

An approach to model the solution growth morphology using a macroscopic diffusion approach

Max Petersen, Accelrys Inc., 10188 Telesis Court, Suite 100, San Diego, CA 92116

Project description

This project deals with understanding morphology of a molecular crystal grown from solution. This problem is relevant to pharmaceutical development as growth from solution is a main mechanism for drug purification. Furthermore, the morphology of the crystallites can crucially affect aspects of drug delivery (delivery via inhalation, dispersion, dissolution, etc.). The general ability to model and predict morphological changes due to the solvent environment critically affects the ability of computational scientists to perform a virtual pre-selection of optimum solvent environment growth conditions, and therefore to guide experiment to reduce time to market in pharmaceutical development.

This project is intended to take place in two phases. Phase 1 will focus on dealing with general aspects of the solvent environment, specifically with solving a diffusion equation involving discontinuous boundary conditions. The growth of facets will be studied using simple model systems. Ideally, creation and annihilation of facets will be addressed during this phase. Phase 2 will take the results and generalize them to realistic growth habits, involving arbitrary symmetry. Furthermore, the team will work on understanding effects of families of virtual facets and their emergence during growth.

Technical description

Understanding the morphology of a molecular crystal grown from solution is one of the key questions pharmaceutical company approach us with when exposing them to our tools to understanding morphologies. These tools are based on the calculation of either surface- or attachment-energies in vacuum. Although this approach often gives valuable insights in certain aspect of a morphology problem, the morphology for crystallites found during growth from solution experiments can deviate dramatically from morphologies predicted for the vacuum environment. In particular, certain molecular crystallites can be found as “needles” or “plates” which can give raise to manufacturing or other technological problems.

This proposal suggests the following way to attack this problem using a macroscopic diffusion approach. To facilitate the discussion, here some definitions:

$f_i(t)$: facet i as determined by a Miller index $[hkl]$ at time t .

$d_i(t)$: distance to the center of the morphology facet $f_i(t)$ at time t .

For the vacuum case the morphology is constructed by determining the $d_i(t)$ either from the surface energy (“equilibrium morphology”) or from the attachment energy (“growth morphology”). The facets $f_i(t)$ are then constructed by generating planes normal to the $d_i(t)$ ’s (note that they also define a direction via the Miller indices [hkl]). The enclosed volume defines the morphology. Facets can be either exposed or hidden, depending on the relative lengths of the $d_i(t)$. In this scenario the $d_i(t)$ ’s and $f_i(t)$ ’s are time independent because they are determined from energetic arguments. This is quite different when the crystallite grows from solution. At any stage during the growth process the facets $f_i(t)$ are in contact with the solvent and ad-molecules. The speed $v_i(t)$ in which $f_i(t)$ grows will depend on the concentration of the ad-molecules present at the boundary of the solution to the facet. This concentration profile can be conveniently described via a diffusion equation

$$\frac{\partial \rho}{\partial t} = D\Delta\rho + F \quad (1) \quad \text{together with the boundary condition}$$

$$\rho|_{f_i(t)} = c_i \quad (2),$$

where D is a diffusion constant and F a flux term that can represent an incoming flux of ad-molecules (typically zero for most experimental scenarios). Note that the diffusion constant that determines the physical properties of the system can be readily determined using Accelrys’ modeling tools (Discover, COMPASS, AmorphousCell). $c_i(t)$ are the boundary condition for (1). These parameters take the role of the attachment energies (or surface energies). They can either be approximated by atomistic simulations (e.g. force-field simulations of the facet-solvent interface or similar) or can be used to reverse engineer a known experimental morphology scenario. The latter could shed light on the currently not well-understood energetics present at the solvent-facet interface.

Once ρ is known, the growth velocity $v_i(t)$ of facet $f_i(t)$ is given by

$$v_i = \frac{\partial \rho}{\partial n_i} \quad (3) ,$$

where n_i is the normal onto facet $f_i(t)$.

At this stage the $d_i(t)$ ’s are updated by a time increment Δt :

$$d_i(t + \Delta t) = d_i(t) + v_i\Delta t \quad (4) .$$

Another important aspect of the growth from solution problem is the dynamical creation/disappearance of facets during time. Depending on the diffusion field, facets might appear or disappear due to the fact that now $d_i(t)$ depends on t . In particular, for zero flux case at late growth stages the morphology will approach thermodynamic equilibrium due to the depletion of ad-molecules in the solvent environment. This typically goes along with the formation of a multitude of facets.

Whereas the disappearance of a facet is trivially accounted for during the update of the morphology, the creation of a new facet is somewhat subtler. A non-exposed facet can be thought of as a one- or two-dimensional object that defines the corners of the morphology object. In the argument of the vacuum “growth morphology” non-exposed facets are interpreted as too fast growing to ever show up since they outgrow slower facets. Therefore, the borders of a given morphology can be viewed as a facet that grows so fast that it is reduced to a one- or two-dimensional object (depending on the bulk crystal symmetry). The list of non-exposed facets that can possibly appear during an update in time-step will therefore be generated taking the distances $l_i(t)$ of the center to the edges and vertices of the morphology object. Also an associated growth velocity has to be determined – otherwise every $l_i(t)$ would be generated at each time step. The growth velocities of the non-exposed facets can be conveniently expressed as

$$v_i^{\text{line}} = \frac{1}{L} \int \frac{\partial \rho}{\partial n_i} dL \quad (5) \quad \text{for 2-dimensional non-exposed facets and}$$

$$v_i^{\text{point}} = \frac{1}{2\pi} \int \frac{\partial \rho}{\partial n_i} d\varphi \quad (6) \quad \text{for 1-dimensional non-exposed facets.}$$

In Eq.(5) the integral runs over the length of the boundary defining the 2-dim facet, and in Eq.(6) it is the radial integral around the point that defines the 1-dim facet.

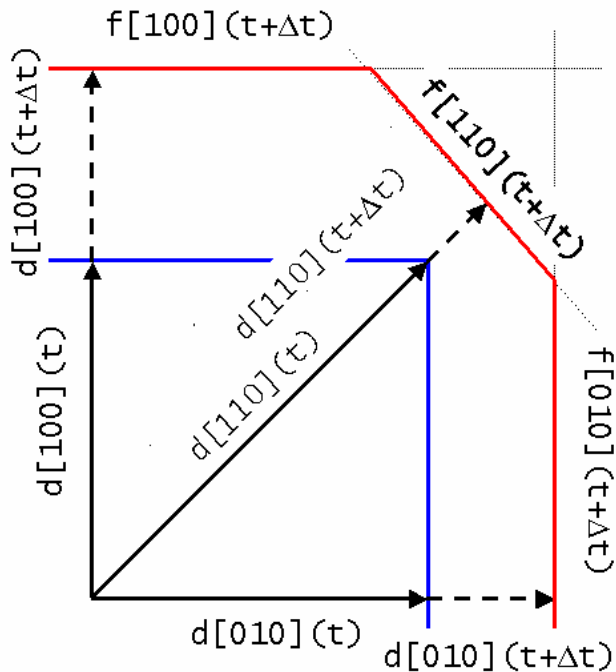


Figure 1: Dynamical update of the morphology. Note that due to the higher growth velocity of $d[100]$ the relative surface area of facet $f[100]$ is reduced. This also leads to the appearance of facet $f[110]$ during this time step.

The updated $d_i(t)$'s together with the $l_i(t)$'s give now raise to an updated morphology. This is schematically illustrated in Fig.1. At this point the algorithm is to be repeated until a final simulation time is reached.