Data-Driven Computational Analysis of PFAS Interactions with Metabolite Receptors

Julia Romanova, University of Sofia

Per- and polyfluoroalkyl substances (PFAS) are persistent synthetic chemicals widely used in industrial and consumer products. Because they resist degradation and accumulate in the body, PFAS exposure through contaminated water and food has been linked to immune suppression, thyroid and liver dysfunction, developmental and reproductive effects, and increased risk of certain cancers. Therefore, the ongoing research aims to clarify long-term health impacts and improve risk management strategies.

Nowadays, there is growing evidence for a link between PFAS and metabolite receptors. It was demonstrated that certain PFAS can interact with metabolite receptors that function as metabolite sensors. Through these receptor-mediated mechanisms, PFAS exposure may disrupt metabolic pathways, contributing to effects such as dyslipidemia, liver toxicity, insulin resistance, and other metabolic disorders.

In this study we used computational chemistry, chemometrics and machine-learning approaches to investigate the molecular level interactions between PFAS and key metabolite receptors. To shed light on the selectivity and binding affinity in the metabolite receptor-PFAS interactions, we have performed large-scale molecular docking screening with eight different metabolite receptors and several hundreds of PFAS. The trends in the binding affinity of PFAS toward specific receptors are interpreted by machine learning (ML) models. To train the ML models we have created dataset comprising structural, quantum-chemical and chemometric descriptors for several hundred PFAS molecules. The study demonstrates the applied potential of data-driven approaches in rationalizing the health impact of PFAS and gives deeper understanding on the structural aspects of PFAS-metabolite receptors interactions.