Loss-in-Weight feeder performance prediction using Machine Learning.

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Abstract

There has been significant drive in recent years to gain greater understanding of unit operations useful for continuous direct compaction, and to leverage data-driven approaches such as Machine Learning to extract trends from large and complex datasets. In this work, an approach using three Machine Learning models to predict the parameters in an equation for Loss-in-Weight feeder performance are presented. Industrially-relevant feeders with multiple screws per feeder are studied, and the approach allows feed factor decay to be predicted using material properties and equipment choice as inputs. Using a wide range of excipients and Active Pharmaceutical Ingredients (APIs) for testing shows good performance against industrially-relevant targets. The approach presented here would be useful for equipment pre-selection activities prior to experimental work.

**Keywords**: feeder, modelling, Machine Learning, powders.

* 1. Introduction

Driven by a need to improve efficiency and ever-increasing R&D costs in the pharmaceutical sector, the use of alternative production methods such as Continuous Manufacturing is gaining ground (Lee et al., 2015; Plumb, 2005; Schaber et al., 2011). Towards this, there is a need to develop mathematical models of key unit operations, as this allows simulations and digital Design-of-Experiments (DoE) to be rapidly carried out (Lee et al., 2020). One such key unit operation is the Loss-in-Weight (LIW) feeder.

LIW feeders are key unit operation in continuous, semi-continuous and batch manufacturing systems. Frequently the first unit operation in secondary processing, in essence they are hoppers of powder sitting above a screw or screws, which mechanically convey powder in a controlled manner as they turn; LIW feeders supply or ‘feed’ material to subsequent unit operations. Differences between designs of feeder can range from hopper size and shape; design of internal agitator; and screw number (e.g. twin-screw as opposed to single screw), design, size, and speed. In the literature there is an extensive body of work characterising feeders and evaluating their mass flow accuracy, reliability, and variability (Bascone et al., 2020; Bostijn et al., 2019; Engisch and Muzzio, 2012; Fernandez et al., 2011; Gao et al., 2011; Yadav et al., 2019).

Literature models for feeder performance typically require regression with experimental data (of feed factor with hopper contents) to determine model parameters, after which the equation can be used for that given material with that given equipment configuration *i.e.* quantities of material are required for testing, and model transferability is limited. In the present work, a Machine Learning-based approach developed, where the inputs are material properties and equipment configuration, and the outputs are model parameters that would otherwise require regression. The dataset used for training and testing spans two types of feeders (GEA Compact Feeder and Gericke GZD200.22) with multiple screws each. Multiple materials are included: 19 excipients and two generic Active Pharmaceutical Ingredients (APIs), which have been further supplemented by the inclusion of literature data (25 APIs/grades, 3 excipients) from Pfizer (Shier et al., 2022).

* 1. Materials, equipment, experiments
     1. Feeders

The GEA Compact Feeder comprises a flat bottom cylindrical hopper with interchangeable twin screws slightly offset from the centre. The operating volume of the hopper is 2 L (total volume is 2.5 L) and has three gearboxes available 455:1 (1-64 rpm), 235: 1 (1-124 rpm) and 63:1 (1-460 rpm) giving a speed range 1-460 rpm for both screws sets: 20 mm pitch double concave (20C) and 10 mm pitch double concave; both screws are 20 mm diameter. The internal hopper agitator rotates horizontally about the hopper axis. The GZD200.22 is a flat-bottomed feeder of 10 L hopper volume, with twin double-concave screws of 22 mm diameter. There are three screws that are represented in the database: the 11 mm pitch 11C screws, the 22 mm pitch 22C screws, and the 33mm pitch 33C screws. The internal hopper agitator rotates horizontally about the hopper axis.

* + 1. Materials

The materials used in the used in the present work include those in the base dataset (19 excipients and a generic API) supplemented by literature data from Pfizer (Shier et al., 2022). The additional literature data is predominantly proprietary substances, many for which there is data (both material characterisation and feeder performance data) for various grades or batches (3 excipients, 25 API grades and batches representing 16 APIs).

* + 1. Material characterisation

Bulk and tapped densities were measured with an AutoTap (Quantachrome). Shear tests were done with a Powder Flow Tester (Brookfield). Stability and Variable Flow Rate were done in a FT4 Powder Rheometer (Freeman Technology), as were compressibility and permeability. A MasterSizer 3000 (Malvern) was used for particle size.

* + 1. Volumetric discharge experiments

Base dataset of GEA Compact Feeder and Gericke GZD200.22 experiments are volumetric discharge runs conducted from an initially full hopper. Screw speeds used depend on feeder: 30, 60, 90 or 230 RPM for the Compact Feeder, and 170, 340, or 510 RPM for the GZD200.22. Runs have been started with screws initially uncharged (empty). Feeders have been run until mass flow stops, and no refills have been conducted. Literature data (Shier et al., 2022) are from gravimetric runs, and whilst this is different to the base dataset (volumetric runs), as subsequent modeling did not consider screw speed as a factor (and treated runs at different screw speeds as replicates) the two datasets are compatible. Some runs in the literature data used mesh grids at the end of the screws to break up any clumps of powder and improve flow, and where there was indication this impacted feeder performance those materials were excluded (not a common occurrence).

* 1. Data processing and Machine Learning approach structure

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| **A** |  | **B** |  |
| **Figure 1.** Decay of feed factor. A: example Eq. (1) decay defined with *ffmax* = 2 g/rev, *ffmin* = 0 g/rev. B: example volumetric discharge data with key 30–80 % hopper fill region highlighted. | | | |

A modified feeder performance equation from literature has been used when regressing parameters using raw data (Wang et al., 2017):

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Where *ff* is feed factor, the mass flow per turn of the screw(s) (g/rev), and *F* is hopper fill fraction. There are two fitting parameters: maximum feed factor *ff*max (g/rev), the initial (typically highest) feed factor when the hopper is full; and rate constant *β* (dimensionless), a measure of how quickly the feed factor decays from *ff*max. High *β* means feed factor is stable for longer and then precipitously decays, while low *β* means a more gradual but earlier decay (Figure 1A).

Raw feeder performance data of feed factor against hopper fill fraction mass (calculated from hopper mass, volume, and material bulk density). This allows a comparison across feeders of different hopper volumes, and allows value ranges of the *β* parameter to be defined: once *β* is at or above 15, the feed factor decay trajectories are functionally the same for the 30%–80% hopper fill region of interest (Figure 1A). This region of interest is used as the modeling efforts are not concerned with the initial rise from zero feed factor (Figure 1B), and the fact that the final decay as the hopper is emptying is likely governed by substantially different powder flow phenomena and moreover would not be experienced in practice as refill would have occurred before this point is reached. As *β* is very sensitive to flat regions of data, a maximum of 15 has been set for this parameter.

* + 1. Machine learning model structure, predictors, algorithms

The goal of the Machine Learning was to predict model parameters *ffmax* and *β*. Three Machine Learning models (developed and implemented in Matlab) have been used: one to predict *ffmax* (ensemble of trees with LSBoost algorithm), one to make an initial coarse estimate of *β* (the *class* of *β*; ensemble of trees with AdaBoost algorithm), and a third model to use this *class* as an additional input predictor and make a refined prediction of *β* (ensemble of trees with LSBoost algorithm). The class of *β* is a rough first estimate, and there are four classes: class 15 (values of *β* at 15), class 10 (values between 10 and 15), class 5 (values between 5 and 10), and class 1 (values between 1 and 5). Class 15 materials have a steady flow with precipitous decay, and class 1 materials have a gradual decay that starts much sooner. Aside from material properties used as predictors to the Machine Learning model, the following equipment properties are also predictors: feeder model (categorical), hopper volume, screw choice (categorical), screw diameter, and screw pitch. There is also ideal feed factor, the product of bulk density and screw free volume; the latter is calculated from geometry assuming the clearance volume around the screw plays no part in material transport (Bascone et al., 2020; Yu, 1997).

Training and test datasets have been split with an approximately 80/20 ratio. Conditions (feeder-screw-material combinations) often have multiple runs, either true replicate runs, or runs conducted at different RPMs. This results in some variability between parameters regressed for that condition, particularly for the *β* parameter. For the training dataset, the average value of regressed parameters has been used, but duplicated equivalent to the number of replicates as weighting. For the testing dataset, averages have been used but they have not been duplicated to not overestimate model accuracy. There are 215 runs in the training set, and 49 in the test set (21 after run averaging). However, there are some material property gaps in the literature data *i.e.* measurements that were not needed or performed for the purposes of that literature data. Excluding these from analysis (missing predictor impact is beyond present work scope) leaves 36 runs (13 after averaging).

* 1. Results and discussion

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| **A** |  | **B** |  |
| **Figure 2.** Training (A) and testing (B) for *ffmax*. Unaveraged data points are shown in a lighter shade. | | | |

Accuracy targets represent practical considerations for feeder operation: for *ffmax* the target was ±0.2 g/rev up to 1.0 g/rev and ±20 % thereafter. For *β* the target was accuracy such that the location of a 10 % drop from *ffmax* is within ± 50 g in terms of hopper contents (this represents different thresholds depending on hopper volume and material density).

The Machine Learning model for *ffmax* has been trained such that 90.2 % of the training data points are within the accuracy targets (Figure 2). In general it was easier to train materials in the base dataset (primarily excipients) than it is for literature data materials (primarily proprietary APIs). The most important predictor is ideal feed factor, the product of screw capacity and bulk density. In testing, a majority (11/13) data points were within the accuracy targets of ±0.2 g/rev or ±20 % (whichever greater). The cases that fell outside the accuracy targets (although only barely outside) were from the literature data, mirroring the more challenging training agreement of this dataset.

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| True class | Class 15 | 5 | 4 | 1 | 1 | Class 15 |  |  |  |  |
| Class 10 | 6 | 80 | 1 | 4 | Class 10 |  | 6 | 3 |  |
| Class 5 |  |  | 114 | 1 | Class 5 |  |  | 4 |  |
| Class 1 |  |  | 3 | 27 | Class 1 |  |  |  |  |
|  |  | Class 15 | Class 10 | Class 5 | Class 1 |  | Class 15 | Class 10 | Class 5 | Class 1 |
|  |  | Predicted class (training) | | | |  | Predicted class (testing) | | | |
| **Figure 3.** Training (A) and testing (B) for classification of *β*. | | | | | | | | | | |

While classification of *β* does not have accuracy targets as such (inaccuracies are passed on to the refined prediction) the classification accuracy can still be assessed (Figure 3). Most data points are either class 5 or 10 *i.e.* few are at the extremes. Training is straightforward (27/30 class 1 correctly classified, 114/115 class 5 correctly classified, 80/91 class 10 correctly classified) although it is slightly challenging for class 15 (5/11 correctly classified). In testing, a majority are correctly classified (6/9 class 10 cases, all four class 5 cases) with no misclassifications greater than one class difference.

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| **A** |  | **B** |  |
| **Figure 4.** Training (A) and testing (B) for prediction of *β*. Data points outside of accuracy thresholds are marked ‘OT’. Unaveraged data points are shown in a lighter shade. | | | |

Finding trends between the predictors and *β* is more challenging than for *ffmax*. Leaving aside the possibility that there is some unmeasured material property or material properties that are required to get a clear picture of the link, the parameter is also simply more variable, even among replicates (Figure 4). Nevertheless, 88 % of training data points (averaged replicates) fall within the specified accuracy threshold for beta (±50 g of material in the hopper to accurately predict location of 10 % drop from initial feed factor). Testing *β* model accuracy using predicted classes as an input (instead of known classes, to accurately gauge the true overall accuracy of the approach) show that a majority of points are within targets (9/13). Of those outside, two are from *β* class model misclassifications (class – the initial coarse estimate of *β* – is the most important predictor for the refined *β* prediction model), one is due to inaccuracy of the *β* model itself, and for the final data point outside targets, this was a run where all other runs of this material (which are in the training set) were of class 5 whereas this data point had a true class of 10. Ultimately, whilst many materials have very stable flow (*i.e.* high *β* values and/or little variability between replicates), there are many instances of significant *β* variability among what the model considers replicates, presenting challenges for *β* prediction.

* 1. Conclusions

Whilst the precise prediction of the likely feed factor decay (*β*) of a feeder is challenging – unsurprising given the variability of this in real data even among replicates – the prediction of the magnitudes of likely feed factor (*ffmax*) is accurate. Taken together, the approaches presented here offer a way to gain insight into likely equipment performance with reduced need for experimentation with the feeders.

Acknowledgements

This work has been funded by the Medicines Manufacturing Innovation Centre project (MMIC), UK (project ownership: Centre for Process Innovation, CPI). Funding has come from Innovate UK and Scottish Enterprise. Founding industry partners with significant financial and technical support are AstraZeneca and GSK. The University of Strathclyde (via CMAC) is the founding academic partner. Pfizer are project partners and have provided key technical input and data. Project partners DFE Pharma have provided materials and technical input, and project partners Gericke AG have provided technical equipment support and advice. Project partners Siemens and Applied Materials have provided key software and software/IT expertise. Andrew Shier (now of GSK) significantly contributed to the present work via the literature data (Shier et al., 2022).

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