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Physics-Constrained Autoencoder Neural Network for the Prediction of Key Granule Properties in a Twin-Screw Granulation Process

Chaitanya Sampat[a] and Rohit Ramachandran[a,*]

[a]*Chemical and Biochemical Engineering, Rutgers, the State University of New Jersey, Piscataway, NJ 08823, USA*
rohitrr@soe.rutgers.edu

Abstract
With the advancement of digitization of industrial manufacturing, there has been an increase in the application of machine learning methods to model these processes. These data-driven models are multivariate in nature and on occasion may not deliver the accuracy that can be obtained from first-principle models. The statistical approach in data-driven models is completely data-dependent and may give erroneous or undesired results due to noisy and incomplete database. Though accurate, first-principle models are often slow to simulate and lack the ability to predict data in real-time (Chen et al., 2020). Thus, to obtain real-time process predictions with accuracy similar to first-principle models, there is a need to develop data-driven models with first principle-based process constraints within their framework. In this study, several experimental datasets for twin-screw granulators (TSG) were considered. The data for 13 different TSGs was collected from previously published studies. The collected data was sorted for process parameters, material properties and geometric conditions of the study. An autoencoder neural network was developed to model these processes. The output from this model not only predicted the data well but also showed granule growth characteristics with the output properties obeying first-principle laws. The encoding section of the neural network helped find correlated inputs creating a reduced order model and captured information about the underlying physics of the process.
Keywords: Physics constrained neural network; autoencoders; twin screw granulation; Physics informed neural networks; PINN; PCNN

1. Introduction
Wet granulation is the process of agglomeration of fine powder into larger granules by adding a liquid binder. These granules help achieve desired quality attributes which can aid in improved flow, better dissolution rates, and better compression characteristics (Iveson et al., 2001). Wet granulation find application in various powder processing industries like mineral processing, agricultural products, detergents, food, and pharmaceuticals. It is an important unit operation in downstream oral dosage manufacturing in the pharmaceutical industry to more uniform distribution and dissolution characteristics. Previously wet granulation has been performed in a batch manufacturing scenario where, powder was mixed using an impeller and a liquid binder was sprayed using a liquid binder. This high-shear granulation can produce less compressible granules and operate in a very narrow range (Kumar et al., 2013). These challenges were overcome by converting this batch process to continuous manufacturing process.
Twin-screw granulation (TSG) is a widely used continuous wet granulation process. This equipment consists of a barrel which contain 2 co-rotating screws along parallel axes helping in the transfer of material along its length (Seem et al., 2015). These

screws are made up of smaller several screw elements which can help alter the flow of the material along the axis and can aid the mixing, breakage and other mechanisms which can affect the CQAs of the final granules. TSG can also support higher production volume compared to a batch granulator. TSGs have a larger design space due to the large number of independent operating parameters. This results in a large design of experiments which needs to be performed for optimization of the process to obtain the desired granule critical quality attributes (CQAs). Performing large number of experiments in early-stage process development when large amounts of active pharmaceutical ingredient (API) may not be available. Thus, there is a need for development of generalized models that can predict the outcome of the TSG. This model would need to be trained on a large data set of experiments which incorporates the effects of various independent operating parameters on the final granule CQAs and process outputs.

Neural networks with their dense structure have proven to be able to capture complicated relationships between inputs and outputs accurately. These neural networks can also be used to create reduce order models for faster prediction of these processes. Recently, to improve the prediction of neural networks for more complex physical processes, physical information about the process has been added to supplement its training (Mao et al., 2020; Raissi et al., 2019). Other studies have focused on constraining outputs of the neural networks with physics-based boundaries to make better informed models which, have the ability to accurately predict process outcomes(Zhu et al., 2019). These physics-based boundaries when incorporated into the loss these neural networks, help the model learn the underlying physics of the process leading to accurate predictions and more reliability under uncertain process conditions (Sampat and Ramachandran, 2021). These physics-based boundaries can be added to both the representation loss as well as the supervised loss, which leads to the addition of an extra loss function to the training. They have also resulted in neural networks requiring less data to train, which is especially useful with TSGs as this would reduce the amount of experimental data required.

In this work, a physics-constrained autoencoder (PCSAE) network was developed to create a reduced order model to represent a complete TSG process. Experimental data from 13 previously published literature was collected for various operating process parameters, process outputs and granule CQAs. The boundary conditions for each output were determined and were added the loss function of the developed PCSAE network. Sensitivity analysis was also performed on the PCSAE to determine whether it was able to capture the physical information about the process.

2. Methods

2.1. Data collection and completion methods

Twin-screw granulators with a wide design space have a large number of process parameters and geometry which can be varied. These variations when combined with changes in formulation can lead to an almost infinite combinations which can make the development of a general model for TSG very complicated. To incorporate all these effects a detailed data collection is required. In this study, data was collected from 9 different previously published experiments encompassing changes in formulation, process parameters and geometry(Dhenge et al., 2013, 2012; Kumar et al., 2016; Meier et al., 2017; Meng et al., 2019; Mundozah et al., 2020; Shirazian et al., 2017; Vercruysse et al., 2012). A total of 227 data points were collected for the creation of the model. Granule growth within a granulation process can be inferred from the process outcomes and critical quality attributes (CQAs) of the granules obtained. Some of the process outcomes of the TSG process commonly studied are residence time distribution (RTD), mixing, torque inside the system, while granule size distribution (GSD) and granule density / porosity are the commonly studied granule quality attributes (Seem et al., 2015). Table 1 lists all the input parameters and outputs collected from each of the sources to develop the PCSAE model for a TSG process. In some literature, outputs had been reported in figures and each figure was processed individually for relevant data. The data from each plot was extracted using WebPlotDigitizer (Rohatgi, 2021). The data was split in the ratio of 3:1 for training and validation.

Table 1: Inputs and output monitored for the development of the PCSAE model

Input Parameters			**Output Parameters**
Geometry	**Process**	**Material**	
Number of CE and KE (nCE,nKE)	L/S ratio	Initial PSD	Granule size distribution
Staggering angle (SA) of KE	Screw Speed	Binder viscosity	Torque
L/D Ratio	Feed Rate	% API in powder	Mean Residence Time
Granulator diameter	Temperature		
Liquid addition position			

In this study, a multivariate linear regression was used since the torque and MRT values for a TSG are dependent on several inputs instead of only a single input. The regression model ($\boldsymbol{Y} = B\boldsymbol{X} + X_i$) was trained using the *sklearn* (Pedregosa et al., 2011) package in Python. The regression model used the existing data for torque and MRT for training. Here, $\boldsymbol{Y}$ is the response matrix of size $n \times p$, $\boldsymbol{X}$ is the matrix containing all predictors with size of $n \times (q+1)$. $\boldsymbol{B}$ is a $(q+1) \times p$ matrix of fixed parameters, X_i is the intercept matrix of size $n \times p$. Here n represents the number of observations, q are the number of inputs or predictors and p represents the number of responses or outputs. This model is often referred to as deterministic regression imputation. Such an imputation can add a bias to the predictions. To remove such biases, uncertainty can be added back to these models.

2.2. Development of Physics-constrained supervised auto-encoders (PCSAE)

An auto-encoder (AE) is a neural network which output are the same as the inputs and during its training for reconstruction, they can extract underlying attributes which can enable accurate predictions (Le et al., 2018). Single-layer AEs with linear activation functions are equivalent to principal component analysis, moreover non-linear auto-encoders have found to extract key attributes (Vincent et al., 2010). A supervised auto-encoder (SAE) is an AE with the addition of a supervised loss on the representation layer. A single linear layer SAE would perform like a partial least square method. The addition of a supervise loss to the AE better directs the representation learning.

The PCSAE model for this study was developed in Python v3.7.6 using Keras (Chollet et al., 2015). Keras is a wrapper used for machine learning package Tensorflow (Martin Abadi et al., 2015) developed by Google. The network had 12 input nodes which were divided into three separate groups as shown in Table 1. This helped create the 3 different reduced dimensional bottleneck layers representing each of the group individually. This bottleneck layer was then used for both reconstruction of the inputs as well as training the outputs with the physical constraints. The output physical constraints were obtained using physics-based boundaries. Maximum value boundaries

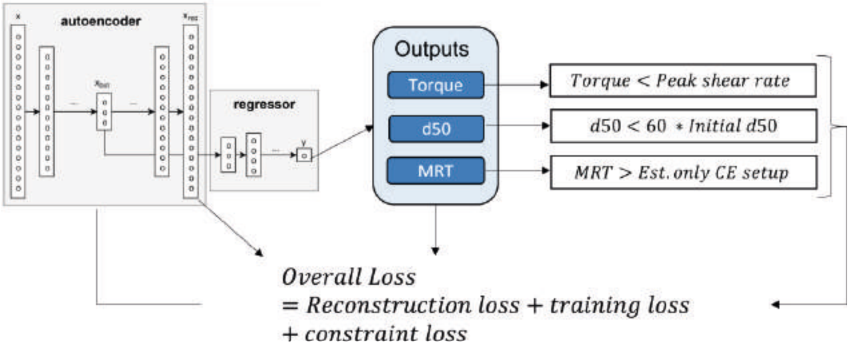

Figure 1: Physics-constrained supervised auto-encoder (PCSAE) model

for the median granule diameter and torque were determined using an empirical correlation and peak shear rate respectively, while a minimum boundary value was determined for the mean residence time (MRT). The minimum value was based on a screw configuration consisting only of conveying elements, which are known to aid conveying of material with little to no back-mixing. No physical constraints were introduced for the reconstruction. Figure 1 contains a schematic detailing the PCSAE model used. A single encoding layer with four nodes was used for the three individual inputs layers, a single decoding layer was used for reconstruction with eight nodes. Four layers were used for prediction of the outputs of the TSG with four nodes in each layer. All layers used the *'tanh'* activation function. The 'Adam' optimizer was used for optimization of the PCSAE with a learning rate of 0.008.

3. Results

3.1. Performance of the PCSAE

The total loss for the system was calculated as the summation of the reconstruction loss, training loss and the error due to the physical boundary constraints. These losses help aid the training of the system and prevent over-fitting of the model. For the PCSAE trained model no over-fitting was observed. The coefficient of determination (R^2) for prediction and reconstruction of outputs and inputs were 0.64 and 0.86 respectively. These values indicate that PCSAE was accurate to reconstruct the inputs to the model while the prediction of the outputs may not always be accurate. Figure 2(a) represents a parity plot for the predicted values of the outputs v/s the actual experimental values and it can be observed that some of the points are away from the $x = y$ line, indicating low accuracy. Figure 2(b) illustrates the parity plot for the reconstruction of the inputs and with an even spread across the $x = y$ line. The accuracy for the output prediction can be

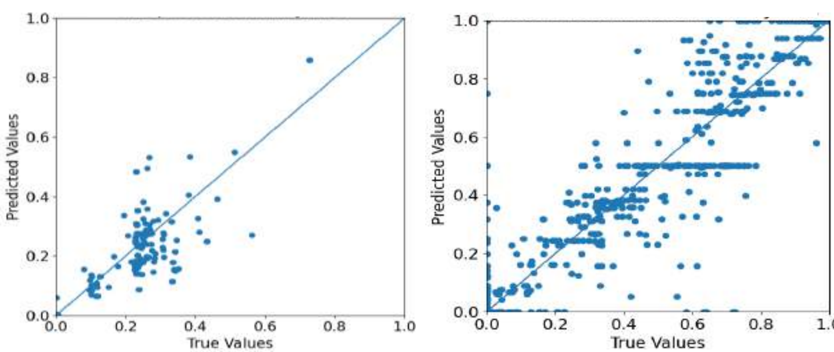

Figure 2: Parity plots for (a) Output prediction (b) reconstruction.

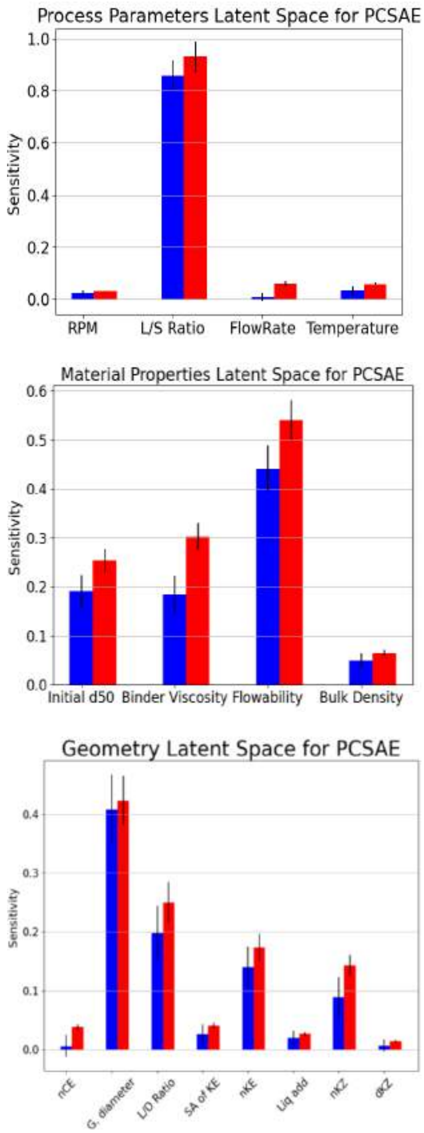

Figure 3: Sensitivity analysis of each input on the reduced dimension layer. The blue bars represent direct effects while the red bars indicate the total effect of the inputs.

improved in several ways including a deeper neural network for regression of the outputs, optimizing the hyperparameters of the neural network, improving the boundaries conditions.

3.2. Sensitivity analysis of PCSAE

To understand the effect of individual inputs on the outputs it is necessary to study their effects on the individual reduced dimension nodes. These nodes in-turn used to predict the outputs as well as reconstruct the inputs. It is vital for a model to capture the physics of the system well such that it considers the effect of each input. In this study, a Sobol sensitivity analysis was performed by varying the inputs across the range of values found in the literature. This sensitivity was compared against a supervised autoencoder without physical boundary constraints, and it was found that the PCSAE's sensitivity captured more physical information about the process than the non-physics constrained autoencoder. Figure 3 shows the sensitivity of the inputs on the reduced dimensions nodes. The effect of L/S ratio and RPM seems to the highest from the process parameters, while the contribution of different material properties seems to be almost equal, and the effect of staggering angle is the most prominent from the geometry parameters. These effects have been studied in literature and are in close accordance with the observed results. The effects of the inputs in the normal autoencoder system were observed to be skewed and did not align with physical observations.

4. Conclusions

Twin-screw granulation is a complicated process with an infinite number of combinations possible for its operation. With the help of developed physics-constrained autoencoder model, we were able to incorporate all the effects into a single model. This robust modelling framework is required could reduce the number of dimensions of the inputs to 3 segregated latent spaces for better process understanding. This framework which has been trained on several experimental datasets was able to capture the underlying physics of the system with accuracy of ~65%. The model was able to identify key inputs affecting the outputs which may not be captured using a regular autoencoder. The overall performance of the model can further be increased by optimizing the neural network structure and including more datasets with larger variations in the inputs. This model can further be used to reduce experimentation by supplementing the design of experiments. Prediction of the latent spaces could be used to assess the granule growth regimes and identify experiments which would yield desired granule CQAs resulting in material and cost saving. This framework could also be adapted to different unit operations with changes in boundary conditions for desired outputs for better cost saving during process development.

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