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PID TEMPERATURE CONTROL FOR THE COMPUTATIONAL STUDY OF CHIRAL CRYSTALLIZATION

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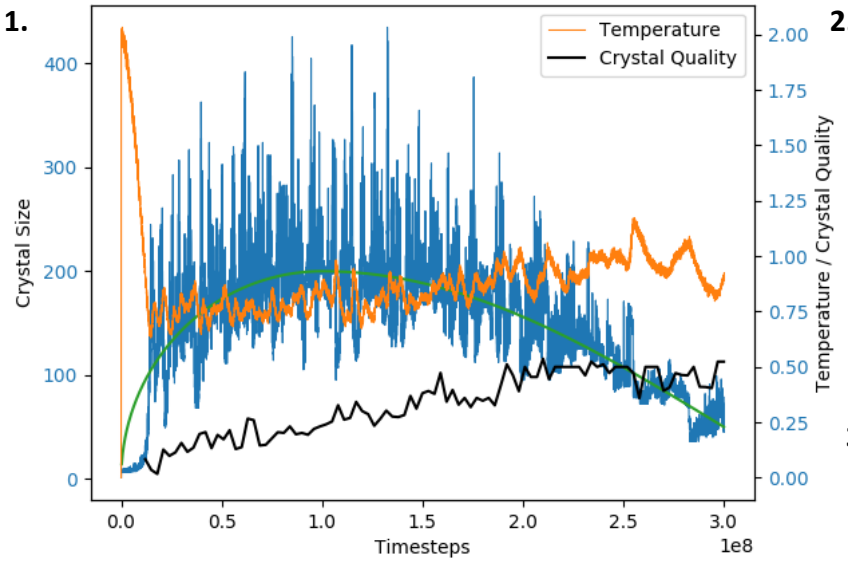
The chirality of a molecule has particular importance in biological processes.[1] A chiral molecule will have enantiomers, mirror-image isomers that cannot be superimposed on each other. Enantiomers with different chirality often have very different medical effects.[2] The separation of enantiomers holds particular importance for the production of many pharmaceuticals.[3] A simple, scalable, and inexpensive method of separating enantiomers is spontaneous chiral resolution, a process where, under the right conditions, a racemic mixture crystalizes into distinct enantiopure crystals. However, the majority of organic racemic mixtures form racemic crystals rather than enantiopure conglomerates.[6] It is still unclear why some molecules can spontaneously resolve into separate enantiopure crystals, while the majority form racemic structures.[4,6]

1.



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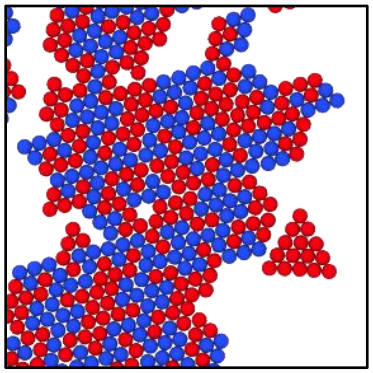
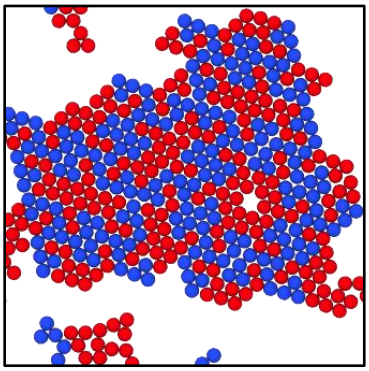


1.0e8 timesteps

3.



2.7e8 timesteps

Figures: (1) The crystallization of a chiral molecule is controlled by the prototype PID controller. The setpoint is the green curve, and represents the cluster size that the PID controller attempts to achieve. The quality of the crystals improves as the crystal is grown and annealed. **(2 & 3)** Examples of clusters found at different times during the simulation.

Computer simulations represent a promising way to better understand the underlying mechanisms behind spontaneous resolution. Simulations can probe the kinetic and thermodynamic factors in the crystallization of chiral molecules[5] and can potentially be used to predict the likelihood of spontaneous separation from the properties of a particular chiral molecule. However, straightforward molecular dynamics computer simulations of the crystallization of molecules are plagued by accessible timescales that are much shorter than those of experimental crystallization studies. As a result, crystallization cannot typically be simulated under experimental conditions of mild supersaturation, even if very simple models are used. Under conditions of strong supersaturation, which must be employed in MD simulations to enhance solidification rates, many systems fail to crystallize well and form disordered solids instead. To address this challenge, we are developing new computational methods to more closely control the simulation conditions to encourage crystallization. We modify the temperature with proportional-integral-derivative (PID) controllers. These controllers monitor a particular aspect of the simulation, such as the maximum cluster size, and iterate the temperature to achieve a target value. If appropriate parameters are chosen for this controller, we can maintain ideal simulation conditions and facilitate crystal nucleation and growth. When optimized, efficient coarse-grained models of chiral crystallization of could provide valuable insight into the guiding principles that determine the crystallization behavior of import chiral molecules.

References

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