disordered regions would be valuable research tools and could form the basis for future therapeutics. Yet, discovery of such molecules is highly challenging using traditional ligand- and drug- discovery methods. Here, we describe two new modalities to target disordered proteins: *de novo* microproteins and *de novo* cyclic peptides. Driven by powerful new technologies for ligand discovery: machine learning-enabled computational design and experimental screening of enormous molecular libraries, respectively. These technologies have the potential to generate much needed research ligands, and open up disordered protein biology to drug discovery.