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# A reduced order PBM–ANN model of a multi-scale PBM–DEM description of a wet granulation process

Dana Barrasso, Ashutosh Tamrakar, Rohit Ramachandran *

*Department of Chemical and Biochemical Engineering, Rutgers, The State University of New Jersey, Piscataway, NJ 08854, USA*

## HIGHLIGHTS

- A computationally efficient PBM–ANN model was developed to substitute for a high fidelity PBM–DEM model.
- The PBM–ANN model demonstrated excellent agreement when compared with the PBM–DEM model. The PBM–ANN model was solved at a fraction of the simulation time of the PBM–DEM model.

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## ABSTRACT

Wet granulation is a particle design process, often used in the pharmaceutical, consumer product, food, and fertilizer industries. A better process understanding is needed to improve process design, control, and optimization. Predominantly, two modeling frameworks are implemented to simulate granulation processes: population balance modeling (PBM) and discrete element methods (DEM). While PBM simulates changes in the number of particles in each size class due to rate processes such as aggregation, DEM tracks each particle individually, with the abilities to simulate spatial variations and collect mechanistic data. In this bi-directional coupled approach, the computational expenditure of the full model is overwhelmed by the high-fidelity DEM algorithm that needs to solve a set of ODEs for each and every particle being handled in the system for very small time intervals. To mitigate this computational inefficiency, reduced order modeling (ROM) is used to replace the computationally expensive DEM step. An artificial neural network (ANN) was trained using DEM results to relate particle size, size distribution, and impeller speed to the collision frequency. Results showed a high correlation between the trained ANN predictions and DEM-generated data. The ANN was coupled with a PBM as a key component of the aggregation rate kernel. The coupled model showed a different development of average particle size and size distribution over time from that of a constant aggregation rate kernel. In addition, the coupled model demonstrated sensitivity to the impeller speed via the ANN rate kernel. When compared with the fully coupled PBM–DEM model for accuracy and computation time savings, the hybrid PBM–ANN model demonstrated excellent agreement with DEM simulations at fractions of the original computational time.



## 1. Introduction

Modeling of particulate systems is of critical importance within the chemical and pharmaceutical industries, and yet it remains relatively poorly understood. Traditionally, the pharmaceutical industry has implemented a Quality by Testing (QbT) approach to product manufacturing which involves sampling the products of empirically designed processes and rejecting out-of-specification batches. In recent years, in a move from batch to continuous processes, the industry has redoubled its efforts to focus on a Quality by Design (QbD) practice to improve controllability, scalability, and profitability. The QbD approach aims to better understand and define the design space and operating parameters that will result in quality products and has elevated the urgency to establish robust particulate system models (Yu, 2008). To develop practical and predictive models of pharmaceutical processes, an effective model-based approach has been proposed in which mathematical process models are developed and validated using experimental data (Glaser et al., 2009; Ramachandran and Chaudhury, 2012). For the highly complex process of wet granulation, which is governed by the rate processes

* Corresponding author. Tel.: +1 848 445 6278; fax: +1 732 445 2581.
*E-mail address:* rohit.r@rutgers.edu (R. Ramachandran).

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of wetting and nucleation, aggregation and consolidation, and breakage and attrition (Iveson et al., 2001), empirical models have limited applicability outside the space of the calibration data set (Barrasso et al., 2014; Chaudhury et al., 2014). To overcome these limitations, a multi-scale modeling approach in which mechanistic information from a discrete element method (DEM) model is provided to the population balance model (PBM) via a reduced order model (ROM).

### 1.1. Modeling powder processes: Population balance models and discrete element methods

Two modeling frameworks are predominantly used to simulate particulate processes: the semi-empirically-driven PBM and the more mechanistic DEM.

Population balance equations have been extensively used to model particulate processes including granulation, crystallization, mixing, milling and drying applications of pharmaceutical products (Reynolds, 2010; Griffin et al., 2010; Mortier et al., 2013; Barrasso and Ramachandran, 2012; Sen and Ramachandran, 2013). The PBM groups the particles into a set of classes based on one or more properties, such as size, liquid content, and porosity. The number of particles in each of these classes, or bins, is tracked over time by evaluating rate processes, such as aggregation, breakage, nucleation, and growth. These rate expressions are often empirical and require ample experimental data to estimate unknown parameters, resulting in poor predictability outside the experimental design space and limited understanding of the effects of process parameters and material processes on the critical quality attributes of the process (Barrasso et al., 2014; Chaudhury et al., 2014).

In contrast, DEM models track each individual particle as it moves through space, colliding with equipment walls, blades, and other particles. Using Newton's laws of physics and supplemental contact models, such as the Hertz–Mindlin model, net forces are calculated and applied to each particle. Although recent studies have demonstrated that DEM can be used to obtain detailed mechanistic information such as collision frequencies, impact velocities and forces (Yang et al., 2003; Gantt and Gatzke, 2005; Hassanpour et al., 2011), more direct investigations are needed to decisively validate these collision-level predictions from DEM. In the study by Freireich et al. (2009), the justification of collision-scale DEM predictions through verification of particle velocity and solid fraction fields using experimental techniques such as particle image velocimetry or positron emission particle tracking was shown to be an insufficient validation (Freireich et al., 2009). Nevertheless, at flow-level the measured macroscopic trends were well captured by DEM models despite the difference in collision-level behavior (Freireich et al., 2009; Di Renzo and Di Maio, 2004). Under these circumstances, the use of DEM simulations to obtain necessary granular flow information in this study has been restricted to approximate only the net collision frequencies between particle size combinations at a flow-scale level. Besides collision frequencies, DEM simulations can provide additional flow-level information such as shear stresses and spatial inhomogeneities. In addition, DEM simulations are highly computationally intensive and generally unsuitable for practical applications such as parameter estimation, control, and optimization (Ketterhagen et al., 2008).

A critical difference between PBM and DEM is the treatment of the rate processes: while DEM simulations cannot independently simulate particle size and property changes resulting from the subprocesses in wet granulation, PBM models also cannot independently capture the detailed granulation behavior without empirical parameters inherent in its kernels. As a result, recent studies have focused on coupling PBM and DEM to take advantage of both models' individual strength. In the study by Reinhold and Briesen (2012), for instance, the aggregation kernel is developed by coupling discrete element simulations with a PBM. Wang et al. (2012) similarly utilizes DEM to obtain collision and dissipation energies during the granule breakage processes in a ball milling operation to link with PBM. Other coupled models have investigated coupling PBM and DEM with Computational Fluid Dynamics (CFD) for particle-fluid interactions in fluidized bed granulation processes (Rajniak et al., 2009; Fries et al., 2011; Sen et al., 2014).

### 1.2. Reduced order models and artificial neural networks

One of the main issues with using a computationally complex model such as a DEM simulation is its inefficiency while being used for overall system analysis which entails iterative calculations. DEM simulations have a high computational cost because they solve a set of ODEs for each and every particle being handled in the system for very small time intervals (usually around $10^{-6}$ s) while also tracking their interactions and spatial movement (Boukouvala et al., 2013; Lucia et al., 2004). Iterative calculations required for system optimization or parameter estimation will thus take a significantly large amount of time because the base model calculations are protracted themselves. This computational inefficiency poses a significant computational challenge to implementing a multi-scale coupled model using PBM and DEM. While a simple PBM can simulate a full process in seconds or minutes, a DEM simulation can take hours or days of computation time, depending on the choice of software and hardware, to solve for only a few seconds of physical time. This problem is exacerbated with large numbers of particles and small particle sizes, often the case in particulate processes (Ketterhagen et al., 2008).

In order to deal with this issue, three popular, computationally-economical approaches are usually implemented as an alternative for modeling the entire granulation system: periodic section DEM simulation, simulation of larger and fewer particles and reduced order models (ROMs). In the periodic section approach, taking advantage of the symmetric geometry of a granulator, simulations of a segment of the granulator are performed rather than the entire system. Since DEM calculations scale non-linearly with the number of particles, running multiple smaller simulations of the entire system is computationally faster than simulating the entire system itself (Dubey et al., 2011; Gao et al., 2012). Another common approach to reduce the DEM calculation time is to mimic the original granulation system in DEM with a system with fewer but larger particles. This reduction entails adjusting the particle densities to maintain similar momentum exchange between particles; however, additional sensitivity studies on the effect of particle size on the powder dynamics needs to be performed before such reduction can be made (Hassanpour et al., 2011). The final alternative approach is to develop ROMs through data fitting techniques to replace the computationally intensive, high-fidelity DEM models. Even though a smaller system of particles are being simulated in the periodic section approach, the fact that DEM algorithm needs to be implemented multiple times for system analysis necessitates investigation into drastically faster reduced order modeling techniques. Various data fitting techniques are available in literature that have been used to replace full scale models including response surface methodology (RSM) (Boukouvala et al., 2010; Jia et al., 2009; Ranjbarian and Farhadi, 2013), Kriging method (Gao et al., 2012; Jia et al., 2009; Ranjbarian and Farhadi, 2013), high dimensional model representations (HDMR) (Banerjee et al., 2010; Banarjee and Ierapetritou, 2004), and artificial neural networking (ANN) (Boukouvala et al., 2010, 2011; Akkisetty et al., 2010; Basheer and Hajmeer, 2000). Developing such reduced-order models not only provide a quantitatively accurate description of the system dynamics which are far less computationally taxing than the original models but also provide a means by which the system dynamics can be readily interpreted for process simulation and optimization purposes (Lucia et al., 2004).