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Development of a Reduced Order Model for Bi-Component Granulation Processes via Laguerre Polynomials

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***Abstract*— This paper presents a model reduction technique for obtaining low order models of wet granulation processes suited for model based control. The fluid bed granulation process is extensively employed by the pharmaceutical industry, in which a binder material is used to create bonds between powder drug particles and form granules. Performing a population balance study for these systems results in models that are usually too complex for control applications. The literature offers various reduced order models that approximate the size distribution dynamics of the process. However, these models either neglect the binder drops or incorporate simplified granulation rate expressions that are not realistic. This paper, in contrast, captures both the size and composition distribution dynamics of the granules and considers the physical and geometrical factors in determining the process rate. Using well known model reduction techniques such as orthogonal projections and the method of moments, we relate the bivariate particle distribution function to the dynamics of a finite number of probabilistic moments of the population. Finally, the accuracy of the model is demonstrated through comparing its predicted results with a constant number Monte Carlo simulation of the process.**

I. INTRODUCTION

This paper presents a scheme for obtaining reduced order models describing the population dynamics of particles in bi-component granulation processes. Wet granulation is a widely used process in many industrial plants, wherein minuscule powder like particles are conglomerated into larger granules [1]–[3]. The heterogeneity of powder particles along with the nonuniformity of the granulation process necessitates a statistical study of the process. Performing a population balance study for these granulation systems results in complex mathematical models. However, in order to reach to a desired output population distribution, application of model-based closed-loop control techniques is critical, which in turn necessitates the development of reduced order models for these processes. This paper addresses this need by focusing on a bi-component agglomeration process and employing well known model reduction tools such as method of moments and orthogonal projection.

The simplest multi-component granulation system conceivable is a two-component one with no chemical reactions. Such systems are frequently encountered in pharmaceutical applications, where through use of an excipient, the particles in a powdered drug adhere together and form granules [4], [5]. The excipient is either used just to bulk up the drug formulation and achieve the desirable dosage or to facilitate drug absorption. Due to the complexity of the process, the granulation models should be able to exclusively capture all the salient dynamics of the process, while they maintain a low order through neglecting the other effects that are less influential. A population balance analysis for bi-component granulation systems determines the time dynamics of a bivariate distribution function in form of an Integro-Differential Equation (IDE). The variables of this distribution function are the size and composition of the aggregates.

The coagulation kernel which reflects the rate of coagulation is a crucial factor in determining the complexity of the resulting coagulation model. This kernel function is also dependent on size and composition and, in the simplest cases, is assumed to be constant or additive [6]. The analytical solution of the IDE for these simple cases is available, however, the real coagulation dynamic is much more complicated. In fact, the coagulation process in the microscopic level consists of two steps: collision and binding. As a result, the *collision probability* and the probability of the particles successfully binding together, namely *collision success factor*, are both involved in the determination of the coagulation rate. In order to simplify the model, some researchers ignore the collision success factor and assume the coagulation kernel between any two particles is only a function of their respective sizes. These works either attempt to directly find a numerical solution to the IDE [7], or they employ random sampling methods such as the constant number Monte Carlo simulation (cNMC) [6], [8]. However, the role the success factor plays in real coagulation systems is too important to ignore. In [9], through considering this factor, Marshall *et al.* obtain cNMC simulation results that closely match the experimental results reported in [10].

One alternative solution for analysis of these dispersed systems is to derive deterministic models that instead of the microscopic behavior of individual elements focus on the bulk statistics of the stochastic process under study. The method of moments is a powerful technique in this regard. It can be used to transform the IDEs governing the coagulation processes into a set of ordinary differential equations (ODEs). Specifically, the direct quadrature method

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of moments (DQMOM) is a very efficient technique to reduce the original model to an ODE set for a single-variable distribution function [11], [12]. However, Marshall *et al.* show this method is not nearly as accurate as cNMC simulation, when the dependency of the kernel function on the composition of granules is taken into account [13].

Furthermore, Yu *et al.* employ Taylor expansions to simplify the results of method of moments and derive a closed finite-dimensional ODE system that models a single-component coagulation process [14]. The accuracy of the model improves with increasing the Taylor expansion's order, which also equals the number of moments considered in the model. A recent work by the authors [15] extends the use of Yu's model to the bi-component processes. This previous work, in addition, designs a moving horizon estimator to obtain the population moments. The estimation is performed in real time and solely from the information of the total number of granules. However, the Taylor expansions of moments cannot be used for problems with a composition-dependent kernel function such as the one used by Liu *et al.* in [16].

One common limitation apparent in the existing literature on reduced order modeling of coagulation processes is their weakness or total inability in incorporating the collision success factor in their formulations. Motivated by the need to address this issue, this paper develops a new model, where the method of moments is used in conjunction with the expansion of the bivariate size and composition distribution function over the set of orthogonal Laguerre polynomials. This idea has been exploited before to approximate the size distribution of crystals in a nucleation example [17], [18]. Incorporating the success factor, our model will be shown to closely approximate the cNMC simulation results.

The remainder of the paper is organized as follows. Section II performs a population balance analysis and explains the dependence of the coagulation kernel function on the size and composition of the particles participating in the process. Next, the two-variable Laguerre polynomials and their orthogonality properties are introduced and used to reduce the population balance equation in Section III. Finally, in Section IV, we give a brief explanation of the cNMC algorithm and compare its performance with our reduced order model in a simulation study.

II. Population Balance and Model Formulation

In this process, the binder, as a liquid adhesive substance causes the particles to glue together and form larger aggregates. With the continuation of the process and continuous injection of the binder to the mixture, the aggregates keep growing in size. Each particle is composed of active drug particles and the inactive binder (excipient) substance. The total mass of a particle is denoted by p, and b represents the mass of the binder content in the particle.

The probability distribution function, $f(p, b)$, describes the population distribution of the particles in the mixture as a function of their mass and binder content. We define $r(p, b)$ as the particle characteristic size vector. This vector fully characterizes a particle and, for notational convenience, this characteristic vector is used in the remainder of this document. Conservation of particle and solute mass leads to the mass balance formulation given below [9].

$$\begin{aligned}\frac{\partial f(r_1)}{\partial t} = \frac{1}{2}\int_0^{r_1} k(r_1 - r_2, r_2) f(r_1 - r_2)\ f(r_2) dr_2 \\ - \int_0^{\infty} k(r_1, r_2) f(r_1) f(r_2) dr_2 + B\end{aligned} \tag{1}$$

where B is the input flow rate of the binder droplets and $k(r_1, r_2)$ denotes the coagulation rate between two particles of sizes r_1 and r_2.

Since the binder mass is less or equal to the particle mass, we define the distribution function so that its value equals zero whenever $b > p$. According to the kinetic theory of granular flow (KTGF), the agglomeration kernel is given by [10]

$$k(r_1, r_2) = k_0 \psi_{12} x_{43}^{\gamma} (p_1^{1/3} + p_2^{1/3})^2 (\frac{1}{p_1} + \frac{1}{p_2}) \tag{2}$$

where k_0 is the coagulation rate constant, ψ_{12} is the probability of two particles remaining stuck together after a collision, and x_{43} is the volume mean diameter of the population (the ratio of the fourth to the third moment for the dried particles) normalized by the size of the binder drop.

Three collision scenarios are conceivable depending on the particles involved: binder-binder, binder-particle, and particle-particle. Due to the configuration of a Wurster fluidized bed reactor, no coagulation occurs between two binder drops (i.e. $k_0 = 0$ for binder-binder coagulation) [9]. Also, the coagulation rate constant between a particle and a pure binder droplet is 100 times faster than this constant rate between two arbitrary particles. Moreover, Marshall *et al.* fits the above expression to experimental data and reports the independence of the kernel on x_{43}, meaning that γ in Eq. (2) equals zero [9]. Finally, the bonding probability, ψ_{12}, is related to both the geometrical and physical properties of the two colliding particles and is given by

$$\psi_{12} = \psi_{geom}\ \psi_{phys}. \tag{3}$$

Physical factor

The dimensionless Stokes number is used to quantify the behavior of the particles suspending in the tank [16] and is defined as follows:

$$St = \frac{4}{9}\frac{\rho u_0}{\mu}\frac{d_1 d_2 (d_1 + d_2)^2}{(d_1^3 + d_2^3)} \tag{4}$$

where d_1, d_2 are the colliding particles' diameters, u_0 is the collision velocity, and ρ and μ are the drug powder density and the binder viscosity, respectively. The collision between two particles is successful when the Stokes number calculated for the pair is below a critical value, St^*. Therefore, ψ_{12} is defined as a switching function of the Stokes number which returns one when the Stokes number of colliding

particles is less than or equal to St^* and is otherwise zero. The critical Stokes value is defined as follows [9].

$$St^* = 2\ln\frac{\lambda_{12}}{h_a} \tag{5}$$

where h_a is the asperity (roughness) of the primary particle surface given in Table II, and λ_{12} is the binder layer thickness obtained from:

$$\lambda_{12} = r_g(\phi_1^{1/3} + \phi_2^{1/3}). \tag{6}$$

In the above equation, r_g is the mean radius of gyration and is assumed to have a constant value equal to 60μm, and

$$\phi_i = \exp\left(f(y_i - g)\right),\ i = 1, 2$$

where y_i is the ratio of the binder mass to the total mass of the $i^{th}-$particle, and f and g are empirical correlation parameters from [10] and their values for a specific excipient, Avicel, are given in Table I.

Geometry factor

The second influential factor for a successful collision resulting in agglomeration is the geometrical success factor. This factor relates the coagulation rate to the amount of accessible binder on the particle surface, surface roughness, and wettability of the powder and is given as:

$$\psi_{geom} = 1 - (1 - \eta_1)(1 - \eta_2) \tag{7}$$

where

$$\eta_i = \frac{1}{1 + \exp(-b(y_i - c))},\ i = 1, 2$$

TABLE I: Parameters for Avicel

Parameter	Value
b	35.1
c	0.129
f	25.9
g	0.327
$h_a[\mu$ m]	6.3
k_0 [m^3/s]	2.510^{-14}

III. Model Reduction Using Laguerre Polynomials

The previous section showed that an IDE governs the evolution of the particle population distribution in a coagulation process. The objective of this section is to obtain a finite order set of ODEs, whose solution approximates the evolutions of the particle population distribution. The moments of the distribution function constitute the variables of this ODE system. The first step in reducing the governing IDE to this ODE set of finite order is to expand the population distribution function on the basis of Laguerre polynomials. Hulburt *et al.* exploit this reduction technique for a mono-component coagulation process [17]. We build on and extend their work by considering the addition of a binder and approximating the bivariate population distribution functions using 2D Laguerre polynomials.

The n^{th} order Laguerre polynomial is defined as:

$$L_n^\lambda(z) = \sum_{i=0}^{n}(-1)^i\binom{n}{i}\frac{\Gamma(n+\lambda)}{\Gamma(n+\lambda-i)}z^{(n-i)} \tag{8}$$

The gamma distribution is used in the construction of these orthogonal polynomials and its probability density function is given as follows

$$w^\lambda(z) = \frac{1}{\Gamma(\lambda)}z^{\lambda-1}e^{-z}. \tag{9}$$

The support for the gamma distribution is limited to positive numbers. This makes these polynomials the preferred choice of basis for the expansion of the particle population distribution function. Defining $L_w^2 = \{f : \int_0^\infty f(x)^2 w(x)dx < \infty\}$, Szego proves that any $f \in L_w^2$ converges to its Laguerre series in the L_w^2-sense [19]. It is straight forward to use the Hölder's inequality and show that any probability density function is of L_w^2 class and is convergent to its expansion.

Let the particle population distribution function be expanded using the generalized Laguerre polynomials as follows

$$\begin{aligned} f(p,b) =& \frac{\lambda}{c}\frac{\gamma}{d}\ w^\lambda(\frac{\lambda p}{c})\ w^\gamma(\frac{\gamma b}{d}) \\ & \cdot\sum_{n=0}^{\infty}\sum_{m=0}^{\infty}\kappa_{n,m}\ L_n^\lambda(\frac{\lambda p}{c})\ L_m^\gamma(\frac{\gamma b}{d}) \end{aligned} \tag{10}$$

where λ, γ, c and d are the parameters of the Laguerre polynomials and required to be positive. Note that in our coagulation system, all the particles have a mass that is strictly positive ($p > 0$), however there may exist particles with no binder content ($b = 0$). By requiring that $\gamma = 1$, we allow for the existence of such particles.

The orthogonality of the expansion terms with respect to a 2D gamma distribution is observed from the following equation:

$$\begin{aligned} &\int_0^\infty\int_0^\infty w^\lambda(x)w^\gamma(y)L_n^\lambda(x)L_m^\gamma(y)L_p^\lambda(x)L_q^\gamma(y)\ dxdy \\ &= \begin{cases} \dfrac{\Gamma(n+\lambda)\ \Gamma(m+\gamma)}{\Gamma(\lambda)\Gamma(\gamma)}n!m! & n = p, m = q \\ 0 & \text{otherwise} \end{cases} \end{aligned} \tag{11}$$

In order to obtain the coefficients $\kappa_{n,m}$ and relate them to the moments of the distribution function, we use the following definition:

$$\langle A(p,b)\rangle = \int_0^\infty\int_0^\infty A(p,b)f(p,b)dpdb. \tag{12}$$

Now, we calculate the expression $\langle L_n^\lambda(\frac{\lambda p}{c})L_m^\gamma(\frac{\gamma b}{d})\rangle$ in two different ways. First, we directly substitute the definition of Laguerre polynomials and the distribution function of

Eq. (10) into Eq. (12). Then, using orthogonality properties described by Eq. (11), we obtain:

$$\langle L_n^{\lambda}(\frac{\lambda p}{c}) L_m^{\gamma}(\frac{\gamma b}{d})\rangle = \kappa_{n,m}\ n!\ m! \frac{\Gamma(n+\lambda)\ \Gamma(m+\gamma)}{\Gamma(\lambda)\Gamma(\gamma)} \tag{13}$$

The second approach is to use the definition of the population distribution function's mixed moments given by the following equation:

$$M_{ij} = \int_0^{\infty}\int_0^{p} p^i s^j f(p,s)\ dpds. \tag{14}$$

For instance, M_{00}, M_{10}, and M_{01} represent the total number of particles, the total mass, and the total solute mass in the volume unit, respectively. Now, we recalculate the left hand side of Eq. (13), but this time the integrand is now expressed in terms of the mixed moments using Eq. (14).

$$\begin{aligned}
&\langle L_n^{\lambda}(\frac{\lambda p}{c}) L_m^{\gamma}(\frac{\gamma b}{d}) > \\
&= \int_0^{\infty}\int_0^{\infty} (\sum_{i=0}^{n} l_{n,i}^{\lambda}(c) p^{n-i})(\sum_{j=0}^{m} l_{m,j}^{\gamma}(d) b^{m-j}) f(p,b) dpdb \\
&= \sum_{i=0}^{n}\sum_{j=0}^{m} l_{n,i}^{\lambda}(c) l_{m,j}^{\gamma}(d) \int_0^{\infty}\int_0^{\infty} p^{n-i} b^{m-j} f(p,b) dpdb \\
&= \sum_{i=0}^{n}\sum_{j=0}^{m} l_{n,i}^{\lambda}(c) l_{m,j}^{\gamma}(d) M_{n-i,m-j}
\end{aligned} \tag{15}$$

where

$$l_{n,i}^{\lambda}(c) = (-1)^i \binom{n}{i} \frac{\Gamma(n+\lambda)}{\Gamma(n+\lambda-i)} (\frac{\lambda}{c})^{(n-i)}$$

Comparing Eq. (13) and Eq. (15), $\kappa_{n,m}$ is given by:

$$\kappa_{n,m} = \frac{\sum_{i=0}^{n}\sum_{j=0}^{m} l'^{\lambda}_{n,i}(c) l'^{\gamma}_{m,j}(d) M_{n-i,m-j}}{n!\ m!} \tag{16}$$

where

$$l'^{\lambda}_{n,i}(c) = (-1)^i \binom{n}{i} \frac{\Gamma(\lambda)}{\Gamma(n+\lambda-i)} (\frac{\lambda}{c})^{(n-i)}$$

So far, we have established a linear relationship between the population distribution function and its probabilistic moments. The rest of this section utilizes this expression of the distribution function to reduce the coagulation model. More specifically, through the application of method of moments to Eq. (1), we derive an ODE system describing the dynamics of the population's statistical moments.

To obtain the rate of change of $M_{ij},\ i,j \in Z^+$, Eq. (1) is multiplied by $p^i s^j$ and then integrated over the region specified by the definition of moments in Eq. (14). After some simplifications we obtain the following expression

$$\begin{aligned}
\frac{d[M_{ij}]}{dt} &= \dot{u}_{i,j} \\
&+ \frac{1}{2}\int_0^{\infty}\int_0^{\infty} [A(r+r') - A(r) - A(r')] f(r) f(r') k(r,r')\, dr dr'
\end{aligned} \tag{17}$$

where r is the characteristic size vector, $A(r) := p^i s^j$ and $\dot{u}_{i,j}$ is the ij mixed moment of the input binder flow. Eq. (17) resembles the result obtained in [6] for the batch processes, but is modified to account for the continuous input flow of the binder.

For a general distribution function, in theory, all the moments are required for reconstruction of the particle population. However, for practicality issues, we limit our attention to only a finite set of the population moments defined as follows

$$\mathcal{M} = \{M_{i,j} | i,j \in \{0,1,...,m-1\}\}$$

As a result, the reduced model consists of m^2 state variables. It is obvious that by increasing the number of the moment states, the distribution function approximation becomes more accurate. Also, in the calculation of the time derivative of M_{ij} and for general coagulation kernels, the right-hand side of Eq. (17) needs to be numerically integrated over an unbounded four dimensional polyhedron. In practice there is an upper bound on the total mass and the binder mass of the particles in the system. This upper bound generally depends on the duration and the initial population distribution of the coagulation process as well as the rate and size distribution with which the binder material is injected to the system.

The next section utilizes a cNMC simulation as the benchmark solution to model a coagulation process. It then obtains the evolutions of the distribution moments for the benchmark and compares it with the results predicted by the reduced order model obtained in this section.

IV. Results and Discussion

This section investigates the size and composition evolutions of Avicel particles in a Wurster fluid bed granulator. This process is simulated first using the stochastic cNMC algorithm as the benchmark solution. From the resulting distribution function, the population moments are then calculated. The section next simulates the reduced order model developed in the last section and predicts the evolutions of the population moments. Finally, the predicted moment trajectories are compared against the results of the benchmark solution.

Constant-Number Monte Carlo Algorithm

Matsoukas *et al.* proposes this specialized Monte Carlo simulation technique for agglomeration processes [9]. This method considers a simulation box containing a constant number of particles denoted by N. Each of the particles in the mixture is characterized by a size vector r. At each time step, first, the probability of two disjoint events are

calculated, namely agglomeration and binder injection. Then, using a random number drawn from the standard uniform distribution, we determine which of these two events is to occur until the next time step.

In case the agglomeration event is selected, first the maximum and average of the kernel functions over all possible pairs of particles are calculated. We denote these two numbers by k_{max} and k_{ave}, respectively. The next step is to randomly pick two particles with indices i, j and evaluate their coagulation kernel k_{ij}. The ratio of k_{ij} to k_{max} shows the agglomeration probability of the selected pair of particles. A random number ρ is then drawn from the standard uniform distribution. The candidate pair is accepted when the calculated coagulation probability is greater than ρ. In order to systematically update the population with the accepted pair, we reassign the properties of the i^{th} particle with $r_i + r_j$.

Because after an agglomeration event the number of the particles in the box decreases, next we need to introduce a new particle into the simulation box. To this purpose, we randomly select an existing particle in the box and use its properties to redefine the j^{th} particle. This addition of a new particle affects the total volume of the box in the following manner:

$$\frac{p_{total}}{p_{total} + p_j} V \to V \tag{18}$$

where p_{total} is the total mass of the particles before the update, and p_j is the total mass of the new j^{th} particle after the update.

In case of the binder injection event, a predetermined number of binder droplets are introduced to the simulation box. In order to maintain the constant number of particles in the box, we randomly choose and remove the same number of existing particles from the simulation box. This event also affects the simulation box volume as follows.

$$\frac{p_{total} + p_b - p_i}{p_{total} + p_b} V \to V \tag{19}$$

where p_b and p_i are the mass of the injected binder drops and deleted particles, respectively.

Matsoukas *et al.* then determine the mean time elapsed before the occurrence of next random event from the following expression.

$$\Delta t = \frac{1}{V(r_b + \sum r_{i,j})} \tag{20}$$

where V is the volume of the simulation box and r_b and $r_{i,j}$ are the rate of the binder injection and agglomeration between particle i and j, respectively (see reference [9] for more details).

Fig. 1 presents the results of the cNMC simulation using the parameters given in Table II. Moreover, the simulation box consists of 10000 particles in. Initially, all the Avicel particles in the tank are assumed to be dry and have an equal diameters of 100.4μm. Also, we assume there are initially 4.5×10^2 binder drops in the tank.

TABLE II: Simulation parameters adopted from [9].

Variable	Notation	Value	Unit
binder droplet diameter	d_b	60	μm
Particle density	ρ	1021	kg/m^3
Binder viscosity	μ	0.762	kg/(ms)
Velocity of particle collision	u_0	5.5	m/s
Reactor Volume	V_R	0.01	m^3
Initial particle concentration	C_0	3.3010^{10}	1/m^3
Binder flow rate	$\dot{Q}$	1.48510^6	1/s

Reduced order model

Section III showed that the Laguerre expansion of the population distribution function is a linear function of the mixed moments. When this expression of the distribution function is substituted in the right hand side of Eq. (17) and after the integrations are carried out, it ultimately becomes a second order function of the population moments. In order to calculate the coefficients of these quadratic terms, we used as the upper bound of the integrals, the maximum particle size and binder content obtained from the cNMC simulation. These values are reported in Table III. Also, this table shows the constant integration increments. To simplify the calculations, we consider only the first nine moments describing the distribution function. In practice, we have to calculate a quadruple integral. To further reduce the computations, we take advantage of the symmetry of the problem to rewrite Eq. (17) as:

$$\frac{d[M_{ij}]}{dt} = \dot{u}_{i,j} + \int_0^{r_{max}} \int_0^{r'=r} dr dr' \alpha(r, r') \tag{21}$$

where $\alpha = [A(r + r') - A(r) - A(r')] f(r) f(r') k(r, r')$.

Fig. 1 depicts the trajectories of the selected population moments obtained from the reduced order model, and compares the against the cNMC simulation results. As is clear from this figure, the two sets of the results are in agreement. The total number of the particles per volume, M_{00}, initially increases due to the entrance of a huge number of binder droplets to the tank. Eventually, the droplets cause many coagulation events and consequently the number of particles starts decreasing. The approximation of the total and the binder mass of the particles (*i.e.*, M_{10}, M_{01}) are observed to be exact. These two trajectories are straight lines with a constant slope equal to the binder's mass flow rate into the tank. With the continually growing size of the aggregates, the higher order moments also monotonically increase during the simulation. The simplicity and performance of the reduced order model proposed in this paper suggests that it can be further used in estimation and control applications.

V. Conclusions

In this paper, we developed a reduced order model for wet granulation processes through use of method of moments and Laguerre expansions. Granulation phenomenon is a complex stochastic process in nature, necessitating model reduction

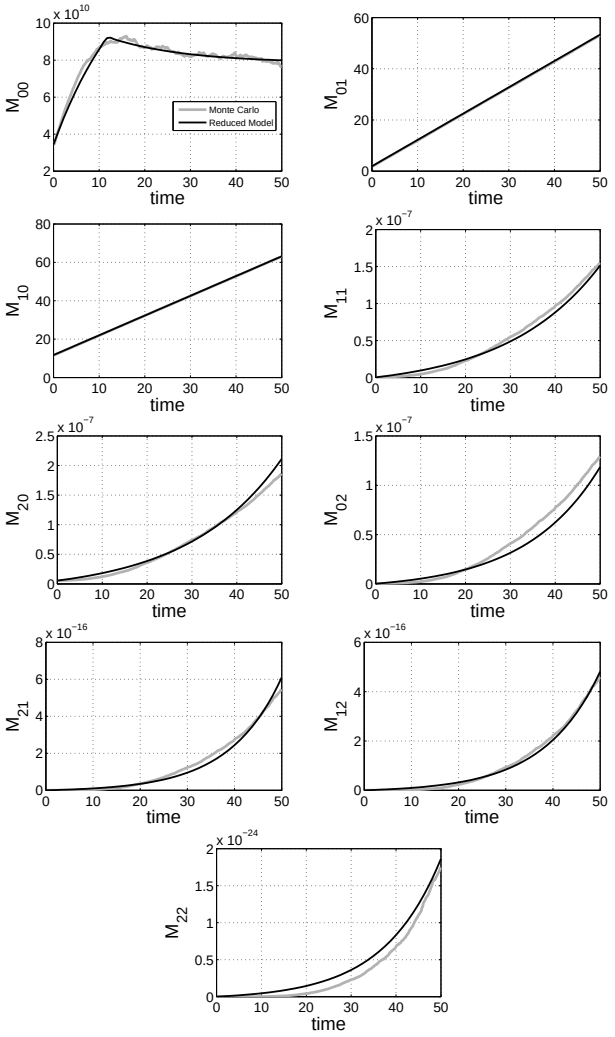

Fig. 1: Moment trajectories; black line represents the reduced order model and gray represents cNMC simulation.

TABLE III: Parameters for the reduced model

Parameter	Value	Parameter	Value
c	10^{-9}	p_{max}	10^{-8}
d	10^{-9}	b_{max}	4×10^{-9}
γ	0.2	Δp	5×10^{-10}
λ	1	Δb	2^{-10}

techniques for process control applications. The model presented in this paper is the first deterministic reduced order model to use realistic coagulation rate expressions and successfully capture the evolutions of both the particle size and composition distributions. The accuracy and simplicity of the resulting low order models renders our model reduction scheme as a promising tool for more effective control of coagulation processes.

REFERENCES

[1] S. M. Iveson, J. D. Litster, K. Hapgood, and B. J. Ennis, "Nucleation, growth and breakage phenomena in agitated wet granulation processes: A review," *Powder Technology*, vol. 117, no. 1-2. pp. 3-39, 2001.

[2] B. J. Ennis, G. Tardos, and R. Pfeffer, "A microlevel-based characterization of granulation phenomena," *Powder Technology*, vol. 65, no. 13. pp. 257-272, 1991.

[3] J. Litster and B. Ennis, *The Science and Engineering of Granulation Processes,* Springer,2004.

[4] A. Faure, P. York, and R. C. Rowe, Process control and scale-up of pharmaceutical wet granulation processes: A review, *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 52, no. 3. pp. 269-277, 2001.

[5] D. M. Parikh, *Handbook of Pharmaceutical Granulation Technology*,3rd ed., CRC Press, 2009.

[6] T. Matsoukas, K. Lee and T. Kim, " Mixing of components in two-component aggregation," *AIChE J.*, vol. 52, no. 9, pp. 3088-3099, 2006.

[7] P. Rajniak, R.T. Chern, F. Stepanek, "Solution of population balance equations for wet granulation and combination with the FLUENT software," *Fifth World Congress on Particle Technology*, vol. 2, 2006.

[8] M. Smith and T. Matsoukas, "Constant-number Monte Carlo simulation of population balances," *Chem. Eng. Sci.*, vol. 53, no. 9, pp. 1777-1786, 1998.

[9] C. L. Marshall, P. Rajniak, and T. Matsoukas, "Multi-component population balance modeling of granulation with continuous addition of binder," *Powder Technol.*, vol. 236, pp. 211-220, 2013.

[10] P. Rajniak, F. Stepanek, K. Dhanasekharan, R. Fan, C. Mancinelli, and R. T. Chern, "A combined experimental and computational study of wet granulation in a Wurster fluid bed granulator," *Powder Technol.*, vol. 189, no. 2, pp. 190-201, 2009.

[11] R. O. Fox, "Optimal moment sets for multivariate direct quadrature method of moments," *Ind. Eng. Chem. Res.*, vol. 48, no. 21, pp. 9686-9696, 2009.

[12] D. L. Marchisio and R. O. Fox, "Solution of population balance equations using the direct quadrature method of moments," *J. Aerosol Sci.*, vol. 36, no. 1, pp. 43-73, 2005.

[13] C. L. Marshall, P. Rajniak, and T. Matsoukas, "Numerical simulations of two-component granulation: Comparison of three methods," *Chem. Eng. Res. Des.*, vol. 89, no. 5, pp. 545-552, 2011.

[14] M. Yu, J. Lin, and T. Chan, "A New Moment Method for Solving the Coagulation Equation for Particles in Brownian Motion," *Aerosol Science and Technology*, vol. 42, no. 9. pp. 705-713, 2008.

[15] N. Hashemian, A. Armaou, "Simulation, model-reduction, and state estimation of a two-component coagulation process," J. AIChE, DOI 10.1002/aic.15146, 2016.

[16] L. Liu, J. Litster, S. Iveson, and B. Ennis, "Coalescence of deformable granules in wet granulation processes," *AIChE J.*, vol. 46, no. 3, pp. 529-539, 2000.

[17] H. M. Hulburt and S. Katz, "Some problems in particle technology: A statistical mechanical formulation," *Chem. Eng. Sci.*, vol. 19, pp. 555-574, 1964.

[18] T. Y. Chiu and P. D. Christofides, "Robust control of particulate processes using uncertain population balances," *Aiche J.*, vol. 46, no. 2, pp. 266-280, 2000.

[19] G. Szego, *Orthogonal Polynomials,* 4th ed., American Mathematical Society, New York, 1939.