IFPRI Project Abstract

Delivery of a Practical Tool for Predicting the Effect of Solvents and Growth Inhibitors on Crystal Morphology

Michael F. Doherty and Tobias Mazal
University of California Santa Barbara
Project Start Date: 1 September, 2017
Abstract Date: 13 May, 2022

Project Objective:

The goal of this research is to develop a practical engineering tool for predicting the relative growth rates (growth kinetics) and morphology of solution-grown faceted crystals, including the effects of solvent, and impurities/additives. The methodology will be tested on a variety of systems, including: paracetamol, olanzapine, adipic acid, naphthalene, and a variety of drug substances, all grown from solution.

Approach:

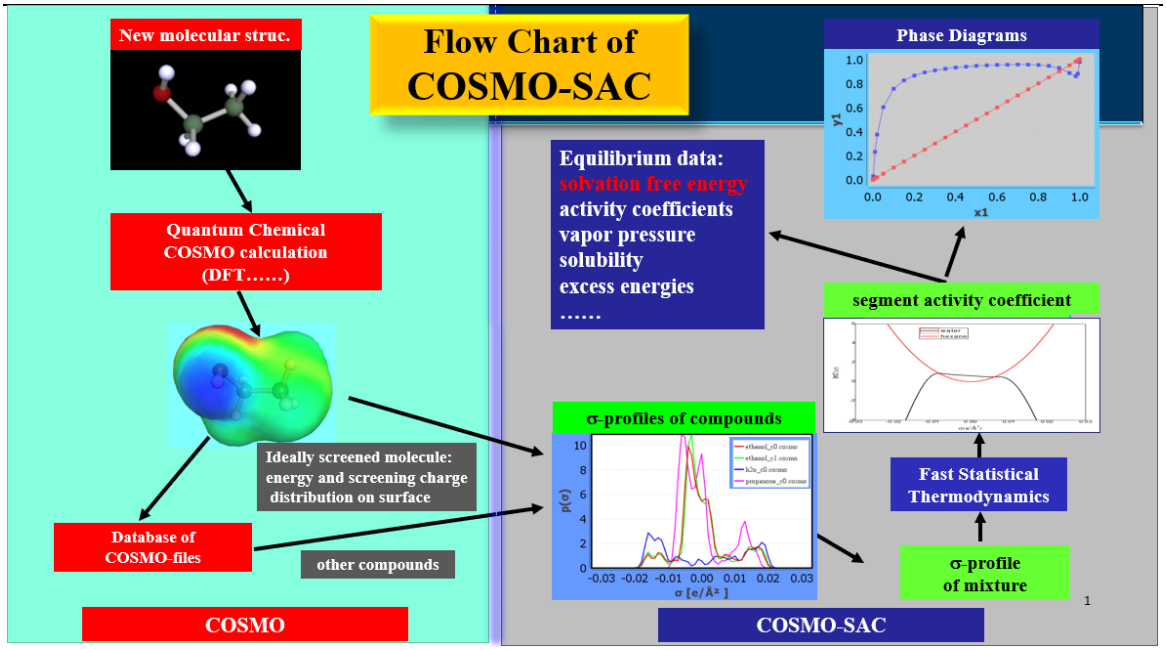
Our approach is to leverage a decade of research & development building our crystal design software tool called ADDICT in order to develop (fast) mechanistic models of crystal growth validated by experiments, molecular simulations and KMC simulations. KMC simulations are utilized for investigating impurity-mediated and noncentrosymmetric crystal growth in conjunction with novel kink density models. Solvent effects are incorporated into the modeling scheme via the use of COSMO-SAC software that we have created ourselves based on literature information.

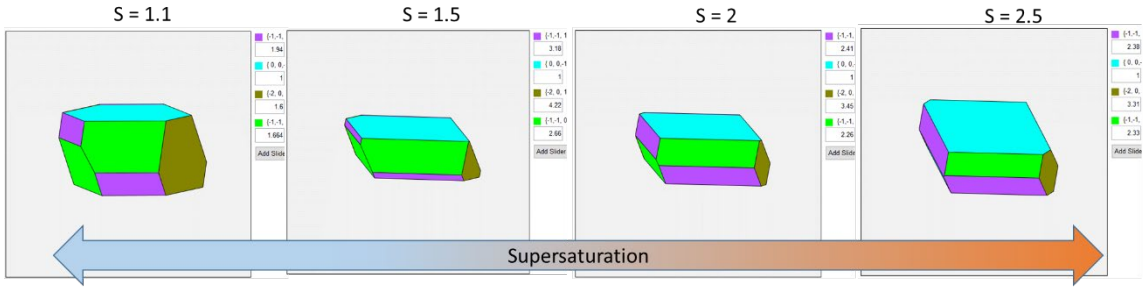
Recent Results:

We have validated and extended our Kinetic Monte Carlo simulations to handle more complex conditions such as impurity-mediated and noncentrosymmetric crystal growth systems. We have completed development of our own version of the COSMO-SAC method and investigated the use of different forcefields as well as improved kink density models to improve morphology predictions. We have also demonstrated the potential of using such inputs to visualize the modified crystal morphology in real time via ADDICT.

Next Steps:

The project will continue to investigate more complex systems (i.e. noncentrosymmetric growth units) and validate novel model developments via KMC simulations. With the help of COSMO-SAC and additional automated forcefields such as CLP, we will look to predict the solvation free energy of solid solutes to enable morphology predictions of mixed solvents and inform antisolvent crystallization. These advances will be adopted within ADDICT to examine the spectrum of crystal morphologies for a range of system growth conditions.





Low	Intermediate	High
All faces slowed significantly Results in Equant Morphology	Fast lower energy / higher kink density faces disappear	Critical length <<< impurity spacing, Impurity-free morphology adopted