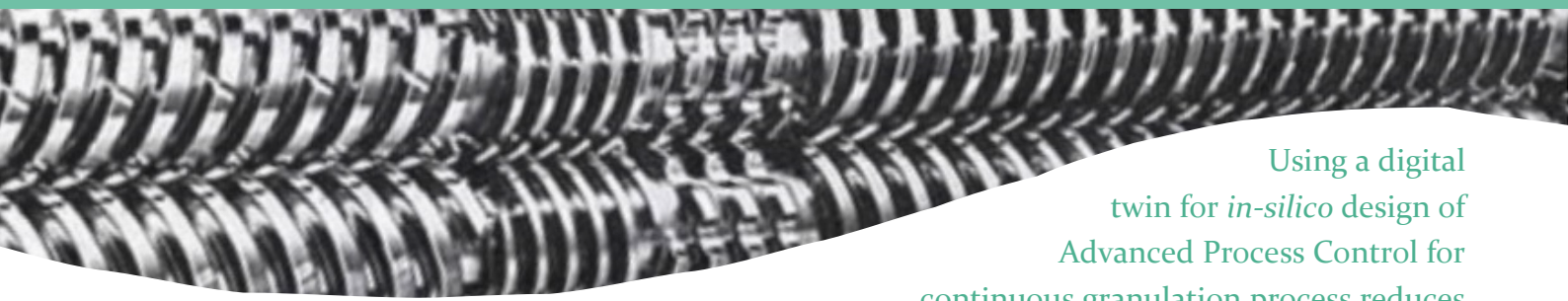


Model Predictive Control of a Twin Screw Wet Granulation Process - A Digital Design Approach

Using a digital twin to control and optimise the twin screw wet granulation process



Drivers

Twin Screw Wet Granulation (TSWG) offers a flexible route for continuous pharmaceutical manufacture. Consistent product with the desired Particle Size Distribution (PSD) can be obtained in the face of raw material variability through the use of an Advanced Process Control scheme such as Model Predictive Control (MPC). Design of data-driven control schemes, however, typically requires experimental effort and material consumption during development.

In the pharmaceutical industry mechanistic models are used mostly for process development and not in routine manufacturing. In this case study, a novel approach was taken by using a mechanistic model as a digital twin for *in-silico* MPC development. Furthermore, the mechanistic model was also used as a soft sensor to provide real-time predictions of PSD.

Approach

An MPC controller was designed to control the PSD D₅₀ to target by manipulating the Liquid-to-Solids (L/S) ratio by interfacing Perceptive Engineering's PharmaMV software to read/write data to and from a TSWG unit at CPI, and a digital twin/mechanistic model implemented in PSE's gPROMS FormulatedProducts software.

Using a digital twin for *in-silico* design of Advanced Process Control for continuous granulation process reduces experimental effort and powder consumption

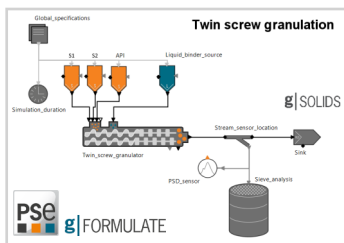
Key Features

- An MPC Advanced Process Control system designed *in-silico* using a mechanistic model
- The MPC and mechanistic model were transferred to a TSWG unit and used to predict and control PSD D₅₀ in real-time
- MPC scheme developed and tested in three trials with less than 10 kg of powder
- Demonstration of how a mechanistic model can be used as a process digital twin to speed up controller design and reduce the experimental effort and cost

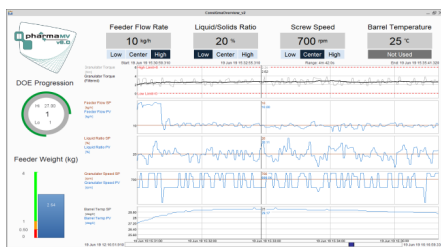
A small number of L/S ratio step tests were first applied to the TSWG unit and a suitable offline sieve analysis was carried out on the collected granules. These measured D₅₀ values were used to target the real-time D₅₀ predictions coming from the digital twin. Thus 'tuned', the digital twin was then exclusively used to design and commission a data-driven MPC controller on the TSWG.

An ADDoPT Case Study featuring collaboration between Perceptive Engineering, PSE, CPI and AZ

MPC Workflow using Digital Twin



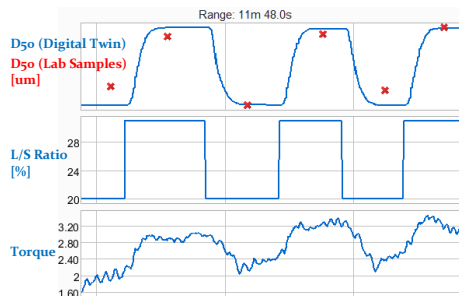
(a) Digital Twin in gPROMS FormulatedProducts



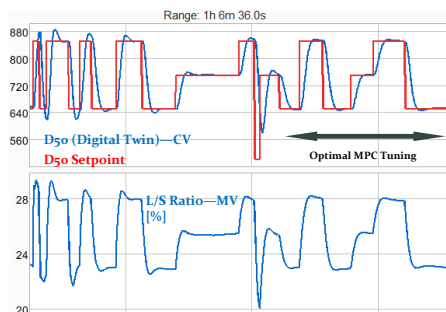
(b) PharmaMV software



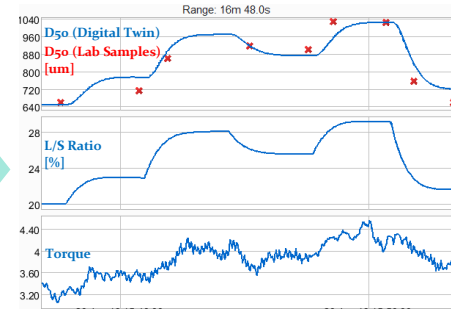
(c) TSWG unit



(d) Step tests for digital twin biasing



(e) MPC modelling and tuning using Digital Twin



(f) Real-time MPC results on physical TSWG Unit

Perceptive Engineering's PharmaMV software (b) was interfaced to the TSWG digital twin (a), implemented in PSE's gPROMS FormulatedProducts, and GEA's TSWG process unit (c). Limited number of L/S ratio step tests were carried out to bias the Digital Twin's D50 predictions (d) to match the offline D50 samples. The MPC scheme was then designed and tuned using only the digital twin (e), which was also used as a D50 software sensor in the real-time commissioning (f).

Up to 60% fewer trials were needed to develop the MPC control scheme resulting in substantially reduced API consumption and experimental effort

Results and Benefits

Using the digital twin to design and commission the MPC scheme reduced the experimental effort and powder consumption for the TSWG process. The proposed advanced control scheme was obtained in 3 trials as opposed to the 6-7 trials required with the traditional data-driven approach, and less than 10 kg of powder was used during the entire process.

The mechanistic model was originally parameterized by running a Design of Experiment set on an AstraZeneca formulation. To transfer the model to a generic compound at CPI, a biasing mechanism was employed and successfully tested. In addition to controller design and soft sensing, the digital twin can also be used with the PharmaMV system for real-time monitoring as well as scale-up studies.

Further Steps

This case study has demonstrated how digital twins can be used to rapidly develop advanced control schemes with reduced experimental effort

and powder consumption. Future work will focus on extending the proposed control scheme to include other critical process variables (e.g. torque and outlet concentration) as well as considering different powder formulations.

Transforming pharmaceutical development and manufacture

Addressing the pharmaceutical industry's desire to deliver medicines more effectively to patients, the ADDoPT project has developed and implemented advanced digital design techniques that streamline design, development and manufacturing processes.



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