



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.

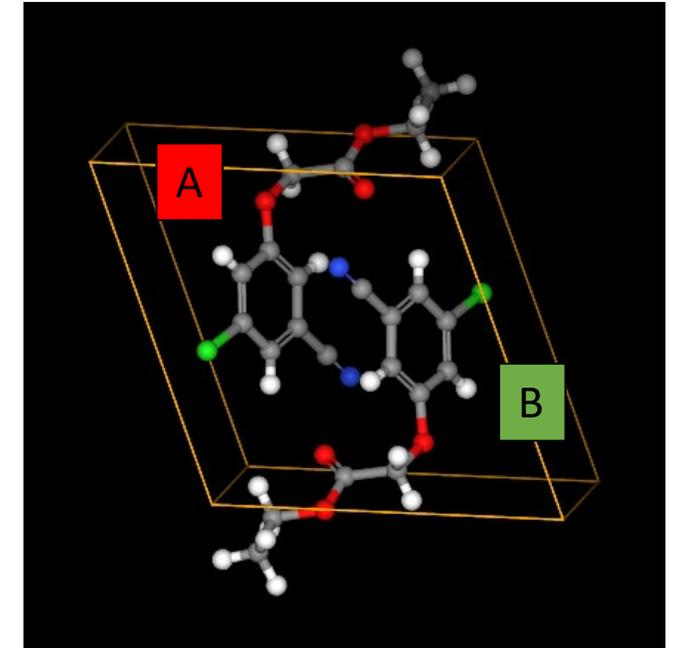
Approach:

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.

Noncentrosymmetry Challenges

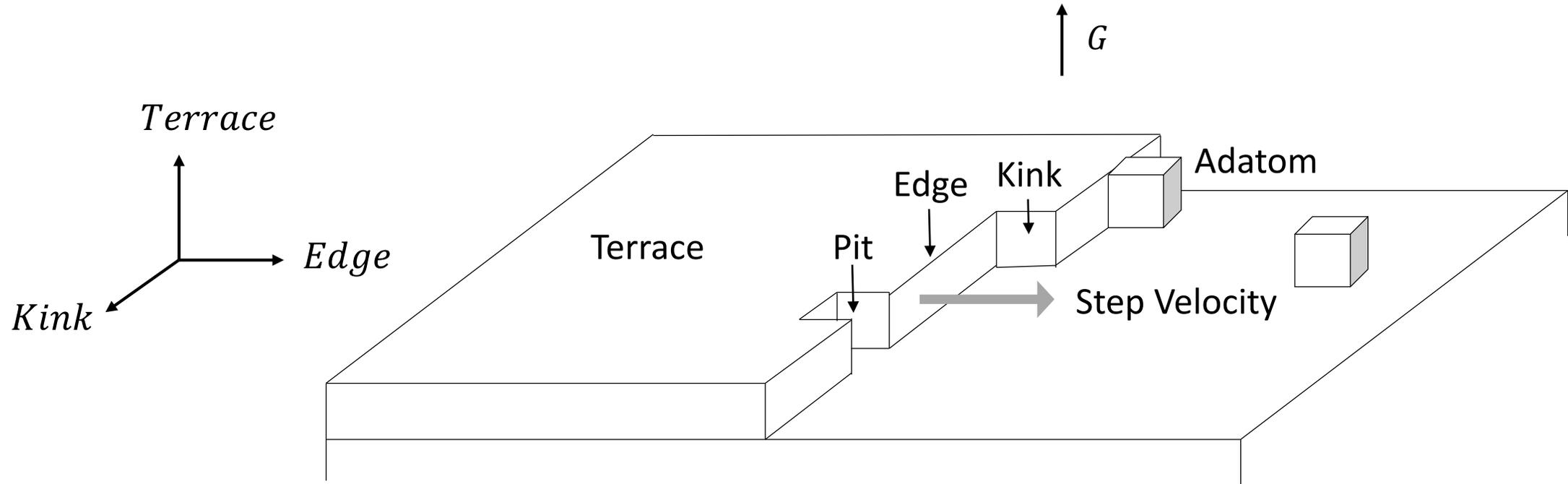
1. Asymmetric molecules generate asymmetric bonding structures, hence complex PBCs – bonds comprising a single bond chain are not necessarily of the same strength.
 - Same molecule can act as *different growth units!*
2. There exist >1 type of kink site so there is no longer an isotropic driving force to incorporate into the solid state structure
3. Sites are no longer statistically independent, hence Boltzmann statistics do NOT apply

[CSD Refcode: OWIVEY]



Doravirine (Z = 2)

Atomistic Modeling : How step velocity depends on growth conditions?



For layered growth mechanisms:

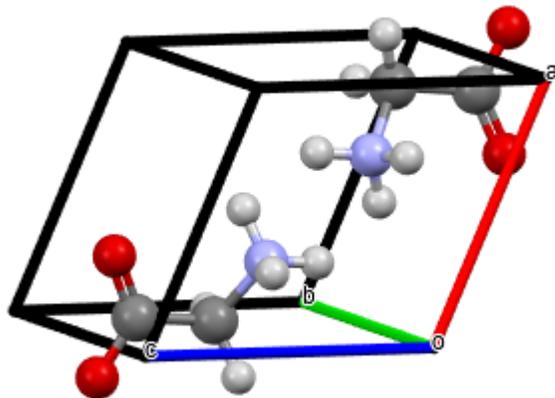
$$\text{Step Velocity } v \propto \text{Kink Density} * \text{Kink Rate}$$

$$\text{Growth Rate } G = \frac{h}{\tau} \longrightarrow \text{Depends on } v$$

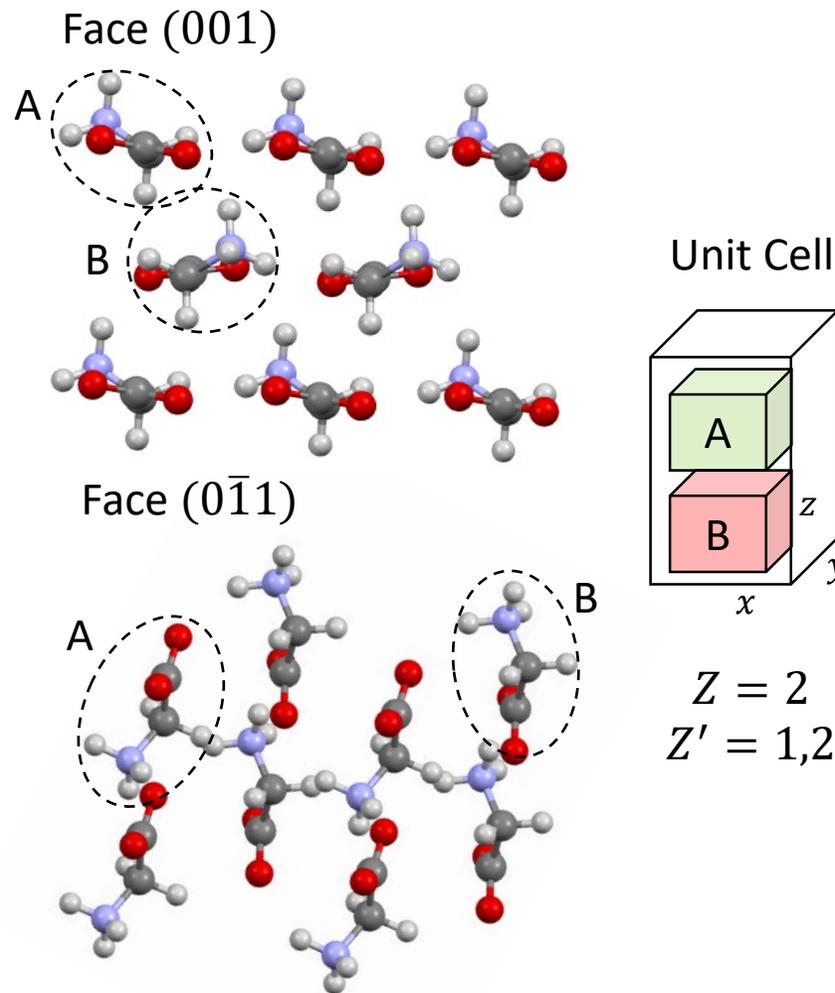
AB Crystals comprise of various face configurations

A & B are the noncentrosymmetric growth units in the unit cell. This results:

1. Multiple face and step configurations.
2. Spatial correlations between different kink types along a step.



GLYCIN (P21) Unit Cell Packing, Mercury
(beta-glycine)



Schematic representation of face configurations

(I)

A	B	A	B	A	B	A	B
A	B	A	B	A	B	A	B
A	B	A	B	A	B	A	B
A	B	A	B	A	B	A	B
A	B	A	B	A	B	A	B

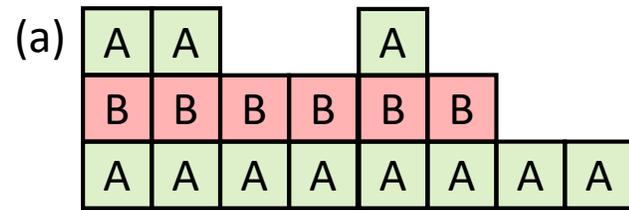
(II)

A	B	A	B	A	B	A	B
B	A	B	A	B	A	B	A
A	B	A	B	A	B	A	B
B	A	B	A	B	A	B	A
A	B	A	B	A	B	A	B

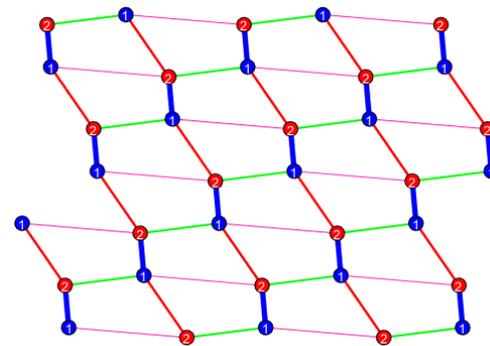
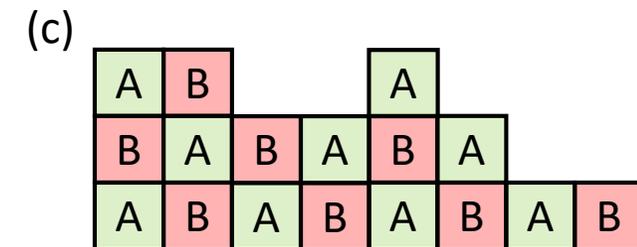
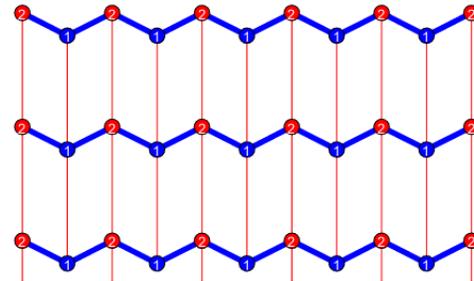
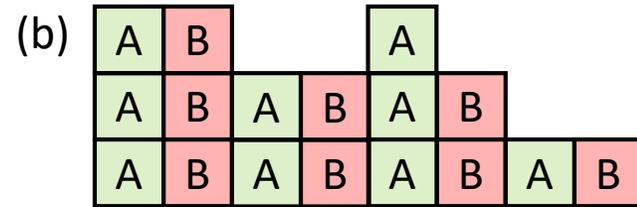
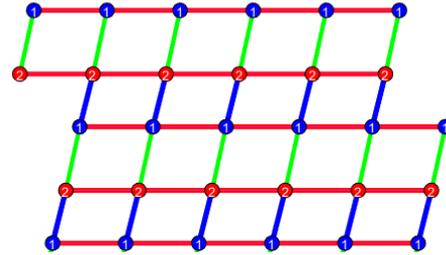
~90,000 AB type organic crystals according to CCDC (Cambridge Crystallographic Data Centre)

Step configurations demonstrate distinct step kinetics

Step Configurations



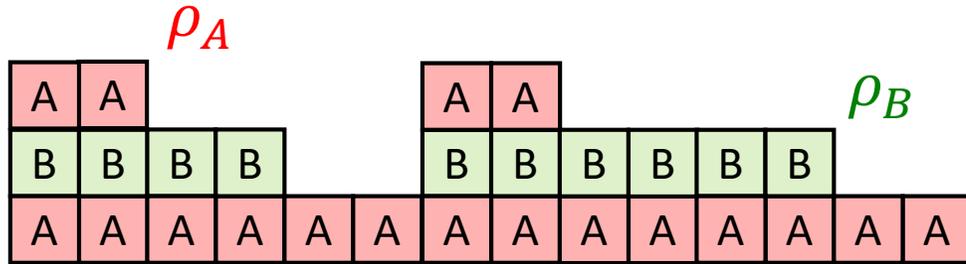
Example PBC networks



“Our results show that the growth of the $A-B$ crystal cannot be described by one universal expression, but that the local structure of the step is of great importance and influences the shape of the step velocity versus supersaturation curve.” - Cuppen et al.

Hence, the steps necessitate independent steady-state analysis.

Why the current equilibrium models for nonKossel crystals are deficient



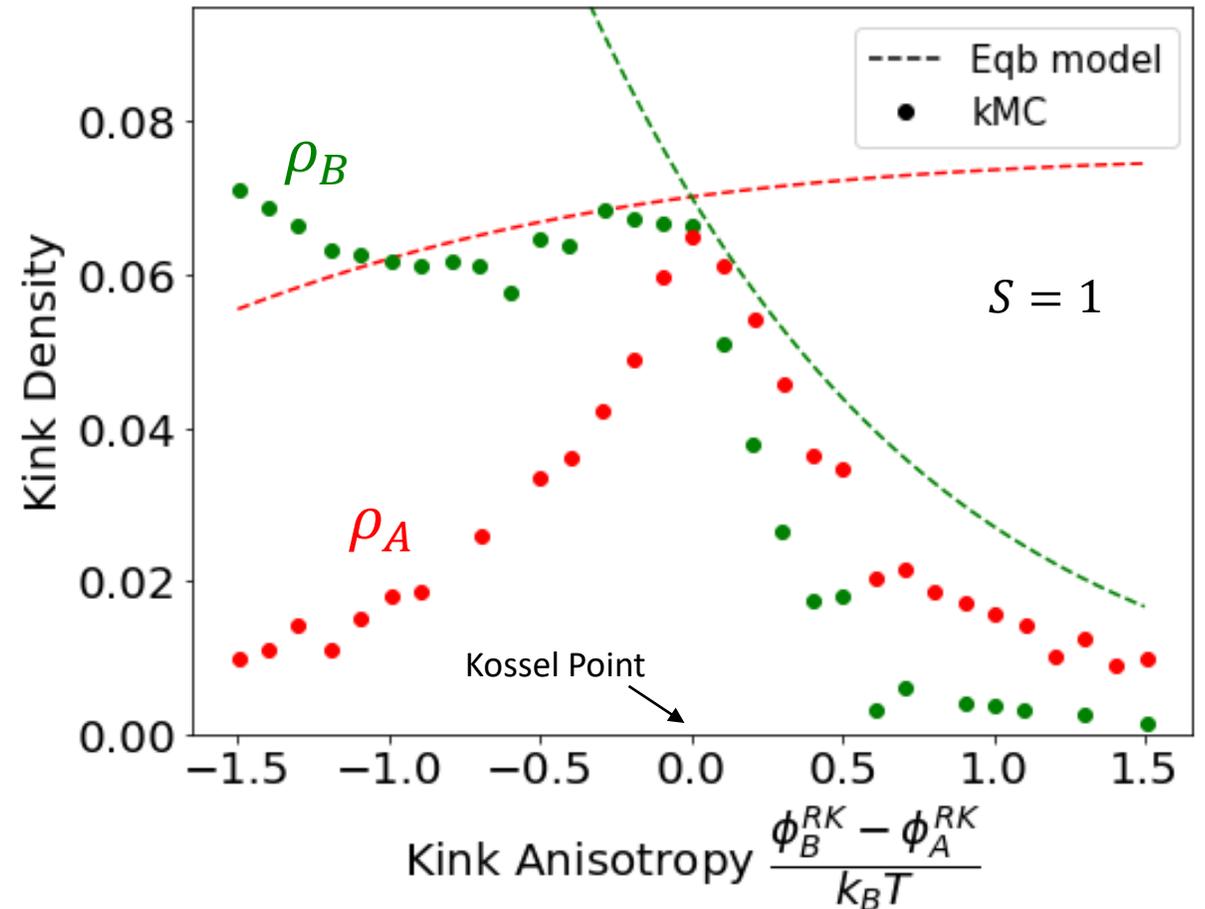
The existing kink density models,
Kink density (ρ_K) \sim equilibrium value

$$= \frac{2e^{-\beta\phi_k}}{Q}$$

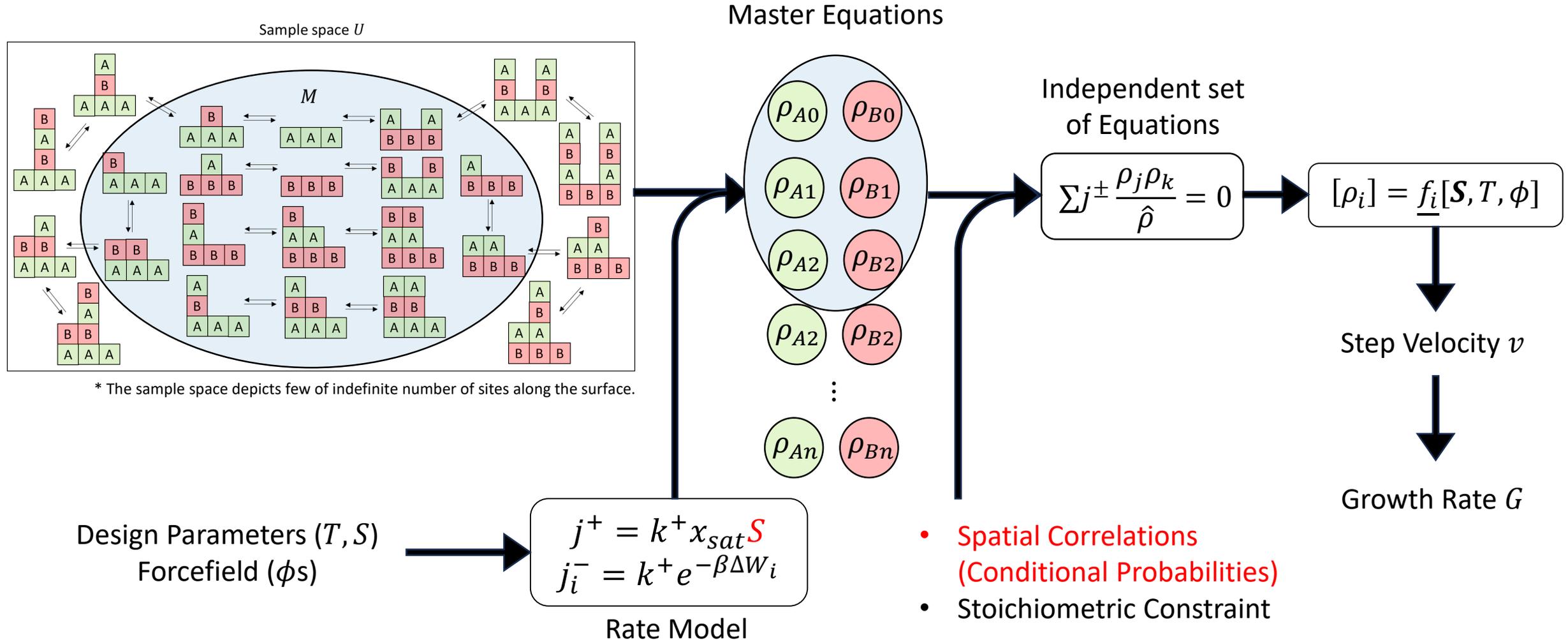
The Boltzmann distribution-based kink density models are deficient even at equilibrium owing to failure to account for spatial correlations.

How ρ_K depends on supersaturation and Interactions?

Anisotropy is a quantitative difference between the interaction spheres of A and B growth units.



Abandon (1) Equilib. Thinking ($S \gg 1$) & (2) Statistical Independence



Our Model overcame limitations in existing equilibrium models

Anisotropy along X-axis, is a quantitative difference between the interaction spheres of A and B growth units.



Dr. Tobias Mazal

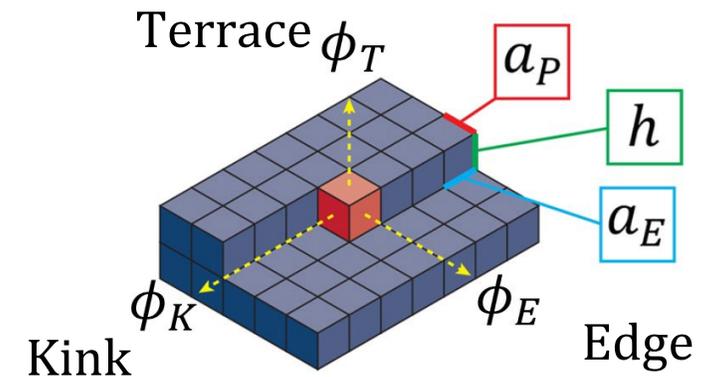
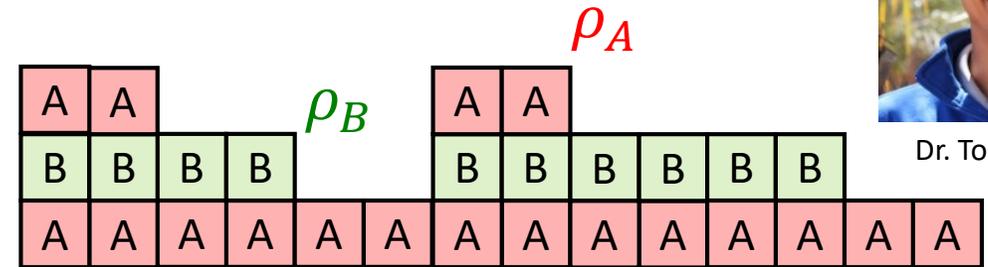
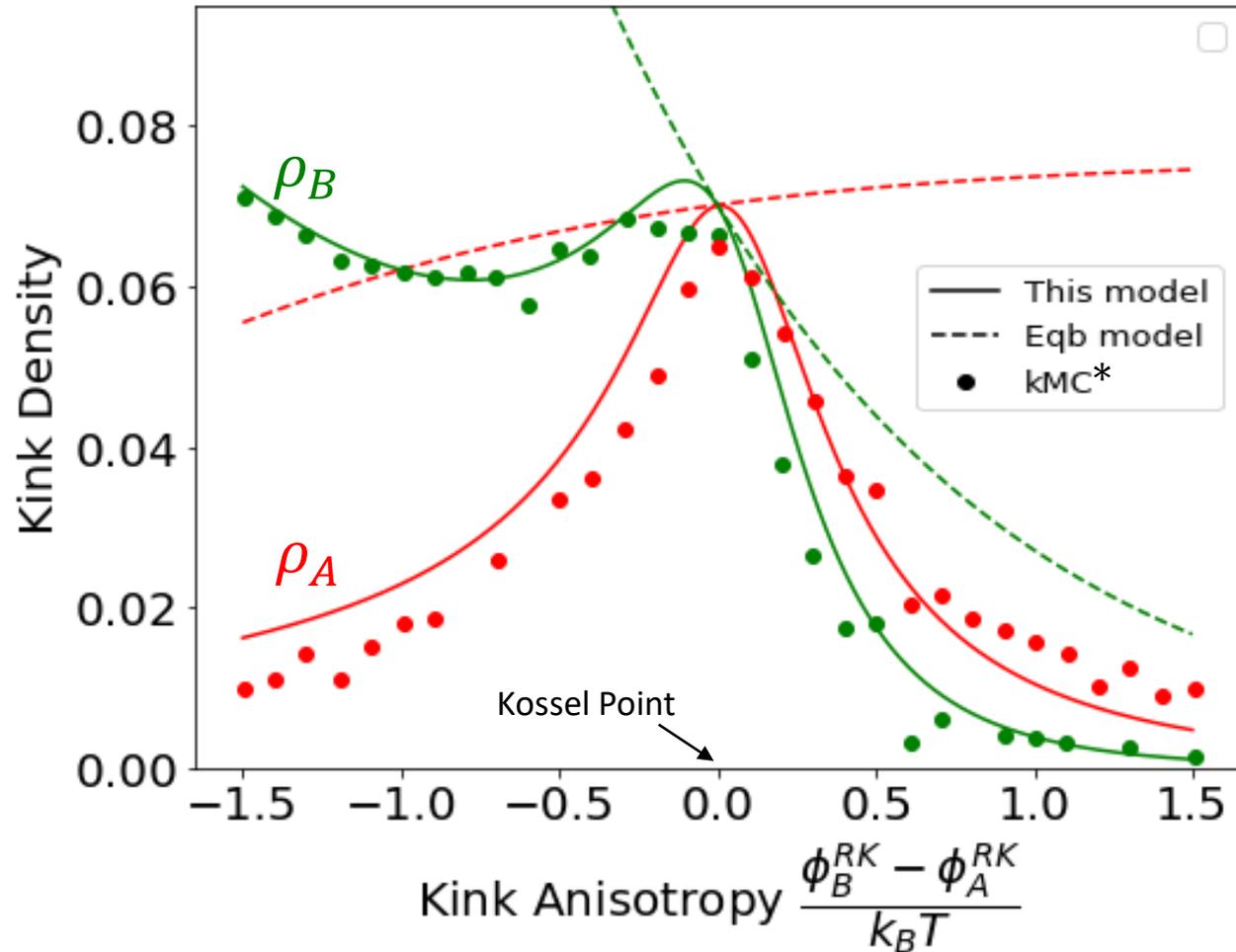
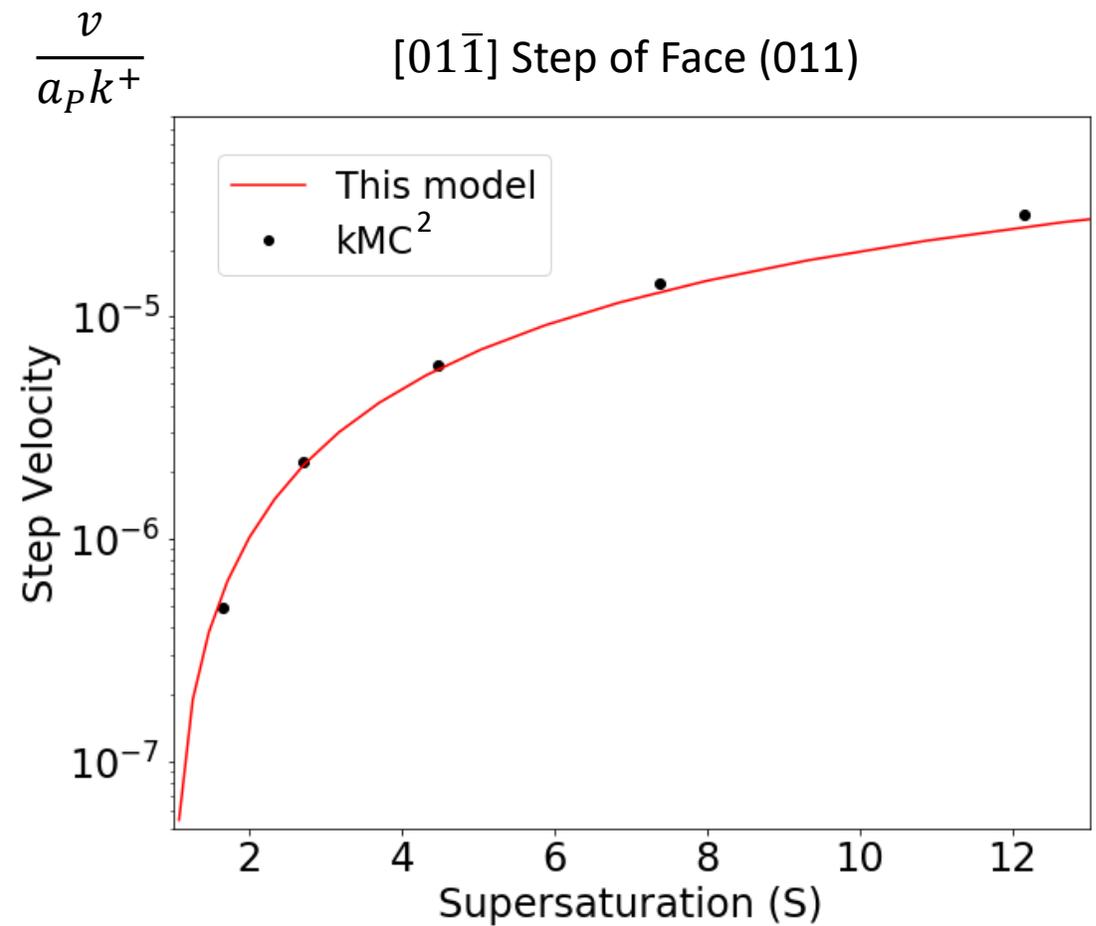
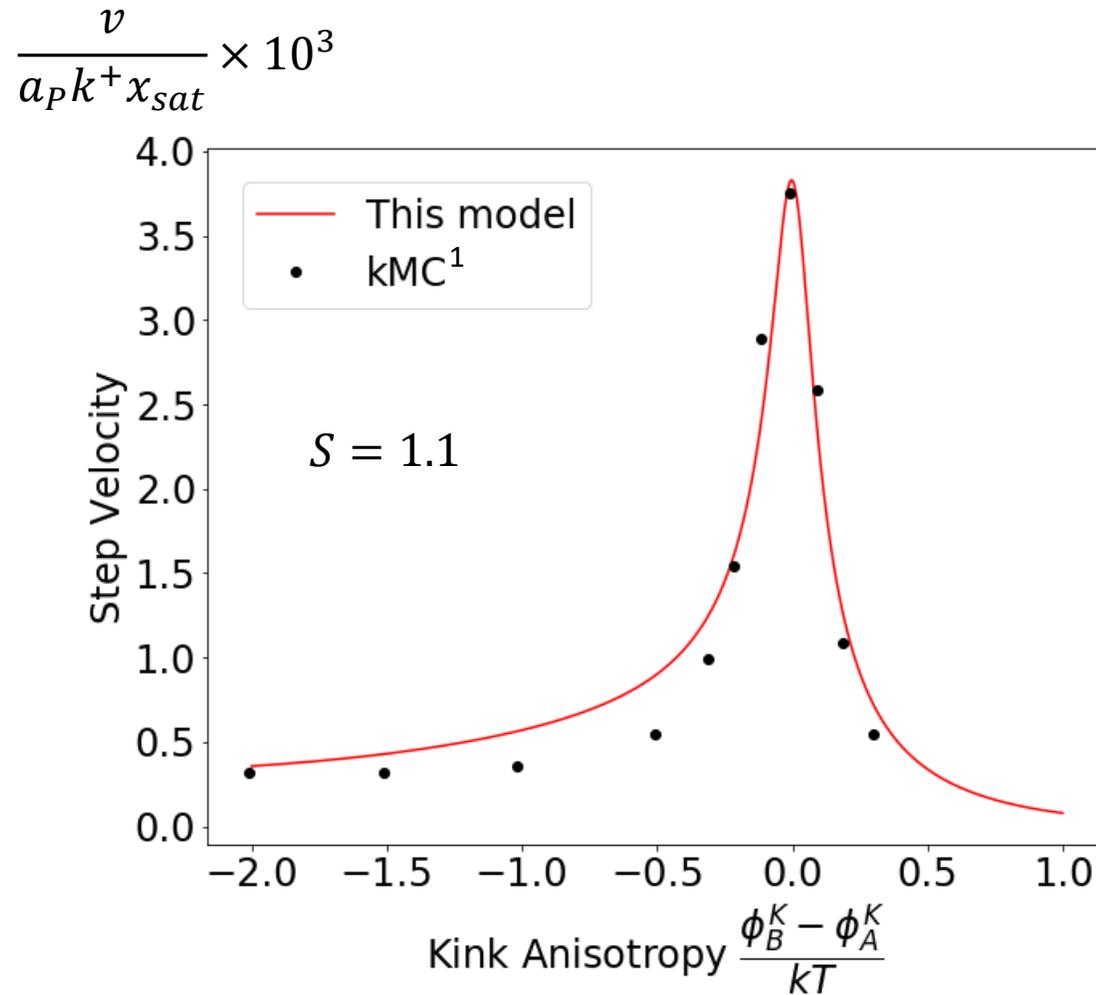


Figure courtesy of Tilbury et al. (2017).

Identified inconsistencies in existing equilibrium AB kink density models since Boltzmann description is based on uncorrelated configurations.

* Simulation data courtesy of Dr. Tobias Mazal.

Step velocity model aligns with kMC for a wide range of supersaturations



1. Tilbury et al., 2017. *Crystal Growth & Design*, 17(4), pp.2066-2080.
 2. Cuppen, et al. 2004. *Surface science*, 571(1-3), pp.41-62.

Morphology Prediction Algorithm from Growth Models

Interpret
Crystallography



Periodic Bond Chains

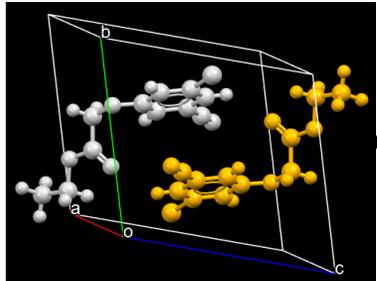
ρ_k, v_k



Growth Kinematics

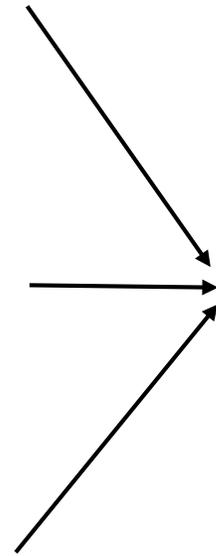
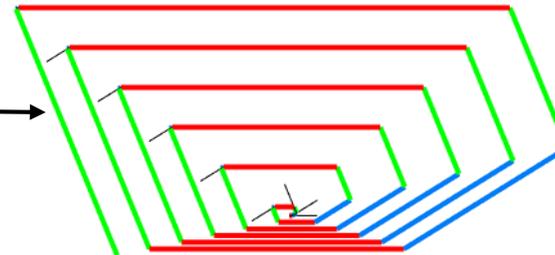
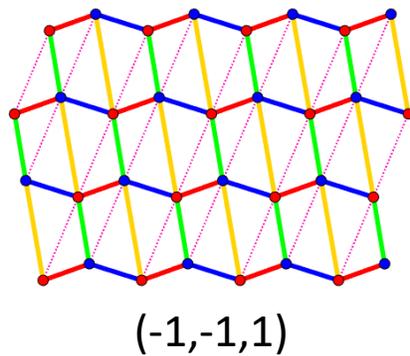
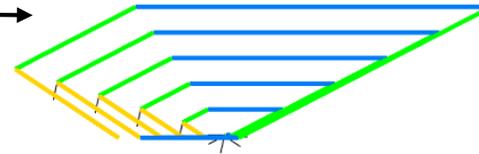
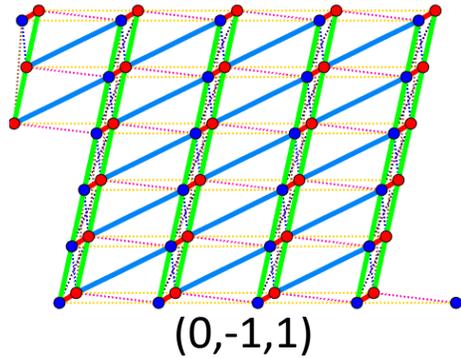
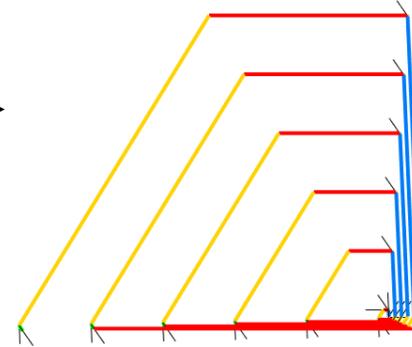
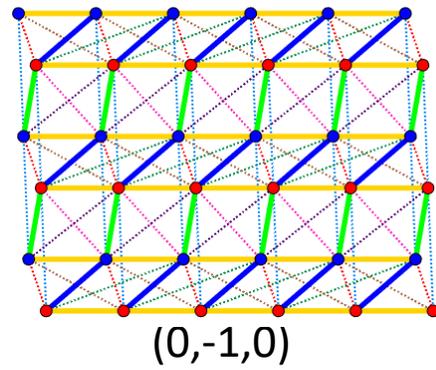


Morphology

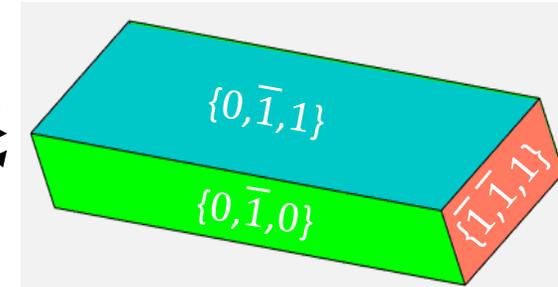


Unit Cell

Cif file
Mol2 files

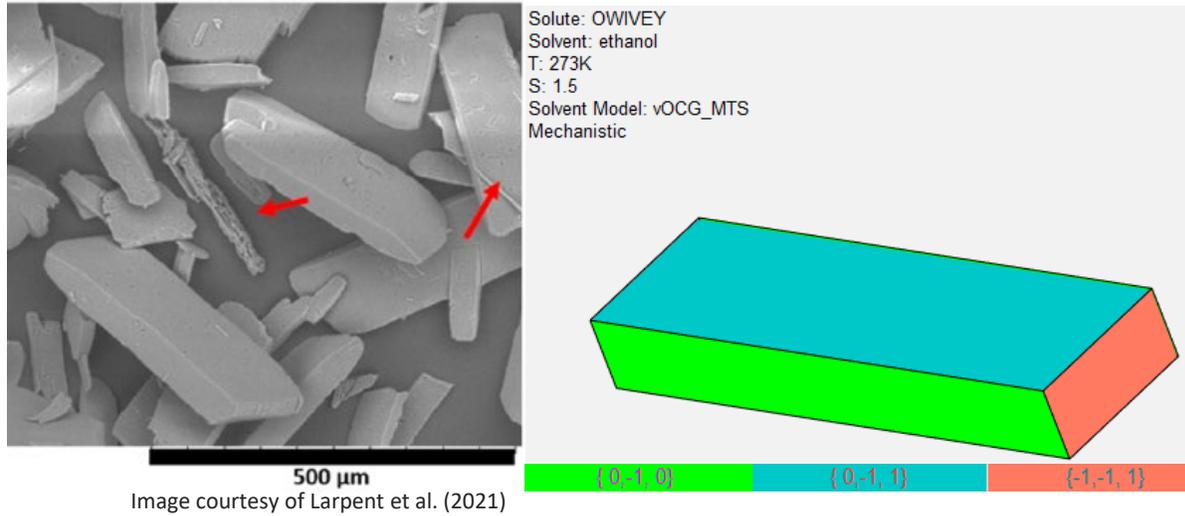


Model Prediction

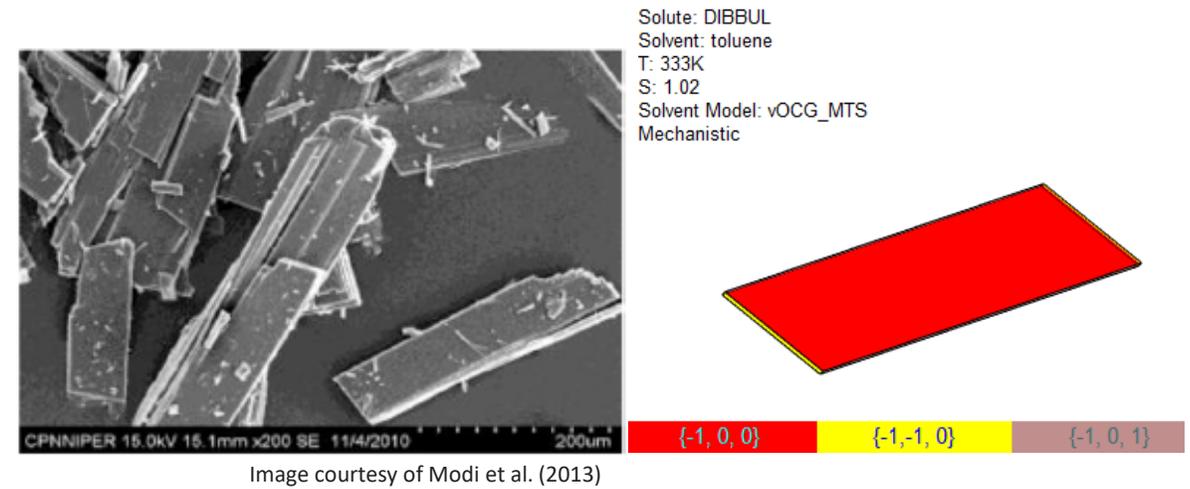


Model-based predictions cover a wide range of morphologies

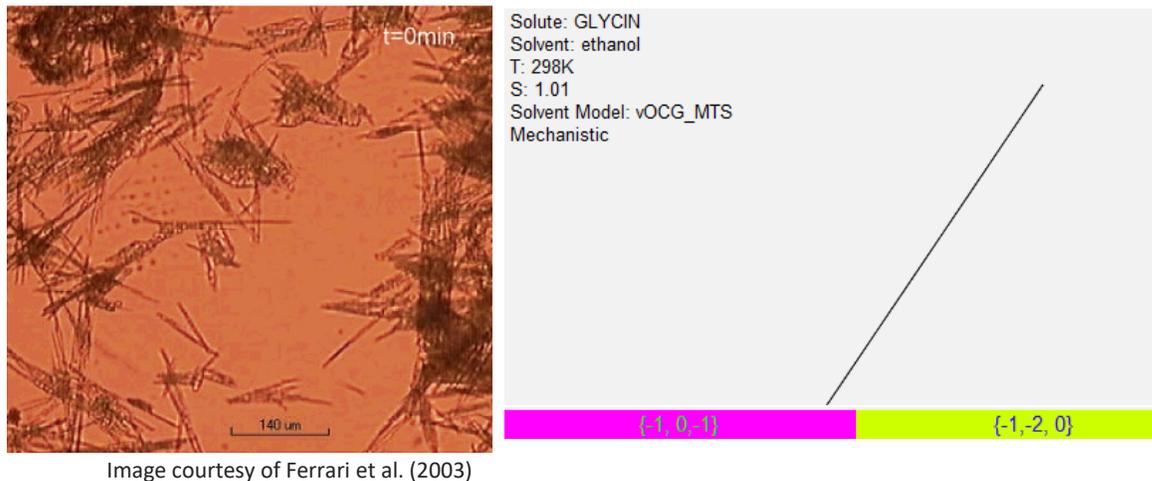
Doravirine precursor (treatment of HIV)



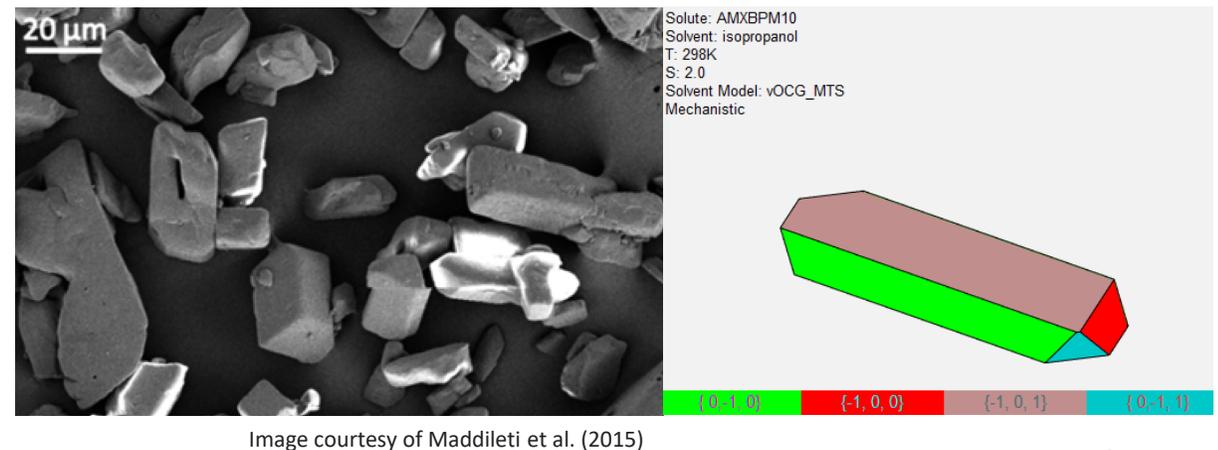
Celecoxib (treatment of arthritis)



β -Glycine (Amino Acid)



Trimethoprim (broad spectrum antibiotic)



How to generalize the framework extension to n growth unit crystals?

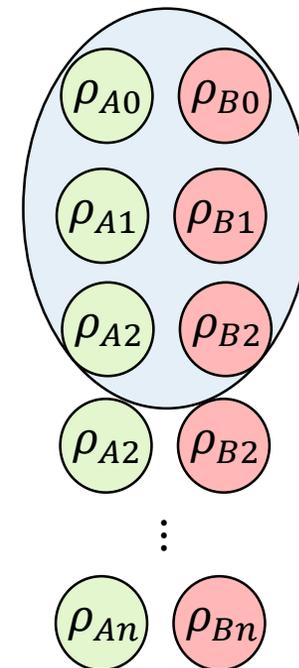
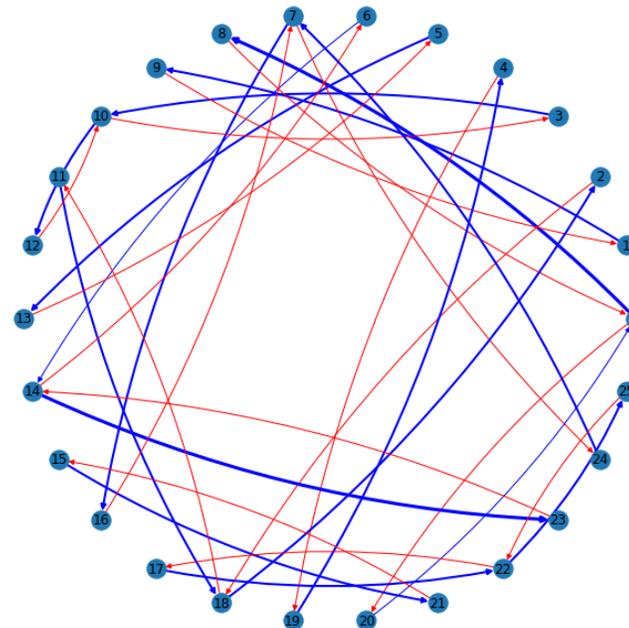
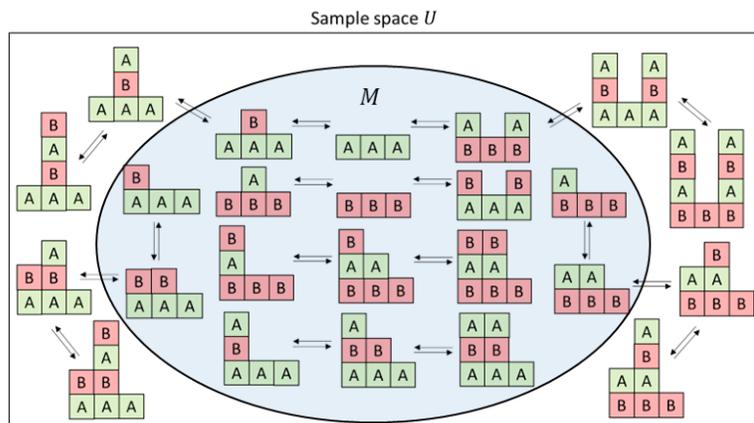
Inputs

Step kinetics

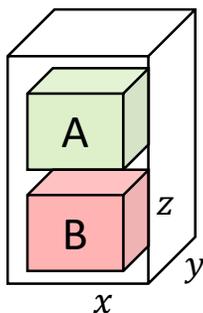
Network Graph

Master Equations

Type of Crystal
Step configuration
Kink density Cut off



Unit Cell

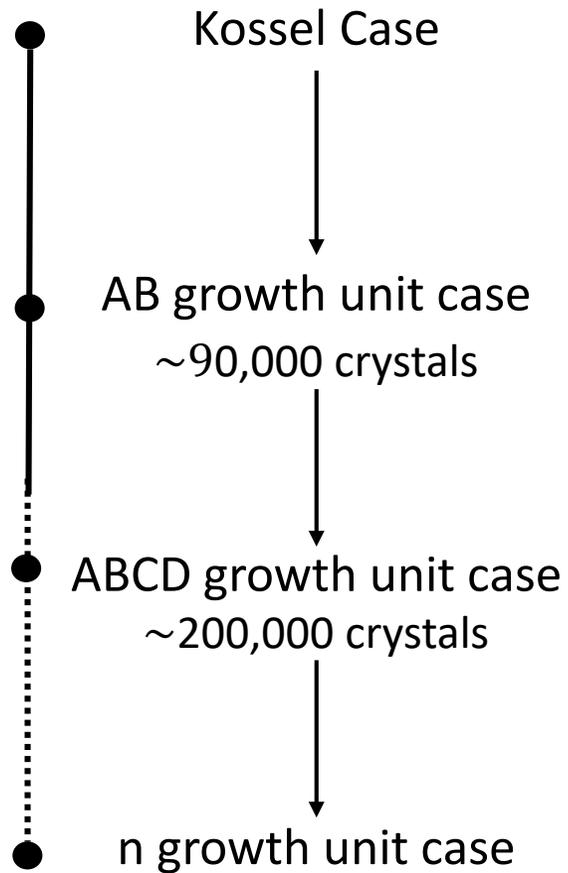


Sites $f(\rho_k) \rightarrow$ Nodes
Events $f(j^+, j^-) \rightarrow$ Edges

Network identification algorithm

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

Current Status



- 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.

Acknowledgements

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