CONFÉRENCE

Dr. Kresten Lindorff-Larsen

University of Copenhagen, Denmark

Stability of proteins

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Abstract:
The rapid decrease in DNA sequencing cost is revolutionizing medicine and science. In medicine, genome sequencing has revealed millions of missense variants that change protein sequences at a single site, yet we only understand the molecular and phenotypic consequences of a small fraction of these. Within protein science and biotechnology, high-throughput multiplexed assays enable us to probe the effects of thousands of variants in a single experiment.
We have used computational and experimental approaches to determine the consequences of missense variants in proteins, with the aim of using such models both for diagnosing genetic diseases, and for providing mechanistic insight into disease. In particular, we have focused on the effects of individual amino acid changes on protein folding and stability, linking biophysical calculations with protein degradation and abundance in cells. By examining a range of proteins and diseases we have found that loss of stability is a common drive for genetic diseases, and that predictions of changes in thermodynamic protein stability are useful to assess the pathogenicity of genetic variation. I will discuss these ideas using recent examples from our laboratories.
At the same time, our work has also revealed areas where our understanding and ability to predict the effect of amino acid changes is still imperfect. I will discuss how we are using sequence analyses and high-throughput, multiplexed assays of variant effects (deep mutational scanning) experiments to understand the origins of loss of function, thus paving the way for more accurate biophysical models and machine learning methods for use in personalized medicine.

Hôte : Christian Landry

Responsable : Christian Landry
Christian.landry@bio.ulaval.ca