Rapid Control Prototyping for Continuous Pharmaceutical Tablet Production Processes

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Abstract

With the advent of continuous processes for solid dosage forms in the pharmaceutical industry, a need for suitable control concepts arises. Even though conventional control algorithms can be tested experimentally, different approaches on the basis of in-depth process analysis in accordance with the Quality by Design principles promise to be more advantageous. In this article, the well-established methodology of Rapid Control Prototyping for simulation based development and testing of control algorithms will be presented. This concept relies on simulation models – mathematical representations of the process that is to be controlled – that serve as a virtual testing environment for the controller or even as an integral part of advanced control concepts (e.g. model predictive control). The procedure of system analysis, modelling and simulation-based controller synthesis is conducted using the example of a continuous direct compression process. This process is part of a continuous production line for pharmaceutical tablets that has been installed by the company L.B. Bohle Maschinen + Verfahren GmbH in Ennigerloh, Germany. The controller synthesis is performed on the basis of experiments with this plant. The development and discussion of two control concepts for the continuous production of pharmaceutical tablets demonstrates the time and cost efficiency of the presented procedure.

Zusammenfassung

Rapid Control Prototyping für kontinuierliche pharmazeutische Tablettenproduktionsprozesse
Mit der Einführung kontinuierlicher Prozesse für feste Darreichungsformen in der pharmazeutischen Industrie ist ein Bedarf an geeigneten Regelungskonzepten entstanden. Auch wenn konventionelle Regelalgorithmen experimentell getestet werden können, versprechen Herangehensweisen auf der Basis eingehender Prozessanalysen in Übereinstimmung mit den Quality-by-Design-Prinzipien Vorteile. In diesem Artikel wird die etablierte Methodik Rapid Control Prototyping für eine simulationsbasierte Entwicklung und Erprobung von Regelalgorithmen vorgestellt. Grundlage dieses Konzepts sind Simulationsmodelle – mathematische Beschreibungen des zu regelnden Systems –, die als virtuelle Testumgebung für den Regler oder auch als integraler Bestandteil fortschrittlicher Regelkonzepte (z. B. modellbasierte prädiktive Regelung) dienen. Die Prozedur der Systemanalyse, Modellbildung und simulationsbasierten Reglerauslegung wird am Beispiel eines kontinuierlichen Direktverpressungsprozesses durchgeführt. Dieser Prozess ist Teil einer kontinuierlichen Produktionslinie für pharmazeutische Tabletten, die von dem Unternehmen L. B. Bohle Maschinen + Verfahren GmbH am Standort Ennigerloh, Deutschland, aufgebaut wurde. Die Reglerauslegung basiert auf Experimenten mit dieser Anlage. Die Entwicklung und Diskussion zweier Regelungsstrategien für eine kontinuierliche Produktion pharmazeutischer Tabletten verdeutlicht die Zeit- und Kosteneffizienz der vorgestellten Prozedur.

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1. Introduction and Motivation

More recently, continuous processes and the idea of continuous production systems have received increased interest in the pharmaceutical industry for solid dosage forms. Batch-oriented production processes – currently state of the art in the pharmaceutical industry – are known to have limited flexibility, higher risks of waste production and reduced capabilities of in-process monitoring. Additionally, regulatory facilities stimulated the pharmaceutical industry by several approaches, including Quality by Design (QbD) and Process Analytical Technology (PAT), to raise its interest in an in-depth understanding of process and product characteristics. To overcome these limitations and implement new quality approaches, integrated continuous production systems have been identified as the key solution – also by the authorities.

The established batch processing machines (unit operations) are to be replaced by continuously operating machines which have been newly developed or adapted from other industries. In contrast to the established production techniques, these machines are being supplied with a mass flow rate of material which is processed continuously before being dispensed. This concept allows assembling multiple unit operations into an entire production chain, in which all machines operate simultaneously in order to provide the desired rate of tablets at the end of the line.

The idea of continuous and simultaneous processing with several unit operations in one production line raises the need for process control on two levels:

- On the level of a single unit operation, the task is to control the machine in such a way that the desired mass flow rate is supplied at the outlet, taking into consideration the incoming flow rate of material from the unit operation upstream and the technical restrictions of the respective machine.
- From a global (production line) perspective, the control task is to coordinate all unit operations in such a way that a smooth operation is guaranteed and a desired rate of tablets is produced.

On both levels, adequate control algorithms have to be chosen considering the dynamic behavior of the respective system and all relevant technical characteristics. Basically, simple control algorithms can be tested and adjusted experimentally. However, these may not be suitable for the given application and the temporal and financial expenditures may be undesirably high: The processes of tablet production are slow and thus time-consuming and testing can require expensive raw material. The well-established methodology of Rapid Control Prototyping (RCP) helps to avoid these problems by substituting experiments with simulations, which also allows for a deeper process understanding and provides the opportunity to find better control solutions in the end.

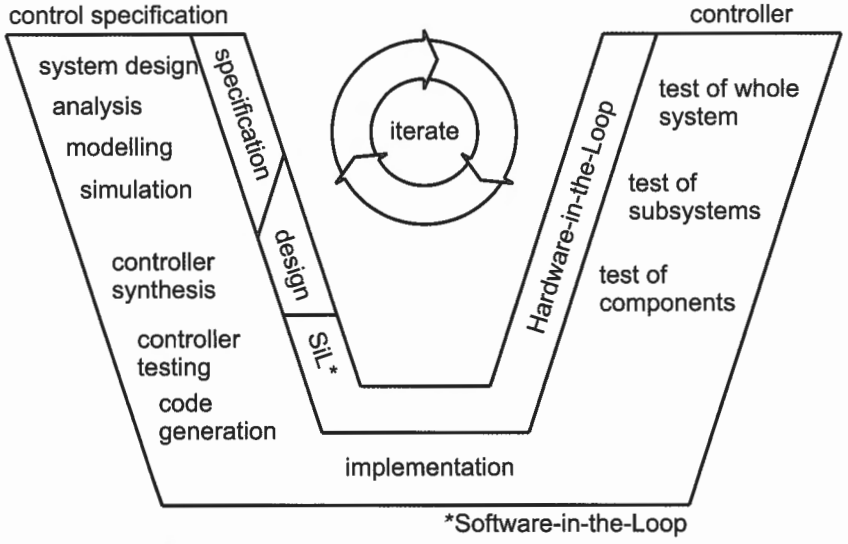

Figure 1: V-model for control engineering [1].

2. Rapid Control Prototyping

The RCP methodology is usually illustrated by the V-model of control theory as depicted in Fig. 1 ([1]; compare to the pharmaceutical validation process: [2]). The basic idea of the procedure is to substitute simulations of the system that is to be controlled for experiments.

For this purpose, the system needs to be analyzed first: Which process variable is to be controlled? Which other variables (system inputs) have a major influence on the controlled variable? Which of these variables can be used as a manipulated variable to influence the system behavior as desired? Corresponding to the principles of the QbD approach, the clarification of these questions forms the basis for a better understanding of the behavior of the whole system and the interrelation of different process variables.

Having identified all relevant system inputs and outputs, the next step towards simulation is to mathematically describe the dynamic relation between these variables via differential (time dependent) equations. This can be done based on physical correlations and/or with the help of experimental data. Usually it is helpful to find at least a suitable structure for the differential equation (type and order), which can then be adapted to the concrete system with few experiments. Afterwards a suitable control algorithm needs to be chosen considering the characteristics of the model and the technical restrictions

of the plant (e.g. limitations of the control signals). Starting from the classical PID control – the control signal is computed based on the sum of proportion, integral and differential of the control deviation – control theory has evolved a large variety of concepts, that often require a mathematical model of the controlled system to be developed [3]. For instance, a Linear-Quadratic Regulator is obtained as the linear result of a mathematical optimization of the control loop with the system model. Many software tools are available that assist the engineer with toolboxes for the design of respective control algorithms.

Apart from being the basis of the control development procedure for many control concepts, the process models serve a very important second purpose: In so called Model-in-the-Loop (MiL) simulations, the derived control algorithm is tested with the model of the plant in the loop. In this way, the closed loop behavior of the controlled plant can be analyzed and controller parameters can be adjusted to ensure the system shows the desired behavior.

When the simulation results are satisfying, the control algorithm can be tested on the real plant. In most industrial applications, the process machines are controlled by programmable logic controllers (PLC [4]). Since the controller synthesis is normally carried out on common development computers, the algorithm needs to be compiled to the desired programming language before it can be transferred to the target hardware. As this complicates the debugging and tuning of the controller, the V-model recommends testing the control performance by directly coupling the plant and the development computer if possible. This approach is commonly referred to as Software-in-the-Loop simulation. When the functionality of the controller has been proven in this way, the algorithm can be transferred to the PLC. The final testing can then be carried out by coupling the target hardware with the simulation model on the development computer. This so called Hardware-in-the-Loop simulation allows the testing of specific and even critical scenarios without any risks.

In the following section, the procedure of system analysis, modelling, simulation and controller synthesis will be demonstrated for a specific pharmaceutical manufacturing process.

3. Exemplary Controller Synthesis with RCP-Methods for a Continuous Direct Compression Process

At its headquarters in Ennigerloh, Germany, the supplier of special process machines for the pharmaceutical industry L.B. Bohle Maschinen + Verfahren GmbH has installed a fully functional, continuous production line for pharmaceutical tablets for demonstration and research purposes. The plant consists of several machines by L.B. Bohle and their partner companies (Korsch AG, Berlin and Gericke AG, Regensdorf). It is designed as a flexible layout concept, allowing for the exchange or removal of single unit operations. In this way, the plant can realize the 3 most commonly used production layouts in the pharmaceutical industry: Direct compression, dry granulation and wet granulation. This section focuses on the control design for a direct compression process which consists of 3 feeders, one blender and the tablet press as illustrated in Fig. 2.

Each of the two unit operations (feeding & blending unit – FBU, tablet press – TP) features a programmable logic controller (PLC) with

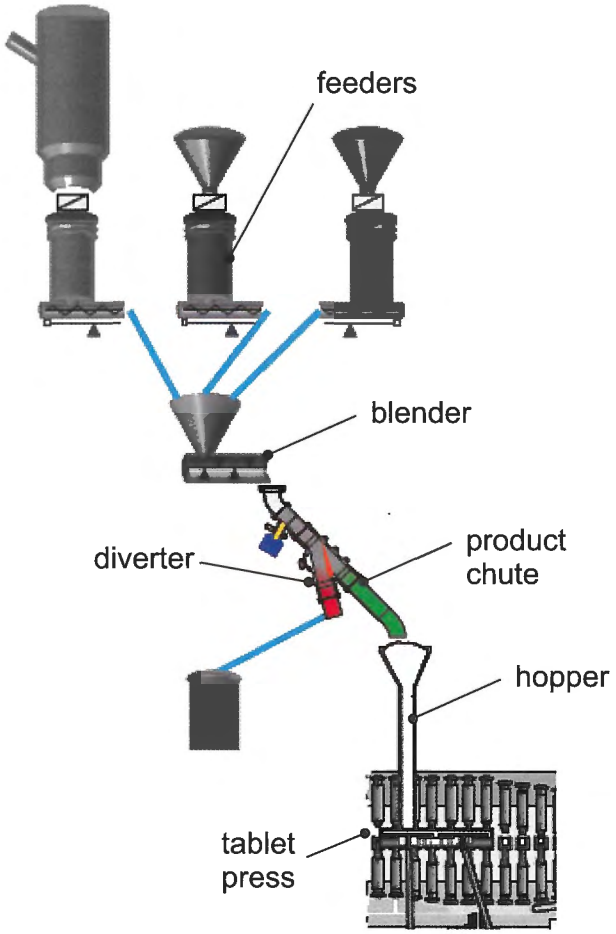

Figure 2: Continuous direct compression process (Source: L.B. Bohle Maschinen + Verfahren GmbH).

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an autonomous automation: The feeders are controlled in such a way that a desired mass flow rate of the respective raw material is supplied to the blender. This is calculated internally by the PLC from a total mass flow rate set point and the mass fractions for all feeders. Inside the blender, rotating paddles stir and transport the blend to its outlet. After being ejected, the blend passes a product chute and is then gathered in the hopper of the tablet press. The PLC of the tablet press controls the rotating speed of the turret which is proportional to the produced rate of tablets. It also provides the filling level of the hopper which is constantly being measured. The product chute features a diverter, which can be used to discharge blend out of specification.

For the demonstration of the RCP methodology, the control problem is formulated as follows: Both unit operations with their underlying, individual automation systems are to be synchronized by a central automation such that a static plant operation is established. Thereby a constant rate of tablets with consistent quality is produced. To achieve this objective, two concepts will be discussed in the following: In order to produce a constant rate of tablets, the rotating speed of the turret of the tablet press is set to a constant value n_{set}. To guarantee constant quality of the produced tablets, the filling level of the hopper h should be kept constant during production. Thus, the filling level is used as control variable of the central process control. Hence, the central control has to find a suitable set point for the total reference mass flow rate of the feeders $\dot{m}_{set}$. The second control strategy also focuses on keeping the the filling level of the hopper constant. However, this time the mass flow rate of the FBU is set to a constant value and thus the rotating speed of the tablet press needs to be adjusted. In this way, a constant output of tablets cannot be guaranteed. However, the constant operating point of the FBU is beneficial for the mixing quality of the blend, as this process is very sensible to operational changes.

For the analysis of the dynamic behavior of the first unit operation (FBU and product chute), an experiment is carried out in which a series of total mass flow rate steps is applied to the automation system of the feeders. The response of the system – the mass output – is measured by a scale which is positioned below the outlet of the product chute. For an easier evaluation of the system response, the curve of the product mass measured by the scale is smoothed and differentiated with respect to time. This yields the mass flow rate of the blend leaving the product chute $\dot{m}_{final\ blend}$ as a function of time. The result of the experiment is plotted in Fig. 3 (for a more extensive analysis of this process see [5]).

It can be seen that the system has a very sluggish behavior: When a set point step is applied to the automation system of the feeders, it takes a lot of time until the response – in the form of a mass flow rate change – is visible at the outlet of the product chute. Besides, the curve of the real mass flow rates $\dot{m}_{final\ blend}$ shows a dampened course. The experimental result is used to motivate a very simple structure for the mathematical description of the system dynamics. A first order differential equation with time delay is chosen that depends on 3 parameters [6]:

$$\dot{m}_{final\ blend} + T \cdot \frac{d\dot{m}_{final\ blend}}{dt} = K \cdot \dot{m}_{set}(t - T_t)$$

The parameters T, K and T_t are adapted for the system with the help of optimization algorithms in such a way that the response of the simulation model to the given total mass flow rate set points $\dot{m}_{set}$ best fits the measured curve. The result of this so called system identification procedure can also be seen in Fig. 3 ($\dot{m}_{Simulation}$). The inert behavior and the large time delay of the system are mainly caused by the blender: The feeders quickly adopt a new mass flow rate set point which is then supplied to the blender. Due to the large volume of the blender and the flow characteristics of the raw materials, it takes some time for the rotating paddles to transport the additional mass flow rate to the outlet. Furthermore, the stirring

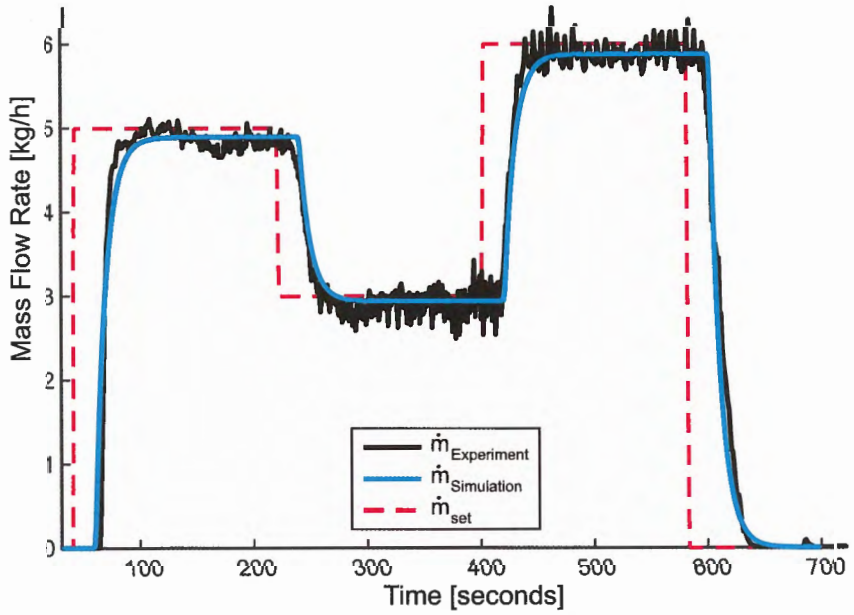

Figure 3: System identification of FBU and product chute (Source of Figures 3–5: the authors).

process in the blender dampens (smooths) the flow in such a way that a (hypothetical) step of the mass flow rate at the inlet will not be seen at the outlet.

To complete the model of the whole direct compression process, a mathematical description is needed for the relation between the mass flow rate of the blend leaving the product chute $\dot{m}_{final\ blend}$ and the filling level h of the hopper of the tablet press. The filling level directly depends on the product mass accumulated in the hopper: $h = f(m_{TP,hold-up})$. However, this is not a linear function as the material cannot be assumed to be incompressible. The accumulated mass in the hopper $m_{TP,hold-up}$ at a certain time t can be calculated with the integral over the sum of all supplied or discharged mass flow rates from the start of production until the considered point in time:

$$m_{TP,hold-up}(t) = \int_0^t (\dot{m}_{final\ blend}(\tau) - \dot{m}_{TP,prod})d\tau.$$

It thus also depends on the mass flow rate $\dot{m}_{TP,prod}$ of the blend which is discharged for the production of tablets. If $\dot{m}_{TP,prod}$ was known exactly, a simple control strategy might use this value as a constant set point for the total mass flow rate of the FBU since both FBU and product chute show no product losses. However, $\dot{m}_{TP,prod}$ can only be roughly estimated; especially the correlation with the rotating speed of the tablet press is not known exactly. A false estimation of n_{set} will lead to a static inequality of $\dot{m}_{final\ blend}$ and $\dot{m}_{TP,prod}$ and thus to a constant drift of the filling level h of the hopper of the tablet press. The result of an exemplary simulation with this simple operating mode is illustrated in Fig. 4.

In order to prevent such behavior, the total mass flow rate set point $\dot{m}_{set}$ of the FBU needs to be adjusted during operation. This can be done by adding a feedback loop to the system that takes the actual control deviation $h(t) - h_{set}$ into consideration. In this example, a PI-controller has been designed for this task. Figure 5 presents the simulation results for the two control concepts. The black curves represent the control result of the ac-

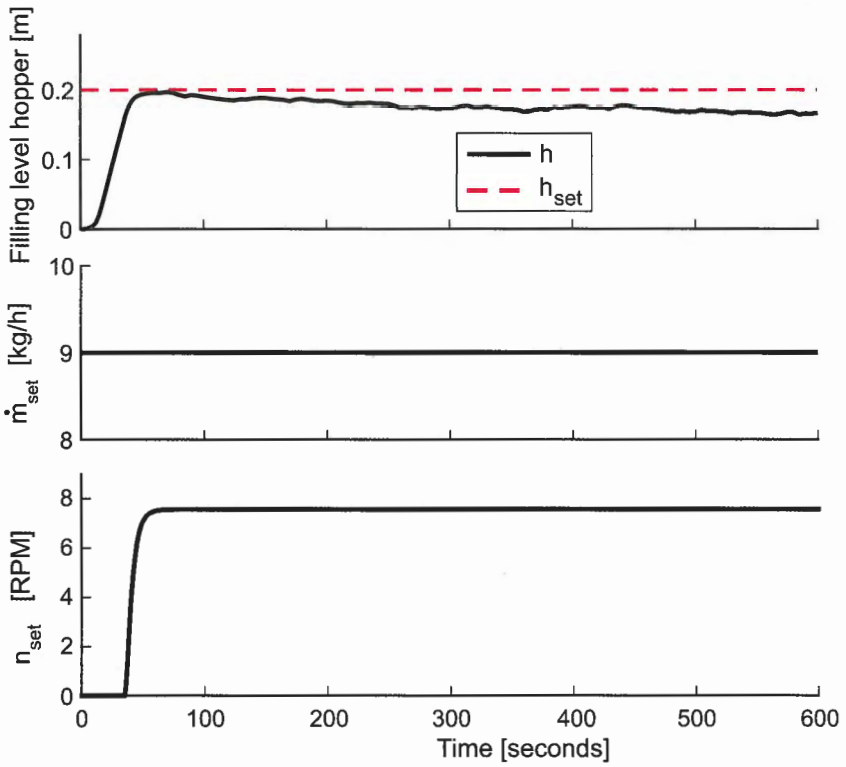

Figure 4: Simulation result – feedforward control.

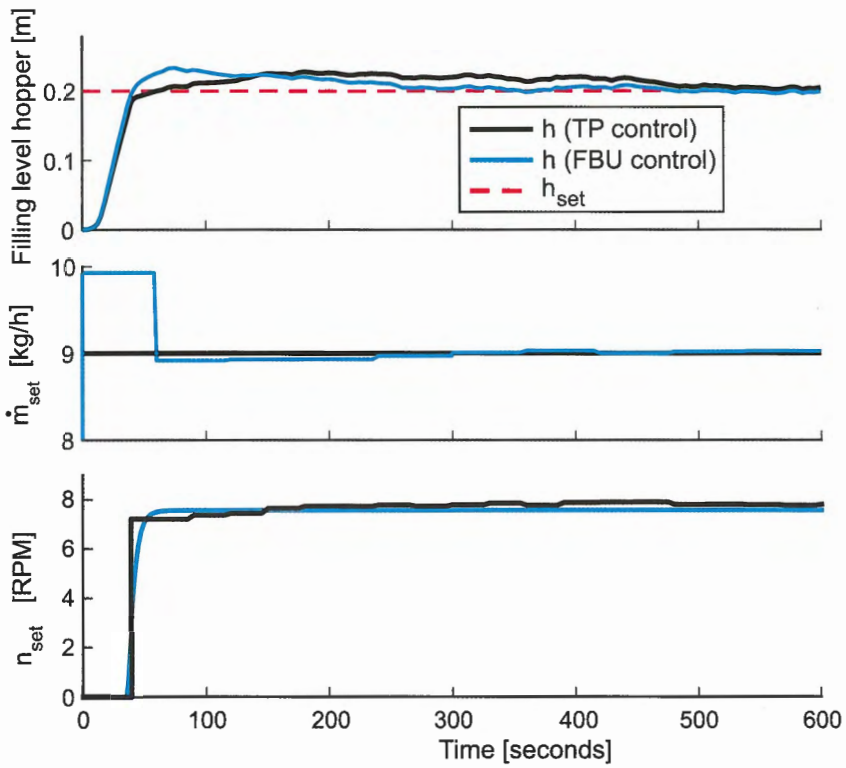

Figure 5: Simulation result – feedforward and feedback control (cyan: TP control, black: FBU control).

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tuation of the tablet press (with a constant set point for the FBU), the cyan ones the result of the FBU (with a constant set point for the TP). A rather large disturbance has been added to the controlled variable h to take modeling and measurement uncertainties into consideration. It can be seen that the controllers adjust the control signals such that the drift of the controlled variable h is prevented.

4. Conclusion

The methodology Rapid Control Prototyping for the simulation-based design of controllers has been described in this article. This concept proves helpful especially for the application for pharmaceutical processes as it allows avoiding time consuming and cost intensive experiments with the plants. It is also in good accordance with the principles of QbD since it features well-established methodologies that encourage and allow for a deeper process understanding. The procedure of system analysis, modelling and simulation-based controller synthesis has been conducted for a continuous direct compression process. The chosen example demonstrates the newly arisen need for feedback control for innovative continuous pharmaceutical processes – not only for the control of individual unit operations, but also for the simultaneous operation of several machines in an entire production line.

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