A Study of One Dimensional Population Balance Modeling Techniques for Crystallization Processes

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CRYSTALS: AN INTRODUCTION

All solid matter may be classified as either amorphous or crystalline. The crystalline state differs from the amorphous state in the regular arrangement of its constituent molecules. Crystals are anisotropic, that is, their mechanical, electrical, magnetic and optical properties vary according to the direction in which they are measured. Crystals belonging to the cubical system are a notable exception.

A crystal consists of a lattice of molecules, atoms or ions whose locations in the lattice are unique to each substance. This regularity in internal structure results in a characteristic crystal shape for each crystalline substance.

Many of the geometric shapes that appear in the crystalline state are readily recognized as being symmetrical and this fact can be used as a means of crystal classification. The three elements of symmetry considered are,

1. Symmetry about a point,
2. Symmetry about a line,
3. Symmetry about a plane

A crystal possesses a centre of symmetry when every point on the surface of the crystal has an identical point on the opposite side of the centre, equidistant from it. One such example is a cube.

A crystal possesses an axis of symmetry if, when the crystal is rotated once around the said axis (i.e., 360º), it appears to have reached its original position more than once. If a crystal has rotated through 180º before appearing to reach its original position, the axis is one of two fold symmetry(Mullin). If it has rotated through 120º, 90º or 60º the axes are of threefold symmetry (triad axis), fourfold

symmetry (tetrad axis) and sixfold symmetry (hexad axis), respectively. A cube has 13 axes of symmetry, 6 diad axes through opposite edges, 4 triad axes through opposite corners and 3 tetrad axes through opposite faces(Mullin).

A plane of symmetry bisects an object such that one half becomes a mirror image of the other half in the given plane. A cube has 9 planes of symmetry, 3 rectangular planes each parallel to two faces, and 6 diagonal planes passing through opposite edges.

Crystal systems: crystals may be grouped into 7 systems(Mullin). These are

1. Regular,
2. Tetragonal,
3. Orthorhombic
4. Monoclinic,
5. Triclinic,
6. Trigonal and
7. Hexagonal

The first six of these systems can be described with reference to three axes, x, y and z. The angle between the y and z axes is denoted by α, that between x and z by β and that between x and y by γ. Four axes are required to describe the hexagonal system. The z axis is vertical and perpendicular to the other three axes (x, y and u), which are coplanar and inclined at 60º to one another.

A brief comparative description of the seven systems is given in the following table(Mullin).

System	Other names	Angles between axes	Length of axes	Examples
Regular	Cubic Octahedral Isometric Tesseral	$\alpha=\beta=\gamma=90^{\circ}$	$x=y=z$	Sodium chloride Potassium chloride Alums Diamond
Tetragonal	Pyramidal Quadratic	$\alpha=\beta=\gamma=90^{\circ}$	$x=y\neq z$	Rutile Zircon Nickel sulphate.7H_2O
Orthorhombic	Rhombic Prismatic Isoclinic Trimetric	$\alpha=\beta=\gamma=90^{\circ}$	$x\neq y\neq z$	Potassium permanganate Silver nitrate Iodine α-Sulphur
Monoclinic	Monosymmetric Clinorhombic Oblique	$\alpha=\beta=90^{\circ}$ $\gamma\neq90^{\circ}$	$x\neq y\neq z$	Potassium chlorate Sucrose Oxalic acid β-Sulphur
Triclinic	Anorthic Asymmetrical	$\alpha\neq\beta\neq\gamma\neq90^{\circ}$	$x\neq y\neq z$	Potassium dichromate Copper sulphate.5H_2O
Trigonal	Rhombohedral	$\alpha=\beta=\gamma\neq90^{\circ}$	$x=y=z$	Sodium nitrate Ruby Sapphire

Hexagonal	None	Z axis is perpendicular to the x, y and u axes, which are inclined at 60º	X=y=u≠z	Silver iodide Graphite Water(ice) Potassium nitrate

Bonding in crystals: Crystalline solids may be classified into four main types according to their method of bonding viz. ionic, covalent, molecular and metallic(Mullin).

Ionic crystals are composed of charged ions held in place in the lattice by electrostatic forces, and separated from the oppositely charged ions by regions of negligible electron density.

In covalent crystals the constituent atoms do not carry effective charges; they are connected by a framework of covalent bonds.

Molecular crystals are composed of discrete molecules held together by weak attractive forces.

Metallic crystals consist of ordered arrays of identical cations. The constituent atoms share their outer electrons as in covalent bonds, but these are so loosely held that they are free to move through the crystal lattice and give metallic properties to the bond.

Polymorphism and Racemism: crystals may exist as isomorphs and polymorphs. Isomorphs are those crystals that crystallize in almost identical forms and are chemically similar. Polymorphs on the other hand are chemically identically crystals that crystallize in different forms.

PHYSICAL AND CHEMICAL PROPERTIES OF CRYSTALS

Growth and nucleation kinetics of crystals depend on the deformation of the crystal lattice. The degree of deformation is a function of the shear modulus, Young's modulus, the Poisson ratio and the fracture resistance. An isotropic material has two elasticity constants, the shear modulus and the Poisson's ratio from which all possible constants can be calculated. Anisotropic materials on the other hand may have between 3 (for the cubic system) and 21 (for the triclinic system) elastic constants depending on the symmetry. Assuming that impacts on a crystal are distributed statistically in all axial directions, the effective (isotropic) elastic properties can be estimated from the constants. The Poisson ratio is give as

$$v_c = E/2\mu - 1$$

where E is the Young's modulus and μ is the shear modulus.

The attrition of crystals due to mechanical impact depends on the brittleness of the material. This brittleness can be described by a ration of the Young's modulus E and the hardness H. materials with a high E/H ratio (>180) are more ductile(Mersmann).

Surface tension of crystals: The interfacial tension Y_{CL} between the solid phase and the surrounding mother liquor is of importance for primary nucleation and for integration limited growth(Mersmann). In both cases, the kinetics is limited by a thermodynamic balance; the free enthalpy, which is gained proportional to the

crystallized volume, must extend the free enthalpy necessary to build the new surface(Mersmann). In principle, Y_{CL} is comparable to the surface tension of a liquid phase in equilibrium with its vapor. However, because of restricted mobility of the molecules in the solid phase, the surface is not usually at minimum free energy. Structural damage that the crystal has undergone will contribute to surface stress, τ_{CL}. The total energy per unit area is given by(AW Adamson)

$$\tau_{CL} = Y_{CL} + A(\delta \tau_{CL}/\delta A)$$

Supersaturation: Crystallization processes are best represented by enthalpy-concentration diagrams. The number of collisions of elementary units like atoms ions and molecules with those in the fluid phase or at the phase interface of the crystalline phase depends on the number of units per unit volume of the fluid phase(Mersmann):

$$\frac{Number\ of\ units}{Volume\ of\ fluid\ phase} = \frac{nNa}{V} = CNa$$

A saturated fluid having concentration C^* is in thermodynamic equilibrium with the solid phase at the relevant temperature. If the solution is liquid, the saturation concentration often depends strongly on the temperature but only slightly on the

pressure(Mersmann). If a fluid phase has more units than C^*Na, it is said to be supersaturated. Crystallization processes can take place only in supersaturated phases, and the rate of crystallization is often determined by the degree of supersaturation. Supersaturation is expressed either as a difference in concentration(Mersmann)

$$\Delta C = C - C^*$$

Or as relative supersaturation(Mersmann),

$$S = C/C^*$$

The fundamental driving force for crystallization is the difference between the chemical potential of a given substance in the transferring and the transferred state, i.e., in solution (state 1) and the crystal (state 2). For an unsolvated solute crystallizing from a binary solution, this may be written as(Mersmann)

$$\Delta\mu = \mu_1 - \mu_2$$

The chemical potential is defined in terms of the standard chemical potential μ_0 and the activity 'a' by(Mersmann)

$$\mu = \mu_0 + RT\ln a$$

the fundamental driving force for crystallization may therefore be expressed as (Mersmann)

$$\Delta\mu/RT = \ln(a/a^*) = \ln S'$$

Where a^* is the activity for a saturated solution, S' the activity supersaturation, R the gas constant, and T the absolute temperature, i.e.,

$$S' = e^{\Delta\mu/RT}$$

For electrolytic solutions, use of mean ionic activity a_+ is more appropriate. This is defined by(Mersmann)

$$a = a^v_{+-}$$

where v is the number of moles of positive and negative ions in one mole of solute. Therefore

$$\Delta\mu/RT = v\ln S_a$$

Where

$$S_a = a_{+-}/a_{+-}^{*}$$

Solubility: The saturation concentration of a substance in a solvent is obtained experimentally by determining the maximum amount that is soluble at a given temperature. Solubility often increases with temperature, but there are also other systems in which the saturation concentration remains approximately constant or decreases with an increase in temperature. The solubility curve for hydrates has a kink where the number of solvent molecules per molecule of dissolved substance changes(Mersmann).

NUCLEATION

Nucleation requires supersaturation, which is obtained usually by a change in temperature (cooling in case of a positive gradient of the solubility curve and heating in case of a negative gradient), by removing the solvent, or by adding a drowning out agent or reaction partners(Mersmann). The system then attempts to attain thermodynamic equilibrium through nucleation. If the solution contains neither solid foreign particles nor crystals of its own type, nuclei are formed only through homogeneous nucleation. If foreign particles are present then nuclei are formed through heterogeneous nucleation. Both homogeneous nucleation and heterogeneous nucleation are classified as primary nucleation. This primary nucleation occurs only when metastable supersaturation is achieved in the system. However, it has been observed that nuclei occur even at very low supersaturation levels (less than metastable supersaturation) when solution-own crystals are present. This type of nucleation is called secondary nucleation. This may result from contact, shearing action, breakage, abrasion, and needle fraction(Mersmann).
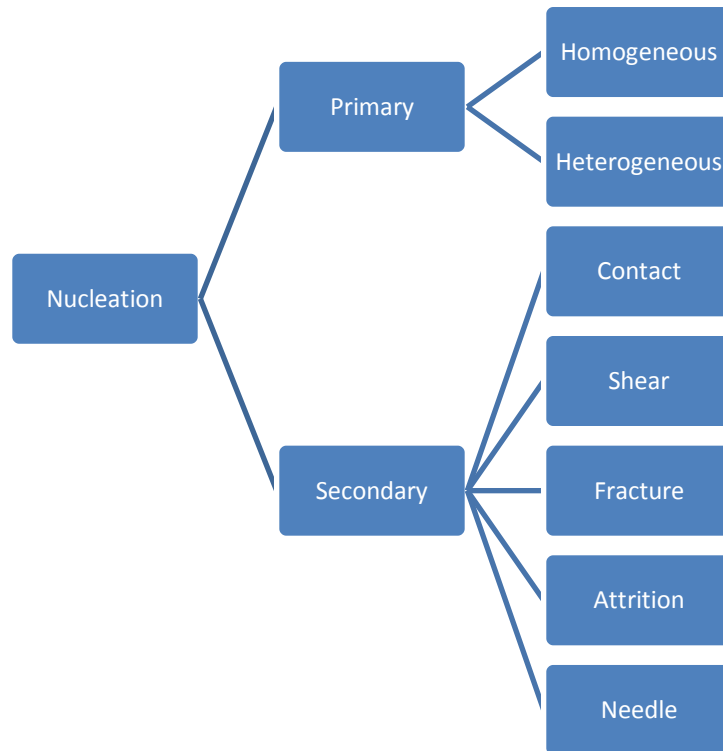
(Mersmann)

Primary Nucleation

Homogeneous nucleation: For the formation of crystal nuclei, the constituent molecules have to first coagulate, resisting the tendency to redissolve, following which they have to become oriented in a fixed lattice. Stable nuclei arise from a sequence of bimolecular additions as follows(Mullin):

$$A + A \leftrightarrow A_2$$

$$A_2 + A \leftrightarrow A_3$$

$$A_{n-1} + A \leftrightarrow A_n \quad \text{(critical cluster)}$$
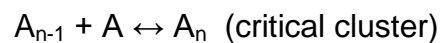
Further molecular additions to the critical cluster result in nucleation and subsequent growth of the nucleus(Mullin). Similarly, ions or molecules in a solution can form short lived clusters. Short chains may be formed initially and eventually a crystalline lattice is built up. The construction process can only continue in local regions of very high supersaturation and many sub-nuclei fail to mature and form nuclei, simply redissolving instead(Mullin). However, if a nucleus grows beyond a certain critical size, it becomes stable. The structure of this critical nucleus is not known, and it is too small to observe directly.

The classical theory of nucleation is based on the condensation of a vapor to a liquid. The free energy changes associated with the process of homogeneous nucleation are as follows(Mersmann).

The overall excess free energy, ΔG, between a small solid particle of solute (assumed to be a sphere of radius r for the sake of simplicity) and the solute in the solution is equal to the sum of the surface free energy, ΔG_S, i.e. the excess free energy between the surface of the particle and the bulk of the particle, and the volume excess free energy, ΔG_V, i.e. the excess free energy between a very large particle (r = ∞) an the solute in solution. ΔG_S is a positive quantity, the magnitude of which is proportional to r^2. In a supersaturated solution ΔG_V is a negative quantity proportional to r^3. Thus

$$\Delta G = \Delta G_S + \Delta G_V$$

$$= 4\pi r^2 \gamma + (4/3)\,\pi r^3 \Delta G_V \text{ (Mullin)}$$

Where ΔG_V is the free energy change of the transformation per unit volume and γ is the interfacial tension i.e., between the developing crystalline surface and the supersaturated solution in which it is located. The two terms on the right hand side of the equation above are of opposite sign and depend differently on r, so the free energy of formation, ΔG, passes through a maximum, which corresponds

to the critical nucleus, r_c and for a spherical cluster is calculated by optimizing the aforementioned equation. Thus,

$$d\Delta G/dr = 8\pi r^2 \Delta G_V = 0$$

therefore,

$$r_c = =2\gamma/\Delta G_V$$

where ΔG_V is a negative quantity. From the above result we get

$$\Delta G_{crit} = 4\pi\gamma r^2_c/3$$

The behavior of a newly created crystalline lattice structure in a supersaturated solution depends on its size. It can either grow or dissolve depending on which process results in a decrease of free energy of the particle. The critical size, r_c therefore represents the minimum size of a stable nucleus(Mullin).

The energy of a fluid system at constant temperature and pressure is constant, however this does not mean that the energy level is same at all parts of the fluid. There will be fluctuations in the energy about the constant value, which is to say that there will be a statistical distribution of energy in the molecules constituting the system (molecular velocity) and in those supersaturated regions where the energy rises temporarily to a high value nucleation will be favored(Mullin).

The rate of nucleation, J, can be expressed as the Arrhenius reaction velocity equation commonly used for the rate of a thermally activated process(Mullin):

$$J = Ae^{(-\Delta G/kT)}$$

Where **k** is the Boltzmann constant.

The basic Gibbs Thomson relationship for a non electrolyte may be written as

$$\ln S = 2\gamma v/kTr \text{ (Mullin)}$$

where S is the supersaturation given by $S = c/c^*$, c being the concentration and c^* being the concentration at supersaturation. N is the molecular volume. Thus,

$$\Delta G_V = 2\gamma/r = kT\ln S/v$$

Hence,

$$G_{crit} = 16\pi\gamma^3 v^2/3(kT\ln S)$$

Finally,

$$J = A\exp(-(16\pi\gamma^3 v^2)/(3\mathbf{k}^3 T^3 (\ln S)^2))$$

This equation shows that three main variables govern the rate of nucleation, temperature, T, the degree of supersaturation, S and interfacial tension, γ.

An empirical approach that expresses a relationship between the induction period, t_{ind} (the time interval between mixing two reacting solutions and the appearance of crystals) and the initial concentration, c of the supersaturated solution may be expressed as follows (Nielsen)

$$t_{ind} = kc^{1-p}$$

where k is a constant and p is the number of molecules in a critical nucleus.

Measurement of homogeneous nucleation: In an early attempt to study nucleation(Vonnegaut) a liquid system was dispersed into a large number of discrete droplets, exceeding the number of heteronuclei present. A significant number of droplets were therefore mote-free and could be used or the study of true homogeneous nucleation.

An expansion cloud chamber was used by Miller Anderson et al (1983) to measure homogeneous nucleation rate of water over a wide range of temperature from 230-290K and nucleation rates of $1-10^{16}$ drops $cm^{-3}s^{-1}$. The comprehensive nature of this data allows for a detailed comparison between theoretical and experimental work. The expansion chamber technique employs continuous pressure measurement and an adiabatic pulse of supersaturation to give the time history of supersaturation and temperature during the nucleation.

The resulting drop concentration is determined using photographic techniques(RC Miller).

Predicting the nucleation rate quantitatively is not a trivial task, and deviations of several orders of magnitude between theoretical predictions and experimentally determined nucleation rates are common. Small angle X-ray scattering experiments have been employed to measure the mean radius, the width of the distribution function and the particle number density as a function of the initial mixture composition. Static pressure trace measurement experiments were conducted to measure the temperature, partial pressure, supersaturation and characteristic time corresponding to the peak nucleation rates and this data was combined with that obtained from SAXS experiments to directly quantify nucleation rate as a function of temperature and supersaturation(D Ghosh).

Heterogeneous nucleation: Even a very small amount of impurities in a solution may affect the rate of nucleation greatly. However, an impurity may have different effects on different solutions and may not have an inhibiting effect in all cases; in fact, it may even act as an accelerator sometimes(Mullin).

It has been observed in many cases that what initially appears to be a case of homogeneous nucleation has actually been induced in some way(Mullin). In that sense there is very sparse occurrence of truly homogeneous nucleation. For example, a supercooled system can be seeded unknowingly by the presence of atmospheric dust containing active particles i.e., heteronuclei.

The presence of a foreign body surface can induce nucleation at degrees of supersaturation lower than those required for spontaneous (homogeneous) nucleation(Mullin). Thus the overall free energy associated with the formation of a critical nucleus under heterogeneous conditions $\Delta G'_{crit}$, should be less than the

corresponding free energy change, ΔG_{crit} associated with homogeneous nucleation. Hence,

$$\Delta G'_{crit} = \varphi \Delta G_{crit}$$

Where the factor φ is less than 1.

Secondary nucleation

A supersaturated solution nucleates more readily when crystals of the solute are already present or deliberately added. This type of nucleation is called secondary nucleation, as opposed to primary nucleation where crystals of the solute are not present initially(Mullin).

Contact nucleation

It has been observed that even at moderate levels of supersaturation, crystal contacts readily cause secondary nucleation. In the secondary nucleation of $MgSO_4.7H_2O$ crystal-crystal contacts gave up five times as many nuclei as did crystal-metal rod contacts(NA Clontz).

Crystal agitator contacts may be a cause for secondary nucleation in crystallizers.

Seeding

Seeding of a supersaturated solution with small particles of material to be crystallized is probably the best method for inducing crystallization. Deliberate seeding may be used to have some degree of control over the product size and size distribution. Seed crystals however, need not necessarily consist of the material being crystallized.

Seed crystal size is considered to be influential in secondary nucleation(RW Rousseau). There may be several reasons for this. Large seeds generate more secondary nuclei than do small seeds because of their greater contact probabilities and collision energies. Very small crystals can follow the streamlines within the turbulence eddies in vigorously agitated solutions, essentially behaving as if they were suspended in a stagnant fluid, rarely coming into contact with the agitator or other crystals(Mersmann).

Unintentional Seeding

Uncontrolled seeding is frequently encountered in the laboratory and in the industry and it is an uncontrolled event that can cause considerable frustration if not checked.

CRYSTAL GROWTH

Crystal growth occurs as soon as nuclei with radius larger than the critical radius have been formed. There are many proposed mechanisms for crystal growth.

The surface energy theories are based on the hypothesis that the shape a growing crystal assumes is such that it has a minimum surface energy. This approach largely fallen out of favor.

Diffusion theories assume that matter is deposited continuously on the crystal face at a rate proportional to the difference in concentration between the point of deposition and the bulk of the solution.

When dealing with crystal growth in an ionizing solute, the following steps can be distinguished (Mullin)

1. Bulk diffusion of solvated ions through the diffusion boundary layer
2. Bulk diffusion of solvated ions through adsorption layer
3. Surface diffusion of solvated or unsolvated ions
4. Partial or total desolvation of ions
5. Integration of ions into the lattice
6. Counterdiffusion through adsorption layer of water released
7. Counterdiffusion of water through the boundary layer

The slowest of these steps are rate determining(Mersmann).

A crystal surface grow in such a way that units in a supersaturated solution are first transported by diffusion and convection and then built into the surface of the crystal by integration or an integration reaction , with the supersaturation, Δc, being the driving force.

The entire concentration gradient, $\Delta c = c - c^*$, is divided into two parts. The first part, $c - c_l$ is responsible for diffusive-convective transport. The second part, $c_l - c^*$ is responsible for the integration reaction within the boundary layer.(Mersmann)

Thus, for growth completely determined by diffusion and convection,

$$c_l - c^* << c - c_l \text{ (Mersmann)}$$

And, when growth is controlled by integration reaction,

$$c_l - c^* >> c - c_l \text{ (Mersmann)}$$

The mass flux density m directed towards the crystal surface is

$$m = k_d(c - c_l) = k_r(c_l - c^*)^r$$

herem k_d is the mass transfer coefficient, k_r is the reaction rate constant and r is the order of the integration reaction(Mersmann).

Reaction rate constant according to the Arrhenius equation is given as follows

$$k_r = k_{r0}e^{(-\Delta E_r/RT)}$$

Where k_{r0} is the reaction constant and ΔE_r is the activation energy. Crystal growth can also be described through the displacement rate of a crystal surface, v, or the overall growth rate, G = dL/dt. The overall growth rate refers to any characteristic length, and generally the diameter of the crystal is used. Consider r is the radius such that r=L/2, where the diameter is that of a sphere corresponding to geometrically similar crystals with volume shape factor $\alpha = V_p/L^3$ and the surface shape factor, $\beta = A_p/L^2$. The following is the relation between mass flux density, m, mean displacement rate, v_{av}, and crystal growth rate, G = $2v_{av}$ (Mersmann)

$$m = A_p^{-1}dM/dt = (6\alpha/\beta)\rho_c dr/dt = (6\alpha/\beta)\,\rho_c v_{av} = (3\alpha/\beta)\rho_c G$$

Diffusion controlled crystal growth:

When the rate of the integration reaction is very fast, the diffusive-convective transfer determines the crystal growth. Thus, $c - c_l \approx c - c^* = \Delta c$ and the following is obtained when the mass flux density is low(Mersmann)

$$M = k_d \Delta c$$

Or

$$G = (\beta/3\alpha)k_d \Delta c/\rho_c$$

If k_d is used to denote purely diffusive or true mass transfer coefficients and $k_{d.s}$ the mass transfer coefficients at a semipermeable interface, the following holds true(Mersmann)

$$k_{d,s} = k_d/(1-w_i)$$

Where w_i is the mass fraction.

G Teqze et al studied freezing to the body-centered cubic (bcc), hexagonal close-packed (hcp), and face-centered cubic (fcc) structures and observed faceted equilibrium shapes and diffusion-controlled layerwise crystal growth consistent with two-dimensional nucleation(G Teqze).

Integration controlled crystal growth:

When the rate of diffusive-convective transport of units is high, integration controlled crystal growth becomes the rate determining step for crystal growth. The individual processes can be diverse and complex, and therefore are difficult to understand.(Mersmann)

POPULATION BALANCE EQUATIONS: AN INTRODUCTION

The analysis of a particulate system seeks to predict the behavior of a population of particles and its environment from the behavior of single particles and their local environments. The population is usually described by the number density of the particles, though on occasion the density of a different extensive variable such as mass or volume may be used(Ramakrishna).

Chemical Engineers have put Population balances to the most diverse use. Applications have covered a wide range of systems such as such as solid-liquid dispersions, and gas-liquid, gas-solid, and liquid-liquid dispersions(Ramakrishna).

Particulate processes today are widely used in the pharmaceutical industry. Such processes include granulation, milling and crystallization. These processes often exhibit a low order of symmetry. In order to obtain constant solid properties in such cases, it is necessary to monitor and to control several distributed parameters(F Puel)

It has been found that the particulate processes mentioned above are best described by the use of population balance equations. Such processes involve formation of entities, growth, breakage or aggregation of particles, as well as dispersion of one phase in another one, and are, therefore, present in a large range of applications, like polymerization, crystallization, bubble towers, aerosol reactors, biological processes, fermentation or cell culture(Caliane Bastos Borba Costa)

The particles under consideration have both internal and external coordinates. The internal coordinates of the particle quantitatively characterize the traits of the particle other than its physical location, which is provided exclusively by the external coordinates. The population balance equation is an equation in the number density of particles and may be regarded as representing a number balance on particles of a particular state(Ramakrishna).

PBEs were first introduced by Hulbert and Katz(HM Hulbert). Later they were tailored for crystallization processes by Randolph and Larson (AD Randolph, Theory of Particulate Processes (2nd Edition)).

Oucherif, Raina et al. employed a population balance model to study the effect of polymer additive hydroxyl propylmethyl cellulose (HPMC) on inhibiting the nucleation and growth of felodipine for supersaturated aqueous solutions(Kaoutar Abbou Oucherif). Seeded and unseeded desaturation experiments were carried out to characterize growth and nucleation kinetics respectively. A mathematical model for the batch crystallization of felodipine was then constructed by using empirical expressions for nucleation and growth, a population balance equation, and a material balance. Kinetic parameters in growth and nucleation expressions were obtained by fitting simulated results to experimental data(Kaoutar Abbou Oucherif).

Ma and Wang have used population balance modeling for crystallization processes to investigate model identification techniques for deriving size dependent facet growth kinetics models as functions of supersaturation and size of the crystal(Y Ma Chao).

THE ONE DIMENSIONAL POPULATION BALANCE EQUATION

Consider a population of particles distributed according to their size, say 'x'. Here 'x' is assumed to be the mass of the particles and it varies between 0 and ∞. The number density of the particles is considered to be independent of the external coordinates(Ramakrishna)).

Let X(x, t) be the growth rate for a particle of size 'x'. The particles may then be viewed as distributed along the size coordinate and embedded on a string deforming with velocity X(x, t). An arbitrary region [a,b] is chosen on the stationary size coordinate with respect to which the string with the embedded particles is deforming. As the string deforms, particles commute through the interval [a, b] across the end points a and b, changing the number of particles in the interval(Ramakrishna).

The number density is denoted as $f_{1(x, t)}$. then, the rate of change of particles at [a, b] is given by

$$X(a, t)f_1(a, t) - X(b, t)f_1(b, t)$$

The first term represents the particle flux at a and the second term represents the particle flux at b. if it is assumed that there is no other way in which particles in the interval [a, b] can change, the number balance for the interval may be written as follows

$$\frac{d}{dt} \int_a^b f1(x,t)dx = X(a,t)f1(a,t) - X(b,t)f1(b,t)$$

Which may then be written as

$$\int_a^b \left[\frac{\partial f1(x,t)}{\partial x} + \frac{\partial}{\partial x}\left(X(x,t)f1(x,t)\right) \right] dx = 0$$

Thus, we have the population balance equation(Ramakrishna)

$$\left[\frac{\partial f1(x,t)}{\partial x} + \frac{\partial}{\partial x}\left(X(x,t)f1(x,t)\right) \right] = 0$$

This equation must be supplemented with initial and boundary conditions. If initially no particles are present, $f_1(x, 0) = 0$. For the boundary condition, let n_0 particles per unit time be the nucleation rate and assume newly formed particles have no mass. This rate would be the same as the particle flux at x = 0. Thus,

$$X(0,t)f_1(0, t) = n_0 \text{(Ramakrishna)}$$

This is the required boundary condition.

If the population balance equation mentioned above is integrated over the entire range of particle masses, the following is obtained

$$\frac{dN}{dt} = \frac{d}{dt}\int_0^\infty f1(x,t)dx = X(0,t)f1(0,t) - X(\infty,t)f1(\infty,t) = n0$$

From the equation above and the boundary condition we get

$$X(\infty, t)f_1(\infty, t) = 0$$

The above is sometimes referred as the regularity condition.

In the above derivation birth and death of particles within the interval [a, b] were not considered. For now let us consider that the net rate of generation of particles in the size range x to x + dx be described by h(x, t)dx where the identity of h(x, t) would depend on the models of breakage and aggregation. In this case, the population balance equation mentioned above becomes

$$\int_a^b \left[\frac{\partial f1(x,t)}{\partial x} + \frac{\partial}{\partial x}\left(X(x,t)f1(x,t)\right) - h(x,t) \right] dx = 0$$

Which gives

$$\left[\frac{\partial f1(x,t)}{\partial x} + \frac{\partial}{\partial x}\big(X(x,t)f1(x,t)\big)\right] = h(x,t)$$

The regularity condition mentioned above also holds true.

All this while it has been assumed that particle behavior is independent of the environment. If this constraint were to be relaxed, consider the continuous phase to be described by a scalar quantity, Y where Y may represent the supersaturation at the surface of the crystals. We introduce the following additional features(Ramakrishna).

1. The nucleation rate depends on Y, i.e., $n_0 = n_0(Y)$
2. The growth rate may be assumed to depend on Y, i.e., $X = X(x, Y, t)$
3. The growth process depletes the supersaturation at a rate proportional to the growth rate of crystals, the proportionality being dependent onparticle size, i.e., at the rate $\alpha(x)X(x, Y, t)$

The net birth rate, h, may or may not depend on Y. in this case the derivation of the PBE shown earlier is not influenced in any way, so the equation will now be

$$\left[\frac{\partial f1(x,t)}{\partial x} + \frac{\partial}{\partial x}\big(X(x,Y,t)f1(x,t)\big)\right] = h(x,Y,t)$$

The initial condition remains the same as before while the boundary condition changes as

$$X(0, Y, t)f_1(0, t) = n_0(Y)$$

A differential equation for Y accounting for its depletion because of growth of all particles in the population is given by

$$\frac{dY}{dt} = -\int_0^\infty \alpha(x)X(x,Y,t)f1(x,t)dx$$

BIRTH AND DEATH FUNCTIONS

In the previous section we had considered systems in which the number of particles changed because of the processes that could be accommodated through the boundary conditions of population balance equations with respect to internal coordinates. Thus, it can be said that the appearance or disappearance of new particles occurred at some boundary of the internal coordinate space. In crystallization processes, the formation of nuclei of zero size by nucleation is a birth process that occurs at the boundary of particle size.

Particles may also appear or disappear at any point in the particle state space. Birth and death of this type occur due to particle breakage and/or aggregation processes.

Birth and death rates at the boundary:

Consider the boundary condition $X(0,t)f_1(0, t) = n_0$ mentioned in the previous section. This represents the birth of new particles at the boundary, which subsequently migrate to the interior of the particle state space. If the birth of new particles represented by the boundary condition mentioned above comes at the cost of existing particles, then the right hand side of the PBE must contain a corresponding sink term(Ramakrishna).

Breakage processes:

'Breakage' in the present context refers not only to those systems where particles undergo random breakage but also those where new particles arise from existing

particles by other mechanisms. One example of this is cell multiplication by asexual means(Ramakrishna).

The breakage function: Consider that the net birth rate is h(x,r, Y, t), where it is assumed to be expressed as a difference between a source term h^+(x,r, Y, t) and a sink term h^-(x,r, Y, t). Assuming that the breakup of particles occurs independently of each other, b(x, r, Y, t) is considered as the specific breakage rate of the particles of state (x, r) at time t in an environment described by Y(Ramakrishna). It represents the fraction of particles of state (x, r) breaking per unit time. Thus, the average number of particles of state (x, r) lost due to breakage per unit time is given as

h^-(x,r, Y, t) = b(x,r, Y, t)f_1(x,r, Y, t) (Ramakrishna)

Consider that v(x',r', Y, t) is the average number of particles formed from the break-up of a single particle of state (x', r') in an environment of state Y at time t and P(x, r|x', r', Y, t) is the probability density function for particles from the breakup of a particle of state (x', r') in an environment of state Y at time t that have state (x, r).

b(x, r, Y, t) is called the breakage function and has the dimensions of reciprocal time. It can be safely be assumed that the breakage occurring is an instantaneous process, which is to say that the time scale over which it occurs is small compared to that in which the particle state varies(Ramakrishna).

The function P(x, r|x', r', Y, t) (Ramakrishna) must satisfy the condition

$$\int_{\Omega x} P(x, r|x', r', Y, t) dVx = 1$$

If m(x) represents the mass of a particle of internal state x, the mass conservation dictates that(Ramakrishna)

$$P(x, r|x', r', \ Y, t) = 0, \qquad m(x) \geq m(x').$$

Also, the following condition must hold(Ramakrishna)

$$m(x') \ \geq \ v(x', r', Y, t) \int_{\Omega x} P(x, r|x', r', Y, t) dVx$$

with the equality holding if there were no loss of mass during breakage.

To calculate the number density of particles originating from break up , consider the following equation(Ramakrishna)

$$h^{+}(x, r, \ Y, t) = \iint_{\Omega x} v(x', r', Y, t) b\,(x', r', Y, t) P(x, r|x', r', Y, t) f1\,(x', r', t) dVx'\, dVr'$$

The net birth rate of particles of state (x, r) is given by $h(x, r, \ Y, t) = h^{+}(x, r, \ Y, t) - h^{-}(x, r, \ Y, t)$ and can be calculated by the definitions of h^{+} and h^{-} given previously.

Particles that are distributed according to their mass or volume are frequently encountered in applications. Consider the breakage process of a population of particles distributed according to their mass (or volume) denoted x.

The breakage functions contain a breakage frequency, b(x), the average number of particles on breakage of a particle of mass x' denoted by v(x') and a size distribution of fragments broken from a particle of mass/volume x' given by P(x|x'), all of which are assumed to be time independent. The following constraints may be applicable for the function P(x|x')(Ramakrishna)

$$\int_0^{x'} P(x|x')dx = 1 \quad P(x|x') = 0, \qquad x > x', \qquad x' \geq v(x')\int_0^{x'} xP(x|x')dx$$

The inequality on the right would become an equality if there were to be no loss of mass due to breakage. If breakage is binary, P(x'-x|x') = P(x|x') because a fragment of mass *x* formed from a parent of mass x' (undergoing binary breakage) automatically implies that the other has mass x' - x so that their probabilities must be the same. For breakage involving more than two particles, the following holds(Ramakrishna)

$$\int_0^z xP(x|x')dx \geq \int_0^z xP(x' - x|x')dx$$

Where z ≤ x'/2.

The population balance equation for the breakage process then becomes

$$\frac{\partial f1(x,t)}{\partial t} + \frac{\partial}{\partial x}\big(X(x,t)f1(x,t)\big) = \int_0^\infty v(x')b(x')P(x|x')f1(x',t)dx - b(x)f1(x,t)$$

Models for breakage frequency:

Luo and Lehr Breakage Kernels: The general breakage rate per unit volume is written as(M Millies)

$\Omega_{br}(V, V') = \Omega_B(V')\eta(V|V')$

Where the original particle has volume V' and the daughter particle has a volume V. $\Omega_B(V')$ is the breakage frequency and $\eta(V|V')$ is the normalized daughter particle distribution function. The general form is the integral over the size of eddies λ hitting the particle with the diameter d (and volume V). the integral is taken over the dimensionless eddy size ε = λ/d. the general form is

$$\Omega_{br}(V,V') = K\int_{\varepsilon min}^{1}((1 + \varepsilon)^2 / \varepsilon^\wedge n)exp(-b\varepsilon^\wedge m)d\varepsilon$$

B, m, n may be determined with the help of Luo Model parameters or Lehr Model parameters.

Coulaloglou and Tavlarides model: the breakage frequency was defined as the fraction of particles breaking divided by a characteristic time. Thus

$$b(\varepsilon) \ = \ \frac{\Delta F(\varepsilon)}{tbF(\varepsilon)} \ \text{(CA Coultalogou)}$$

where, b is the breakage frequency, ε is the characteristic parameter (eg. Volume) tb is the characteristic time and $\Delta F(\varepsilon)/ F(\varepsilon)$ is the fraction of particles breaking(CA Coultalogou).

Furthermore,

$$\Delta F(\varepsilon)/ F(\varepsilon) = \exp(-E_c/E)$$

With E_c being the surface energy and E the mean turbulent kinetic energy. Also(CA Coultalogou),

$$Tb \propto \varepsilon^{2/3} \, \varepsilon^{-1/3}$$

Ghadiri breakage Kernels: this model is used to calculate only the breakage frequency. The breakage frequency, f is related to the material properties and impact conditions(M Ghadiri):

$$f = \frac{\rho s E^{\frac{2}{3}}}{\Gamma^{\frac{5}{3}}} v^2 L^{\frac{5}{3}} = Kb v^2 L^{\frac{5}{3}}$$

Where ρs is the particle density, E is the elastic modulus of the granule, and Γ is the interface energy. v is the impact velocity and L is the particle diameter prior to breaking. Kb is the breakage constant and is defined as

$$Kb = \frac{\rho s E^{\frac{2}{3}}}{\Gamma^{\frac{5}{3}}}$$

Aggregation processes:

Aggregation must occur at least between two particles. It covers a variety of processes ranging from coalescence in which two particles completely merge along with their interiors, to coagulation, which features a "floc" of particles loosely held by surface forces without involving physical contact. In intermediate situations particles may be in physical contact with each other without merger of their interiors(Ramakrishna).

The Aggregation Frequency: The aggregation frequency represents the probability per unit time of a pair of particles of specified states aggregating. Let the aggregating particles be described by the state vector (x, r) in a continuous phase of state Y. The probabiltity that a particle at state (x, r) and another particle

at state (x', r'), both present at time t will aggregate in the time interval t to t + Δt
is given as(Ramakrishna)

$$a(x, r;x', r'; \ Y, t)dt$$

Alternatively, a(x, r;x', r'; Y, t) may be considered the fraction of particle pairs of
states (x, r) and (x', r') aggregating per unit time.

a(x, r;x', r'; Y, t) satisfies the symmetry property

$$a(x, r;x', r'; \ Y, t) = a(x', r';x, r; \ Y, t)$$

Consider a population of particles distributed according to their masses (or
volumes), denoted x. the aggregation frequency for particle masses x and x' is
a(x, x'). The source term for formation of particles through aggregation is given
as (Ramakrishna)

$$h^+(x, t) = \frac{1}{2}\int_0^x a(x - x', x')f1(x', t)dx'$$

the sink term for formation of particles through aggregation is given
as(Ramakrishna)

$$h^{-}(x, t) = f1(x, t) \int_0^\infty a(x, x')f1(x', t)dx'$$

Aggregation Kernels:

Luo Aggregation kernel: The general aggregation kernel (Luo) is defined as the rate of particle volume formation as a result of binary collisions of particles with volumes V_i and V_j

$$\Omega_{ag}(V_i, V_j) = \omega_{ag}(V_i, V_j)P_{ag}(V_i, V_j)$$

Where $\omega_{ag}(V_i, V_j)$ is the frequency of collision anf $P_{ag}(V_i, V_j)$ is the probability that the collision results in coalescence. The frequency is defined as follows:

$$\omega_{ag}(V_i, V_j) = (\pi/4)(d_i^2 + d_j^2)n_in_ju_{ij}$$

where u_{ij} is the characteristic velocity of collision of two particles with diameters d_i and d_j and the number densities n_i and n_j.

$$u_{ij} = (u_i^2 + u_j^2)^{1/2}$$

where

$$u_i = 1.43(\varepsilon d_i)^{1/3}$$

the expression for the probability of aggregation is

$$P_{ag} = exp\{-c_1 \frac{\left[0.75\left(1 + x_{ij}^2\right)^{\frac{1}{2}}\right]}{\left(\frac{\rho_2}{\rho_1} + 0.5\right)^{\frac{1}{2}}\left(1 + x_{ij}\right)^3} We_{ij}^{\frac{1}{2}}\}$$

Where c_i is a constant of order unity , $x_{ij} = d_i/d_j$, ρ_1 and ρ_2 are the densities of the primary and secondary phases, respectively and the weber number is defined as

$$We_{ij} = \frac{\rho_1 d_i\left(u_{ij}\right)^2}{\sigma}$$

Free Molecular Aggregation Kernel: Real particles aggregate with frequencies characterized by complex dependencies over particle internal coordinates(Schmoluchowski). Very small particles aggregate because of collisions due to Brownian motion. In this case the frequency of collision is size dependent and usually the following kernel is implemented.

$$a\left(L_i, L_j\right) = \frac{2k_B T}{3\mu}\frac{\left(L_i + L_j\right)^2}{L_i L_j}$$

where k_B is the Boltzmann constant, T is the absolute temperature, μ is the viscosity of the suspending fluid.

SOLUTION METHODS FOR POPULATION BALANCE EQUATIONS

Method of classes:

This method discretizes the size domain in N intervals in a free of choice grid. Due to this discretization one obtains a complete set of N ordinary differential equations (ODE) which can be solved numerically.

Hounslow Ryall et al applied discretization techniques to the modeling of in-vitro growth and aggregation of Kidney stones(MJ Hounslow).

John and Suciu employed discretization techniques to the solution of a bi-variate population balance model for the nucleation and growth of Potassium Dihydrogen Phosphate (KDP) particles(Volker John).

Consider the following one dimensional PBE

$$\frac{\partial f(V,t)}{\partial t} + \frac{\partial(G(V,t).f(V,t))}{\partial V} = \int_V^\infty \gamma(V')b(V')p(V,V')f(V',t)dV' + b(V)f(V,t)$$

For simplicity, let us assume G(V, t) = G and γ(V) = 2

Consider the particle growth term $\frac{\partial(G(V,t).f(V,t))}{\partial V}$. This can be written as(Ramakrishna)

$$\frac{\Delta(G.f(V,t))}{\Delta V}$$

$$= G . \frac{f(V_i+1,t)-f(V_i,t)}{V_i+1-V_i}$$

Similarly, the breakage birth term $\int_V^\infty \gamma(V')b(V')p(V,V')f(V',t)dV'$ may be written as

$$2 \sum_{j=i}^{j=imax} b(V_j)p(V_i,V_j)f(V_j,t)$$

And, the breakage death term $b(V)f(V,t)$ may be written as $b(V_i)f(V_i,t)$. The PBE is then converted into a system of N ordinary differential equations (ODEs) given as(Ramakrishna)

$$\frac{\partial f(V,t)}{\partial t} = -G . \frac{f(V_i+1,t)-f(V_i,t)}{V_i+1-V_i} + 2 \sum_{j=i}^{j=imax} b(V_j)p(V_i,V_j)f(V_j,t) + b(V_i)f(V_i,t)$$

Method of Moments:

The moment of the number distribution f is defined as:

$$\mu_j(t) = \int_0^\infty \varepsilon^j . f(\varepsilon,t)d\varepsilon \text{ (Ramakrishna)}$$

The zeroth moment represents the total number of particles. The total volume of the particulate phase is inferred from the first moment (j = 1) if the volume V is chosen as the internal coordinate. Consider the following PBE

$$\frac{\partial f(V,t)}{\partial t} + \frac{\partial(G(V,t).f(V,t))}{\partial V} = \int_V^\infty \gamma(V')b(V')p(V,V')f(V',t)dV' + b(V)f(V,t)$$

We need to transform the above equation into a set of ODEs. For this purpose, we first multiply the equation by V^j, and then integrate from 0 to ∞. Thus, for the first term

$$\int_0^\infty V^j \frac{\partial f(V,t)}{\partial t} dV = \frac{\partial \mu_j(t)}{\partial t}$$

For the growth term,

$$\int_0^\infty V^j \frac{\partial (G(V,t).f(V,t))}{\partial V} dV = jG\mu_{j-1}$$

For the breakage birth term

$$\int V^j . \int_V^\infty \gamma(V')b(V')p(V,V')f(V',t)dV'dV$$

$$= 2[\int_0^1 \left(\frac{V}{V'}\right)^j p\left(\frac{V}{V'}\right) d\left(\frac{V}{V'}\right)] \int_0^\infty V^j b(V)f(V,t)dV$$

For the breakage death term,

$$\int V^j b(V) f(V, t) dV = b\mu_j$$

Thus, the PBE now becomes

$$\frac{\partial \mu_j(t)}{\partial t} = \mu_j b(2\pi_j - 1) - jG\mu_{j-1}$$

Where $\pi_j = \int_0^1 \left(\frac{V}{V'}\right)^j p\left(\frac{V}{V'}\right) d\left(\frac{V}{V'}\right)$

Case Study - One Dimensional Population Balance Model of a Batch Cooling Crystallization Process

A seeded batch cooling crystallization process of model Active Pharmaceutical Incipient (API) in a model solvent was considered as a case study for the development of a Population Balance Mode simulation and a solver was developed in MATLAB. The relevant material properties and process settings are described in the following table.

Material constants	Value	Description
Molecular weight API	$MW_{API} = 180.16 \ [g/mol]$	Molecular weight of acetylsalicylic acid (Aspirin®)
Molecular weight solvent	$MW_{Sol} = 46.07 \ [g/mol]$	Molecular weight of ethanol
Density crystalline phase	$\varrho_{cp} = 1 \ [kg/L]$	For simplification we assume an equal density for the crystalline phase, the pure solvent and the solvent containing dissolved species of the crystalline phase
Density pure solvent	$\varrho_{sol} = 1 \ [kg/L]$	
Density solvent with dissolved species	$\varrho_{sol+ds} = 1 \ [kg/L]$	
Reactor volume	$V_r = 1 \ [L]$	In the present work We used the same the initial mass for the solvent and the API (solid & dissolved) for all simulated experiments
Overall mass of pure solvent in the reactor	$m_{sol} = 0.5 \ [kg]$	
Overall mass of API in the reactor	$m_{API} = 0.5 \ [kg]$	

In this case study only crystal growth was considered. Aggregation and breakage were not considered in the simulation.

To establish the solubility of model API in model solvent the solubility of acetylsalicylic acid dissolved in pure ethanol was used. This is given by the following equation.

$$\log(X_{cp}) = N_1 + \frac{N_2}{T} + N_3 \cdot \log(T)$$

Where N_1 = 27.769, N_2 = -2500.906 and N_3 = -8.323(GD Maia).

The supersaturation is defined as

$$S = \frac{c \, [mol/L]}{c^*[mol/L]}$$

Where c^* is the solubility of API in the solvent and c is the current concentration.

A common size independent growth rate shown below is used for the model under study(AD Randolph, Theory of Particulate Processes)(Mersmann)

$$G(S,T) = k_{g1} \cdot \exp\left(\frac{-k_{g2}}{R \cdot T}\right) \cdot (S-1)^{k_{g3}}$$

The parameters for the above equation are given below(Mersmann), (AD Randolph, Theory of Particulate Processes)

Model parameters (growth)	value
k_{g1}	$= 10 \ [\dfrac{m}{s}]$
k_{g2}	$= 10^4 \ [\dfrac{J}{mol}]$
k_{g3}	$= 1 \ [-]$

The initial seed mass of the model API $m_{cp\ initial}$ and the initial concentration of dissolved species $c_{API\ initial}$ depend only on the solubility as the initial temperature $T_{initial}$.

$$c_{\text{API initial}} \left[\frac{\text{mol}}{\text{L}}\right] = \left(\frac{\varrho_{sol+ds} \cdot X_{cp}(T_{initial})}{MW_{cp} \cdot (X_{cp}(T_{initial})) + \left(1 - X_{cp}(T_{initial})\right) \cdot MW_{sol}}\right) \cdot 10^3$$

$$m_{\text{cp initial}} \ [\text{kg}] = m_{cp0} - c_{cp\ 0} \cdot MW_{cp} \cdot 10^{-3}$$

The total mass of the API in the system, m_{cp0} is assumed to be 500g. the initial CSD was assumed to be a logarithmic distribution as follows.

$$n(L) = \frac{1}{\text{L} \cdot \sigma_{ln} \cdot \sqrt{2 \cdot \pi}} \cdot \exp\left(-\frac{1}{2}\left(\frac{\ln\ (L/L_{50})}{\sigma_{ln}}\right)^2\right)$$

Where σ_{ln} = 0.4 and L_{50} = 100μm. Furthermore, crystals were assumed to be cubic and were defined by their characteristic lengths L. Thus, the following constraint involving m_{cp} may be imposed.

$$\int_0^{L_{max}} n(L) \cdot L^3 \cdot \varrho_{cp} \stackrel{\text{def}}{=} m_{cp\ 0}$$

For the current simulation L was varied from 0 to 400μm. This relation was used for the normalization of the initial assumed distribution. Thus, if the normalization constant was assumed to be con,

$$\int_0^{L_{max}} con.\, n(L) \cdot L^3 \cdot \varrho_{cp} = m_{cp\ 0}$$

Process settings of simulation experiments :

$T_{initial}\ [^oC]$ = 45

$m_{cpinitial}$ = 0.388

$t_{process}$ = 1666

Discretization was employed for the solution of the resulting population balance equations. The characteristic length L was varied from 1 to 400µm with a step size of 1. Thus the PBE given as
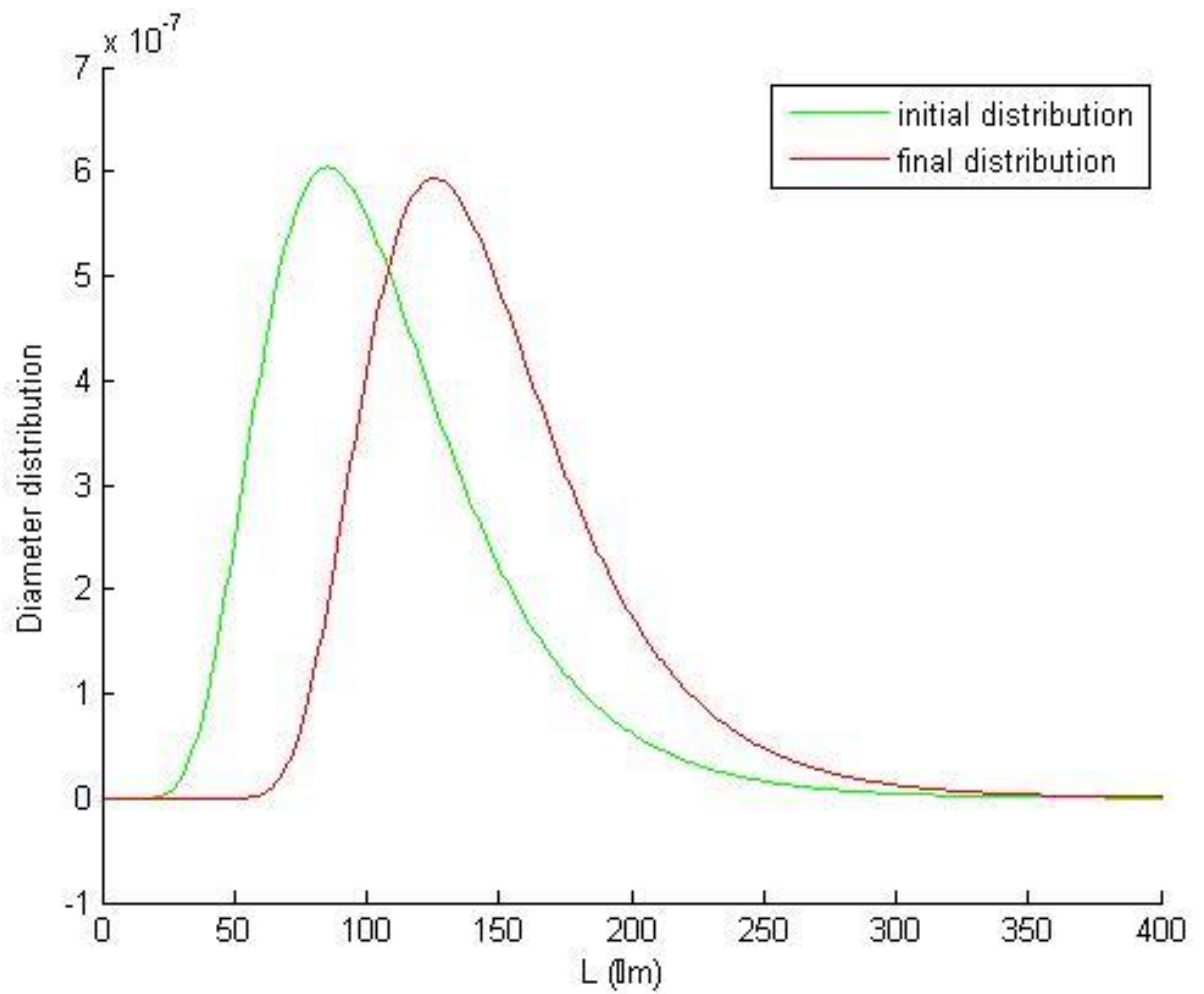
$$\frac{\partial n(L,t)}{\partial t} + \frac{\partial(G(L,t).n(L,t))}{\partial L} = 0$$
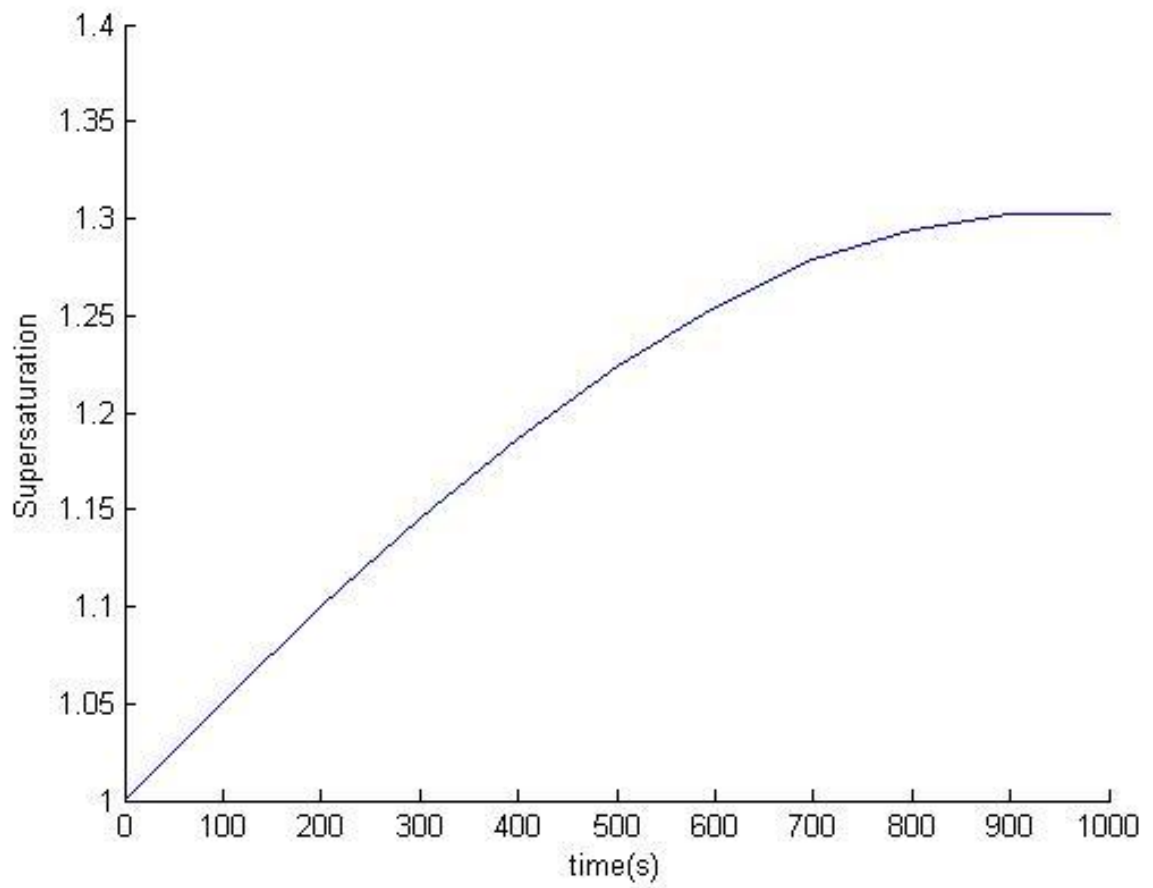
Was discretized as

$$\frac{\partial n(L,t)}{\partial t} = -\frac{G(n(L_{i+1},t) - n(L_i,t))}{(L_{i+1} - L_i)}$$
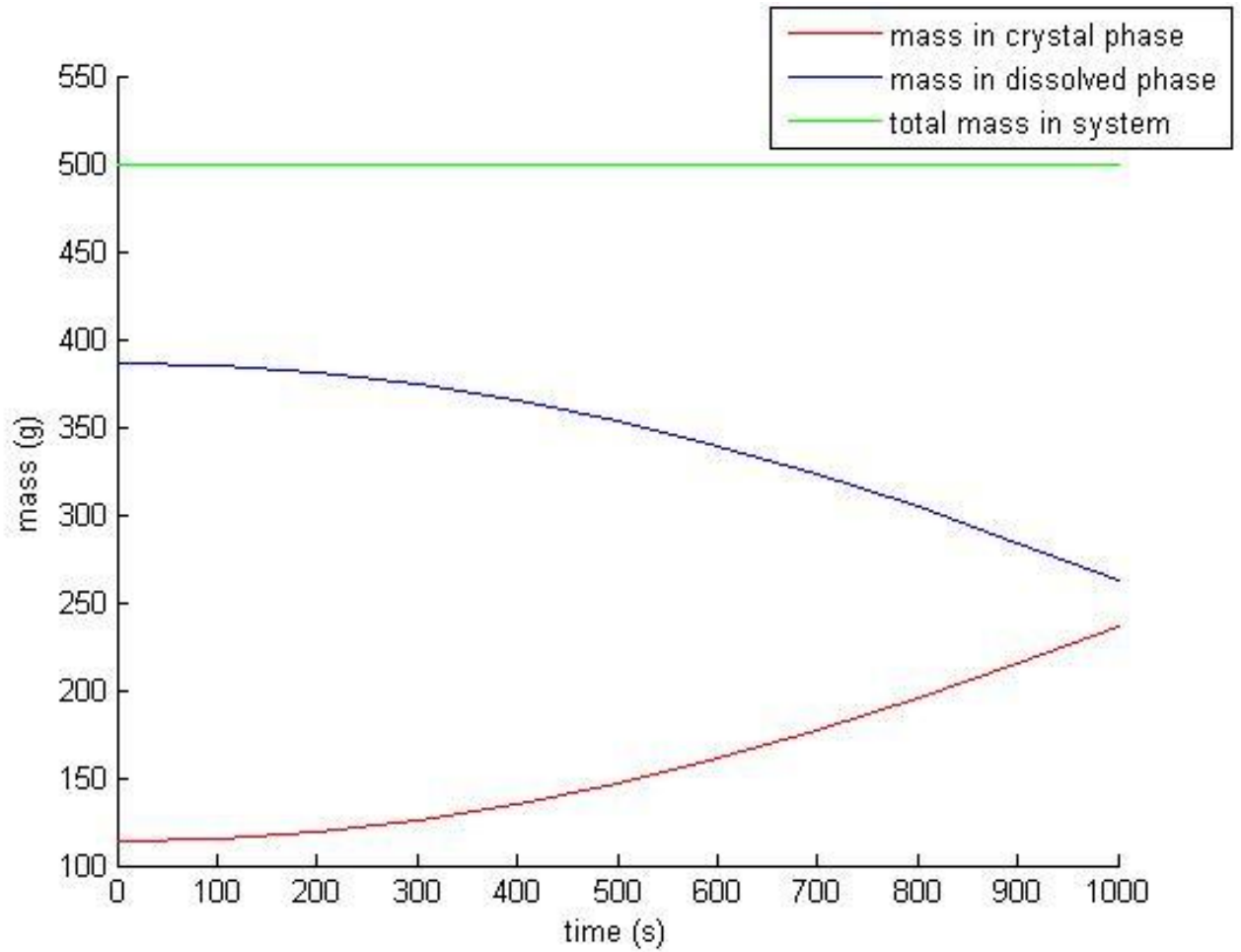
Results:

The initial and final crystal size distribution is given as follows.

The supersaturation profile is shown as follows

The following graph validates the simulation through mass balance. It can be seen that total mass of the system remains constant at 500g. This is the initial assumed total mass of the system.

CONCLUSION

This report consists of a literature review of crystallization and Population Balance Modeling followed by a case study of a crystallization process. This has helped me gain a good knowledge base in PBM techniques so that I may pursue further research in the field. In the case study a one dimensional PBM was employed. I aim to work with multi-dimensional PBM simulations in the future. Through the course of my research at TU Graz I have gained a starting point for the research I aim to pursue during my Masters course at Rutgers University.

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