

Crystal Growth Cessation Revisited: The Physical Basis of Step Pinning

James F. Lutsko,^{*,†} Nérido González-Segredo,[†] Miguel A. Durán-Olivencia,[‡] Dominique Maes,[#] Alexander E. S. Van Driessche,[#] and Mike Sleutel[#]

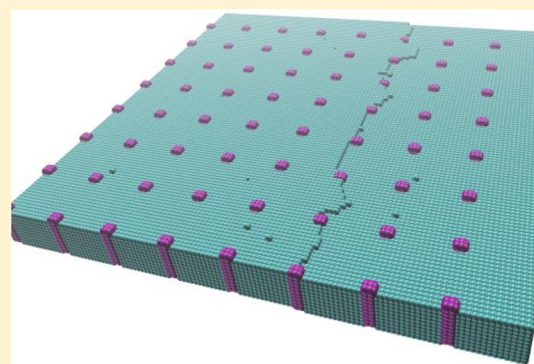
[†]Center for Nonlinear Phenomena and Complex Systems, Code Postal 231, Université Libre de Bruxelles, Boulevard du Triomphe, 1050 Brussels, Belgium

[‡]Laboratorio de Estudios Cristalográficos, Instituto Andaluz de Ciencias de la Tierra. CSIC-UGR, Avenida de las Palmeras, 18100 Granada, Spain

[#]Structural Biology Brussels, Vrije Universiteit Brussel, Pleinlaan 2, 1050, Elsene, Belgium

S Supporting Information

ABSTRACT: The growth of crystals from solution is a fundamental process of relevance to such diverse areas as X-ray diffraction structural determination and the role of mineralization in living organisms. A key factor determining the dynamics of crystallization is the effect of impurities on step growth. For over 50 years, all discussions of impurity–step interaction have been framed in the context of the Cabrera–Vermilyea (CV) model for step blocking, which has nevertheless proven difficult to validate experimentally. Here we report on extensive computer simulations which clearly falsify the CV model, suggesting a more complex picture. While reducing to the CV result in certain limits, our approach is more widely applicable, encompassing nontrivial impurity–crystal interactions, mobile impurities, and negative growth, among others.



INTRODUCTION

No crystal is formed in a completely pure environment: a key factor affecting crystallization is the effect of impurities on step growth,¹ which, depending on thermodynamic and kinetic factors,² can lead to growth-rate enhancement³ or inhibition.⁴ The growth of impure crystals from solution is fundamentally a nanoscopic process, of relevance to such diverse areas as biomineralization^{2–4} and templated nanoparticle growth.⁵ This is particularly true for protein crystals and biominerals, which are typically grown from very heterogeneous mother-liquor solutions. Even more extreme are interfacial fluids, for which crystallization may only be achieved by impurity adsorption.^{6,7} In protein crystals, the heterogeneity is a remnant of the imperfections of the purification protocol: the protein of interest is typically separated from hundreds if not thousands of other proteins, and 90–95% (w/v) final purity grades are the norm. The foreign protein species are regarded as impurities because they perturb the quality of the crystal, as typically judged from X-ray diffraction characteristics. In biominerals, the compositional heterogeneity is a biological necessity, and therefore it should not be surprising that the formation of these highly complex materials requires the presence of additives to regulate the final morphology and composition. Quantitative understanding of the kinetic impurity effect can contribute to overcoming protein–crystal size limits and to the development of new bioinspired composite materials. A

fundamental measure of this effect is the dependence of the rate of advancement of unfinished crystal layers (i.e., steps) on the concentration of impurities adsorbed onto the surface.

This well-known problem was addressed over 50 years ago by Cabrera and Vermilyea (CV) with the now-classic CV model.⁹ The model considers the rate of step growth as $v(\Delta) = v_0(1 - 2R_c/\Delta)^{1/2}$, where v_0 is the step velocity in the absence of impurities, Δ is the typical distance between impurities, and R_c is the critical radius for 2-d nucleation on the crystal surface.⁹ It is motivated by assuming the impurities are distributed as a regular, square array. When a flat step meets a row of impurities along its growth direction, the step is broken up into a number of fingers, each projecting between a pair of neighboring impurities (see Figure 1). Step blocking occurs if the radius of curvature of these fingers, which is at most $\Delta/2$, is less than R_c . The square root in $v(\Delta)$ arises from using a geometric mean to combine the effects of free step propagation on the impurity-free terraces, v_0 , and impeded-step velocity, taken to be $v_0(1 - 2R_c/\Delta)$ due to an assumed linear dependence on the effective supersaturation and the Gibbs–Thomson (GT) effect,^{10,11} whereby the effective supersaturation across a curved interface is reduced proportionally to the curvature. Other processes,

Received: September 2, 2014

Revised: October 8, 2014

Published: October 23, 2014

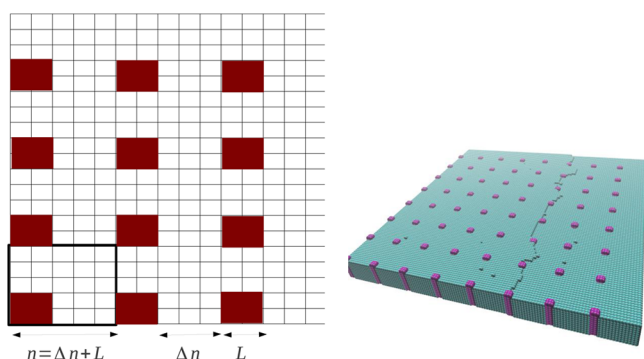


Figure 1. Left panel shows a schematic diagram of the simulation cell for the case of a regular array of static impurity clusters (red). The quantities defined are the cluster size, L , the separation between clusters, Δn , and the length of the repeating unit, n . The right panel shows a snapshot from a simulation of a growing step, illustrating the formation of fingers penetrating from left to right between the impurity clusters. (Simulations visualized using VMD.⁸)

such as liquor depletion, can also affect the step velocity,^{12,13} but the CV model has been the starting point for many discussions of step blocking.^{14,15}

As it stands, there are two elements to the CV model: the critical impurity separation (CIS) to cause complete step blocking, $\Delta_c = 2R_c$, and the arguments leading to the form of the function $\nu(\Delta)$. While the latter has been the subject of much discussion leading to several proposed modifications (see, e.g., Kuboto and Mullin¹⁶ and Weaver et al.¹⁷), it is clearly the former, the CIS, that is of most conceptual importance: once this is known, the exact manner in which $\nu(\Delta)$ goes from $\nu(\infty) = \nu_0$ to $\nu(\Delta_c) = 0$ is less relevant vis-à-vis deriving a step-blocking criterion. Potapenko proposed an adjustment leading to $\Delta_c = (5/3)R_c$ to take account of the fact that impurities are distributed randomly,¹⁸ while Weaver et al. recently treated such an adjustment as empirical.¹⁹

Despite these refinements, the literature includes a bewildering collection of both supportive^{20,21} and disputative^{22,23} experimental evidence (see the survey of experimental literature given in the Supporting Information); indeed, there are a number of fundamental flaws and limitations intrinsic to the physical picture underpinning the CV model. First, the concept of impurity-induced step bending is no longer relevant in the low kink-density limit: De Yoreo et al.²⁴ have demonstrated that the predominant mode of retardation of the so-called stiff steps, of low kink density, is kink blocking (“poisoning”) rather than the GT effect associated with step bending. Second, there is a clear irreconcilability of two different length scales in the CV model: impurities are considered to be molecular, whereas the step is treated macroscopically via invocation of the GT effect. Third, the operational regime of the CV model, as motivated by De Yoreo et al.,²⁴ is restricted to nonstiff steps in the high kink-density limit. However, it is precisely this step flexibility that limits the energetic cost of creating local step fluctuations, which for the case of molecular impurities can lead to morphological shortcuts that bypass the blocking effect of the impurity (see Supplementary Videos S1 and S2, Supporting Information).

In this paper we revisit the classic CV model and some of its variations by taking step fluctuations at the molecular level explicitly into account in a kinetic Monte Carlo (kMC) computational model^{11,25,26} (for details of our simulations, see Supporting Information). On the basis of both thermodynamic

and kinetic considerations, we discuss the CIS for step blocking and show that the CV model only applies in precisely defined, rather restrictive circumstances. In addition, given the unrealistic idealization by the CV model that impurities have infinite surface-residence times and zero surface diffusion, we expand our analysis to also include impurity kinetics.

COMPUTER SIMULATIONS

We performed kMC simulations of a Kossel (i.e., cubic) lattice of lattice parameter a and containing two species, the crystal molecules, c , and the impurities, i . The crystal–crystal molecule binding energy is $\epsilon < 0$. Impurities have different binding energies that we allow in general to be anisotropic. Vertical binding of an impurity with either an impurity or a crystal molecule has energy $\epsilon_{ii}^{(v)}$ and $\epsilon_{ic}^{(v)}$, respectively, while horizontal (in-plane) binding has impurity–impurity energy $\epsilon_{ii}^{(h)}$ and impurity–crystal energy $\epsilon_{ic}^{(h)}$.

To begin, we work with *static* impurities which are put in place at the start of the simulation and which thereafter do not move (they effectively have infinite vertical binding energies, $\epsilon_{ii}^{(v)} = \epsilon_{ic}^{(v)} \rightarrow -\infty$) and zero binding with the crystal, $\epsilon_{ic}^{(h)} = 0$. A schematic diagram of the simulation cell is shown in Figure 1. We then consider a solution bath that contains only the majority species, c . With the impurities distributed in a regular array, the configuration adheres to the assumptions of the CV model, a somewhat artificial arrangement, as discussed below. At zero supersaturation, thermal roughening occurs in this model at a temperature $k_B T_R \approx 0.6|\epsilon|$, where k_B is Boltzmann’s constant. We typically work well below thermal roughening, e.g., in the range $0.20 \leq k_B T/|\epsilon| \leq 0.30$.³² At this temperature, the velocity varies linearly with the supersaturation up to about $\Delta\mu = 0.05|\epsilon|$ (see Supporting Information) where $\Delta\mu$ is the difference between the chemical potential of a crystal molecule in solution and that of the molecule in the bulk crystal. To make a comparison to experiment, we note that thermal roughening temperatures for metals are typically on the order of 1000 K, so the temperatures set for our simulations, being near about $T_R/3$, would be on the order of room temperature.

RESULTS AND DISCUSSION

Figure 2 shows typical results for the dependence of step velocity on the interimpurity distance measured in lattice units, $\Delta n \equiv \Delta/a$, defined as the number of unoccupied lattice sites between impurities. In this particular case, the critical impurity separation at which blocking occurs is approximately $\Delta n = 6$. To compare to the CV model and in order to eliminate any uncertainty arising from the application of classical nucleation theory to these small length scales, we have *empirically* determined from simulation that the critical radius is $R_c = 9.3a \pm 0.2a$ (Supporting Information). The fundamental assumption of CV, namely, that the CIS is twice the critical radius (about 18 lattice units in this example), is thus clearly unsupported. Note that this discrepancy is not due to the regular, artificial impurity arrangement imposed by the CV model, criticized by other authors. Indeed, see also Figure 2, results for a random impurity distribution closely approximate those for the regular impurity array, suggesting that such effects are small. On the other hand, Figure 2 shows equivalent data for the case of nonzero impurity–crystal in-plane binding energy, $\epsilon_{ic}^{(h)}$, which shows (a) that the CIS is a sensitive function of this energy and (b) that deviations from CV are even greater as this energy grows. Last but not least, our results show

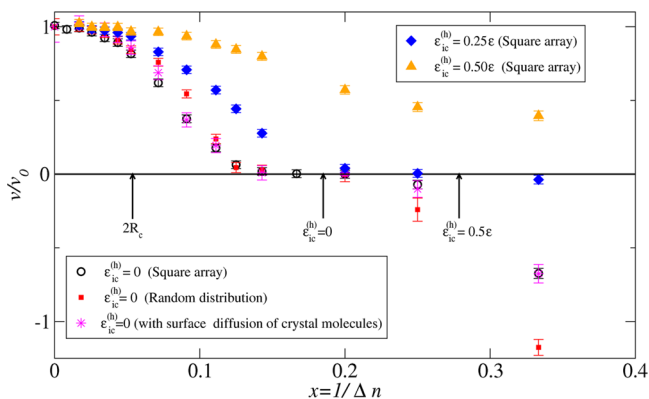


Figure 2. Step velocity as a function of the inverse separation between impurities for $k_B T = 0.25\epsilon l$ and $\Delta\mu = 0.05\epsilon l$. Results are shown for point impurities with no horizontal interaction with crystal molecules (for a square array, a random distribution, and a square array with surface diffusion of crystal molecules with no Schwoebel barrier), and for impurity–crystal binding energies of $\epsilon_{ic}^{(h)} = 0.25\epsilon$ and 0.5ϵ . The arrows indicate, from left to right, the CIS predicted by the CV model, the CIS determined from our thermodynamic condition for $\epsilon_{ic}^{(h)} = 0$ and $\epsilon_{ic}^{(h)} = 0.5\epsilon$ (using the zero-temperature estimate for the line tension); for $\epsilon_{ic} = \epsilon$, the thermodynamic prediction is that blocking does not occur: there is nevertheless a slowdown of step growth due to the need to nucleate kinks between each pair of blockers (see, e.g., ref 24). In the case of diffusion, the diffusion constant is chosen to allow for approximately 20 diffusive jumps during the residency time of a monomer and results in a step velocity in the pure system of approximately 9 times that without diffusion.

negative step velocities (crystal dissolution) for sufficiently small impurity separation, i.e., sufficiently high impurity surface concentrations. This is possible because our simulation begins with impurities already incorporated into the crystal surface; see Figure 1. The smooth transition from positive to negative velocities is outside the scope of the CV model and suggests that the physics behind it is incomplete.

Our simulations (see Supplementary video, Supporting Information) reveal the true cause of the CV–CIS failure: it is very likely for a small thermal fluctuation on the border of a finger to close the gap around a point ($L = 1$) impurity and coalesce with an adjacent finger. This is related to the fact that the critical radius as an absolute threshold is a macroscopic concept. Microscopically, rather, the critical radius is defined as the radius for which clusters have a 50% probability of growing or shrinking. In other words, the microscopic criterion allows both smaller clusters to grow and larger clusters to evaporate, as explicitly shown in Supporting Information. We therefore repeated our simulations with impurity clusters consisting of blocks of size $L \times L$ for $L = 2, 4, 8,$ and 16 lattice sites so that the finger–finger gaps to be bridged were larger. Typical results are shown in Figure 3. It is evident that the CIS approaches the expected CV value as the size of the clusters increases. These results are for the particular conditions $k_B T = 0.25\epsilon l$, $\Delta\mu = 0.05\epsilon l$, a square lattice of size 120 – 240 (ref 33) and runs of 10^7 – 10^8 surface updates (ref 34)—we have verified that our results are insensitive to the precise values chosen for the lattice size and run length (Supporting Information). Similar behavior was observed for lower and higher temperatures and both lower and higher supersaturations (Supporting Information). Allowing for surface diffusion of the crystal molecules has no significant effect, as is apparent in Figure 2.

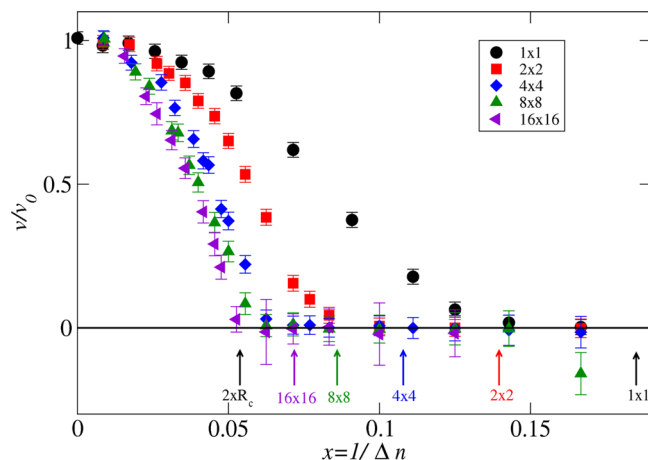


Figure 3. Step velocity as a function of the inverse separation between impurity clusters of various sizes for $k_B T = 0.25\epsilon l$ and $\Delta\mu = 0.05\epsilon l$. The impurity clusters are square with sides of length 1, 2, 4, 8, and 16. The zero-temperature approximation for the line tension was used to estimate the CIS with the results, indicated by the arrows on the figure, in good agreement with the simulation data. The CV limit is also shown. The approach of the limit of the dead-zone to the CV value and the slower approach of the CIS are both in evidence. Note that all curves systematically show negative velocities as $1/\Delta n$ increases beyond the range of this plot.

Analytical Criterion for Step Pinning. Our results clearly demand a new approach to characterizing the CIS. Whether the crystal grows or dissolves ultimately depends on what final state has the lowest free energy. We therefore consider the free-energy difference between adding a layer of molecules to the crystal and having the same number of molecules in solution. If a surface layer comprises N sites and if there are N_i impurities on the surface, each one occupying S lattice sites, then the number of molecules needed to form one crystal layer is $N - N_i S$. If the impurity–crystal bond energies, $\epsilon_{ic}^{(h)}$, were identical to the crystal–crystal bond energy, ϵ , there would be a free energy difference of $-(N - N_i S)\Delta\mu$, where $\Delta\mu > 0$ for growth. However, the defining characteristic of an impurity is that $\epsilon_{ic}^{(h)} \neq \epsilon$, thus introducing an excess free energy proportional to $N_i C$, where C is the number of crystal–impurity bonds per impurity, which in turn is the circumference of the impurity, in lattice units. The resulting free energy difference is $\Delta F = -(N - N_i S)\Delta\mu + N_i C \gamma_{ic}$, where γ_{ic} is the crystal–impurity line tension. In the simple case that the number of unoccupied sites between impurities is Δn and that the impurities are square with the side of length L lattice units, then $S = L^2$, $C = 4L$, and the CIS for which $\Delta F = 0$ is $\Delta n_c = L((1 + 4\gamma_{ic}/L\Delta\mu)^{1/2} - 1)$. There are several important features of this estimate. First, the thermodynamic argument readily explains the occurrence of negative step velocities: they arise because the effective supersaturation, $\Delta\mu_{\text{eff}} \equiv -\Delta F/(N - N_i S)$, is lowered to the point of undersaturation by the impurities already incorporated into the solid. Second, at low temperatures the line tension can be roughly estimated as the bond-energy difference per each molecule of the pair, i.e., $\gamma_{ic} \approx (\epsilon_{ic}^{(h)} - \epsilon)/2$. This way, an explicit dependence on the bonding characteristics of the impurity can be taken into account: this correctly predicts decreasing CIS with increasing $\epsilon_{ic}^{(h)}$. Third, in the limit of large impurities the CIS becomes $\lim_{L \rightarrow \infty} \Delta n_c = -2\gamma_{ic}/\Delta\mu$, which is precisely twice the critical radius predicted by classical nucleation theory for 2-d island nucleation¹¹ if γ_{ic} is the same as that of the

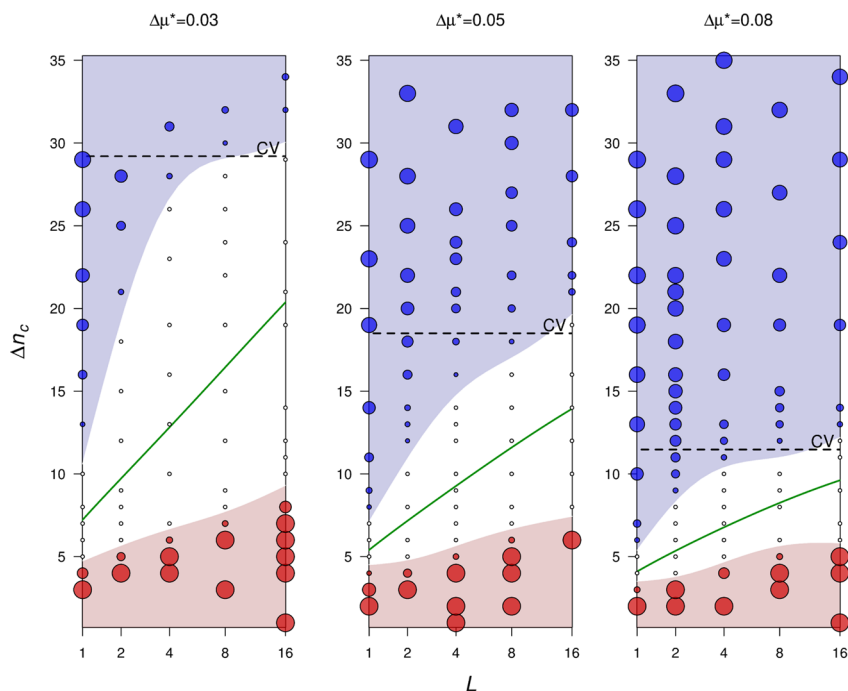


Figure 4. Critical impurity separation, Δn_c for blocking as a function of cluster size (in primary growth units), L , for three reduced supersaturations, $\Delta\mu^* \equiv \Delta\mu/|\epsilon|$. Each data point is represented by a circle the size of which is proportional to the absolute value of the velocity (up to a maximum imposed for clarity and a minimum needed for visibility). Blue indicates that the velocity was positive, red that it was negative, and white that the velocity was within the 95% confidence interval around zero. The green lines are the thermodynamic CIS calculated using the zero temperature line tension. The dashed horizontal lines are the CV predictions.

impurity-free step; this condition is true at low temperatures and a reasonable approximation at higher temperatures if $\epsilon_{ic}^{(h)} = 0$. In other words, the CV model is only valid in the limit of large impurities with zero horizontal bonding to crystal molecules.³⁵ Fourth, since the argument is based on thermodynamics, we would expect that neither a random distribution of impurities on the surface nor diffusion of crystal molecules will affect the CIS, in accord with the simulation results. Our results can be easily generalized to apply to a distribution of cluster sizes and geometries.

Many of these points are illustrated in Figure 4, which shows the step velocity as a function of impurity size and separation, for three different supersaturations. Our theoretical prediction for the critical impurity separation, based on the zero-temperature estimate for the crystal-impurity line tension, falls in all cases in the center of the “dead zone”, defined as the domain in which the measured velocity is less than the statistical error and, so, indistinguishable from zero. There is a dead zone because growing past a blocker requires a thermal fluctuation of sufficient size: for smaller blockers and/or higher temperatures these are frequent and the dead zone is narrow, while for larger blockers and/or lower temperatures they are less frequent and the dead zone is broader. Given that experimental observations and computer simulations are made over a finite time scale, step growth appears to cease sufficiently near the thermodynamically prescribed limit. True cessation only occurs for impurity separations equal to or below the thermodynamic limit unless, as in our case, the crystal already contains impurities, in which case it only occurs precisely at the CIS. Growth cessation above the CIS in a pure crystal and below the CIS in a crystal with embedded impurities is, rather, an experimental artifact determined by the time scale over which observations are made.

Dynamic Impurities. We have also investigated the same questions in the context of dynamic impurities that adsorb from solution and can evaporate. Figure 5 shows results for the same temperature and supersaturation as in Figures 2 and 3. The impurity vertical binding energy $\epsilon_{ic}^{(v)}$ is an additional variable.

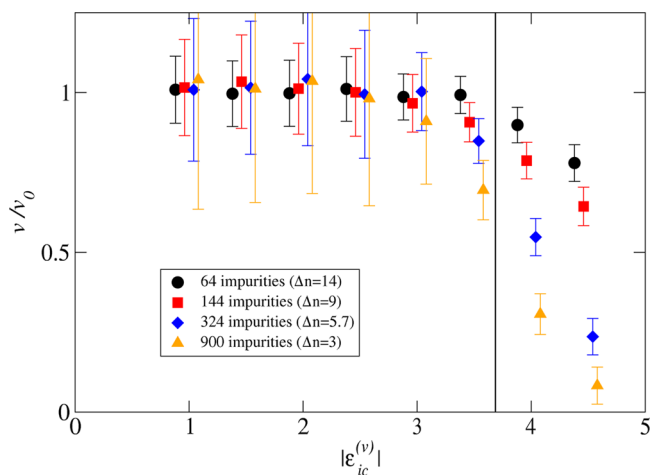


Figure 5. Step velocity as a function of the binding energy of impurities to the surface, $\epsilon_{ic}^{(v)}$, for a lattice of size 120×120 , temperature $k_B T = 0.25|\epsilon|$ and crystal supersaturation $\Delta\mu = 0.05|\epsilon|$. As the binding energy is varied, the concentration of impurities in solution (i.e., their supersaturation) is adjusted so as to result in the desired average number of impurities on the equilibrated surface. The legend gives in each case the average separation between impurities, Δn . The energy for which the velocity is equal to a lattice spacing divided by the residency time of an impurity is indicated by the line. The points have been slightly shifted horizontally to make the individual values apparent.

We therefore adjusted the supersaturation of impurities such that the average equilibrium density of impurities on the surface for a given value of $\epsilon_{ic}^{(v)}$ had a prescribed value. The figure shows that for small $|\epsilon_{ic}^{(v)}|$ the step velocity is almost completely unaffected, even if the average density is in the blocking regime for static impurities. It is only if the $|\epsilon_{ic}^{(v)}|$ is sufficiently high so that the impurities have sufficient residency time to be incorporated into the growing crystal and thereby lowering the effective supersaturation that blocking can occur. The threshold is therefore *that binding energy for which the residency time of an impurity is comparable to the time required for a step to grow by one lattice unit*. Since the residency time varies as $\exp(\epsilon_{ic}^{(v)}/k_B T)$, this creates the rather sharp threshold observed in the simulation. We can immediately deduce that impurity surface diffusion will have a similar effect on step blocking: blocking will only occur if the net residency time of an impurity in a given position is greater than this threshold. This again illustrates the thermodynamic origin of step blocking.

■ CONCLUDING REMARKS

We have reported on kinetic Monte Carlo simulations examining the effect of impurities on step growth. Our simulations circumvent many uncertainties inherent in experimental tests of the CV model that make its direct verification difficult, namely, assuming the validity of classical nucleation theory, uncertain values of physical quantities (e.g., line tension, impurity residency time, the impurity–crystal interaction, supersaturation at the crystal surface), the role of diffusion, the relation between impurity concentration in solution and the impurity density on the surface, and the effect of step interactions.

We have designed a setup which, in principle, maximizes the applicability of the CV model: it features impurities organized in a regular array, stationary impurities, impurities of identical size. We found, nevertheless, that the CV model only applies in the case of effectively large impurity clusters with long surface-residency times. A clear realm where this large-impurity limit holds is protein-mediated biomineralization, where the polypeptide impurity species can be several orders of magnitude larger than the main growth species (e.g., peptide adsorption on COM^{27} and CaCO_3^{28}). Another one is the clustering of impurities present in lysozyme solutions prepared from commercial sources (e.g., Sigma-Aldrich HEWL²⁹).

Experimentally, effectively large impurities can be realized by means other than impurity clusters. For example, an impurity with a positive horizontal binding energy will tend to oppose the occupation of its nearest neighbor sites by crystal molecules, which will in turn lower the probability of second nearest neighbor and further sites, the presence of the impurity therefore affecting an extended neighborhood. Another possibility is a point impurity that is incommensurate with the lattice, which results in the creation of a relatively long-range disturbance.

Smaller clusters and point impurities require much higher impurity densities to induce step blocking because thermal fluctuations are likely to drive the system past the limit implied by the GT effect. In fact, blocking is a result of two effects: an absolute, thermodynamic critical CIS dictated by the free-energy cost of removing a surface layer, and a larger, kinetically determined critical CIS that is the result of the classical arguments based on the GT effect and that therefore (a) depends on temperature, line tension, supersaturation, etc. and

(b) can be expected to scale as a function of these variables as activated processes do.

Our results are not completely unanticipated: Van Enckevort and Van den Berg made an early simulation study of step blocking,³⁰ but their systems were very small in comparison, and as noted by De Yoreo et al.²⁴ they worked either above the roughening transition or in a regime subject to surface nucleation. De Yoreo et al.²⁴ worked in a regime comparable to ours and also noted the importance of thermal fluctuations, but they concentrated on the kinetics of kink nucleation and did not put forward a dependence of the CIS on impurity concentration as given here, which includes a crossover to CV behavior for large clusters with no horizontal interactions. In this sense, our study is complementary to theirs. Anklam and Firozabadi³¹ recognized the importance of thermodynamics rather than the kinetic role of the GT effect, but did not apply this insight into the question of the role of the size dependence of impurities. To the best of our knowledge directly comparable experimental data are not available, since most of the published works measure step velocity and do not know the actual impurity spacing, as explained in detail in the Supporting Information, section “The experimental state-of-the-art”.

Our results were obtained for the case of a Kossel (i.e., simple cubic) lattice, and it is fair to wonder if this choice limits the generality of our conclusions. On the one hand, the CV theory is itself generic and is supposed to apply to all lattices: having demonstrated its failure for a specific lattice is therefore sufficient to put it into doubt for all cases. On the other hand, the reasoning that underlies our explanation of our results, namely, that it is the thermodynamics of impurity incorporation that ultimately leads to step blocking, is also quite generic and can reasonably be expected to hold generally. What may prove to be system specific is the difference between the CV and thermodynamic criterion and the dynamics of fluctuations. It is worth noting that the detailed prediction of the thermodynamic criterion will, in general, depend on specifics such as the number of neighbors, the range of the interaction, etc. and will have to be re-evaluated for other lattice types.

The interaction between steps and impurities depends on many factors: the size of the impurities, their residency time, and the strength of the crystal-impurity bonding, to mention a few. The Cabrera–Vermilyea critical impurity separation is actually an upper limit to step blocking and growth cessation: it is certainly true that greater separations between impurities cannot lead to growth cessation. In general, however, it is neither an accurate measure of the absolute limit of growth cessation, which is actually determined by the thermodynamics of impurity incorporation into the crystal, nor an accurate measure of the upper limit of the dead zone for growth, which depends, rather, on kinetic considerations vis-à-vis time scale of fluctuations versus observation times.

■ ASSOCIATED CONTENT

Supporting Information

Additional text (Methods and Materials, Additional Simulation Results, and Survey of the Experimental Literature) and two videos. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jlutsko@ulb.ac.be.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

J.F.L., A.E.S.V.D., D.M., and M.S. are grateful for the support by the Belgian PRODEX Programme under Contract Number ESA AO-2004-070. M.D. acknowledges support from the Spanish Ministry of Science and Innovation (MICINN), FPI Grant BES-2010-038422 (Project AYA2009-10655).

■ REFERENCES

- (1) Dandekar, P.; Doherty, M. F. *Science* **2014**, *344*, 705.
- (2) Orme, C. A.; Noy, A.; Wierzbicki, A.; McBride, M. T.; Grantham, M.; Teng, H. H.; Dove, P.; De Yoreo, J. J. *Nature* **2001**, *411*, 775.
- (3) Teng, H. H.; Dove, P. M.; Orme, C. A.; De Yoreo, J. J. *Science* **1998**, *282*, 724.
- (4) Rimer, J. D.; An, Z.; Zhu, Z.; Lee, M. H.; Goldfarb, D. S.; Wesson, J. A.; Ward, M. D. *Science* **2010**, *330*, 337.
- (5) Wei, H.; Wang, Z.; Zhang, J.; House, S.; Gao, Y.-G.; Yang, L.; Robinson, H.; Tan, L. H.; Xing, H.; Hou, C.; Robertson, I. M.; Zuo, J.-M.; LuHui, Y. *Nat. Nanotechnol.* **2011**, *6*, 93.
- (6) González-Segredo, N.; Nekovee, M.; Coveney, P. V. *Phys. Rev. E* **2004**, *69*, 061501.
- (7) González-Segredo, N. In *Soft Condensed Matter: New Research*; Dillon, K. I., Ed.; Nova Science: New York, 2007.
- (8) Humphrey, W.; Dalke, A.; Schulten, K. J. *Mol. Graphics* **1996**, *14*, 33–38.
- (9) Cabrera, N.; Vermilyea, D. *Growth of Crystals from Solution*; Proceedings of the International Conference, Cooperstown, NY, Wiley: New York, 1958; pp 393–410.
- (10) Burton, W. K.; Carbrera, N.; Frank, F. C. *Philos. Trans. R. Soc. London Ser. A* **1951**, *243*, 299.
- (11) Saito, Y. *Statistical Physics of Crystal Growth*; World Scientific: Singapore, 1998.
- (12) Davis, K. J.; Dove, P. M.; De Yoreo, J. J. *Science* **2000**, *290*, 1134.
- (13) Sleutel, M.; Willaert, R.; Wyns, L.; Maes, D. *Cryst. Growth Des.* **2009**, *9*, 335–343.
- (14) De Yoreo, J. J. *Biomolecular Modification of Inorganic Crystal Growth*; Lawrence Livermore National Laboratory: Livermore, CA, 2007; <https://e-reports-ext.llnl.gov/pdf/346930.pdf>.
- (15) De Yoreo, J. J. *Physical Mechanisms of Crystal Growth Modification by Biomolecules*; Selected Topics on Crystal Growth: 14th International Summer School on Crystal Growth. AIP Conference Proceedings; AIP Publishing: Melville, NY, 2010; Volume 1270, Issue 1, pp 45–58.
- (16) Kubota, N.; Mullin, J. J. *Cryst. Growth* **1995**, *152*, 203–208.
- (17) Weaver, M. L.; Qiu, S. R.; Hoyer, J. R.; Casey, W. H.; Nancollas, G. H.; De Yoreo, J. J. *Chem. Phys. Phys. Chem.* **2006**, *7*, 2081–2084.
- (18) Potapenko, S. Y. *J. Cryst. Growth* **1993**, *133*, 141–146.
- (19) Weaver, M. L.; Qiu, S. R.; Hoyer, J. R.; Casey, W. H.; Nancollas, G. H.; De Yoreo, J. J. *J. Cryst. Growth* **2007**, *306*, 135–145.
- (20) Nakada, T.; Sazaki, G.; Miyashita, S.; Durbin, S.; Komatsu, H. *J. Cryst. Growth* **1999**, *196*, 503–551.
- (21) Wang, L.; De Yoreo, J. J.; Guan, X.; Qiu, S.; Hoyer, J.; Nancollas, G. *Cryst. Growth Des.* **2006**, *6*, 1769–1775.
- (22) Land, T.; Martin, T. L.; Potapenko, S.; Palmore, G.; De Yoreo, J. *Nature* **1999**, *399*, 442–445.
- (23) Thomas, T. N.; Land, T. A.; Casey, W. H.; De Yoreo, J. J. *Phys. Rev. Lett.* **2004**, *92*, 216103.
- (24) De Yoreo, J. J.; Zepeda-Ruiz, L.; Friddle, R.; Qiu, S. R.; Wasylenki, L. E.; Chernov, A. A.; Gilmer, G.; Dove, P. M. *Cryst. Growth Des.* **2009**, *9*, 5135–5144.
- (25) Chatterjee, A.; Vlachos, D. G. *J. Comput.-Aided Mater. Des.* **2007**, *14*, 253–308.
- (26) Gilmer, G. H. *Science* **1980**, *208*, 355–363.
- (27) Friddle, R. W.; Weaver, M. L.; Qiu, S. R.; Wierzbickid, A.; Casey, W. H.; De Yoreo, J. J. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 11–15.
- (28) Elhadj, S.; De Yoreo, J. J.; Hoyer, J. R.; Dove, P. M. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 19237–19242.
- (29) Sleutel, M.; van Driessche, A. *Cryst. Growth Des.* **2013**, *13*, 688–695.
- (30) van Enckevort, W. J. P.; van den Berg, A. C. J. F. *J. Cryst. Growth* **1998**, *183*, 441–455.
- (31) Anklam, M. R.; Firozzabadi, A. *J. Chem. Phys.* **2005**, *123*, 144708.
- (32) In choosing parameters, there is always a trade-off: for low temperatures and/or low supersaturations, crystal growth is too slow and therefore computationally expensive, whereas for a given temperature there is a maximum supersaturation above which 2-d nucleation occurs, the consequent presence of multiple terraces making it difficult to determine, e.g., the step growth velocity.
- (33) In order to have a regular array, the lattice size in each direction must be commensurate with the repeating unit n in Figure 1. We therefore make small adjustments of the lattice size depending on the chosen value of n . For example, for clusters of size 4×4 and $n = 25$ we use a lattice of size 125×125 . The lattice-size dependence of our results is discussed in the Supporting Information.
- (34) In all cases, we monitor the estimated error of our measurements as discussed in the Supporting Information. For lower (respectively higher) temperatures or chemical potentials, we do longer (respectively shorter) runs so as to have roughly consistent estimated errors.
- (35) Note that this is only true for square clusters: circular clusters, for example, give a result that is one-half this value.