Systems & Control Transactions

Research Article - Peer Reviewed Conference Proceeding
ESCAPE 35 - European Symposium on Computer Aided Process Engineering
Ghent, Belgium. 6-9 July 2025
Jan F.M. Van Impe, Grégoire Léonard, Satyajeet S. Bhonsale,
Monika E. Polańska, Filip Logist (Eds.)

PSE PRESS

Closed-Loop Data-Driven Model Predictive Control For A Wet Granulation Process Of Continuous Pharmaceutical Tablet Production

Consuelo Del Pilar Vega Zambrano[a], Nikolaos A. Diangelakis[b], and Vassilis M. Charitopoulos[a]*

[a] Department of Chemical Engineering, The Sargent Centre for Process Systems Engineering, University College London, Torrington Place, London WC1E 7JE, UK
[b] School of Chemical and Environmental Engineering, Technical University of Crete, Chania, Crete, GR 73100, Greece
* Corresponding Author: v.charitopoulos@ucl.ac.uk.

ABSTRACT

In 2023, the International Council for Harmonisation (ICH) guideline for the development, implementation, and lifecycle management of pharmaceutical continuous manufacturing (PCM), was implemented in Europe. It promotes quality-by-design (QbD) and quality by control (QbC) strategies as well as the appropriate use of mathematical modelling. This development urges a harmonizing understanding across academia and industry for adoption of interpretable models instead of black-box models for advanced control strategies such as model predictive control (MPC), especially when applied in Good Manufacturing Practice (GMP) regulated areas. To this end, we first propose a comprehensive model development using Dynamic Mode Decomposition with Control (DMDc)to represent complex dynamics in a lower-dimensional space, disambiguating between underlying dynamics and actuation effects. Using data from a digital twin of PCM, our model demonstrates low computational complexity while effectively capturing nonlinear dynamics with significant improvements observed in the performance metrics. Additionally, we demonstrate enhanced uncertainty propagation performance when compared to state-space models obtained with N4SID and Sparse Identification of Nonlinear Dynamical systems with control algorithms. Finally, we develop a closed-loop workflow that seamlessly connects data exchanges between Python (DMDc), GAMS (MPC optimisation) & gPROMS to evaluate the controller performance with setpoint tracking and disturbance rejection studies achieving high accuracy in real-time monitoring and control of granule size. This study offers a novel, interpretable control strategy for PCM. The results demonstrate the potential for real-time release testing, reduced reliance on end-product testing, and improved process control in the pharmaceutical industry.

Keywords: Quality by control, Data-driven control, Continuous pharmaceutical manufacturing

INTRODUCTION

For pharmaceutical continuous manufacturing (PCM)applications, model predictive control (MPC) was first used in 2010 [1] to control a continuous roller compaction process comparing a PID, linear MPC (DMC), and nonlinear MPC. The nonlinear MPC showed better performance, but it was found not practical due to the high computational cost whereas the linear MPC could track the set point change and reject the disturbances of roll speed and in the inlet bulk density. Obregón et al. (2013) addressed the control of a fluidized bed dryer (FBD) using MPC alongside inline near-infrared (NIR) moisture sensors while maintaining optimal moisture content, minimizing energy consumption, and adhering to physical constraints such as air flow and temperature limits [2]. They showcased MPC's advantages in achieving the desired set points faster and more efficiently than traditional control methods. However, the model required adjustments when operating conditions deviate from the original fitting parameters showing inability to generalize to unseen data. The application of MPC for controlling blending units in continuous pharmaceutical manufacturing has also been investigated [3]. The authors described

the use of the System Identification Tool in MATLAB to develop the blending model, focusing on outlet mass flow and holdup as key outputs. The linear MPC incorporated constraints on blender speed and mass flow to enhance process performance. Although it demonstrated superior control capabilities compared to conventional methods, it was considered disadvantageous for systems with high sampling frequencies. Additionally, they indicated that measuring the outlet mass flow to estimate the states of the blender model may not be feasible in a continuous production line. A novel control concept utilizing MPC with a local linear model tree (LOLIMOT) algorithm for hopper levels in the tablet press was developed previously [4]. Recently, a hybrid model integrating mechanistic and machine learning approaches to optimize a continuous dry granulation process with MPC was developed [5]. Artificial Neural Networks (ANN) and Nonlinear Model Predictive Control (NMPC) showed effectiveness in managing the granulation process.

The implementation and assessment of MPC strategies, tailored for a holistic plant-wide control framework in continuous pharmaceutical manufacturing, have been proposed [6]. This work was conducted at the Novartis-MIT Center for Continuous Manufacturing. Two distinct MPC designs were proposed, employing different modeling approaches: subspace identification and linearization of nonlinear differential-algebraic equations. These approaches resulted in low-dimensional and high-dimensional state-space models, respectively. The simulation results demonstrated that the plant-wide MPC effectively regulates critical quality attributes (CQAs) while accommodating various uncertainties, including fluctuations in reaction kinetics and disturbances in filtration unit efficiency. Additionally, the approach incorporated quality-by-design principles by integrating input and output constraints, ensuring that the process remains compliant with regulatory requirements. The findings demonstrated that the MPC framework not only improves operational efficiency but also ensures consistent product quality.

While some applications of MPC for pharmaceutical continuous manufacturing have been reported, barriers to the adoption of this advanced process control exist [7]. Celikovic et al. (2020) identified two challenges in implementing MPC algorithms: i) handling potentially high computational burden to solve the control problem fast enough within the small sampling intervals and, ii) having the reliable process analytical technology (PAT) equipment for real-time monitoring of CQAs [3]. An implementation issue arises that when nonlinear models are used, this leads to non-convex optimization problems with multiple local optima, which requires much more computational power and offers no guarantees for global optimality and stability of the solution.

Given that MPC is employed to regulate a dynamic process system whilst considering constraints that can include operational limits on the controlled variables and rate-of-change limits on the manipulated variables, undoubtedly a key part on adopting this control strategy is mathematical modelling. As an alternative to computationally demanding mechanistic models, reduced Order Models (ROMs) offer an entirely data-driven means to represent reliable yet computationally intensive models in a lower-dimensional space. ROMs representations can be deduced with several system identification techniques, many of them based on a form of dynamic regression that fits models based on input- output data. These techniques have been examined since the 1950s and some examples include autoregressive moving average with exogenous inputs (ARMAX) models, Multivariable Output- Error State Space (MOESP), Observer Kalman Identification (OKID), Sparse identification of nonlinear dynamics (SINDy) and Dynamic Mode Decomposition with Control (DMDc) [8]. Particularly, DMDc has been increasingly recognized for its ability to systematically uncover simplified relationships within intricate systems operating using discrete-time snapshots of the states and corresponding control inputs of the system to extract the underlying effect of both on the system dynamics.

Our approach differs from previous surrogate models for two reasons. First, the interpretability in our framework comes from the algorithmic or mathematical transparency of how a dynamic model is obtained with Dynamic Mode Decomposition with control which avoids the black-box nature of data-driven techniques found in the literature such as LoLiMoT, ARMA or neural network models. Second, to enhance interpretability, the reduced-order model is formulated as a simple linear discrete-time state-space equation, for which we also quantify its uncertainty propagation performance.

METHODOLOGY

Data-driven model identification with DMDc

Dynamic mode decomposition with control (DMDc) was introduced in 2016 [8] as a modal decomposition technique that extracts dynamically relevant spatial structures and whose goal is to disambiguate between the underlying dynamics and the effects of actuation.

Since the mathematical foundations of DMDc lie on the assumption that the next state of a dynamic system $y_t \in R^n$ is determined from a function of the current state $y_{t-1} \in R^n$ and current input $u_{t-1} \in R^p$, a dynamic system can be then approximated by a linear state-space model described in equation (1) for n observed snapshots, where A $\in R^{nxn}$ is the system matrix and B $\in R^{nxp}$ is the control matrix.

$$y_t^{DMDc} = Ay_{t-1} + Bu_{t-1} \quad (1)$$

$$where\ y_t \in R^n, u_{t-1} \in R^p,\ A \in R^{nxn}\ and\ B \in R^{nxp}$$

We tested the performance of DMDc to identify a model, as part of an offline stage of our proposed framework (Fig. 1), to predict four granule size distribution quantiles D5, D10, D50, and D90 for a twin-screw granulation process with three control variables Avicel (AFR), binder (BFR), and lactose flow rates (LFR). Data was collected from simulations using a gPROMS FormulatedProducts® 2023.2.1 process model flowsheet of integrated TSG and fluidized bed drying which was customized for the GEA ConsiGma™-25 Continuous Tableting Line CTL, at the Diamond Pilot Plant (DiPP) of the University of Sheffield. The TSG consists of a feeding section for powder transport and a working section for mixing powder with granulation liquid. Dry powders and granulation liquid are delivered via loss-in-weight dosing units. Wet granules are transferred to a six-segment fluidized bed dryer, where they are dried sequentially and discharged for further processing, enabling continuous operation until tableting is complete. For the full details of the process flowsheet, we refer the interested reader to [9].

Duration of the simulations was 3000s, with 1 dataset for training and 3 datasets for validation, varying randomly the powder (lactose and Avicel) and binder (water) flowrates. Noise was added to all data imposing periodical disturbances on the flowrates with a frequency 1 min-1 and a minimum/maximum deviation of 5% directly in gPROMS. For the uncertainty quantification study, 1000s extra were sampled for the training dataset.

Alternative system identification methods were used to compare the performance of DMDc. First, a state-space equation is obtained with a data-driven method called Sparse Identification of Nonlinear Dynamical systems with control (SINDyc), which regresses the coefficients for a nonlinear ordinary differential equation [10]. Second, the N4SID tool for Multivariable Output Error State Space (MOESP) from the MATLAB system identification toolbox [11] was employed.

Uncertainty quantification for state-space models

After identifying A and B matrices for the DMDc, SINDyc and MOESP models, the covariance matrix of the process noise and posterior covariance, as detailed in Digital Supplementary Material, was calculated for each model following:

$$\Sigma_\varepsilon = \frac{1}{n}\sum_{t=2}^{n} \left(y_t - \hat{A}y_{t-1} - \hat{B}u_{t-1}\right)^T \left(y_t - \hat{A}y_{t-1} - \hat{B}u_{t-1}\right) \quad (2)$$

$$V\left[y_{t*+1}|Y,\hat{A},\hat{B},\hat{\Sigma}_\varepsilon\right] = \sum_{i=0}^{t*-n} \hat{A}^i \hat{\Sigma}_\varepsilon \left(\hat{A}^i\right)^T + \sum_{i=0}^{t*-n} \hat{A}^i \hat{B} \hat{\Sigma}_u \hat{B}^T \left(\hat{A}^i\right)^T \quad (3)$$

For simplicity, $\hat{\Sigma}_u$ was assumed to be a diagonal matrix containing the standard deviations of each component (independent of the others) of the control input vector used for the training dataset.

Then, 95% confidence interval (CI) are calculated as:

$$CI = y_{t*} \pm 1.96 \cdot diag\left(V\left[y_{t*}|Y,\hat{A},\hat{B},\hat{\Sigma}_\varepsilon\right]\right) \quad (4)$$

The numerical criteria include the predictive root of mean squared error (RMSE) and the average length of the 95% predictive intervals (L(95%)):

$$RMSE = \left(\sum_{j=1}^{m}\sum_{t*=n+1}^{n+n*}\left(\hat{y}_{j_{t*}} - y_{j_{t*}}\right)^2\right)^{\frac{1}{2}} \quad (5)$$

$$L(95\%) = \frac{1}{mn*}\sum_{j=1}^{m}\sum_{t*=n+1}^{n+n*} \text{length}\{\text{CI}_{j,t*}(95\%)\}) \quad (6)$$

where $\hat{y}_j(x_{t*})$ is the prediction of the output for state j and length $\{\text{CI}_{j,t*}(95\%)\}$ denotes the length of the 95% predictive interval.

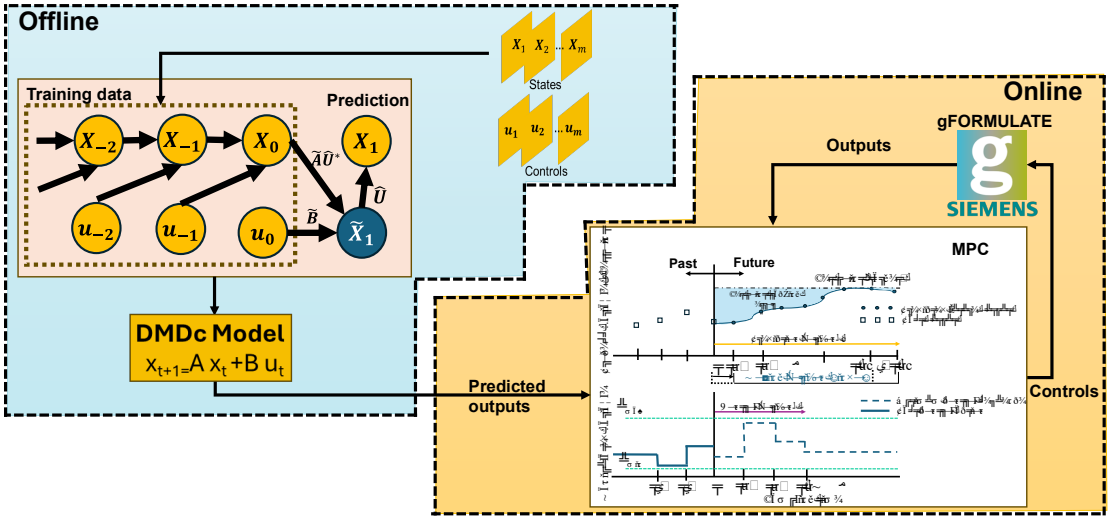

Figure 1. Proposed framework for a model predictive control (MPC) with a DMDc model

Closed-loop data-driven control framework

The DMDc model developed offline was integrated into a linear model predictive control in an online stage (Fig. 1), coded in General Algebraic Modelling System (GAMS®) using the solver Gurobi 11.02, in a closed-loop manner. A prediction horizon of 30 seconds and a control horizon of 10 seconds were empirically tuned to balance control performance and computational efficiency.

Every control period of 1 second, a customized gPROMS FormulatedProducts® flowsheet sent data employing gO:Python, which used the model as an estimator to predict future states of the system. These predicted outputs were sent to the optimizer using GAMSPy to find optimal control inputs in real time by solving an optimization problem with an average computation time of 0.034 ± 0.01s that minimized the error between predicted and desired setpoints. At each time step (1s), the optimization was repeated, updating the control sequence over the control horizon and applying the first control action to the system using gO:Python + GAMSPy. The interaction between the process, estimator, and optimizer ensured that the system operates efficiently, maintaining stability and optimizing performance in response to changing process conditions.

Setpoint tracking and disturbance studies were conducted, to evaluate the MPC, introducing white Gaussian noise on the states with 1% standard deviation. Stepwise changes of the granule size references were introduced at certain times, and the solid/liquid feed rate control moves were analyzed.

Three types of disturbance scenarios were explored separately: binder flow rate disturbance, lactose flow rate disturbance, and Avicel flow rate disturbance. To conduct this study, each disturbance simulation, was applied as two manual step changes using gO:Python of either +10% or +20% of the flowrate at 40 seconds and either -10% or -20% of the flowrate at 80 seconds. The objective was to assess the controller's ability to detect, respond, and adjust control actions to maintain the desired reference values.

RESULTS AND DISCUSSION

Model comparison

The model obtained for DMDc in Python, MOESP in Matlab and SINDyc in Python has the form of a discrete-time first-order state-space equation where matrix A was the system matrix and determined how state variables change over time and B was the control matrix which determines how the system inputs affected the state change.

The model performance can be visualized in Fig. 2 where the DMDc model demonstrates enhanced accuracy and performance when dealing with unseen values (validation phase) even when working with noisy data. The deteriorated performance for MOESP can be related to its algorithmic complexity and overfitting trend and for SINDyc because of elimination of coefficients of the A matrix in the ROM that described, for example, the effect of D90 on D10 state, as detailed in Digital Supplementary Material.

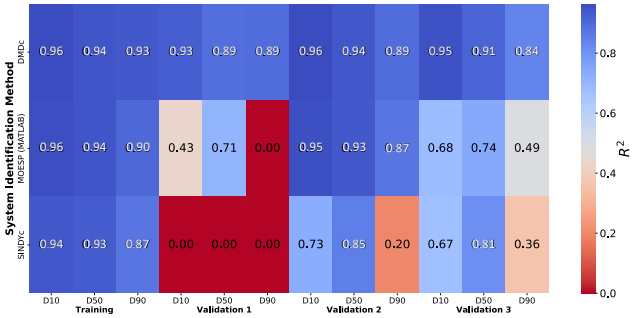

Figure 2. Heatmap for error metrics study R^2

The eigenvalues of the generated system state space models are shown in Table 1. Following conventional control theory, the DMDc eigenvalues provide stability guarantee on the model performance.

Table 1: Eigenvalues of ROMs.

Method	Description
DMDc	$[0.63\,;\ \ 0.99\ ;\ 0.99\,;\ \ 0.97]$
SINDyc	$[0.6-0.13i\,;0.6+0.13i;\ 0.9\,;1.0005\,]$
MOESP	$[0.3+\ 0.2i;\ \ 0.3-0.2i\,;\ \ 0.99\,;\ 0.97\,]$

Regarding the uncertainty study, as displayed in Table 2, DMDc was found to be the most accurate method because it had a small predictive error quantified by RMSE and shorter average length of 95% predictive interval, also shown in Fig. 3.

High RMSE and wide confidence intervals for SINDyc and MOESP methods suggest that these models are more sensitive to noise and could be overfitting or underfitting the data, with very large uncertainty.

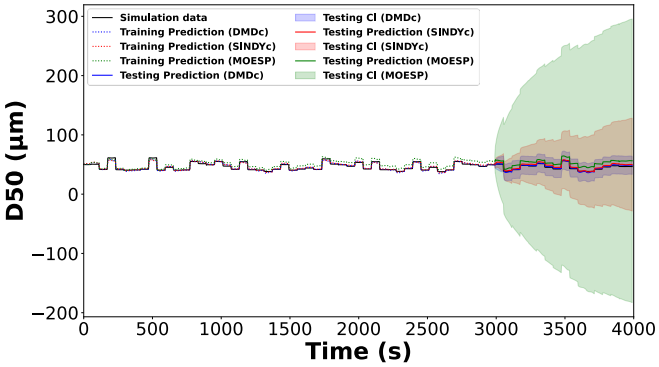

Figure 3. Uncertainty measurement for D50 for a prediction of 1000 steps by DMDc (blue), SINDYc (orange) and MATLAB (green) after 3000s for training.

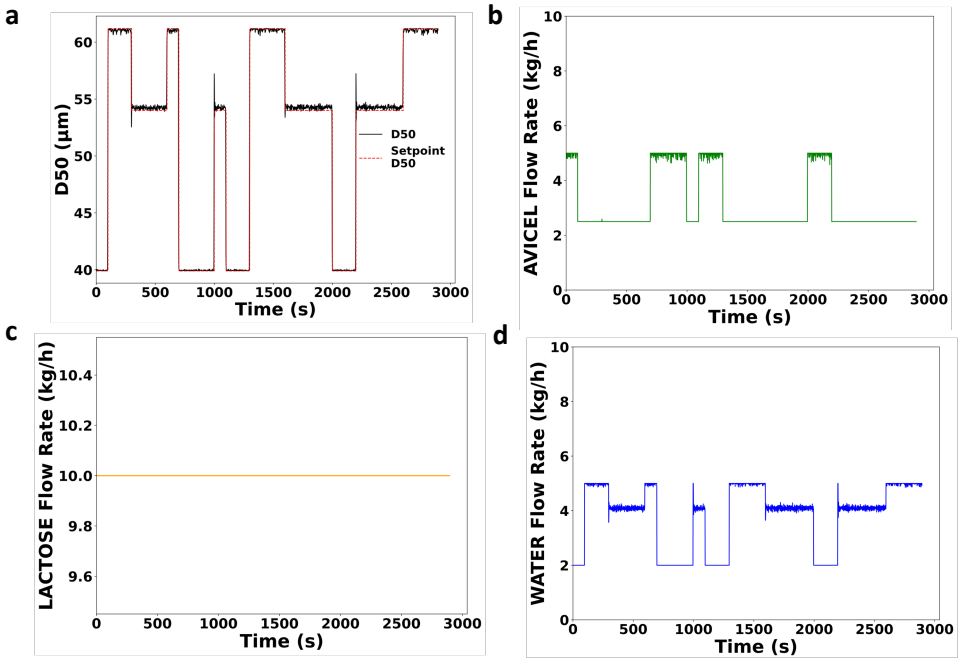

Figure 4. Setpoint tracking study for DMDc-MPC: a. Controlled variable (D50 shown) b-d. Manipulated variables

The 95% predictive intervals per each model are envisaged as shaded areas.

Table 2: Uncertainty quantification

1000-steps test		
	RMSE	**L(95%)**
DMDc	6.18	57.85
SINDyc	13.29	424.66
MOESP(MATLAB)	57.17	1548.82
2000-steps test		
	RMSE	**L(95%)**
DMDc	6.89	58.98
SINDyc	16.08	717.86
MOESP(MATLAB)	66.95	1981.83

Closed-loop MPC performance

As shown in Suppl. Table 1, the selected prediction and control horizons provided the best trade-off for a control interval of 1s. As we can see in Suppl. Fig. 1, the setpoint for the controlled variable D50 is better reach with strategy H3 and longer horizons (PH = 100s, CH = 20s) led to over-tuning, as evidenced by increased peaks in the Avicel flowrate and higher CPU times."

The choice of a 1-second control interval was justified by the granulation process dynamics, which require frequent adjustments to maintain stability because it is known the binder concentration control is extremely important to maintain a desired oversized fraction of granules for lactose/Avicel-based formulations, also deviations in powder mass flow rate which might occur during volumetric feeding must be considered [12]. Nevertheless, less frequent sampling rates can be facilitated.

For the closed-loop evaluation, performance monitoring methods were used to assess how effectively the control system follows setpoint changes. Fig. 4 confirms the MPC's capability to track the reference by adjusting the input flow rates (D50 shown as an example)

Furthermore, the controller's ability to handle introduced disturbances was analyzed, especially because regulatory-level process control loops are commonly used in plants to respond to variations in binder flow rates.

In all cases, the disturbances were well rejected, as shown in Suppl. Figs. 2-4. The interested reader can refer to Digital Supplementary Material for other graphs. The most interesting aspect revealed is that introducing disturbances to the Avicel flowrate does not affect the other manipulated variables (MVs). In contrast, disturbances applied to either the lactose or binder flowrates affect both. In all cases, the manipulated flow rates stabilize after a short transient period.

CONCLUSION

This study highlights the effectiveness of DMDc as an explainable machine learning method for CM. The DMDc-MPC system not only maintained desired process conditions and granule size but also demonstrated superior performance in uncertainty analysis, outperforming other data-driven models. This approach enhances transparency, reliability, and regulatory acceptance, potentially accelerating the adoption of predictive models in pharmaceutical manufacturing. Future work in our group is focusing on exploring the application of DMDc to more

complex unit operations that exhibit highly nonlinear dynamics. This will allow us to further explore potential limitations of the proposed method and fuel further developments.

DIGITAL SUPPLEMENTARY MATERIAL

Digital materials can be found with this LAPSE:2025.0010.

ACKNOWLEDGEMENTS

Financial support from grant EPSRC EP/V034723/1 and Peruvian Government through PRONABEC is gratefully acknowledged.

REFERENCES

1. Hsu SH, Reklaitis GV, Venkatasubramania V. Modeling and control of roller compaction for pharmaceutical manufacturing: Part ii: Control system design. J. Pharm. Innov. 5, 24–36(2010) https://doi.org/10.1007/s12247-010-9077-z
2. Obregón L, Quiñones L, Velazquez C. Model predictive control of a fluidized bed dryer with an inline nir as moisture sensor. Control Eng. Pract. 21, 509–517 (2014) https://doi.org/10.1016/j.conengprac.2012.11.002]
3. Celikovic S, Kirchengast M, Rehrl J, Kruisz J, Sacher S, Khinast J, Horn M. Model predictive control for continuous pharmaceutical feeding blending units. Chem. Eng. Res. Des. 154, 101–114 (2020) https://doi.org/10.1016/j.cherd.2019.11.032
4. Sacher S, Celikovic S, Rehrl J, Poms J, Kirchengast M, Kruisz J, Sipek M, Salar-Behzadi S, Berger H, Stark G, Horn M, Khinast J. Towards a novel continuous hme-tableting line: Process development and control concept. European J. Pharm. Sci. 142 (2020) https://doi.org/10.1016/j.ejps.2019.105097
5. Huang YS, Lagare RB, Bailey P, Sixon D, Gonzalez M, Nagy ZK, Reklaitis GV. Hybrid model development and nonlinear model predictive control implementation for continuous dry granulation process. Comput. Chem. Eng. 183 (2024) https://doi.org/10.1016/j.compchemeng.2024.108586
6. Mesbah A, Paulson JA, Lakerveld R, Braatz RD. Model predictive control of an integrated continuous pharmaceutical manufacturing pilot plant. Org. Process Res. Dev. 21, 844–854 (2017) https://doi.org/10.1021/acs.oprd.7b00058
7. Nașcu I, Diangelakis NA, Muñoz SG, Pistikopoulos, EN. Advanced model predictive control strategies for evaporation processes in the pharmaceutical industries. Comput Chem Eng 173, 108212. (2023) https://doi.org/10.1016/j.compchemeng.2023.108212
8. Proctor JL, Brunton SL, Kutz JN. Dynamic mode decomposition with control. SIAM. 15, 142–161 (2016) https://doi.org/10.48550/arXiv.1409.6358
9. Wang, LG, Omar, C, Litster, J, Slade, D, Li, J, Salman, A, Bellinghausen, S, Barrasso, D, Mitchell, N. Model driven design for integrated twin screw granulator and fluid bed dryer via flowsheet modelling. Int J Pharm 628, 122186 (2022) https://doi.org/10.1016/j.ijpharm.2022.122186
10. Fasel U, Kaiser E, Kutz JN, Brunton BW, Brunton SL. Sindy with control: A tutorial. 2021 60th IEEE Conference on Decision and Control (CDC) 2021-Decem, 16–21 (2021) https://doi.org/10.48550/arXiv.2108.13404
11. Van Overschee, P, & De Moor, B. N4SID: Subspace algorithms for the identification of combined deterministic-stochastic systems. Automatica, 30(1), 75-93 (1994) https://doi.org/10.1016/0005-1098(94)90230-5
12. Vega-Zambrano C, Diangelakis NA, Charitopoulos VM. Data-driven model predictive control for pharmaceutical continuous manufacturing. Int J Pharm 125322 (2025) https://doi.org/10.1016/j.ijpharm.2025.125322

© 2025 by the authors. Licensed to PSEcommunity.org and PSE Press. This is an open access article under the creative commons CC-BY-SA licensing terms. Credit must be given to creator and adaptations must be shared under the same terms. See https://creativecommons.org/licenses/by-sa/4.0/