Model order reduction of a multi-scale PBM-DEM description of a wet granulation process via ANN

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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. Two modeling frameworks are available to simulate granulation processes: population balance modeling (PBM) and discrete element methods (DEM). PBM simulates changes in the number of particles in each size class due to rate processes such as aggregation, often relying on empirical rate kernels or require additional mechanistic information, such as flux data, collision frequencies, and impact forces. DEM tracks each particle individually, with the abilities to simulate spatial variations and collect mechanistic data. DEM does not inherently simulate particle size changes and is highly computationally expensive. While DEM can determine collision rates between particles of various sizes, PBM can use this data to determine aggregation rates and calculate a net change in the number of particles in each size class. As the size distribution develops, the collision rates change, resulting in a time- and size-dependent aggregation rate kernel. To solve this complex model, 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.

Keywords: Wet Granulation; Discrete Element Modeling; Population Balance Modeling; Reduced Order Modeling; Artificial Neural Networks

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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 [1]. To develop practical, predictive models of pharmaceutical processes, a model-based approach has been proposed in which mathematical process models are developed and validated using experimental data [2,3]. For the highly complex process of wet granulation, which is governed by the rate processes of wetting and nucleation, aggregation and consolidation, and breakage and attrition [4], empirical models have limited applicability outside the space of the calibration data set [5, 6]. 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. 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 [5, 6].

In contrast, DEM models track each individual particle as it moves through space, colliding with equipment 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 DEM simulations can provide detailed mechanistic information such as collision frequencies and forces, shear stresses, and spatial inhomogeneities, they cannot independently simulate particle size and property changes resulting from the subprocesses in wet granulation. In addition, DEM simulations are highly computationally intensive and unsuitable for practical applications such as design, control, and optimization [7].

1.2. Reduced order modeling and artificial neural networks

Computational inefficiency poses a significant computational challenge to implementing a multi-scale 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 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 [7].

As an alternative approach, ROMs can be developed through data fitting techniques to replace the intensive, high-fidelity DEM models. Various data fitting techniques are available in literature that can be used to replace the full scale model including response surface methodology (RSM), Kriging method, high dimensional model representations (HDMR), and artificial neural networking (ANN) [8].

ANN, in particular, is a popular modeling technique to address complex problems and develop empirical process models [9]. ANNs mimic the learning systems of the brain, using a trained set of weighted neurons to predict output values from input data. In pharmaceutical science, ANNs can be used to model analytical data, molecular drug design, modeling pharmacokinetic and pharmacodynamics profiles, optimizing manufacturing processes, [10] and to model pharmaceutical unit operations [11]. In a previous study, Akkisetty, et al [11] used an ANN within a PBM to represent the breakage kernel in an industrial milling process. ANNs are particularly well suited for modeling non-linear problems and can be evaluated rapidly, making them a suitable candidate to model DEM data within a PBM.
1.3. Objectives and approach

DEM modeling can provide useful mechanistic information to comparatively semi-empirical PBMs. Simulating DEM models of multi-scale and multi-dimensional wet granulation processes is a computationally expensive procedure that is not feasible for practical purposes of optimization, control or flowsheet modeling. An alternative to running DEM simulations is to develop a reduced order model (ROM) that will substitute the intensive calculations of DEMs with faster black box models. The ROM investigated in this study utilizes the data generated from DEM models to train an artificial neural network (ANN) which is used within a PBM. A schematic of this approach is shown in Figure 1. The objectives of this study are to:

- Present a one-dimensional PBM for a batch wet granulation process representing the aggregation rate kernel as the product of the collision frequency and efficiency.
- Characterize the effects of particle size, size distribution, and impeller speed on the collision frequencies in a batch granulator using DEM.
- Based on the results from DEM simulations, train ANNs to predict the collision frequency from some or all of the following: colliding particle sizes and number frequencies, overall size distribution, and impeller speed.
- Compare the accuracies of the ANNs to predict the collision frequencies from their subsets of input variables and select the optimal ANN configuration.
- Perform simulations using a hybrid PBM-ANN for a dynamic, size-, size distribution-, and impeller speed-dependent aggregation kernel, and compare the results of the hybrid model to those of the uncoupled PBM.

Fig. 1. Schematic of bi-directional coupled PBM-DEM model (top) and PBM-ANN reduced order model (bottom).

2. Model development

2.1. Population balance model development

A one-dimensional PBM was developed, tracking distributions in particle size over time due to aggregation. The rate of change of the number of particles, \( F \), as a function of particle size \( x \), is given in Equation 1 [12].

\[
\frac{dF(x)}{dt} = \mathcal{R}_{agg}(x) = \frac{1}{2} \int_{0}^{x} \beta(x - x', x') F(x - x') F(x') dx' - \int_{0}^{\infty} \beta(x, x') F(x) F(x') dx' \quad (1)
\]

The net aggregation rate source term is given by \( R_{agg} \), and the aggregation rate constant is given by \( \beta \). A linear grid with respect to volume was implemented to discretize the size domain. The discretized form of this PBM is given in
Equation 2, where \(i\) and \(j\) are the indices of the bins and \(N\) is the total number of bins, given in Table 1.

\[
\frac{dF(i)}{dt} = \frac{1}{2} \sum_{j=1}^{N-1} \beta(i-j, j) F(i-j) F(j) - \sum_{j=1}^{N-1} \beta(i, j) F(i) F(j)
\]  

(2)

The volume \((V)\) and diameter \((d)\) of the particles in each bin are given by Equations 3, where \(V_0\) is the volume of the first bin. The size of all initial particles was equal to that of the first bin, and the initial number of particles is given in Table 1, along with the volume of the first bin.

\[
V(i) = V_0 i \quad d(i) = \left(6V_0i/\pi\right)^{1/3}
\]  

(3)

Several aggregation rate kernels have been proposed in the literature, including dependencies on size [13], liquid content [14], and composition [15]. The aggregation rate can be represented as the product of the collision frequency \((C)\) and the collision efficiency \((\Psi)\) between two particle classes [16].

The collision efficiency represents the likelihood or probability that a single collision will result in coalescence. This value depends on the sizes, masses, and surface liquid of the colliding particles, as well as their relative velocities [16, 17]. For the purposes of this study, a constant, size-independent collision efficiency was assumed in order to investigate the collision frequency in detail. The value for the collision efficiency is given in Table 1.

The collision frequency is the rate at which collisions occur between two bins per particle in each class. As shown in Equation 4, the collision frequency can be calculated from the number of collisions \((N_c)\) between the two classes over a time interval \((\Delta t)\) and the number of particles in each class [16, 18].

\[
C(i, j) = \frac{N_c(i, j)}{F(i) F(j) \Delta t}
\]  

(4)

In order to estimate the collision frequency, DEM simulations can be performed, and the number of collisions can be counted. It has previously been demonstrated and is shown here that the particle size distribution in the system affects the collision frequency functions [18]. Because of this effect, a single DEM simulation is not sufficient to characterize the aggregation kernel, which may change over time as the state of the system changes. Bi-directional coupling between PBM and DEM has been proposed and demonstrated [18]. However, these detailed models are limited by their computational expense. Further, process parameters, such as impeller speed, may affect the collision frequency and should be considered in the aggregation rate kernel.

In this study, DEM simulations were performed to gather data relating particle size, size distribution of the system, and impeller speed \((v)\) to the collision frequency. An ANN was trained and validated using the results from the DEM simulations to describe the collision frequency as a function of these input parameters. The resulting size-, size distribution-, and impeller speed-dependent aggregation kernel is given in Equation 5. Because this kernel depends on the state of the system, it changes over time, resulting in a dynamic aggregation rate.

\[
\beta(i, j, v, F(x)) = C(i, j, v, F(x)) \Psi
\]  

(5)

The PBM was solved for a total batch time of 3 minutes using MATLAB. First-order Euler integration was used to solve the resulting system of ordinary differential equations.

| Parameter                  | Value                        | Parameter                  | Value |
|----------------------------|------------------------------|----------------------------|-------|
| Number of bins (\(N\))     | 125                          | Batch time                 | 180 s |
| Volume of first bin \((V_0)\) | 4.19e-12 m³ (200 μm in diameter) | Integration time step     | 0.25 s |
| Initial number of particles in first bin \((F(1))\) | 1e4 particles                  | Collision efficiency \((\Psi)\) | 0.03% |
2.2. Discrete element method

To generate the training data set for ANN development, DEM simulations were performed, tracking the collision frequency of particles in the system. In a batch granulator with a four-blade impeller, fifteen particle distributions were simulated at three impeller speeds. Collision rates between particles were recorded according to the sizes of the colliding particles. EDEM 2.5 (DEM Solutions) was used to perform the DEM simulations in this study.

As shown in Figure 2 (a), the geometry for a batch granulator with an impeller was created in EDEM. The walls of the tank were represented by a vertical cylinder, and four impeller blades were created to agitate particles at the bottom of the tank. The dimensions of the geometry and rotational speeds of the impeller are listed in Table 2. All particles were created in random locations above the impeller at a rate of 1e6 particles/s until the specified number of particles was created. Figure 2 (b) shows a snapshot of a DEM simulation with particles.

![Equipment geometry, DEM simulation, and size distributions](image)

The standard Hertz-Mindlin contact model was used [19], and the values for material properties and contact parameters are shown in Table 2. These parameters were obtained from previous literature studies [20, 18].

| Parameter                        | Value   | Parameter                        | Value   | Parameter                        | Value   |
|----------------------------------|---------|----------------------------------|---------|----------------------------------|---------|
| Poisson’s ratio                  | 0.25    | Density                          | 1 g/cm³ | Tank diameter                    | 40 mm   |
| Shear modulus                    | 2 MPa   | Grid cell size                   | 1 mm    | Tank height                      | 40 mm   |
| Coefficient of restitution       | 0.1     | Fixed time step                  | 5e-6 s  | Blade width                      | 8 mm    |
| Coefficients of static, rolling friction | 0.5, 0.01 | Total DEM simulation time       | 10 s    | Blade angle                      | 30°     |

In order to develop an ANN that can accurately predict the nonlinear relationships between the different variables of the particulate system, the ANN must be trained using a substantial dataset relating selected input and output variables that encompasses most realistic scenarios. To generate such a dataset, fifteen particle size distributions were generated using the PBM presented in Section 2.1, assuming a constant and uniform collision frequency of 0.01 collisions/particle²-s. The 125 bins in the PBM were grouped into nine particle classes, ranging from 200 to 1000 μm. The normalized mass frequency in each of the nine classes was calculated over time, and distributions were selected based on the mass frequency of the smallest class. Distributions were selected when the mass frequency of this class reached the following values: 1, 0.8, 0.6, 0.4, 0.2, 0.15, 0.1, 0.05, 0.025, 0.01, 0.0075, 0.005, 0.004, 0.003, and 0.002. The resulting distributions are shown in Figure 2 (c).

Nine corresponding spherical particle types were created in EDEM with different diameters representing each size class. The number of particles in each class was varied for each simulation according to the distributions obtained from the PBM. Each distribution was simulated once with an impeller speed of 60 RPM and again with an impeller speed of 30 RPM or 90 RPM. The high and low impeller speeds were alternated for odd and even numbered distributions. The number of collisions between each particle type over a ten-second interval was recorded, and the collision frequency was calculated according to Equation 7.
Simulations were performed on a Dell Precision T1650 desktop using four Intel Core i7-3770 (3.4GHz) processors with 32GB RAM. The fixed DEM time step and grid cell size are given in Table 2, and each distribution was simulated for a total time of 10 s. The computation time for these simulations ranged from 4 days for the first distribution, which contained 100,000 particles, to 2.5 hours for the fifteenth distribution, which contained 3500 particles.

2.3. Artificial neural network architecture and training techniques

The data sets obtained from the DEM simulations were used to generate an ROM, relating inputs of particle sizes, size distribution, and impeller speed to collision frequencies. For this purpose, ANN was chosen as a suitable ROM. ANNs are particularly well suited for addressing non-linear problems. Given the non-linear nature of granulation processes, ANNs are a strong candidate for approximating DEM simulations.

The ANN developed in this study is used as a part of the aggregation rate kernel in the PBM. Four alternative ANNs were generated from the DEM dataset, representing four types of aggregation kernels. The inputs and outputs of each ANN are listed in Table 3. By using various inputs for these ANNs, the kernels can be compared for their ability to capture physical behavior using only a subset of inputs. For example, when omitting the impeller speed from the input dataset, the ANN may perform more poorly, indicating that the impeller speed has a significant effect on the collision frequency and must be considered in the aggregation rate kernel. All four ANNs had a single output: the square root of the collision frequency.

Table 3. Four ANN alternatives for describing collision frequencies.

| ANN# | Dependencies | No. of inputs | Inputs |
|------|--------------|---------------|--------|
| 1    | Particle size, impeller speed | 3             | Diameters of A and B, impeller speed |
| 2    | Size distribution, impeller speed | 10            | CSD of nine classes, impeller speed |
| 3    | Particle size, size distribution | 13            | Diameters of A and B, normalized number frequencies of A and B, CSD of nine classes |
| 4    | Particle size, size distribution, impeller speed | 14            | Diameters of A and B, normalized number frequencies of A and B, CSD of nine classes, impeller speed |

The first ANN only considers the sizes of the two colliding particles, denoted as A and B, and the impeller speed, resulting in a size- and impeller speed-dependent aggregation rate kernel. This ANN does not consider the state of the system (the size distribution), and results in a kernel that is not dynamic. The second ANN considers the size distribution and impeller speed, but not the particle size. All particles are treated equally as if their size does not affect the collision rate, but the state of the system is considered, resulting in a dynamic rate kernel. The third ANN includes the sizes of A and B and the size distribution of the system, as well as the normalized number frequency of the classes A and B in particular, resulting in a dynamic rate kernel that does not account for impeller speed. Finally, the fourth ANN represents the full kernel, with size, size distribution, and impeller speed dependencies. This ANN uses the sizes of the two particles involved in the collision as well as their relative number frequency of these particles in the system. The cumulative mass frequencies of the nine size classes are also provided as inputs, and the single output is the square root of the collision frequency for the two particles.

All ANNs were structured to contain a single hidden layer of 10 neurons, as shown for the fourth ANN in Figure 3. The input and target data from the DEM simulations were randomly divided into training (70%), validation (15%), and test sets (15%). This division of dataset ensures that different samples of input/target matrices are being used to improve and test the ANN developed. The training set is used to teach the network. Training continues as long as the network continues improving on the validation set. The mean-squared is calculated over different epochs, or iterations, of training. The test set provides an independent measure of network accuracy.

The ANNs in this study were generated using the neural network toolbox in MATLAB using the Levenberg-Marquardt training algorithm. The target values specified were the square-roots of the collision frequencies generated in DEM simulations. The square root transformation was used to ensure that data points of lower collision frequencies were predicted accurately and no negative collision frequencies would be predicted. The resulting output
of the ANNs represented the estimated square root of the collision frequency, and as such, these values were squared before use in the PBM to invert the square root transform and retain their physical meaning.

3. Results and discussion

3.1. Particle size distributions and collision rate functions from DEM

The DEM simulations showed that the collision frequency of any two classes depends on the sizes of those classes, the impeller speed, and the size distribution of the system. Figure 3 shows plots of collision frequency versus particle sizes for four simulations using various distributions and impeller speeds.

![DEM results: Distribution 8 at 60 RPM](image1)

![DEM results: Distribution 15 at 60 RPM](image2)

![DEM results: Distribution 15 at 90 RPM](image3)

In general, larger particles collide more frequently than smaller particles. The collision frequency increases at larger impeller speeds. These effects are demonstrated more clearly in Figure 4, which plots all of the collision frequency data points versus (a) the size distribution number (from Figure 2 (b)), (b) the impeller speed, and (c) the size of the aggregate particle. As the distribution number increases, the average particle size increases and the size distribution widens. Greater collision frequencies are observed for the higher distribution numbers, suggesting that the state of the system influences the collision frequency, and a dynamic aggregation rate must be considered. It is also evident that an increase in impeller speed results in slightly greater collision frequencies, which can be attributed to the increased agitation of the system. Further, larger particles engage in more frequent collisions. Figure 4 also shows the effects plots for the fourth ANN overlaid with the DEM dataset.

![DEM results and ANN predictions versus distribution number](image4)

![DEM results and ANN predictions versus impeller speed](image5)

![DEM results and ANN predictions versus aggregate particle diameter](image6)

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3.2. ANN training and predictability

The performance of a neural network developed can be measured by plotting the regression of the square root of the collision frequencies predicted by the ANN (known as the output) versus those calculated by DEM simulations.
(known as targets). The coefficient of determination ($R^2$) values for the regression plots of the four neural networks are listed in Table 4 for the training, validation, and testing subsets, in addition to the overall value.

Table 4. Coefficients of determination ($R^2$) for each ANN, by data set.

| ANN# | Training | Validation | Testing | Overall | ANN# | Training | Validation | Testing | Overall |
|------|----------|------------|---------|---------|------|----------|------------|---------|---------|
| 1    | 0.7859   | 0.7167     | 0.8516  | 0.7810  | 3    | 0.8657   | 0.8393     | 0.8871  | 0.8643  |
| 2    | 0.1057   | 0.1360     | 0.1220  | 0.1121  | 4    | 0.9780   | 0.9715     | 0.9600  | 0.9751  |

These results show that the accuracy of the fourth ANN is much higher than that of the first three. Two conclusions can be drawn from this observation; either, the architecture is insufficient to describe the input-target relationships for the first three ANNs, or the inputs used for these ANNs are not extensive enough to describe the target collision frequencies generated from the DEM simulations. Based on the results of the DEM simulations, shown in Figure 4, it is clear that the impeller speed, particle size, and size distribution affect the collision frequency. As a result, the fourth ANN was selected as the optimal ANN for use in the aggregation rate kernel, and all subsequent results are based on this ANN.

The regression plots for the ANN are shown in Figure 5, and an overlay of the effects plots for the target and output collision frequencies is shown in Figure 4. The ANN predictions show strong correlation to the target values, or DEM results, suggesting that the training was successful and the ANN captures the trends observed. The validation and testing data sets were also strongly correlated, suggesting that the ANN is not over-fitting the data and has predictive capabilities beyond the data points used in training. Based on the overlay of the effects plot (Figure 4) the ANN captures the overall relationships between the input and target variables.

![Regression plots for ANN #4](image)

**Fig. 5.** Regression plots for ANN #4. Target values are collision frequencies, in collisions/particle\(^2\)-s, from DEM results. Output values are the corresponding predicted collision frequencies from ANN.

Figure 6 shows the ANN-predicted collision frequency as a function of the sizes of the colliding particles for the three distributions and impeller speeds shown in Figure 3. These plots show similar shapes trends to those from the DEM data sets (Figure 3).

![Collision frequency predictions](image)

**Fig. 6.** ANN collision frequency predictions for (a) distribution 8 at 60 RPM and distribution 15 at (b) 60 RPM and (c) 90 RPM.
3.3. PBM-ANN results

The ANN provides a dynamic, size-, size distribution-, and impeller speed-dependent collision frequency function to the PBM, and when combined with the constant collision frequency, completes the aggregation rate kernel. To use the PBM-ANN model, the ANN was evaluated at every time step during the PBM simulation to determine a predicted collision frequency between each pair of bins based on their diameters and number frequencies, the overall size distribution of the system, and the impeller speed. Figure 7 shows the results of the uncoupled PBM and PBM-ANN models.

Figure 7 (a) shows the average diameter ($d_{4,3}$) over time for the constant and dynamic collision frequencies. The constant collision frequencies resulted in sharp increases in size initially, but the size starts to level off after the first minute. However, in the simulations using the dynamic and size-dependent collision frequency (via ANN), the size increase is more gradual initially, but steadier throughout the process. This result can be attributed to the size and size distribution dependencies of the aggregation rate kernel when using the ANN. As larger particles develop, the collision frequencies increase, resulting in more aggregation.

Figure 7 also demonstrates the effect of impeller speed on the granulation process. The PBM-ANN was simulated at five impeller speeds ranging from 30 to 90 RPM and with a step change in impeller speed from 90 to 30 RPM at 60 seconds. Greater impeller speeds result in larger particles due to the increase in collision frequency.

In the step change simulation, the particle size initially increases quickly. When the impeller speed is reduced at 60 seconds, the aggregation rate reduces. This result demonstrates the ability of the PBM-ANN model to respond to changes in a process parameter, which may be useful in process design, control, and optimization.

By using the ANN, the computation times of the multi-scale simulations were drastically reduced compared to those of a full PBM-DEM model. While the DEM simulations required hours or days to solve only 10 seconds of simulation, the PBM-ANN model was solved in approximately 15 seconds. In comparison, the uncoupled PBM was solved in less than one second. The increase in computation time when using the ANN can be attributed to the evaluation of the ANN based on the current input parameters at each time step. Additionally, the calculation of some of those input parameters (such as particle size distribution) was not required at every time step in the uncoupled PBM since they had no impact on the results. Unlike the full PBM-DEM model, the 15-second PBM-ANN simulation can be used for iterative calculations, such as parameter estimation, optimization, and model-based control.

4. Summary and conclusions

The QbD approach to solving complex problems in science and engineering demands a model-based method to understand process design and parameters. For a highly complex process of wet granulation, developing a predictive model that is dependable beyond the space of calibration data set is critical in aiding process control and
optimization. A multi-scale model where the mechanistic information from a DEM model is provided to the empirical PBM calculations can be used to simulate multi-dimensional wet granulation processes. Simulating DEM models, however, is a computationally taxing procedure and one that is not very feasible for practical purposes of optimization, control or flowsheet modeling.

An alternative to running DEM simulations is to develop a ROM that will substitute the intensive calculations of DEMs for a faster approach of black box models. The reduced order model investigated in this study utilizes DEM results to train an artificial neural network (ANN) which can relate particle size, size distribution, and impeller speed to the collision frequency. The trained ANN showed a high predictive ability with respect to DEM generated data. A coupled PBM-ANN bi-directional model was subsequently developed using ANN predictions 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. The computational time required to solve the PBM-ANN model was observed to be drastically lower compared to the full PBM-DEM bi-directional model, which illustrates the potential of this ROM for iterative calculations.

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