Jerome Tubiana
Blavatnik School of Computer Science, Tel Aviv University

Title: Harnessing sequence generative models for inhibitory peptide design: a case study

Abstract:
Peptides that efficiently bind a target protein and interfere with its native protein-protein interactions are attractive tools for basic research and therapeutic applications. However, the vast search space and the physio-chemical properties of protein-peptide interactions make rational design challenging. I will present an integrative peptide design protocol based on a generative model trained on native protein interaction partners of the target. We tested our protocol on Calcineurin, a serine/threonine phosphatase involved in multiple cellular pathways such as T-cell activation. We showed that the generative model i) inferred sequence motifs related to binding, ii) predicted binding affinity changes upon mutation, and iii) generated diverse candidate sequences. After filtering via molecular docking and high-throughput binding assays, we found that 70% of the designed peptides successfully interfered with Cn-substrate interactions. Altogether, our work suggests that generative modeling is a promising strategy for discovering peptide inhibitors.