Dynamic Quantum Crystallography and Machine Learning for Better Understanding Thermodynamic Stability and Solubility of Drug Cocrystals

Humanity has always strived to develop increasingly better and more effective medicines. However, the journey from discovering an active pharmaceutical ingredient (API) to creating a finished drug is fraught with challenges. One of the key issues is **bioavailability**, which refers to the ability of a drug to be absorbed by the body. Many APIs suffer from low solubility or poor membrane permeability, which complicates their industrial applications. These challenges can often be addressed by selecting an appropriate solid-state form of the drug, such as salts, solvates, or cocrystals.

Cocrystals are formed when two or more different molecules are combined into a single crystal lattice. Typically, these consist of an API, the molecule responsible for the drug's therapeutic effect, and a coformer. The coformer may be another active substance (in the case of API-API cocrystals) or other compounds deemed safe for pharmaceutical use. Interestingly, drug formulations containing cocrystals often exhibit better bioavailability than those using pure APIs. Currently, the first cocrystal-based drugs are becoming available on the market, with several cocrystal systems in various stages of clinical trials.

Unfortunately, obtaining the thermodynamic properties of cocrystals—such as stability and solubility—remains a significant challenge from experimental and theoretical point of view. Experimental determination of solubility for cocrystal is not a trivial task, as it requires a large amount of sample and numerous experiments. From theory, even when the structure of a cocrystal is known, it is difficult to predict its solubility with high accuracy.

The primary goal of this project is to address this issue by proposing new theoretical models that, based on data obtained from single-crystal X-ray diffraction (SCXRD) measurements and theoretical calculations, will allow for the determination of thermodynamic properties, including solubility, of cocrystals. The refinement methods for normal mode vibrations, which we have developed in relation to X-ray data, will be further enhanced to enable their application in determining the thermodynamic properties of cocrystals.

In addition to theoretical methods used to predict the solubility of cocrystals, machine learning approaches are increasingly being applied. These methods allow us to obtain preliminary models much more rapidly, which can then be refined using our proposed methodology. In this way, the procedure for determining the thermodynamic properties of cocrystals is significantly accelerated and, for larger systems beyond the reach of accurate quantum-chemical methods, becomes feasible.

The project will also involve extensive experimental efforts to discover new cocrystals of APIs. Using the latest crystallization techniques, including crystallization robots, ball mills, and crystallization reactors, we plan to produce new cocrystals of several carefully selected APIs. We will then determine the structures of these cocrystals and study their solubility. The experimental results will be compared with those obtained using our theoretical methods.

The methods we propose will enable faster estimation of the solubility and thermodynamic stability of cocrystals and, consequently, will contribute to the development of more effective drugs.