IFPRI Project Abstract

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

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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 is being tested on a variety of systems including 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 to develop (fast) mechanistic models of crystal growth validated by experiments, molecular simulations and kMC simulations. Kinetic Monte Carlo 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-therm software that we have created ourselves based on literature information.

Recent Results:

We have developed a new model of crystal growth for asymmetric solute molecules that abandons the old thinking of (1) thermodynamic equilibrium, and (2) statistical independence of surface sites. We have compared its predictions for kink density and step velocity against kinetic Monte Carlo simulations and find good agreement. The new model has been used to predict crystal morphologies of many API-like molecules grown from solution and has been validated as satisfactory for use in engineering work flow (see figure below). The model is currently being incorporated into our digital design aid ADDICT.

Next Steps:

The IFPRI-sponsored project will end at UCSB later this year. However, it will continue at CCDC in Cambridge, England where the scientists there are using ADDICT as a platform to develop their own crystal morphology digital design aid.

Model-based predictions cover a wide range of morphologies

Doravirine precursor (treatment of HIV)

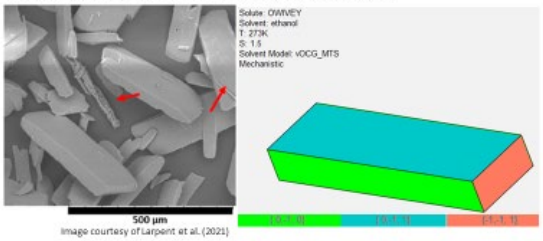

Image courtesy of Larpent et al. (2021)

Celecoxib (treatment of arthritis)

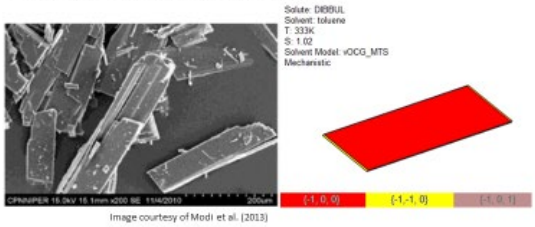

Image courtesy of Modi et al. (2013)

β-Glycine (Amino Acid)

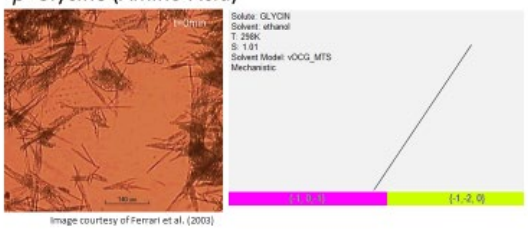

Image courtesy of Ferrari et al. (2003)

Trimethoprim (broad spectrum antibiotic)

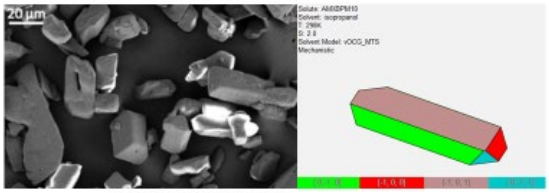

Image courtesy of Maddileti et al. (2015)