Investigating the Effect of Solvents and Impurities on Crystal Growth

IFPRI AGM 2020

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Project Objective:

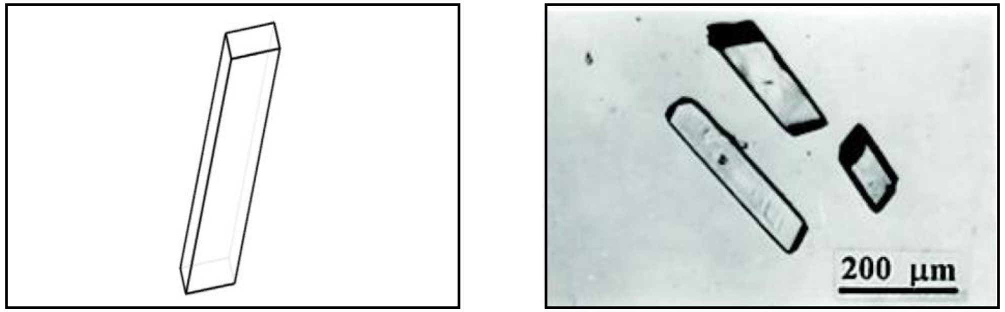
The goal of this research is to develop a practical engineering tool for predicting the relative growth rates (growth kinetics) and morphology of solution-grown faceted crystals, including the effects of solvent, and impurities/additives. The methodology will be tested on a variety of systems, including: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

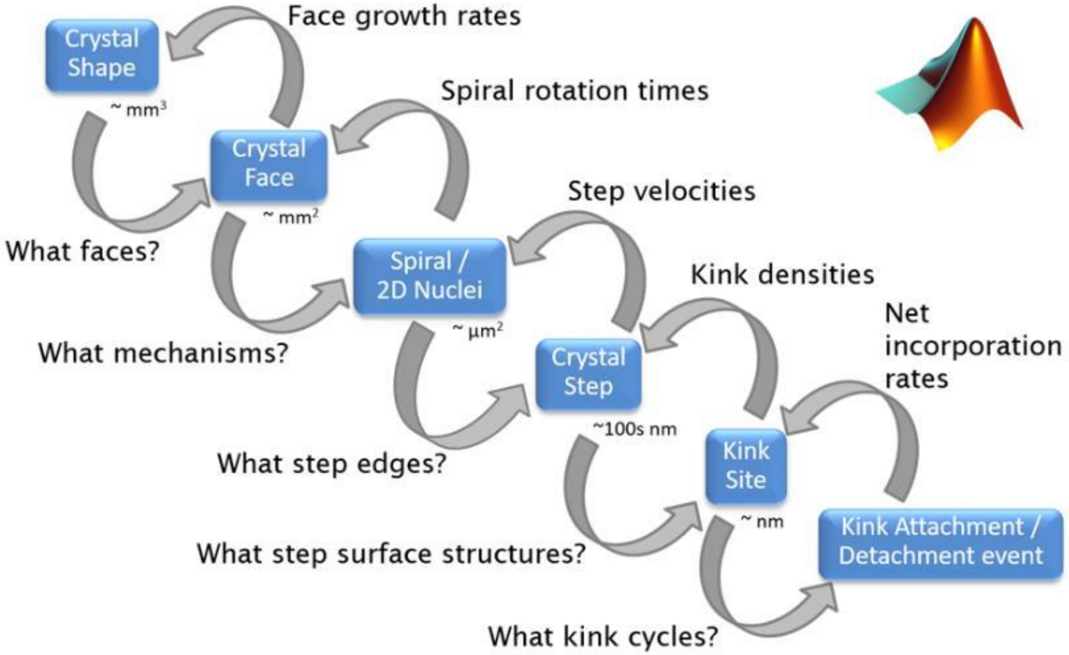
Background - ADDICT

- Mechanistic framework developed by Doherty group models layered growth
- Predicts crystal morphology for given .cif file and growth conditions[3]



(a) Predicted shape of paracetamol in Vapor ⟷ (b) Observed shape of paracetamol in Vapor

Images adapted from Li et al. (**2016**)



Scheme works well when implemented case-by-case by expert.
Software implementation for general user is a challenge.

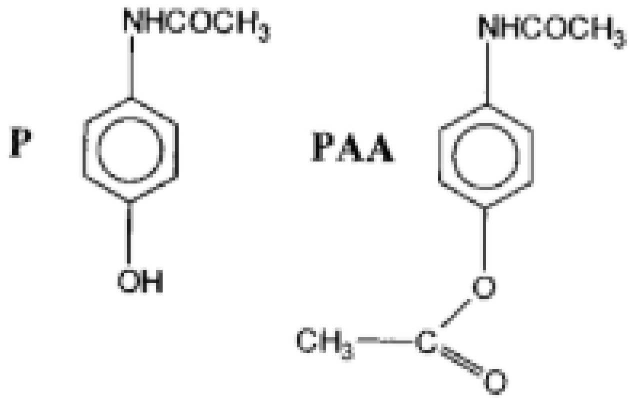
Background - Impurities

- Anti-freeze proteins within Antarctic fish inhibit ice crystal formation
- Antimalarial medications inhibit β-hematine crystallization
- Inhibition of L-cystine kidney stones through structural mimics
- Metacetamol/PAA inhibition of paracetamol production

- This can occur at **ppb concentrations!**

Background - Impurities

- PAA inhibits growth of **paracetamol** crystals
- Distinct faces inhibited by different amounts by introduction of PAA



PAA = p-acetoxyacetanilide

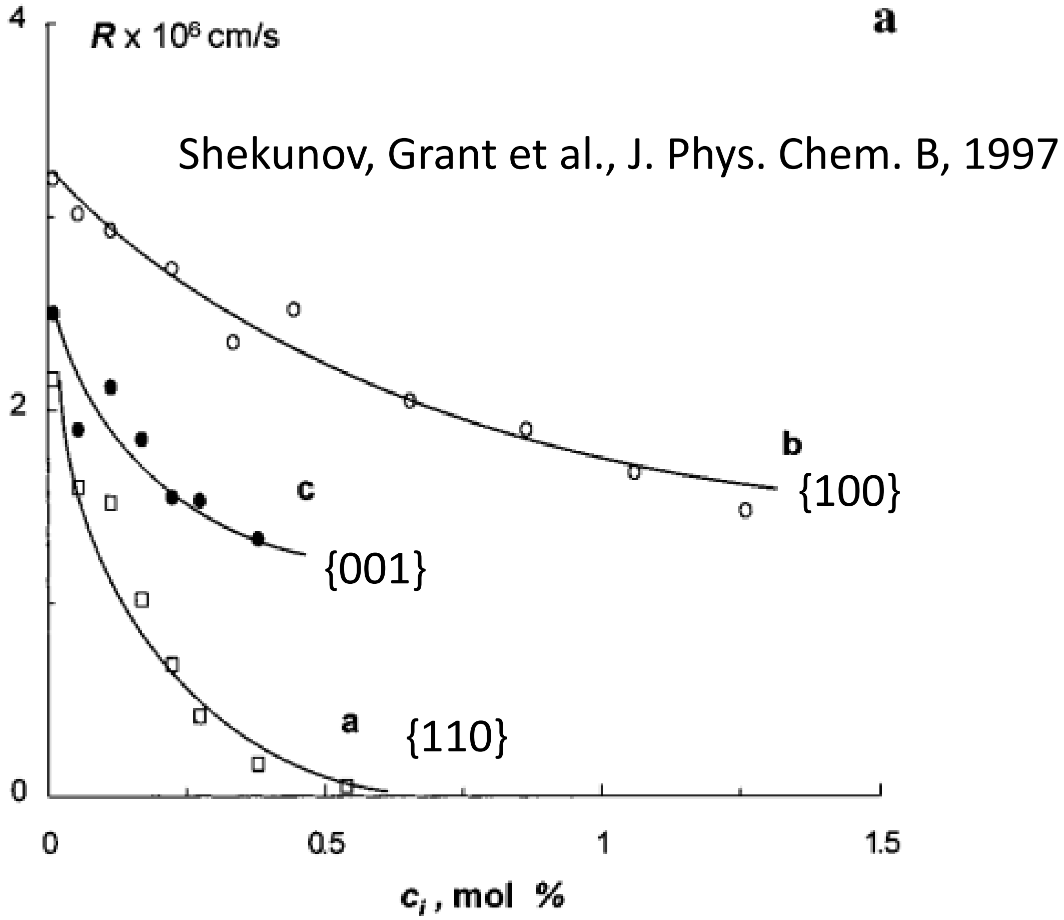


Figure 1. Dependencies of (a) normal growth rate, R as functions of concentration c_i of PAA in solution. Curves correspond to the crystal faces {110} (a, □), {20$\bar{1}$} (b, ○), and {001} (c, ●). $\sigma = 0.1$. $T = 35.5$ °C.

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Three Inhibition Mechanisms

1. Step pinning (main focus of current work). Influences critical length of step front

2. Spiral pinning. Influences critical length of step side

3. Kink blocking. Influences the number of growth sites (kinks)

Step Pinning

- Cabrera and Vermilyea (1958): **Step Pinning Mechanism**[5]
- Segments of the step edge are halted as edge encounters impurities spaced apart distance less than the critical length

$$v = v_{\infty}(1 - 2l_c d^{1/2})^{1/2}$$

Critical Length of Step

Density of Adsorbed Impurities

$$d \propto \theta_I$$

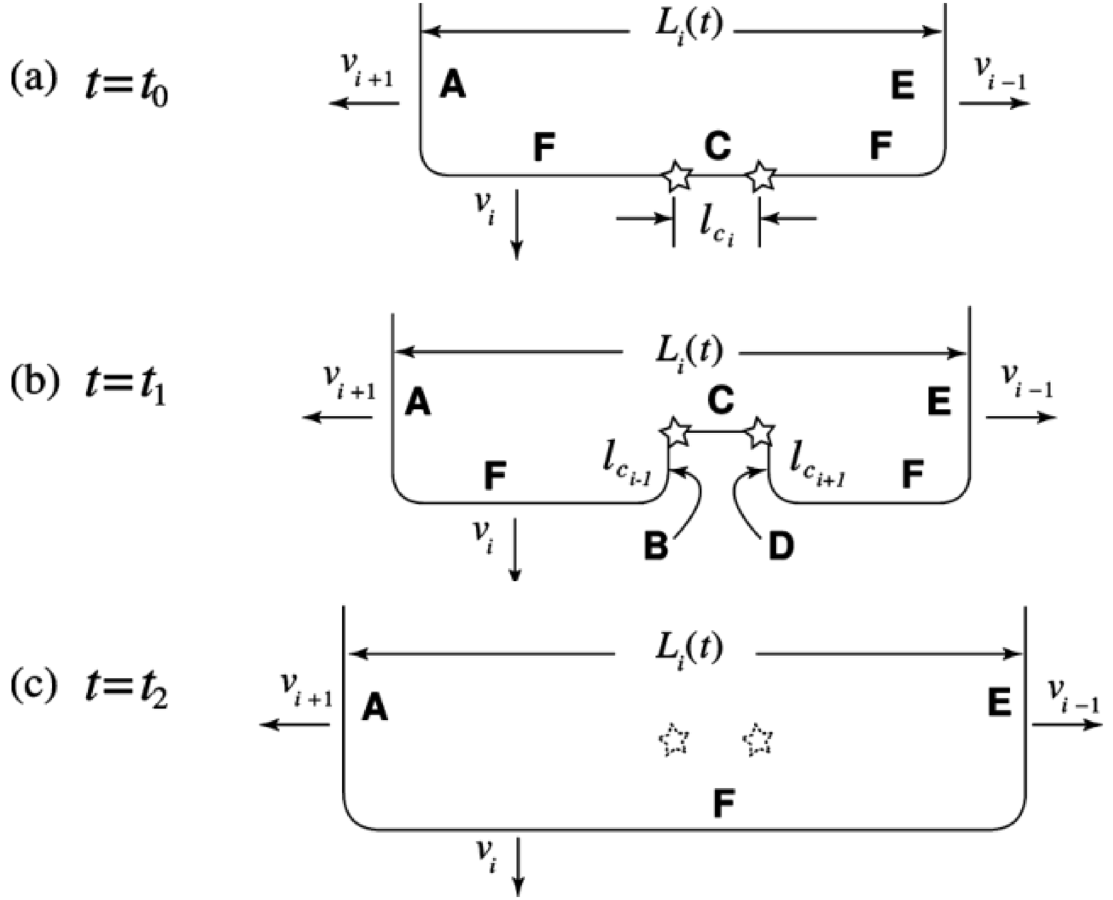

Image adapted from J. Sizemore, M. F. Doherty (**2009**)

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Kinetic Monte Carlo (KMC)

- KMC used to simulate growth of a Kossel crystal, starting with a flat step edge[6]
- Attachment and detachment events are defined as transport of growth units:
  - Bulk solution ↔ Terrace
  - Terrace ↔ Edge
  - Edge ↔ Kink
  - Terrace ↔ Kink

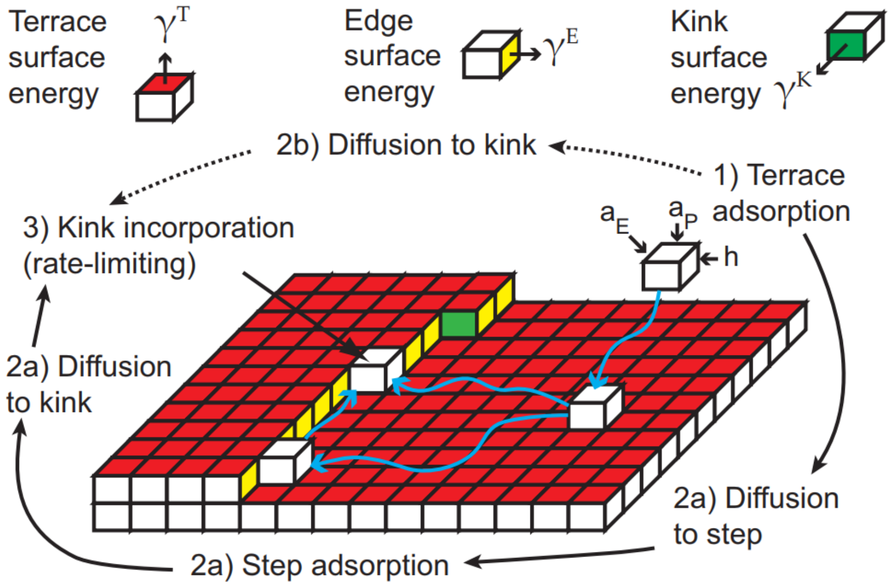

Image adapted from Tilbury et al. (**2016**)

KMC Algorithm

1. Define possible events and their corresponding rates.

KMC - Microkinetic Rate Expressions

	Attachment Rates (1/s)	Detachment Rates (1/s)
Edge ↔ Kink	$j_{K,i}^{+} = k_{K,i}^{+}\ \theta_{E,i} = v_0 \exp\left(\frac{-\Delta U_{K,i}^{\ddagger}}{k_B T}\right)\theta_{E,i}$	$j_{K,i}^{-} = k_{K,i}^{-} = v_0 \exp\left(\frac{-(\Delta U_{K,i}^{\ddagger} + \Delta W_{K,i})}{k_B T}\right)$
Terrace ↔ Edge	$j_{E,i}^{+} = k_{E,i}^{+}\ \theta_{T,i} = v_0 \exp\left(\frac{-\Delta U_{E,i}^{\ddagger}}{k_B T}\right)\theta_{T,i}$	$j_{E,i}^{-} = k_{E,i}^{-}\ \theta_{E,i} = v_0 \exp\left(\frac{-(\Delta U_{E,i}^{\ddagger} + \Delta W_{E,i})}{k_B T}\right)\theta_{E,i}$
Terrace ↔ Kink	$j_{KT,i}^{+} = k_{KT,i}^{+}\ \theta_{T,i} = v_0 \exp\left(\frac{-(\Delta U_{K,i}^{\ddagger} + \Delta U_{E,i}^{\ddagger})}{k_B T}\right)\theta_{T,i}$	$j_{KT,i}^{-} = k_{KT,i}^{-} = k_{KT,i}^{+} \exp\left(\frac{-(\Delta W_{E,i} + \Delta W_{K,i})}{k_B T}\right)$
Solution ↔ Terrace	$j_{T}^{+} = k_{T}^{+}\ x = v_0 \exp\left(\frac{-\Delta U_{T}^{\ddagger}}{k_B T}\right)x$	$j_{T,i}^{-} = k_{T}^{-}\ \theta_{T,i} = v_0 \exp\left(\frac{-(\Delta U_{T}^{\ddagger} + \Delta W_{T})}{k_B T}\right)\theta_{T,i}$

$$x = x_{sat} S$$

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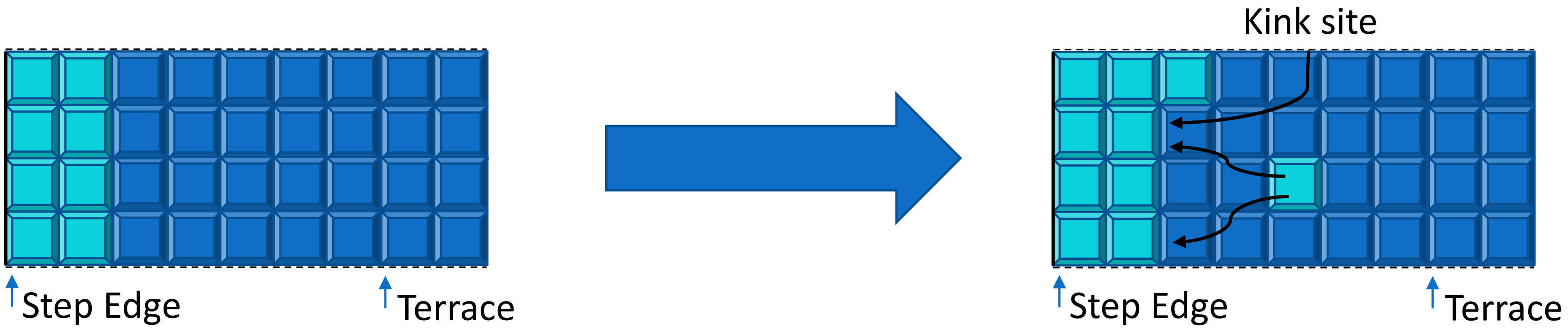
KMC Algorithm

1. Define possible events and their corresponding rates.
2. Set initial system state.



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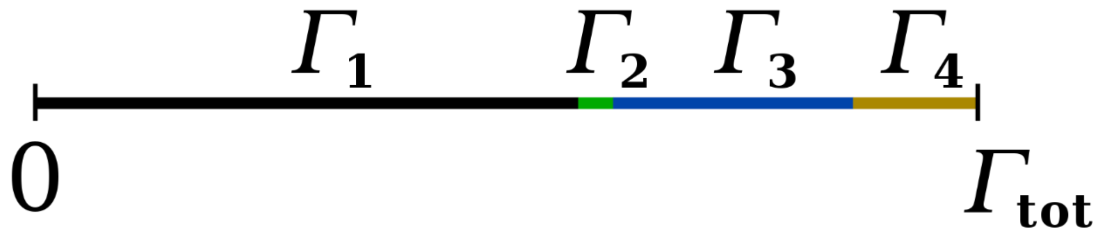
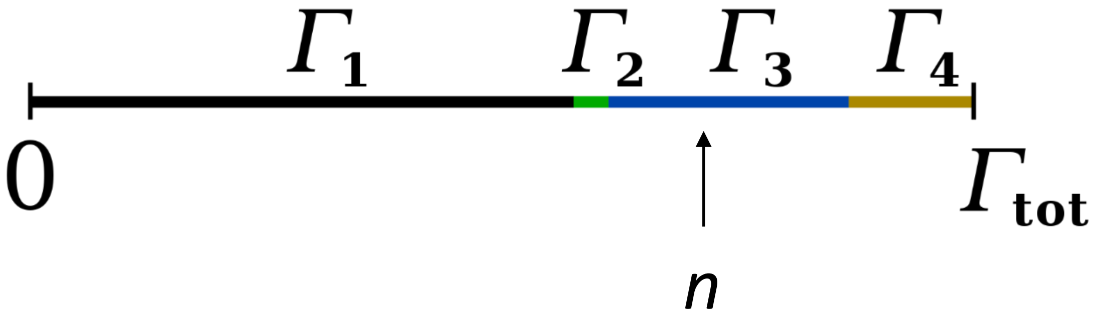
KMC Algorithm

1. Define possible events and their corresponding rates.
2. Set initial system state.
3. At each site, determine the number of nearest neighbors and occupation status. Then, compute cumulative rate functions, Γ_i, and the total rate constant, Γ_{tot}.



KMC Algorithm

1. Define possible events and their corresponding rates.
2. Set initial system state.
3. At each site, determine the number of nearest neighbors and occupation status. Then, compute cumulative rate functions, Γ_i, and the total rate constant, Γ_{tot}.
4. Draw a random number *n* between 0 and Γ_{tot} to determine which event to execute:

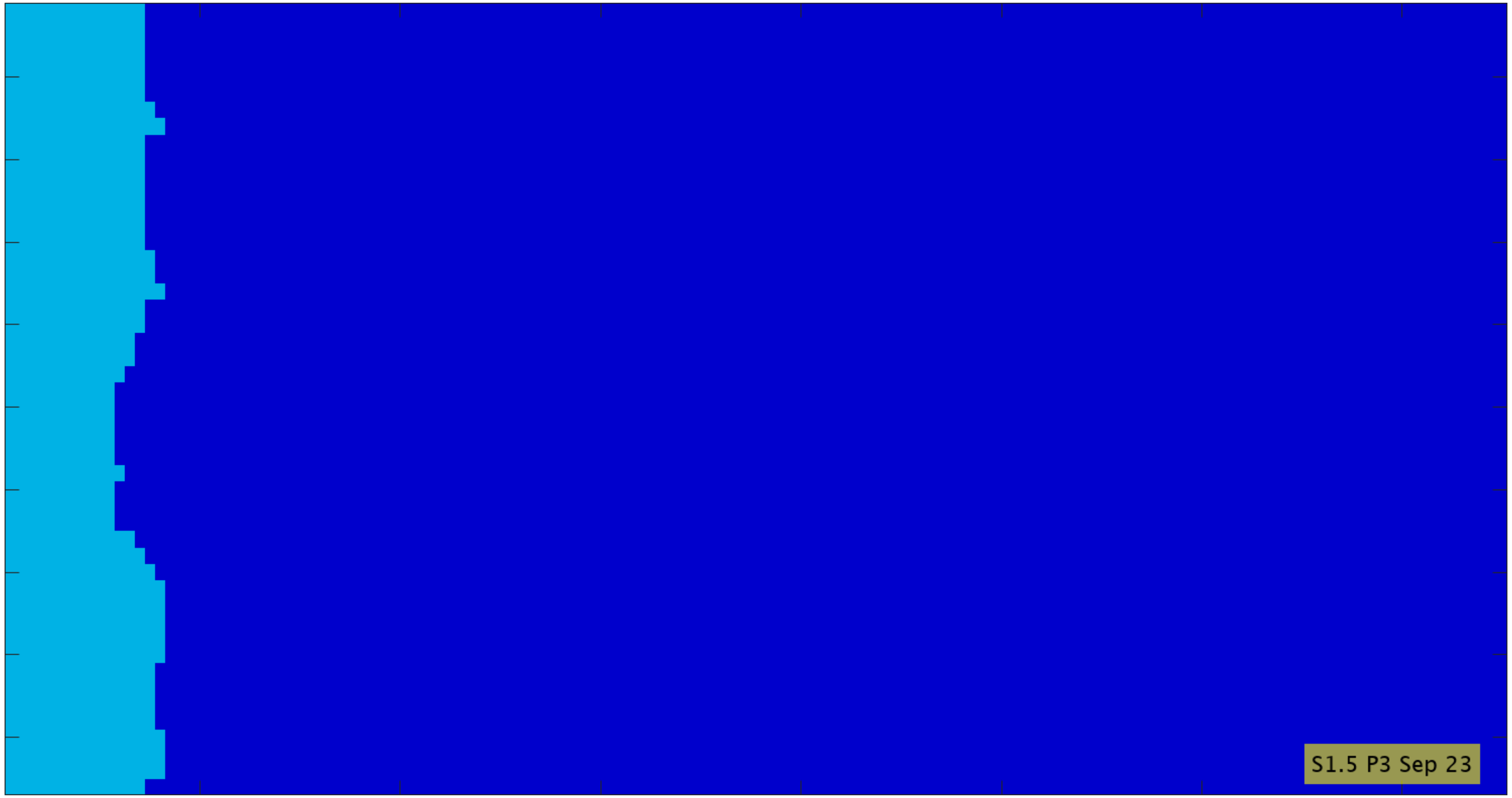


KMC Algorithm

1. Define possible events and their corresponding rates.
2. Set initial system state.
3. At each site, determine the number of nearest neighbors and occupation status. Then, compute cumulative rate functions, Γ_i, and the total rate constant, Γ_{tot}.
4. Draw a random number *n* between 0 and Γ_{tot} to determine which event to execute (e.g., 3). Pick a random site where event 3 is possible and implement event 3 at that site.

KMC Simulation

- S = 1.5
- $\phi = 3\ k_B T$
- 15,000 MC steps



KMC Simulations (production runs)

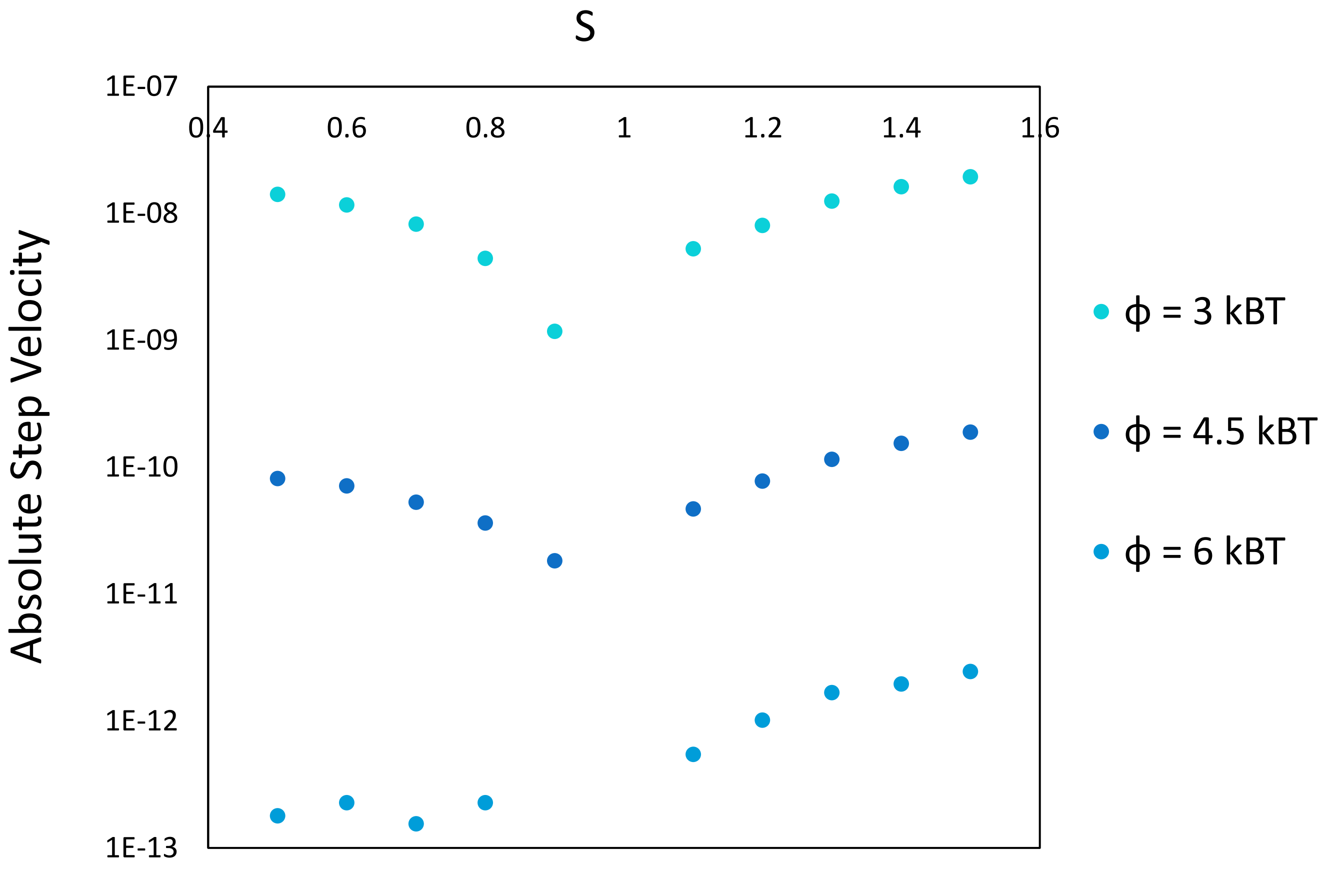
- Simulations run for 75,000 MC steps at various energies; S = 1.5

$\phi = 1.5\ k_BT$ $\phi = 3\ k_BT$ $\phi = 6\ k_BT$

- Higher energy penalty corresponds to slower edge but “smoother” front

Step Velocity Dependence

- Sensible agreement of step velocity with both ϕ and S
- What if we introduce **impurity molecules?**



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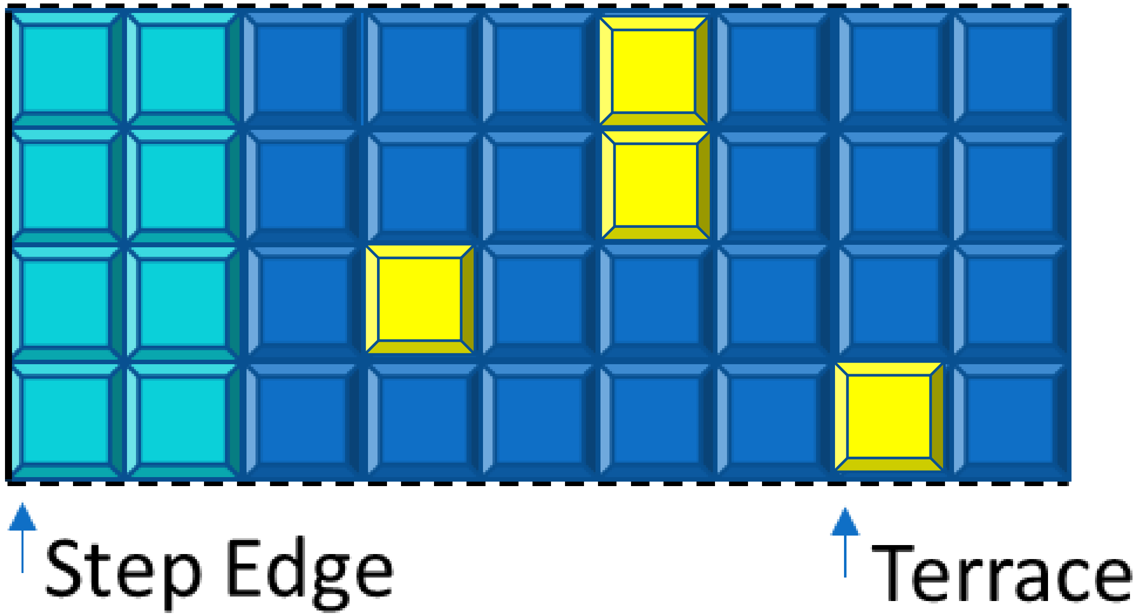
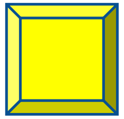
Introducing Impurities



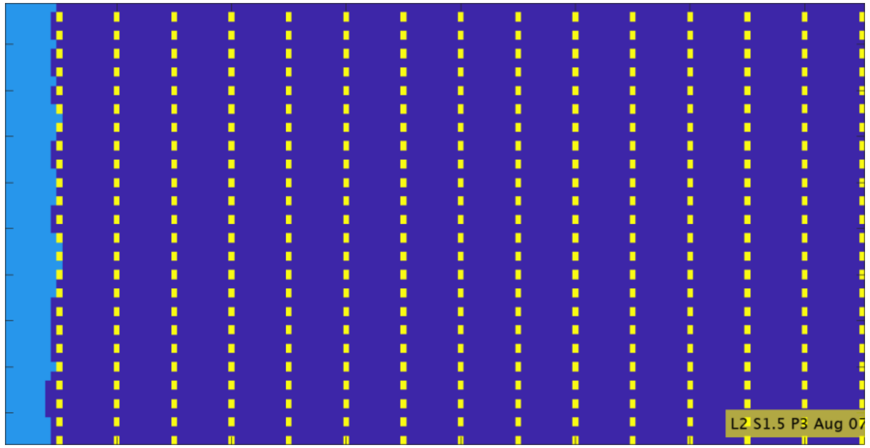

= impurity

θ_I - fractional coverage of impurities on the terrace

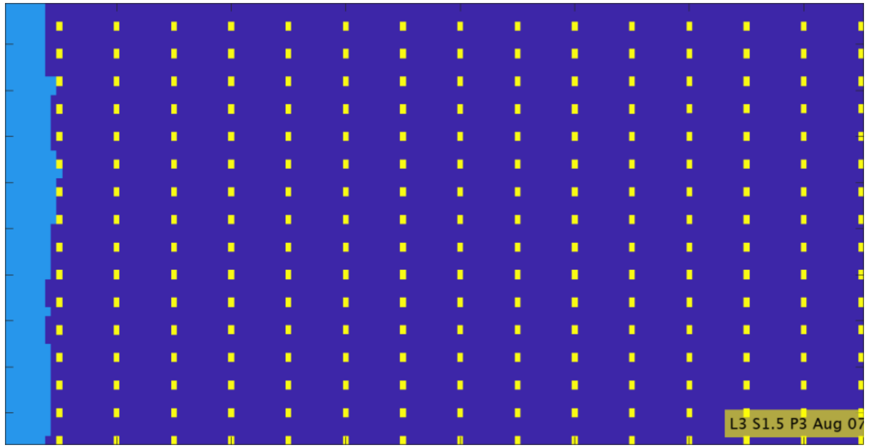
Impurities on a Lattice

θ_I - fractional coverage of impurities on the terrace

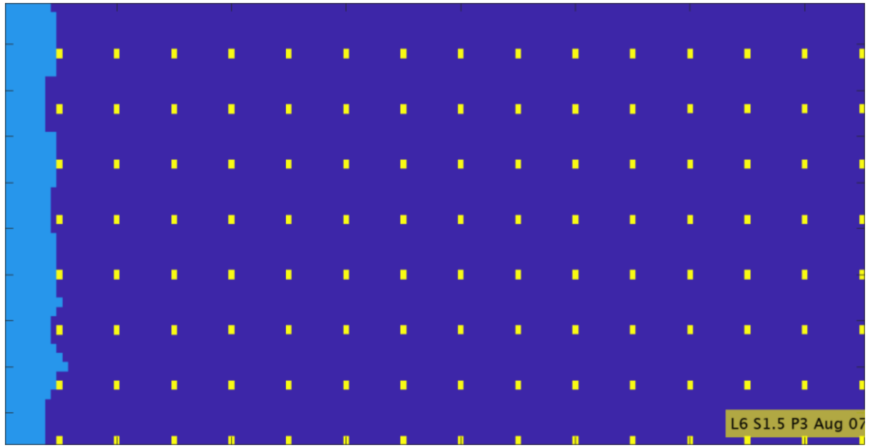
- S = 1.5
- $\phi = 3\ \mathrm{k_B T}$
- 15,000 MC Steps

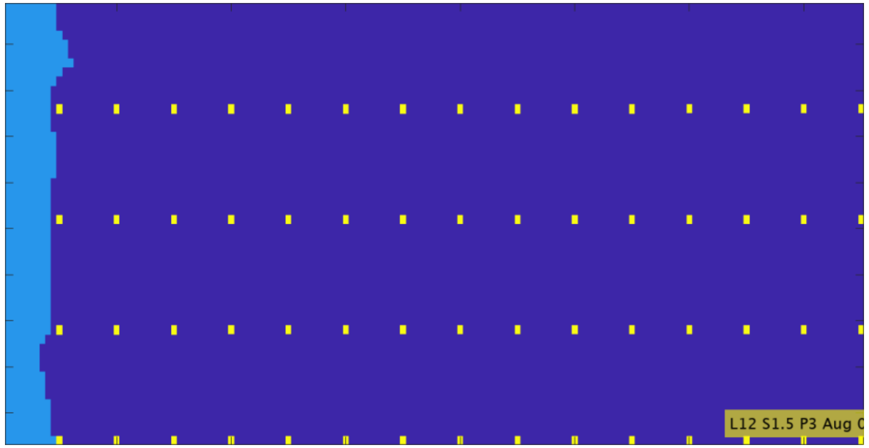


$\theta_I = 0.017$ / 0.057



$\theta_I = 0.038$ / 0.068





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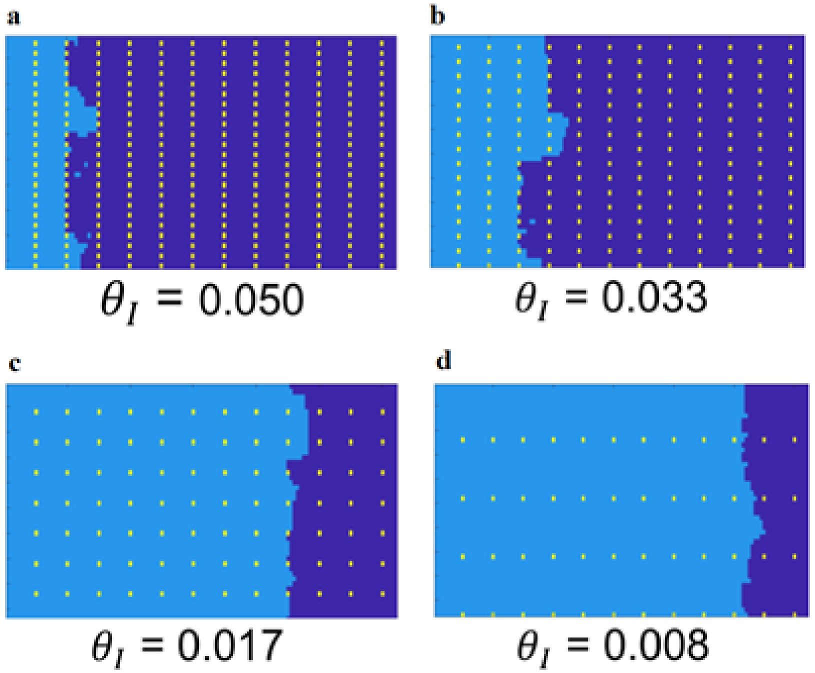
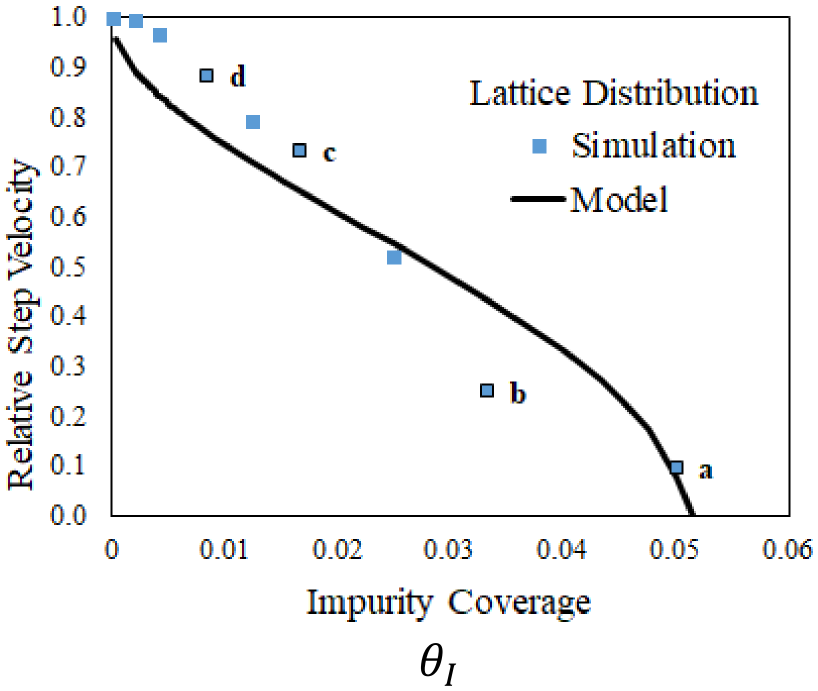
Impurities on a Lattice

- Imposters close together significantly diminish step velocity and thus reduce growth rate
- Monotonic decrease with increasing coverage

CV Model equation:

$$v = v_{\infty}(1 - 2l_c d^{1/2})^{1/2}$$





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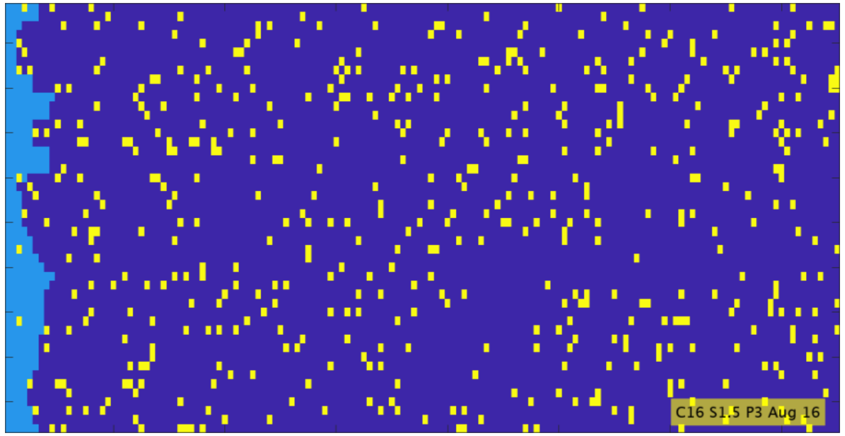
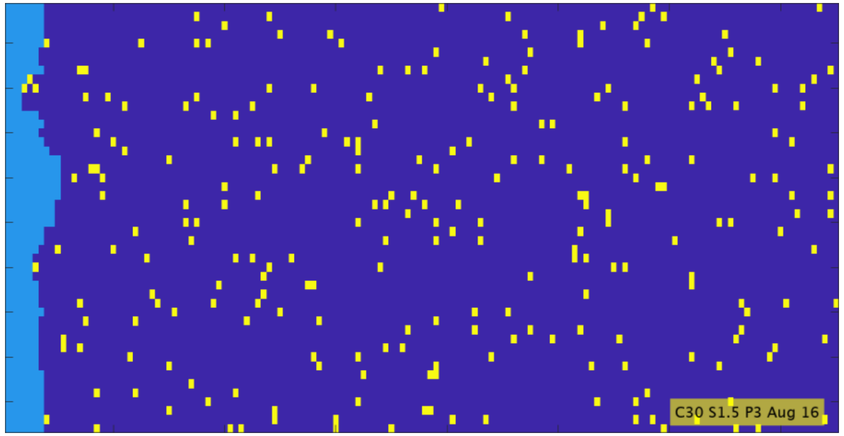
Impurities Distributed Randomly

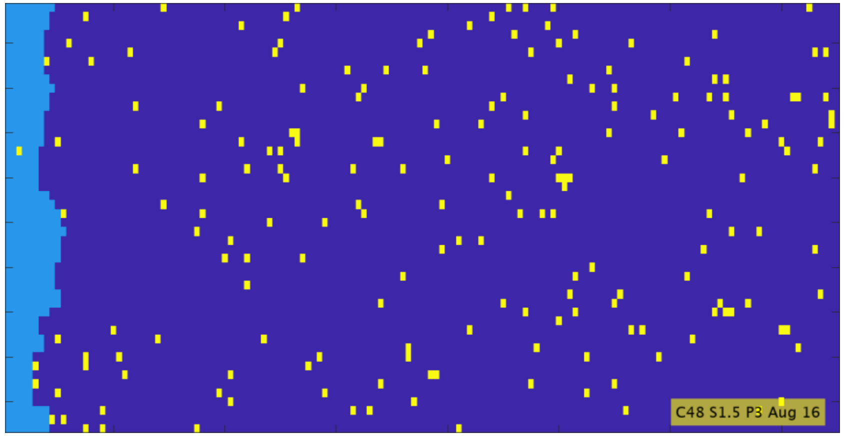
- S = 1.5
- $\phi = 3\ \mathrm{k_B T}$
- 15,000 MC steps

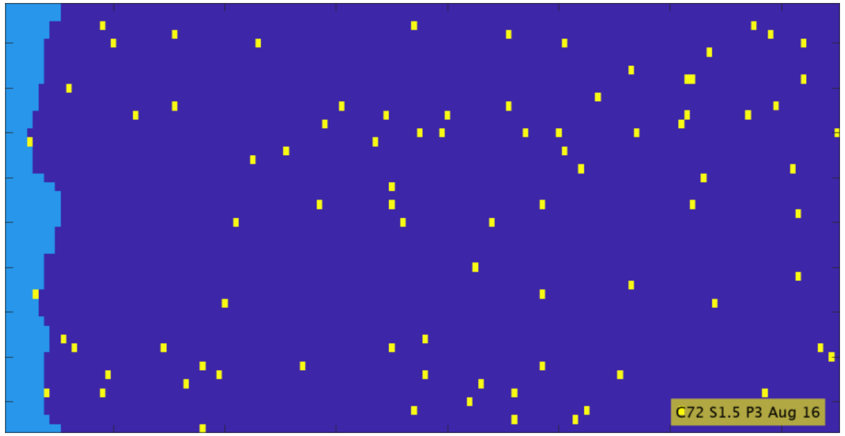


$\theta_I = 0.042$



$\theta_I = 0.028$





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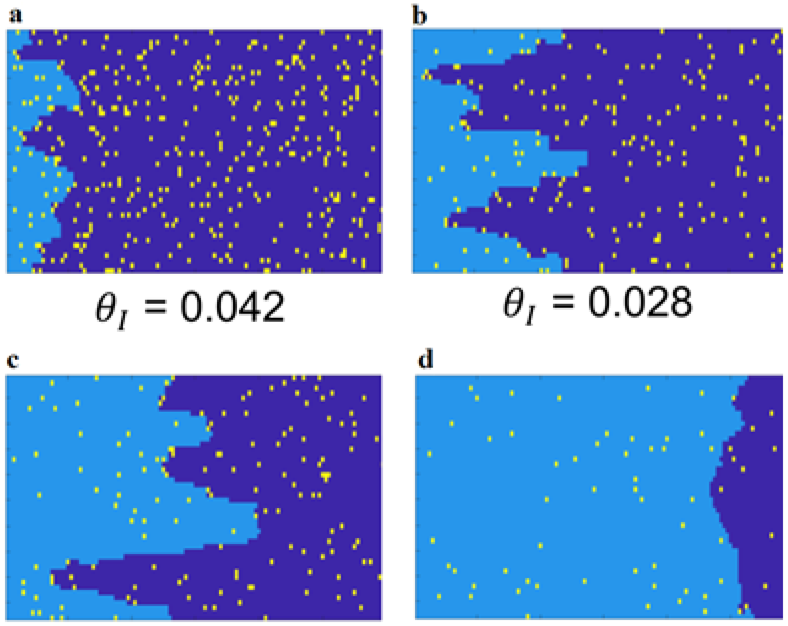
Impurities Distributed Randomly

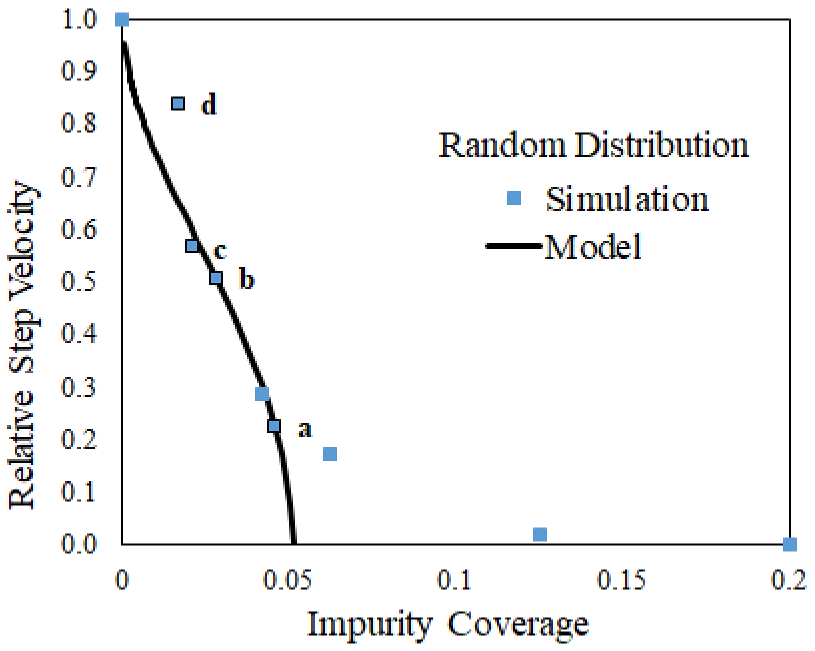
- Model equation captures monotonic decrease but not all curve characteristics
  - Predicts dead zone prematurely (error bars?)
- Are KMC results & CV model sensitive to the **impurity distribution?**

CV Model equation:

$$v = v_\infty (1 - 2 l_c d^{1/2})^{1/2}$$



θ_I = 0.042 θ_I = 0.028 θ_I = 0.021 θ_I = 0.014



θ_I

Future Work

- **2020-21:** Implement KMC for more realistic systems
  - Mobile impurities
  - Include finite energetic interactions amongst solute and imposter species
- **2020-21:** Investigate other mechanisms by which impurities may inhibit crystal growth (step-pinning, kink death)
- **2020-21:** Compare inhibitor mechanisms through KMC simulation to determine the range of validity of each mechanism and the transitions between them
  - – Compare KMC results to experimental inhibitor results before implementing validated mechanisms into ADDICT
- For mobile impurities consider the formation of inhomogeneous terrace with 2D islands of impurities at higher coverage fractions? MD simulations to examine how impurities affect energetics and surface coverage on the crystal surface

Acknowledgments

- Doherty Group
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