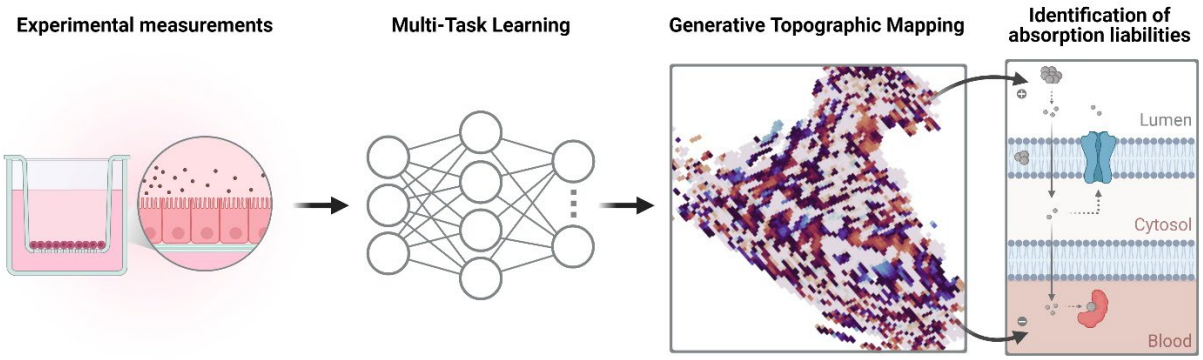
Drug absorption, a multi-task solution to a multi-parametric problem

Pierre Llompart[1,2], Claire Minoletti[2], Gilles Marcou[1,*], Alexandre Varnek[1]

[1]*Laboratory of Chemoinformatics, UMR7140, University of Strasbourg, Strasbourg, France*
[2]*IDD/CADD, Sanofi, Vitry-Sur-Seine, France*

Lead optimization failures are often linked to poor absorption, compounded by strong efflux transport and low recovery. This study first examines the relationship between critical permeability parameters, using comparative analysis of one pharma-industrial chemical space. Our findings highlight misconceptions in the transport route characterization. We herein demonstrate the importance of considering recovery, distribution coefficient, and total potential surface area during Multi-Parameter Optimization. Then we employ a Multi-Task Learning approach for predictive model development, we validate public models against industrial data, revealing key discrepancies influenced by variation in experimental protocols. Our analysis emphasizes the need for proprietary data in industrial absorption evaluations to avoid applicability domain issues and standardized measurement protocols. Finally, the integration of predictive models with Generative Topographic Mapping for chemical space exploration introduces a novel strategy to explain the origins of optimization challenges. This work proposes a visual approach for MPO to improve drug discovery efficiency.



Research workflow of the study, progressing from data acquisition to chemical space mapping through data analysis, curation, and Machine Learning integration.