Delivery of a Practical Tool for Predicting Crystal Morphology of Complex Molecules

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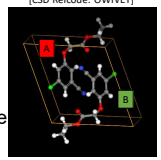
Objectives

- 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

Noncentrosymmetry Challenges

- Asymmetric molecules generate asymmetric bonding structures, hence complex PBCs – bonds comprising a single bond chain are not necessarily of the same strength. Same molecule can act as different growth units!

[CSD Refcode: OWIVEY]



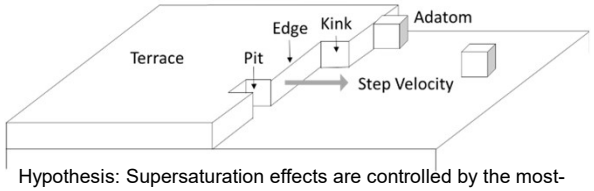
Doravirine (Z = 2)

- Kink Rates – there exist >1 type of kink site so there isotropic driving force to incorporate into the solid-state structure

- Sites are no longer statistically independent, hence Boltzmann statistics do NOT apply

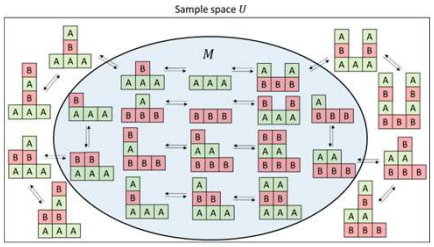
Simplified Steady-State Framework

- Attachment at *kinks* is crucial to flow of steps along crystal surfaces

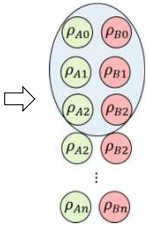


- Hypothesis: Supersaturation effects are controlled by the most-probable surface processes.

Step kinetics



Master Equations



1. Padwal and Doherty, 2022. Crystal Growth & Design, 22(6), pp.3656-3661.
2. Padwal, N. and Doherty, M.F. 2024 *Crystal Growth & Design*.

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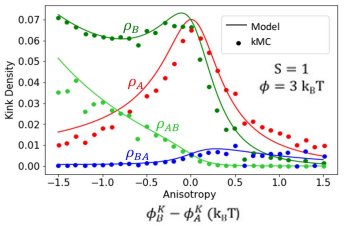
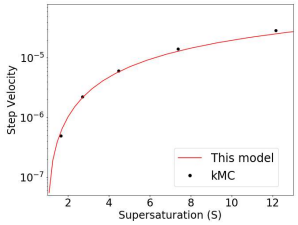
Model-based Morphology Predictions

Kink density and Step Velocity Predictions

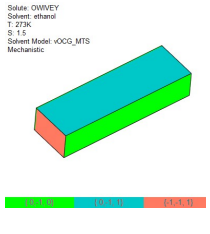
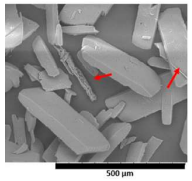
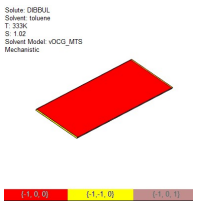
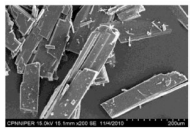
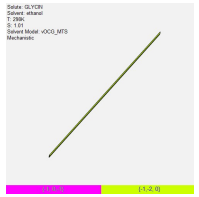
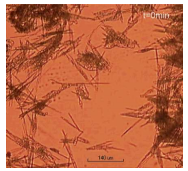
- Kink density and step velocity predictions demonstrate good agreement with kMC simulations





kMC courtesy of Cuppen et al. (2004)

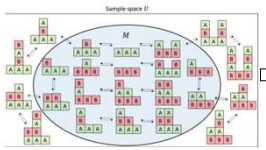
- Application of the model to APIs demonstrate excellent agreement with experimental observations.

Crystal Species/Solvent	Morphology Prediction	Experimental Morphology
Doravirine precursor [OWIVEY]		 Image courtesy of Larpent et al., (2021)
Celecoxib [DIBBUL]		 Image courtesy of Modi et al., (2013)
β-Glycine [GLYCIN]		 Image courtesy of Ferrari et al., (2003)

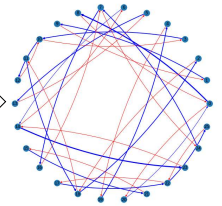
Computational model development

Symbolic Engine

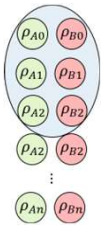
Step kinetics



Network Graph



Master Equations

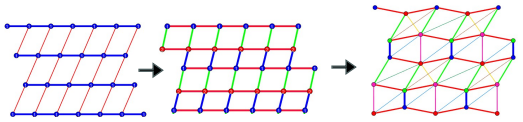


Sites $f(\rho_k) \rightarrow$ Nodes
Events $f(j^+, j^-) \rightarrow$ Edges

Network identification algorithm
1. Identify major sites → nodes
2. Subject nodes to j^+ and j^- events and parse through the major sites.
3. Most-probable events then form the network edges

Numerical Engine

Parametric continuation to target specific steady-states.

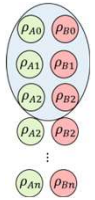


Kossel Crystal
- With simple PBCs

Intermediate Crystal

Final Crystal
-with complex PBCs

Master Equations



Steady-state solution

$$\sum j^{\pm} \frac{\rho_j \rho_k}{\hat{\rho}} = 0$$

Non-linear Equation Solver

Least-square minimization

Dependent set of Equations

Nonequilibrium kink densities

$$[\underline{\rho}] = \underline{f}[\boldsymbol{S}, T, \phi]$$

Future Work

- Symbolic-numeric tool implementation: The symbolic engine is complete, robust numerical engine implementation in progress.

- Transfer of ADDICT technology and source code to CCDC complete.

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