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Sensitivity analysis of a pharmaceutical tablet production process from the control engineering perspective

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ABSTRACT

This paper presents a sensitivity analysis of a pharmaceutical direct compaction process. Sensitivity analysis is an important tool for gaining valuable process insights and designing a process control concept. Examining its results in a systematic manner makes it possible to assign actuating signals to controlled variables. This paper presents mathematical models for individual unit operations, on which the sensitivity analysis is based. Two sensitivity analysis methods are outlined: (i) based on the so-called Sobol indices and (ii) based on the steady-state gains and the frequency response of the proposed plant model.

1. Introduction

Switching from batch to continuous production is one of the highly publicized trends in pharmaceutical manufacturing. This transition is encouraged by the U.S. Food and Drug Administration (FDA) (Chatterjee, 2012) due to multiple advantages (e.g., easier scale-up, reduction of waste material, better exploitation of patent exclusivity period and improved product quality).

However, continuous operation at a manufacturing plant poses new challenges with regard to the required measurement and control system. The structure of control system has to be tailored to suit the process properties. However, it is crucial to *quantitatively* identify the interactions between the actuators and the controlled variables. To that end, sensitivity analyses may be used. In (Singh et al., 2015) the authors described an experimentally based sensitivity analysis for a direct compaction process (Singh et al., 2014) in order to evaluate the effects of powder bulk density on critical quality attributes and critical process parameters. In (Singh et al., 2009) and (Singh et al., 2010), the authors emphasized the importance of sensitivity analysis and proposed a step-wise approach to perform this analysis without detailing the required steps. Singh et al. (Singh et al., 2012), Boukouvala et al. (Boukouvala et al., 2012) and Sen et al. (Sen et al., 2013) carried out a dynamic sensitivity analysis for a tablet production process involving feeding, blending, roller compaction and tablet press. They accomplished sensitivity analysis via extensive simulation studies. The results were used to assign actuators to critical process variables, providing essential information about the design of a control system for the process and facilitating the assignment of actuating signals to the controlled variables. In this paper, we compare this approach (hereinafter referred to as Approach I, see Section 3.3.1) to our approach (hereinafter referred to as Approach II, see Section 3.3.2) that uses the mathematical plant model to analytically perform the sensitivity analysis. Approach II is based on the steady-state gains from the model inputs to the model outputs of a linearized plant model and on the respective Bode magnitude plots. Both methods were applied in a continuous direct compaction process that involved four feeders, a blender and a tablet press. Mathematical models of the above-mentioned unit operations are presented in this paper as well. Some of the model outputs are closely related to the critical quality attributes (CQAs) of the end product and must remain within certain limits. With that regard, it is crucial to establish the model inputs/critical process parameters (CPPs) that have a significant impact on these model outputs. The methods presented in this paper make it possible to perform such an analysis in a rigorous system-theoretic manner. Our approach allows to draw additional conclusions based on the frequency response of the system.

The paper is structured as follows: In Section 2, the problem setup is described. Section 3 explains modeling of the unit operations and introduces the two approaches that we used to perform the sensitivity analysis. The software framework, which

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Nomenclature

A	System matrix of the linearized system
API	Active pharmaceutical ingredient
BIN	Binder
B	Input matrix of the linearized system
C	Output matrix of the linearized system
CQA	Critical quality attribute
CPP	Critical process parameter
D	Feed through matrix of the linearized system
DIS	Disintegrant
ε	Tablet porosity
EXC	Excipient
GSA	Global sensitivity analysis
$\dot{m}$	Mass flow in kg/h
m_{hu}	Mass hold-up of the blender in kg
$m_{hu,cj}$	Mass hold-up of compartment j in kg
ω	Blender speed in rpm
pdf	Probability density function
SA	Sensitivity analysis
$\mathbf{S}_{ss}$	Matrix with steady-state sensitivities
$\mathbf{S}_{dyn}$	Matrix with dynamic sensitivities
S_i	First order Sobol indices
S_{Ti}	Total order Sobol indices
X	Input factors
Y	Output

was set up in order to perform the sensitivity analysis according to Approach I and the selected values of the model inputs for Approach II are provided subsequently. The next part highlights Approach II. Finally, the results are discussed and conclusions are provided.

2. Problem setup

The direct compaction setup considered in our work is shown in Fig. 1. It consists of four feeders, a blender and a tablet press. The investigated formulation consisted of the following four materials:

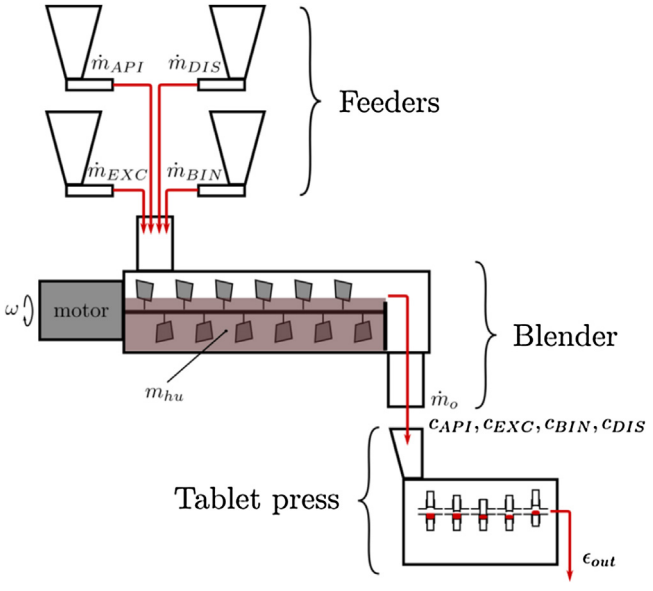

Fig. 1. Direct compaction setup.

Table 1
Bulk and true densities of the studied materials.

material	ρ_{bulk} in kg/m^3	ρ_{true} in kg/m^3
Paracetamol (API)	357	1290
Dicafos (EXC)	750	2310
Kollidon VA 64 Fine (BIN)	150	1180
Kollidon CL (DIS)	400	1180

5% Paracetamol (API), 80% Dicafos (EXC), 5% Kollidon VA 64 Fine (BIN) and 10% Kollidon CL (DIS). The bulk and true densities of the materials are summarized in Table 1. Knowing these values is important for developing a tablet press model (Section 3.2). The operating point used in our analysis, which is described by the mass flows of the materials, the blender speed and the tablet press compaction pressure, and the resulting system outputs are shown in Table 2. The outlet mass flow of the blender at the operating point is equal to the sum of the inlet mass flows. The mass hold-up in the blender and the tablet porosity are computed via models presented in Sections 3.1 and 3.2, respectively. The next section describes mathematical modelling of the investigated unit operations.

3. Mathematical modeling and sensitivity analysis

In order to simulate the system, mathematical models of the unit operations are required. Since the feeder outlet mass flows are given (i.e., are treated as system inputs), modeling the feeders is outside the scope of this paper. Fig. 2 shows a block diagram of the investigated setup. The models of blender and tablet press are presented in the following subsections.

3.1. Blender

Developing the blender model consisted of two parts. The first one deals with modeling of the outlet mass flow and the mass hold-up in the blender, i.e., $\dot{m}_o$ and m_{hu}, respectively. The blender is separated into several compartments, with a mass-balance equation solved for each one. The mass hold-ups of the individual compartments $m_{hu,cj}$ are considered state variables and their time derivatives are given by the difference between the inlet mass flow $\dot{m}_{cj,i}$ and the outlet mass flow $\dot{m}_{cj,o}$, i.e.,

$$\frac{dm_{hu,cj}}{dt} = \dot{m}_{cj,i} - \dot{m}_{cj,o}. \quad (1)$$

Table 2
Operating point of the direct compaction setup.

input/output	operating point	unit
blender speed ω	100	rev/min
mass flow API $\dot{m}_{API}$	1	kg/h
mass flow EXC $\dot{m}_{EXC}$	16	kg/h
mass flow BIN $\dot{m}_{BIN}$	1	kg/h
mass flow DIS $\dot{m}_{DIS}$	2	kg/h
compaction pressure p	$2{\cdot}10^8$	Pa
mass hold-up blender m_{hu}	0.296	kg
outlet mass flow blender $\dot{m}_o$	20	kg
mass fraction API c_{API}	5	%
mass fraction EXC c_{EXC}	80	%
mass fraction BIN c_{BIN}	5	%
mass fraction DIS c_{DIS}	10	%
tablet porosity ε_{out}	0.0812	–