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

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Project Objective:

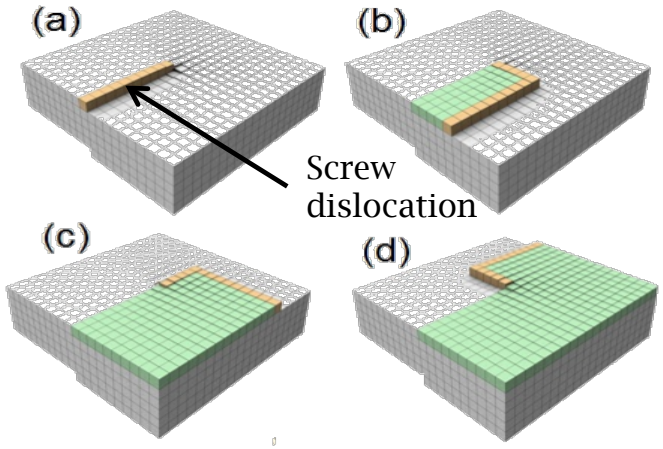
The goal of this research is to develop a practical engineering tool for predicting the relative growth rates (growth kinetics) and morphology of solution-grown faceted crystals, including the effects of solvent, and impurities/additives. The methodology is being tested on a variety of systems including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

Approach:

Our approach is to leverage many years of research & development building our crystal design software tool called ADDICT. Our approach is to develop (fast) mechanistic models of crystal growth validated by experiments and both molecular simulations and kMC simulations.

Layered Growth Mechanism

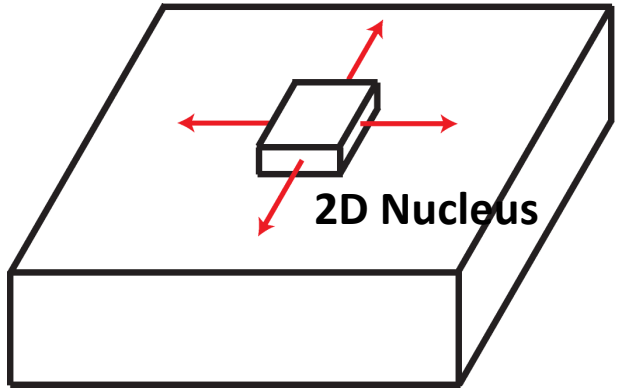
Spiral Growth



Absolute growth rate

$$G = \frac{h}{\tau}$$

2D Nucleation and Growth



Screw dislocations are the sources of steps

$$\tau_s = \sum_{i=1}^{N} \frac{l_{c,i+1} \sin\left(\alpha_{i,i+1}\right)}{\mathrm{v}_i}$$

Step velocity v depends on[1]

- Density of kink sites along the edge (ρ)
- Net rate of attachment into kink sites (u)

$$\mathrm{v} = a_p \rho u$$

2D Nuclei are the sources of steps

$$\tau_{2D} = \left(\mathrm{v}^2 I\right)^{-1/3}$$

h : Height of a layer
$l_{c,i+1}$: Critical length of edge i+1
$\alpha_{i,i+1}$: Angle between edge i and edge i+1
a_p : Propagation length
I : Nucleation rate

[1] Li et al., "Rate Expressions for Kink Attachment and Detachment During Crystal Growth," *Cryst. Growth Des*. 16, 3313 (2016)

Layered Growth Mechanism

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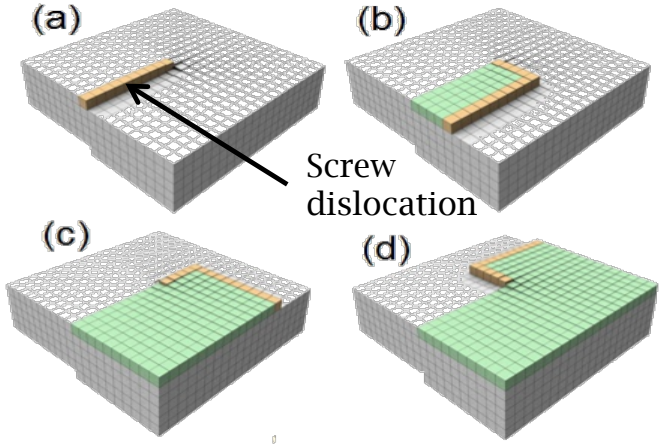

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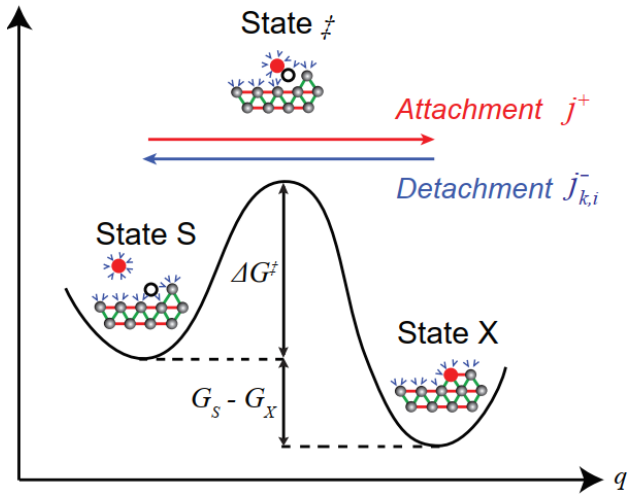
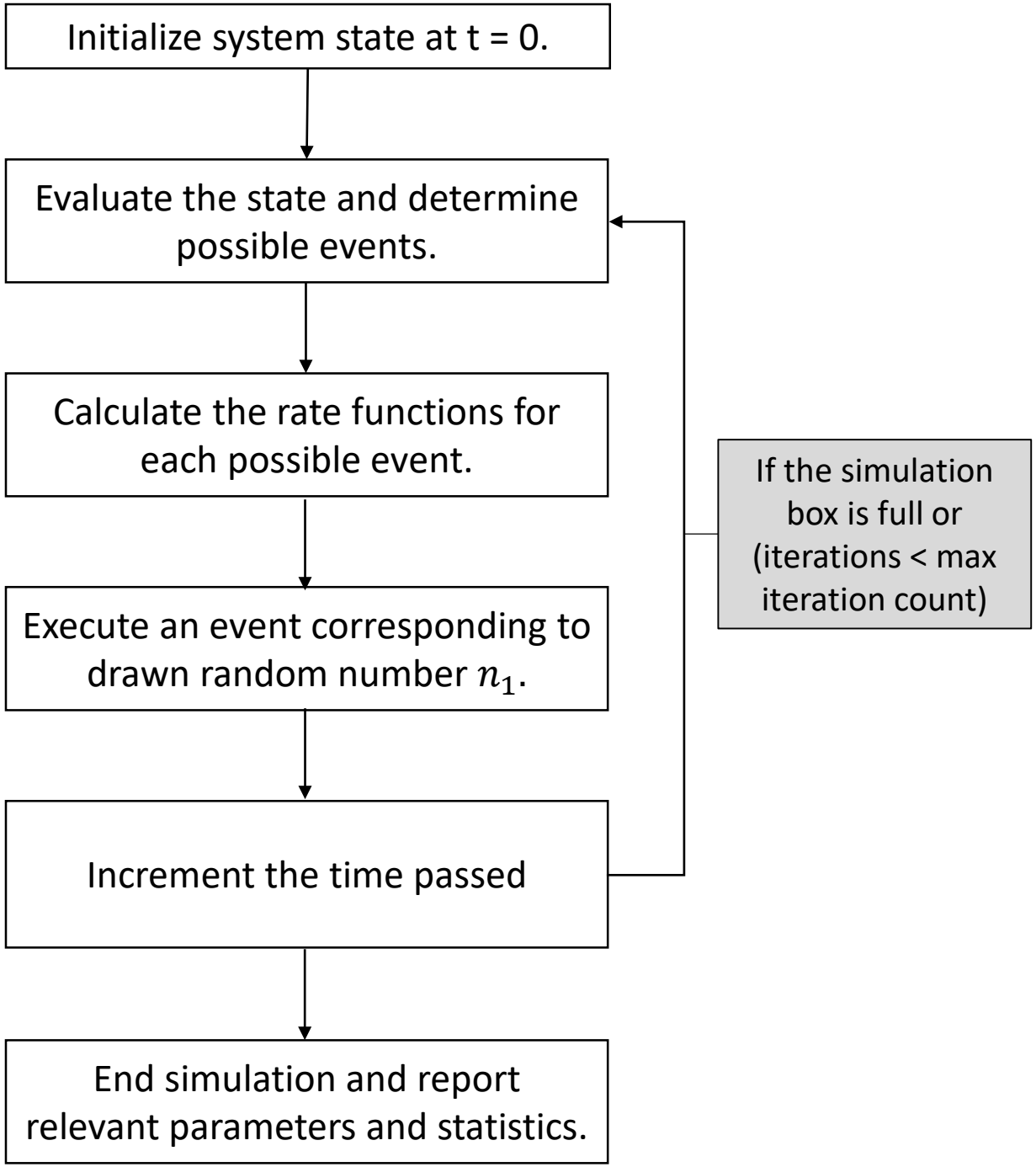
Kinetic Monte Carlo Algorithm



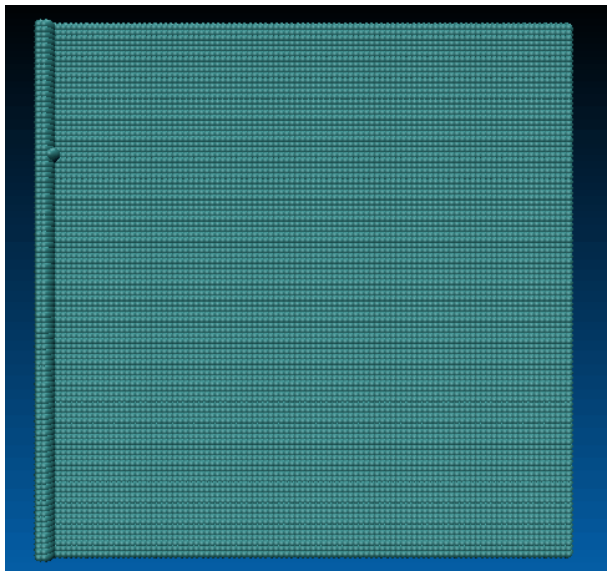
$$j^+ = k^+ x = k^+ x_{sat} S$$

$$j^-_{k,i} = k^- \cong k^+ \exp\left(\frac{-\Delta W_{k,i}}{k_B T}\right)$$

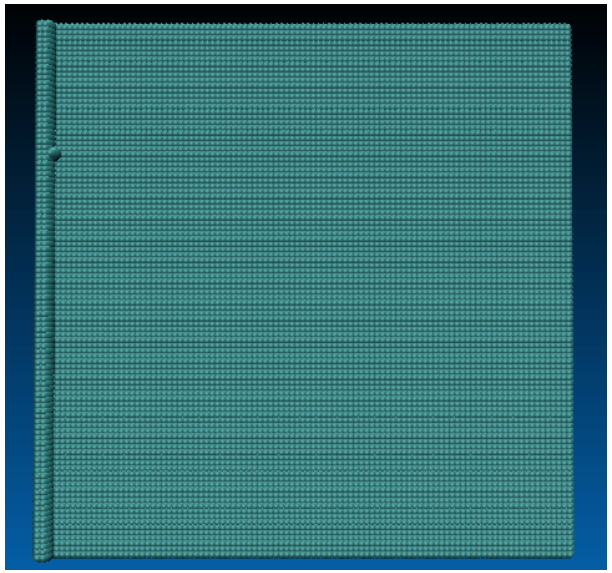


kMC Simulations in Pure Solutions

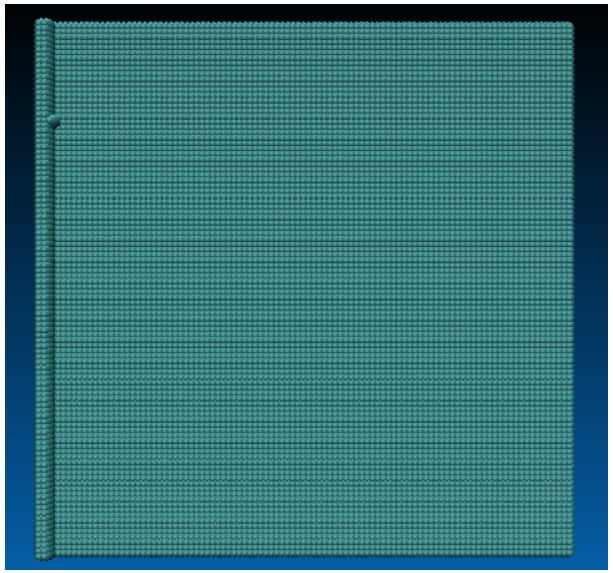
- Kinetic Monte Carlo growth simulations of a Kossel crystal, starting with a flat step edge in supersaturated solution (S = 1.2)



$\phi = 1.5\ k_B T$



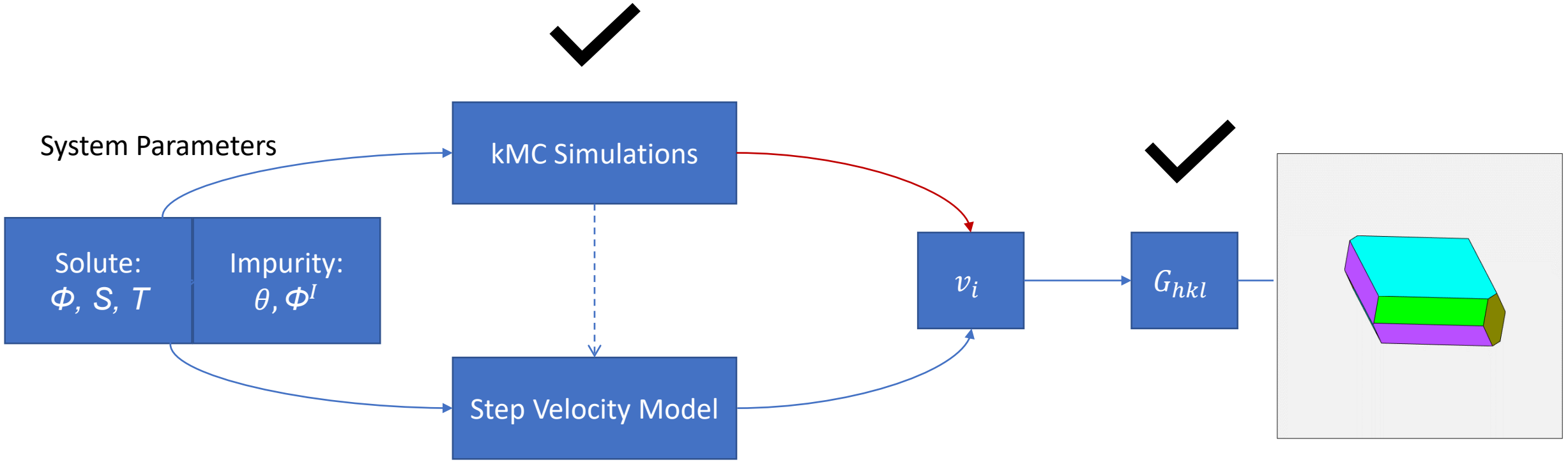
$\phi = 3\ k_B T$



$\phi = 4.5\ k_B T$

- Higher energy penalty corresponds to slower edge but smoother front

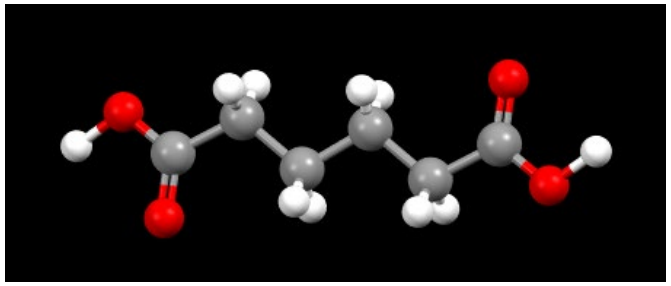
Crystal Morphology Prediction Framework



- Validated kMC simulations; corroborated with existing step velocity models
- Existing ADDICT framework allows rapid morphology predictions and visualization given $\{v_i\}$

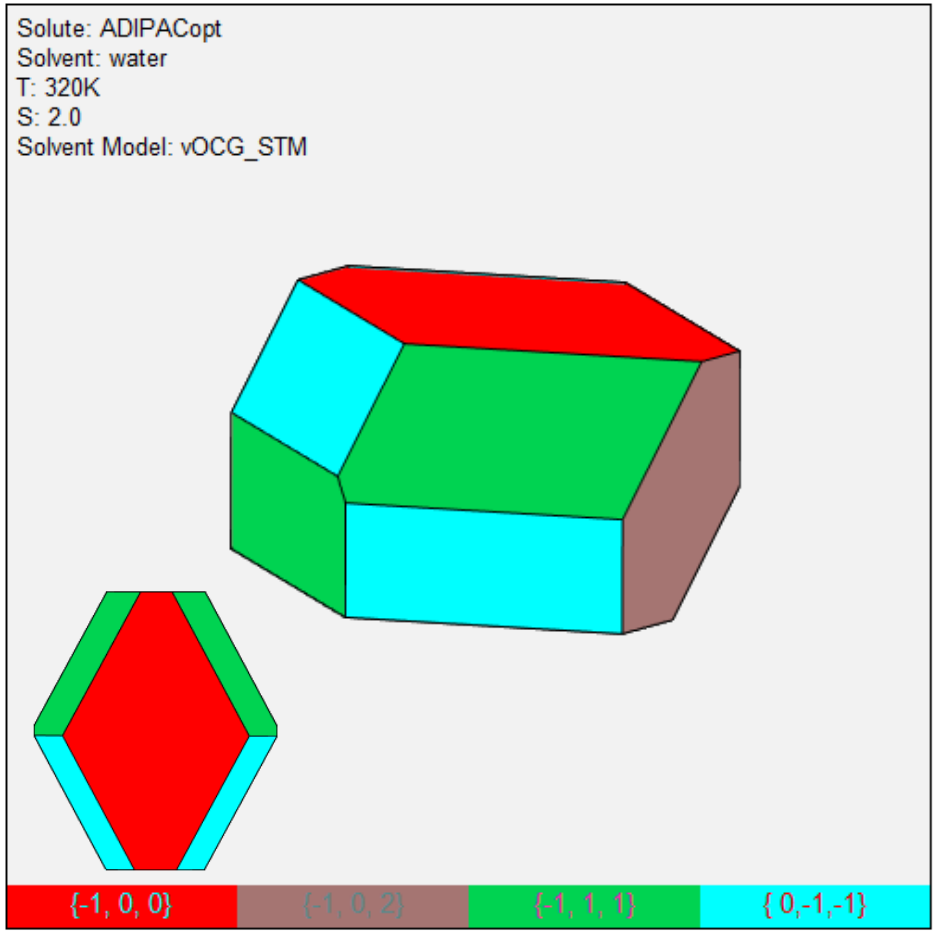
Adipic acid grown from water

[CSD Refcode: ADIPAC]

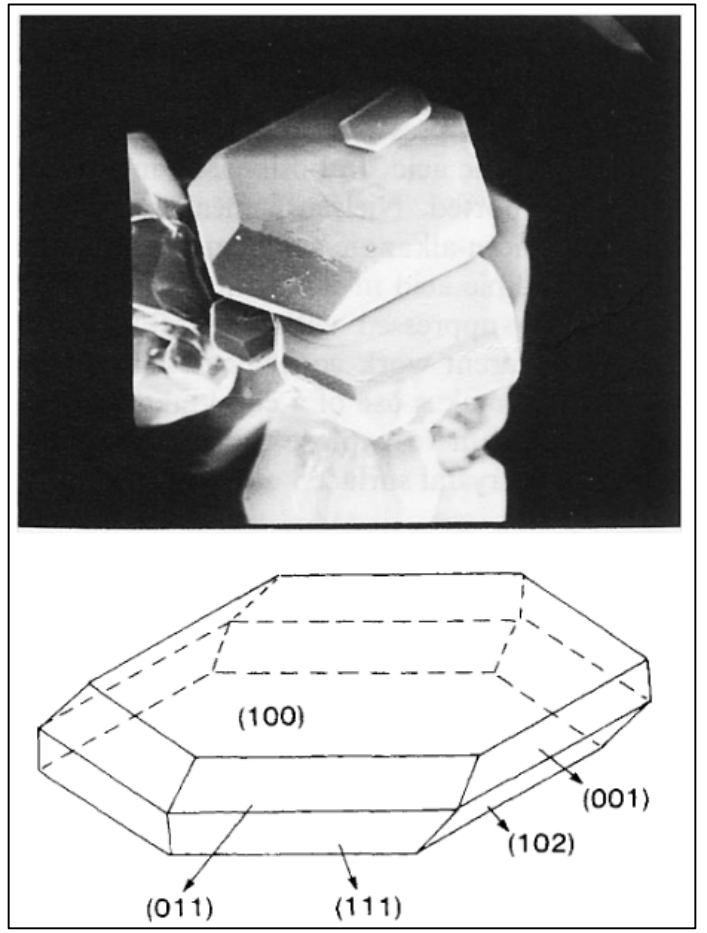


- Precursor to Nylon 6,6; 2500 kta produced
- Lifson forcefield used to generate PBCs and determine $\{\phi\}$ for 11 unique edges

kMC-Based
Morphology Prediction



Experimental Morphology @
T = 307K , S = 1.26



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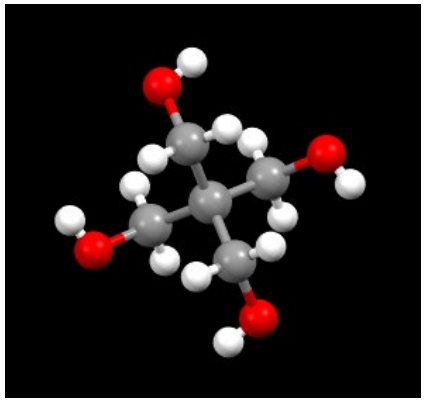
Davey, R. J. *et al. J Chem Soc Faraday Trans* **88**, 3461–3466 (1992).

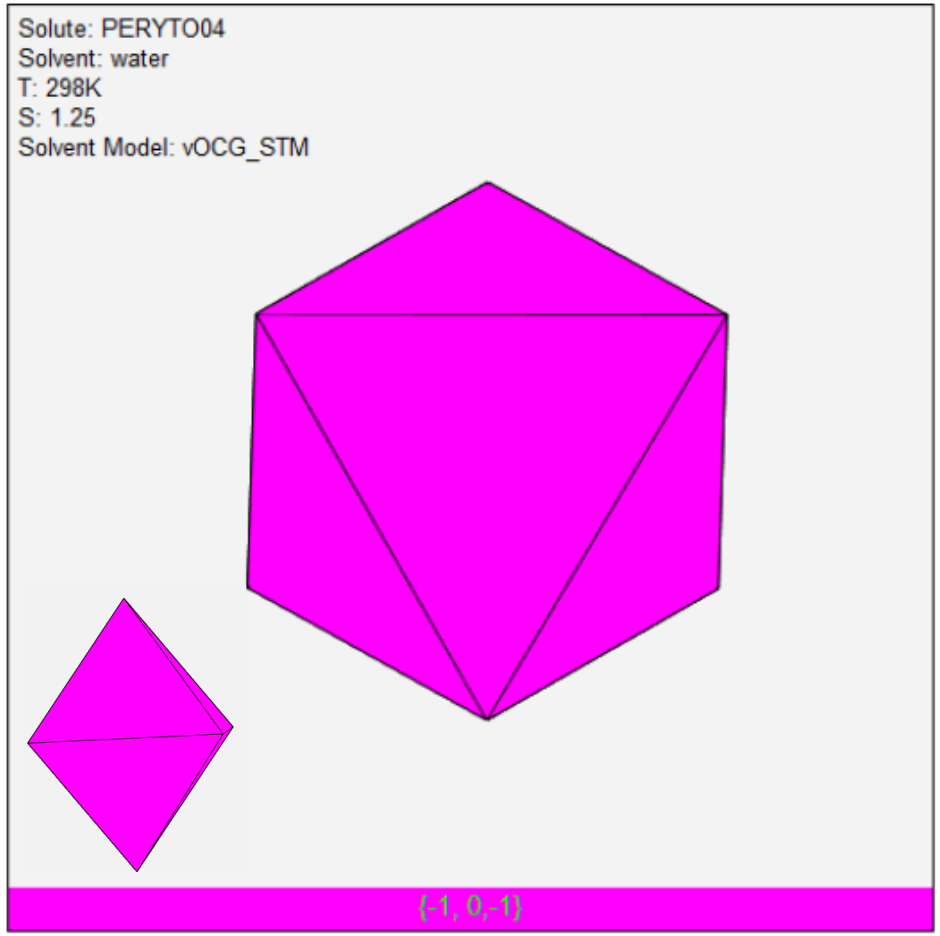
Pentaerythritol grown from water

[CSD Refcode: PERYTO04]

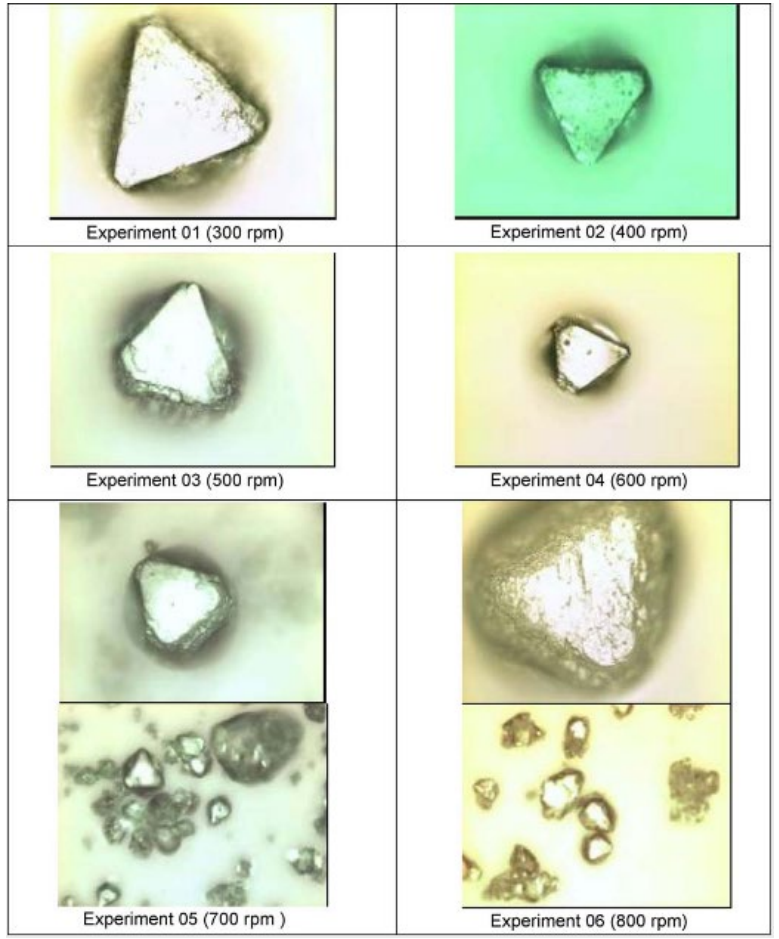


- Fire retardant and precursor to plastics and energetic materials
- CLP forcefield used to determine $\{\phi\}$ for 4 unique edges

kMC-Based
Morphology Prediction



Experimental Morphology



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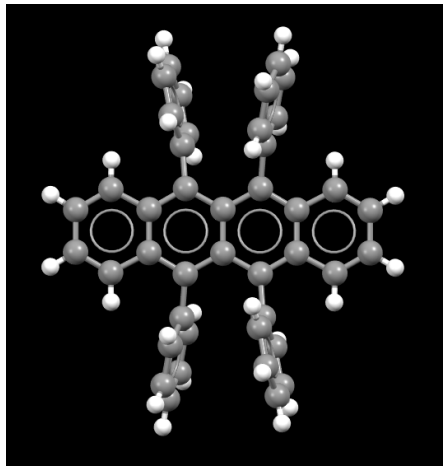
Bernardo, A. & Giulietti, M. *Chem Eng Res Des* **88**, 1356–1364 (2010).

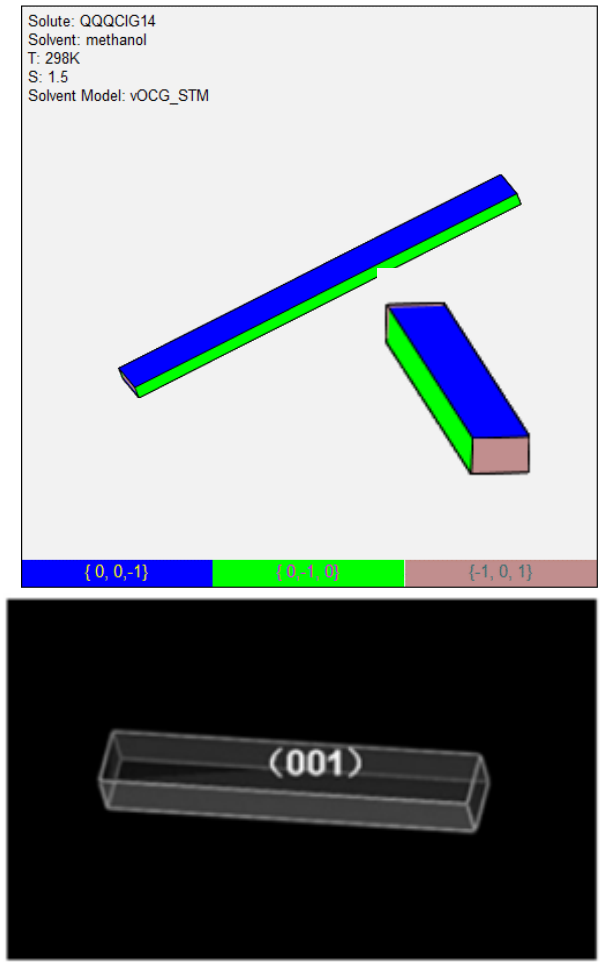
Rubrene polymorphs grown from methanol

[CSD Refcode: QQQCIG13/4]

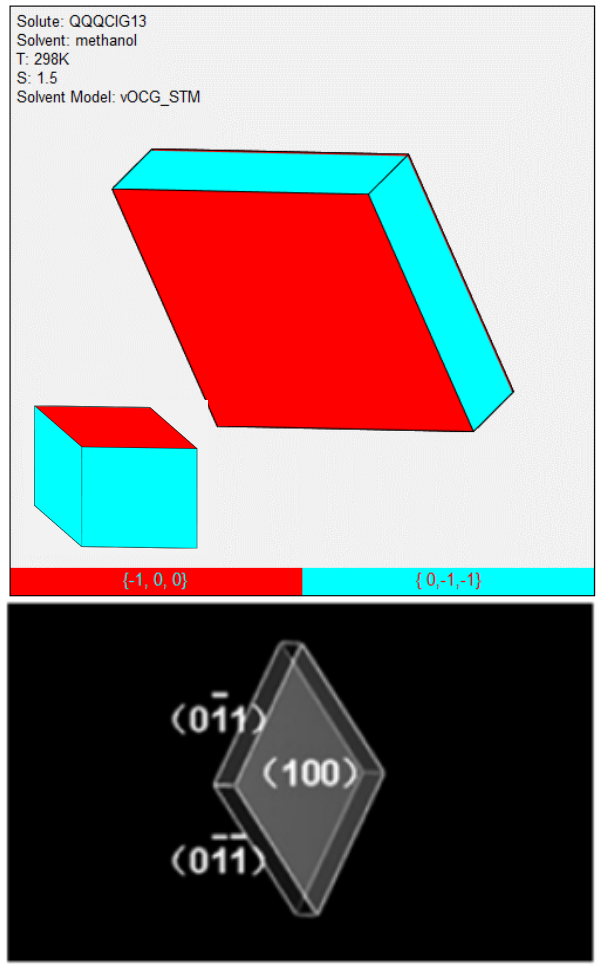


- Organic semiconductor used for OLEDs
- CLP forcefield used to determine $\{\phi\}$ for 12/24 unique edges

kMC-Based Morphology Predictions



(b) Experimental ribbon morphology of triclinic crystals



(b) Experimental rhombus morphology of monoclinic crystals

Huang, L. *et al. J Mater Chem* **20**, 159–166 (2010).

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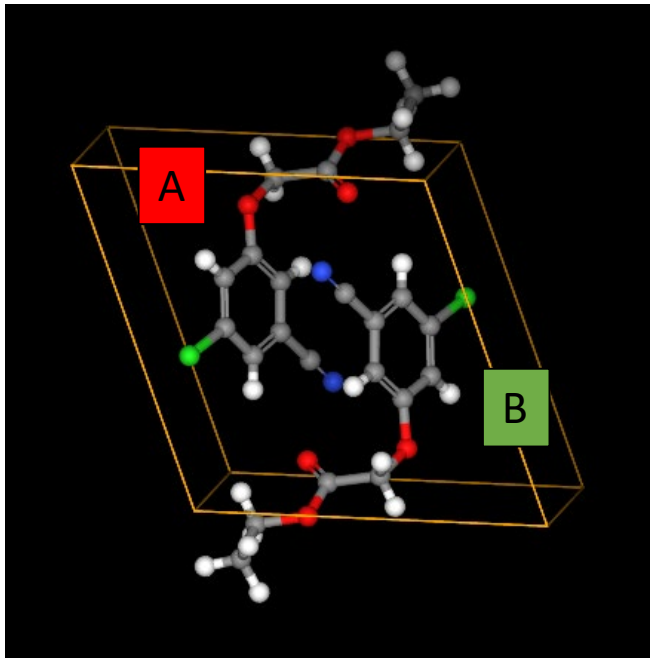
Noncentrosymmetry Challenges

1. Complex PBCs – bonds comprising a single bond chain are not necessarily of the same strength.
   - Same molecule can act as *different growth units!*

2. Kink Rates – there exist >1 type of kink site so there is no longer an isotropic driving force to incorporate into the solid state structure

3. Stable/Unstable Edges – complex bonding structures introduce the idea that certain edges may not be stable

[CSD Refcode: OWIVEY]



Doravirine (Z = 2)

Larpent, P. *et al. Cryst Growth Des* **21**, 4207–4219 (2021).

Next Steps

- Incorporate kMC simulations into ADDICT for step velocity prediction and integration into morphology prediction
- Automate CLP force-field in ADDICT
- Complete kMC simulations for AB crystals with and without impurities in solution
- Extend COSMO-SAC to solvent mixtures (antisolvent crystallization)
  - Benzoic acid dimer GUs grown from ethanol + water ; Tetra (4 aminophenyl) porphyrin (TAPP) from xylene + ethanol
- Non-equilibrium kink density model is finished (Neha Padwal) - write “special code” for AB systems ADDICT – test and compare with experiment and kMC

Red means complete. Black means we are working on it now.