IFPRI
International Fine Particle Research Institute

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

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Project Objective:

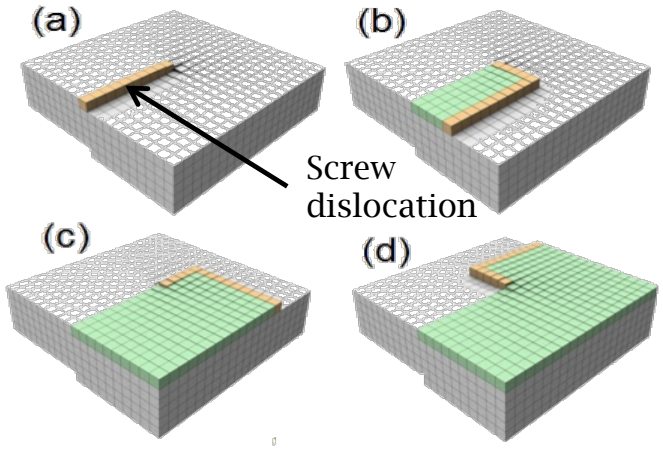
The goal of this research is to develop a practical engineering tool for predicting the relative growth rates (growth kinetics) and morphology of solution-grown faceted crystals, including the effects of solvent, and impurities/additives. The methodology is being tested on a variety of systems, including: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



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]

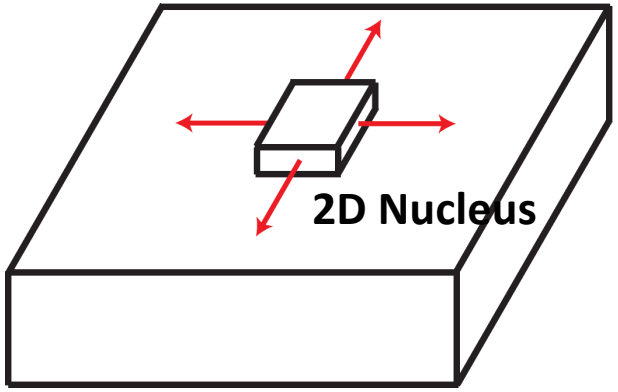
- Density of kink sites along the edge (ρ)
- Net rate of attachment into kink sites (u)

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

Absolute growth rate

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

2D Nucleation and Growth



2D Nuclei are the sources of steps

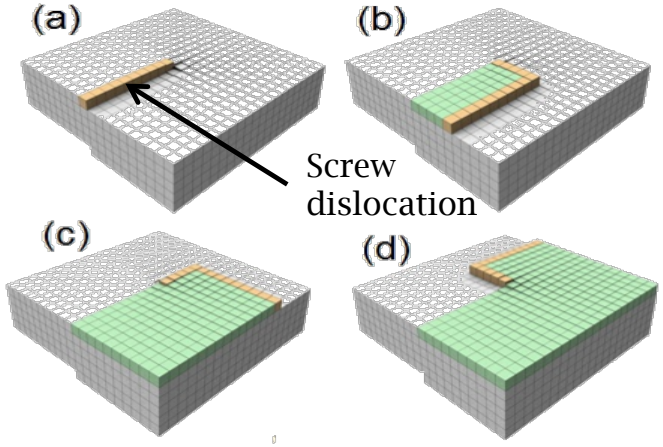
$$\tau_{2D} = \left(\mathrm{v}^2 I\right)^{-1/3}$$

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

Spiral Growth



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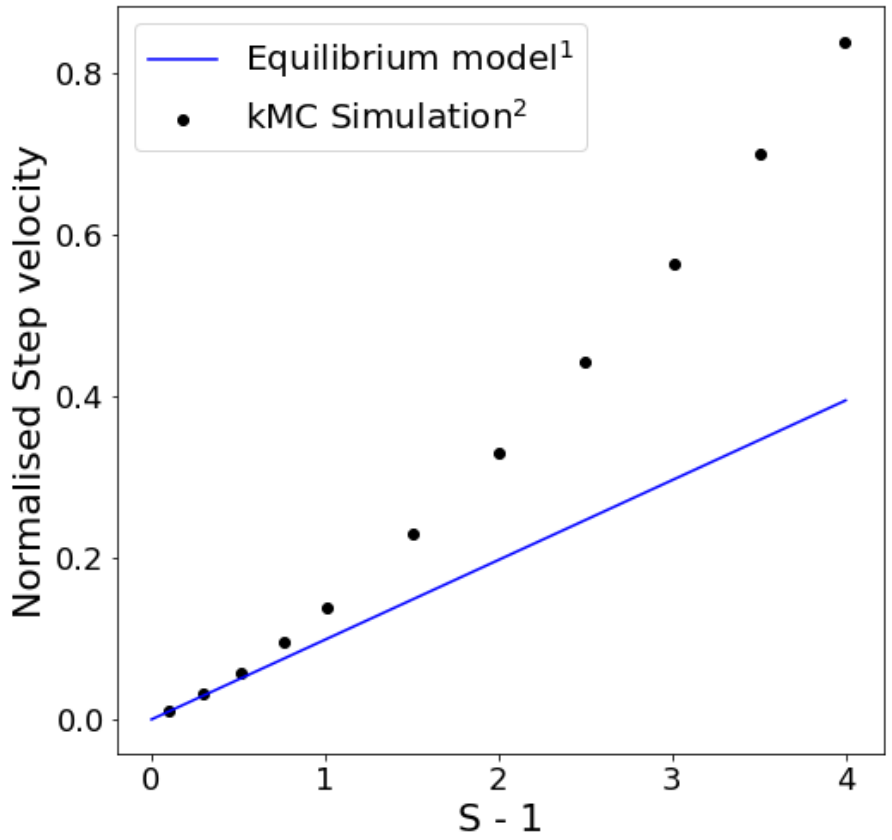
Non-equilibrium Kink Density Modeling

Step Velocity $\propto$ Kink Density $*$ Kink Rate



Master Equation Formulation

$$\left.\begin{array}{l}\text{Rate of } \textbf{creation} \pm \text{Rate of } \textbf{transformation} - \text{Rate of } \textbf{annihilation} \\ {}^{*} = 0\end{array}\right\}$$

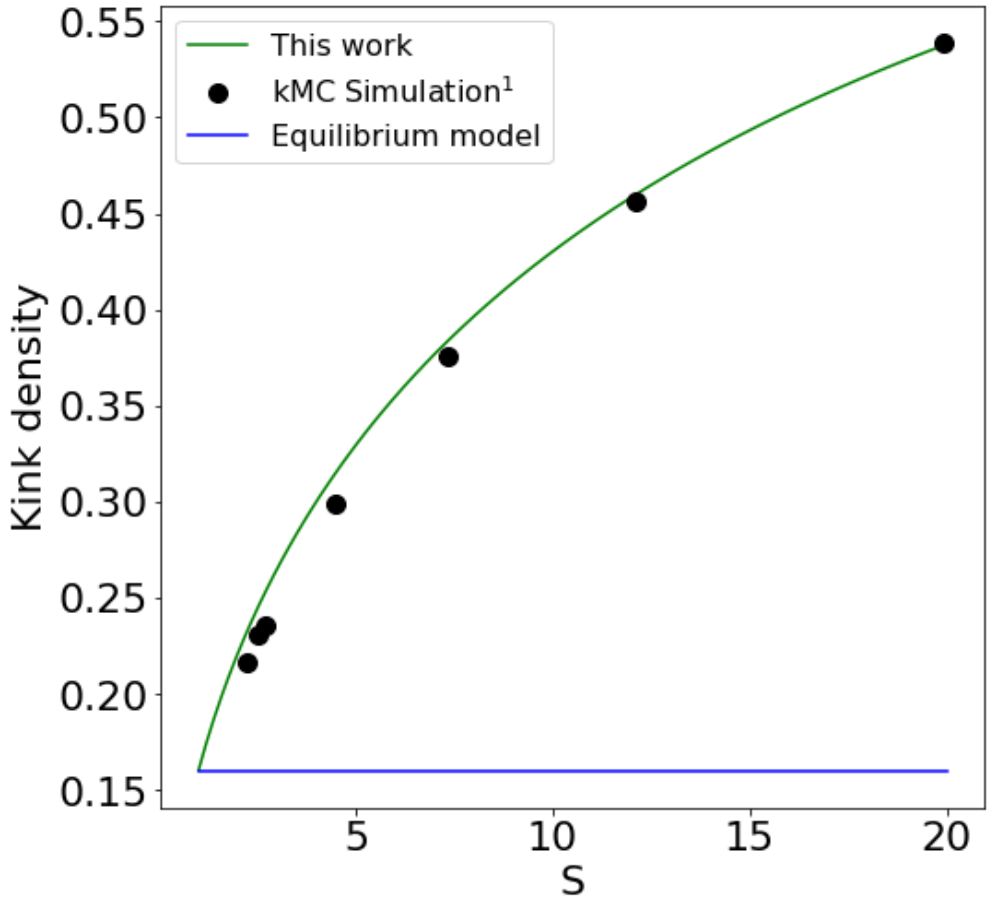
$$\sum_{n} F_n \pm T_n - A_n = 0$$

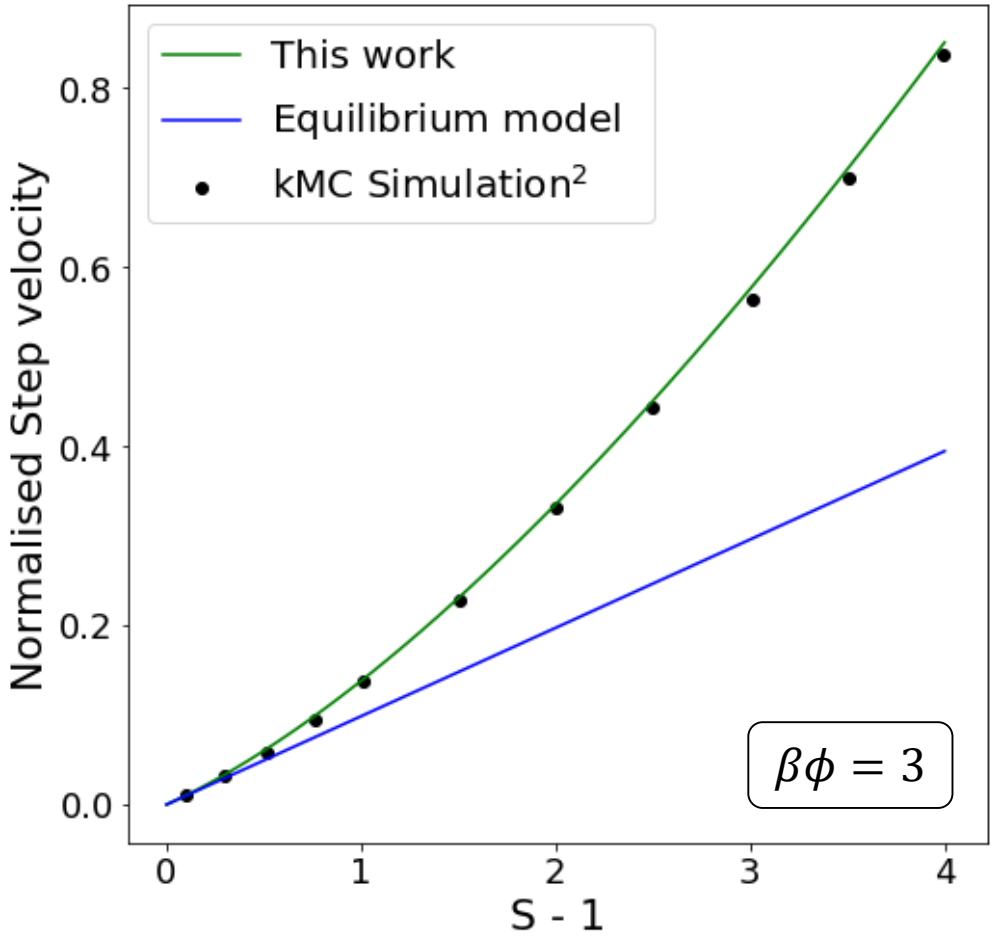
* Most likely events

1. J. Frenkel., 1945. Journal of Physics USSR, 9:392.
2. Joswiak, M.N., Peters, B. and Doherty, M.F., 2018. *Crystal Growth & Design*, *18*(2), pp.723-727.

Kink density and Step velocity plots align with kMC

Comparison of NEQ kink density model with equilibrium kink density



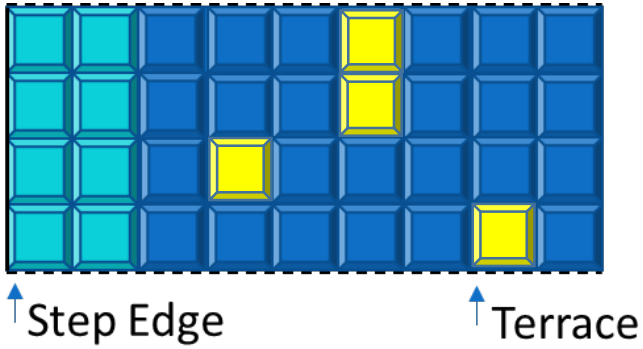


1. Cuppen et al., 2002. *Surface science*, *506*(3), pp.183-195.
2. Joswiak, M.N., Peters, B. and Doherty, M.F., 2018. *Crystal Growth & Design*, *18*(2), pp.723-727.

Introducing Impurities

- Impurity

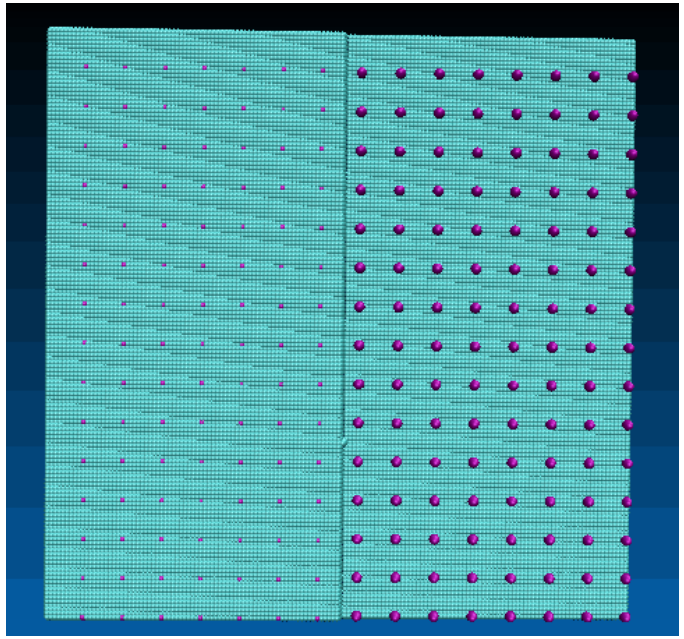
θ_I - fractional coverage of impurities on the terrace



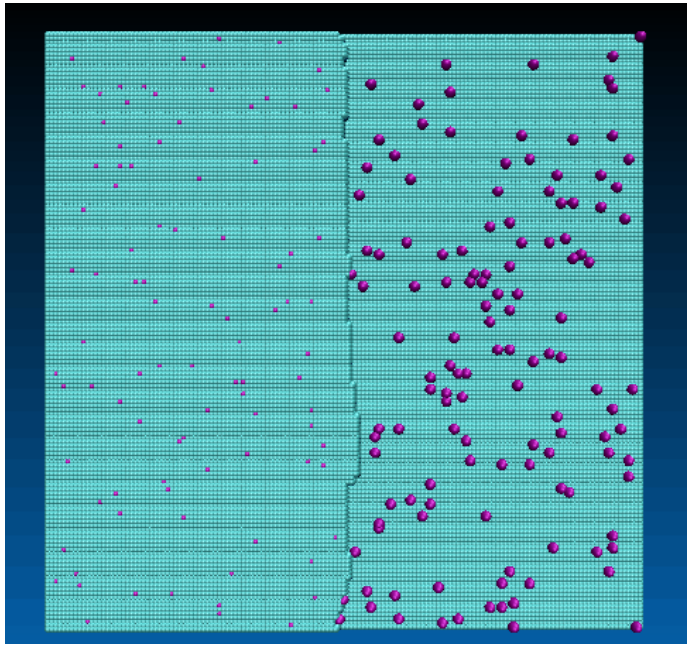
$$\phi_T^I = \infty$$
$$\phi_E^I = 0$$
$$\phi_K^I = 0$$

$S = 1.5$
$\phi = 3\ k_B T$
$\theta_I = 0.01$

Lattice Distribution



Random Distribution



- Terrace-bound impurities serve to pin the step

Impurity Modelling

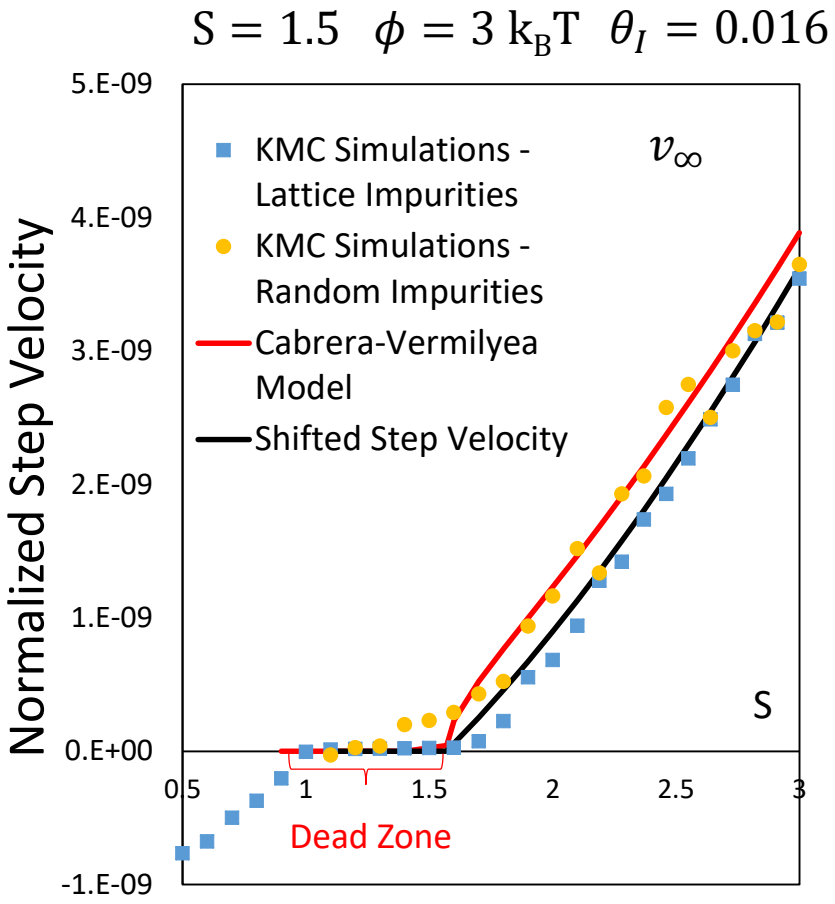
Cabrera-Vermilyea (C-V) Model (1958):

- Assumes that strongly adsorbed impurities pin the step to reduce the effective local supersaturation

$$v = v_\infty \left(1 - \frac{l_C}{\Delta}\right)^{0.5}$$

- Growth halted when the distance between impurities (Δ) is less than the critical length (l_C)

$$v = 0 \qquad 1 \le S \le S^*$$
$$v = a_P \rho u \qquad S > S^*$$
$$u = k^+ x_{sat}(S^* - 1)$$



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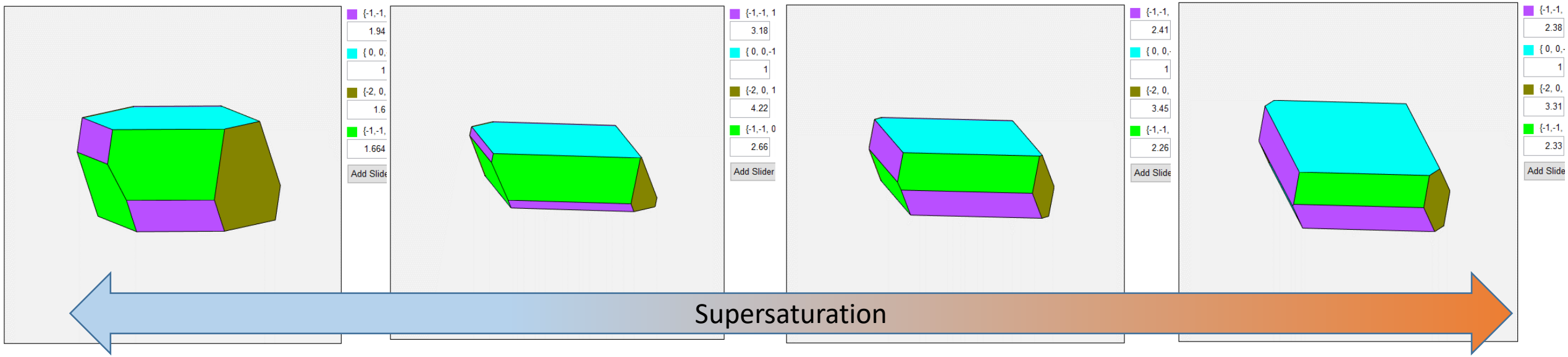
Insights from KMC Driven Morphologies

- Naphthalene system containing impurities at $\theta_I = 0.005$
- For centrosymmetric systems containing impurities, increasing S mitigates impurity effects

S = 1.1 | S = 1.5 | S = 2 | S = 2.5



Low

All faces slowed significantly
Results in Equant Morphology

Intermediate

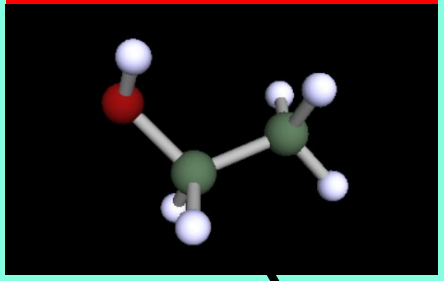
Fast lower energy / higher kink density faces disappear

High

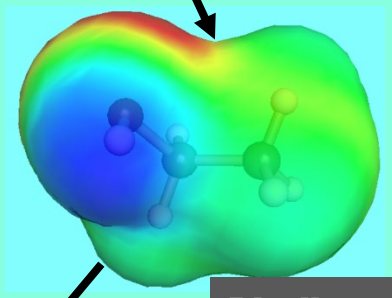
Critical length <<< impurity spacing,
Impurity-free morphology adopted

Flow Chart of COSMO-SAC

New molecular struc.



Quantum Chemical COSMO calculation (DFT……)



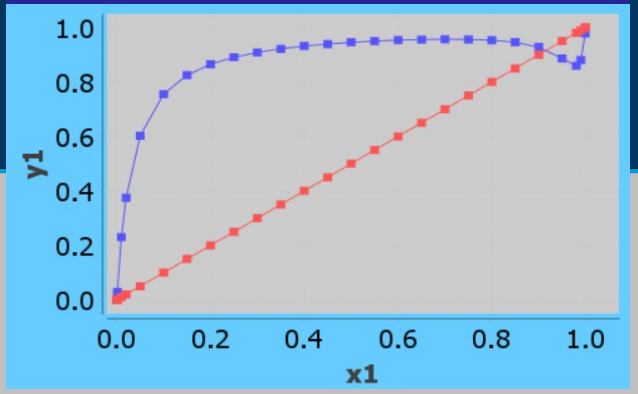
Ideally screened molecule: energy and screening charge distribution on surface

Database of COSMO-files

other compounds

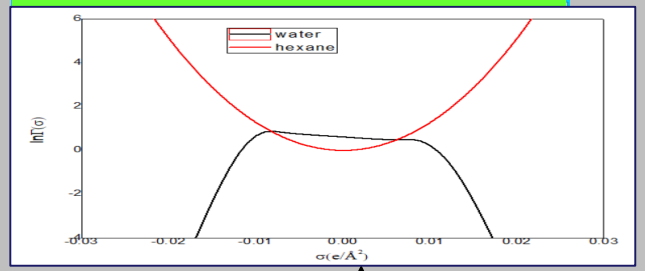
COSMO

Phase Diagrams

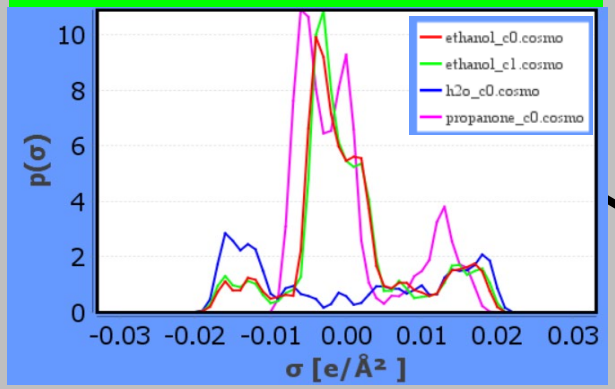


Equilibrium data:
solvation free energy
activity coefficients
vapor pressure
solubility
excess energies
……

segment activity coefficient



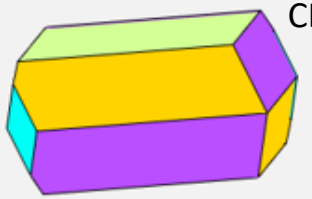
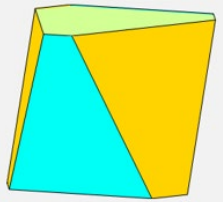
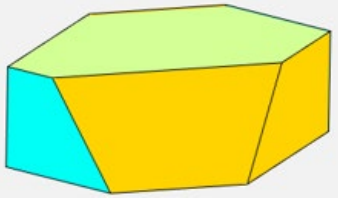
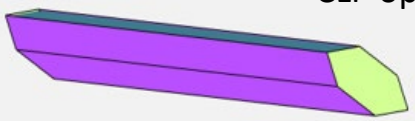
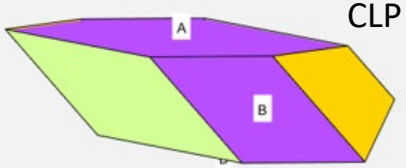
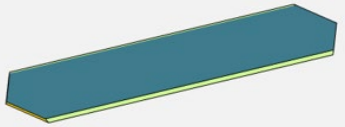
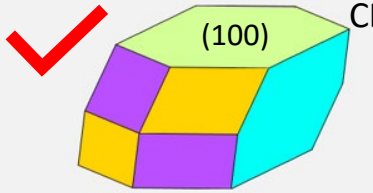
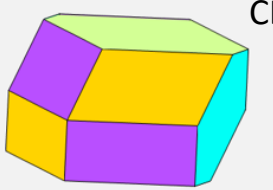
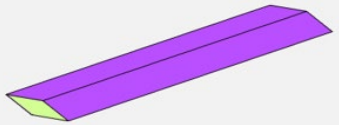
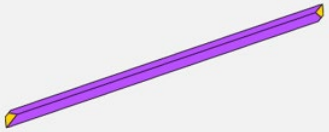
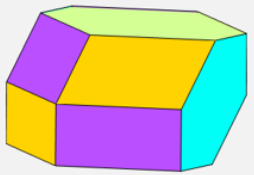
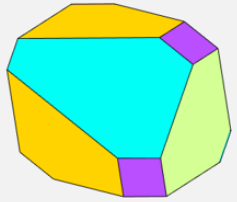
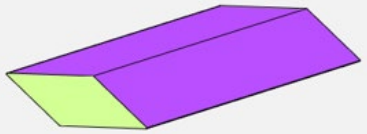
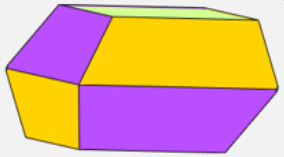
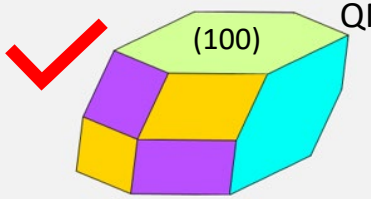
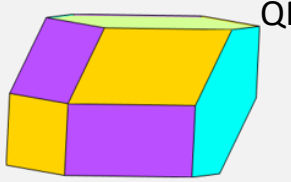
σ-profiles of compounds

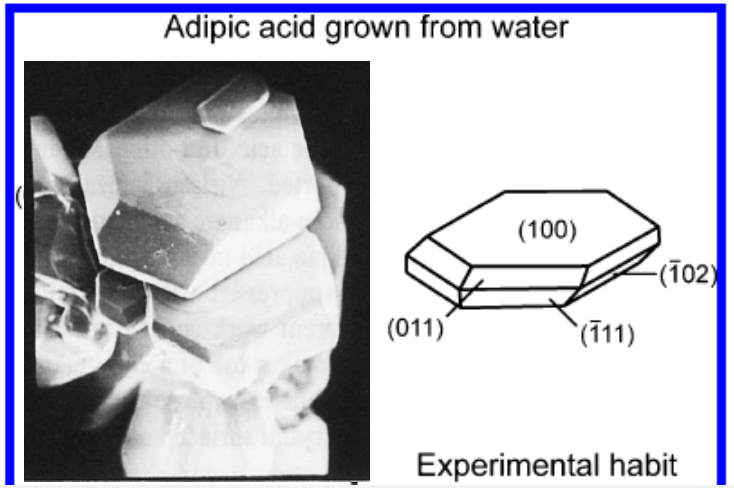


Fast Statistical Thermodynamics

σ-profile of mixture

COSMO-SAC

FF	COSMO	vOCG	COSMO	vOCG
CLP	CLP opt. 	CLP opt. 	CSD 	CSD 
Amber	CLP opt. 	CLP opt. 	CSD 	CSD 
Lifson	CLP opt. 	CLP opt. 	CSD 	CSD 
CLP	QM opt. 	QM opt. 		
Amber	QM opt. 	QM opt. 		
Lifson	QM opt. 	QM opt. 		



Cryst. Growth Des. 2016, 16, 2590−2604

Next Steps

- Extend COSMO-SAC to solvent mixtures (antisolvent crystallization)
  - Benzoic acid dimer GUs grown from ethanol + water ; Tetra (4 aminophenyl) porphyrin (TAPP) from xylene + ethanol
- Automate CLP force-field in ADDICT
- Non-equilibrium kink density model is finished - write “special code” for AB systems ADDICT – test and compare with experiment and kMC
- Generalize non-equilibrium kink density model to any number of growth units
- Complete kMC simulations for AB crystals with and without impurities in solution
- Incorporate kMC simulations into ADDICT for step velocity prediction and integration into morphology prediction
- Build an optimization code to optimize the positions of hydrogen atoms in the unit cell by minimizing the lattice energy of the crystal with the same atom-atom force field that will subsequently be used to make shape predictions
- Automatic assignment of oligomer growth units (monomer, dimer, trimer, etc.) then apply to solvates and organic salts

Red means we are working on this topic now. Black means it is a future project