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Engineering Research Center for Structured Organic Particulate Synthesis (ERC-SOPS)

Arun Giridhar, Gintaras V. Reklaitis and Venkat Venkatasubramanian

***Abstract*— The ERC-SOPS is an NSF-funded collaborative effort to improve existing manufacturing processes and develop new ones for the pharmaceutical industry. Participants include four universities and several industrial partners, including pharmaceutical companies and vendors of equipment and control systems. A primary goal of the Center is to demonstrate continuous and real-time control of pharmaceutical manufacturing processes, which have hitherto been restricted to batch operations. This document describes some of the efforts that have been made towards achieving this goal.**

I. INTRODUCTION

The ERC-SOPS is an NSF-funded collaborative effort to improve existing manufacturing processes and develop new ones for the pharmaceutical industry. Participants include Purdue University, Rutgers University, New Jersey Institute of Technology, the University of Puerto Rico at Mayaguez, and several industrial partners, including pharmaceutical companies and vendors of equipment and control systems, such as Emerson.

A. Overview and Focus

A primary goal of the Center is to demonstrate continuous and real-time control of pharmaceutical manufacturing processes, which have hitherto been restricted to batch operations. Such processes include currently existing ones such as tablet-making, and will eventually include processes such as making gels and drop-on-demand technologies.

This work will focus on Testbed 1 of the ERC, which deals with tablet manufacture. Two other testbeds (not covered in this document) deal with gels and drop-on-demand respectively, whose processes are not yet understood well enough to have good online control strategies.

B. Process Description

The selection of a process (wet granulation, direct compression, or dry granulation) depends largely on drug loading (the weight fraction of a tablet that is the actual drug and not inert excipients), with roller compaction preferred for large drug loading ($\geq 50\%$), wet granulation for low drug loading ($\leq 5\%$), and direct compression for intermediate ranges (20% to 40%).

In wet granulation, a mixture of API and excipients is subjected to a liquid spray containing a binder, forming aggregates of granules, which are dried, mixed with a lubricant and then compressed into tablets in a tablet press. In direct compression, the API and excipients are blended together as dry powders, and the blend is compressed into tablets. For high drug loadings, the blend segregation may be unacceptable; to preclude it, the blend is compacted under high pressure into a ribbon without delay. The ribbon is broken down into granules which are then compressed in a tablet press (the granules are small enough to fit in a tablet press's die but much coarser than the powders that are blended together, so that segregation is prevented). The control problems are summarized in Table I.

TABLE I
PROCESSES AND THEIR CONTROL GOALS

Process	Control Problem
Wet granulation	Segregation
Direct compression	Segregation, Tablet weight and composition
Roller compaction	Tablet weight and composition

II. CONTROL SYSTEM OVERVIEW

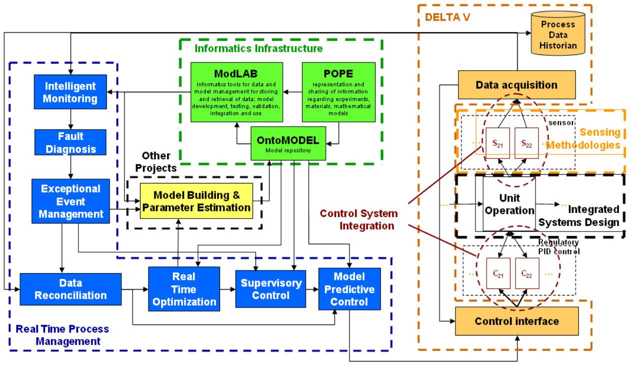

Fig. 1. Control System Overview

As shown in Fig. 1, the overall control system is based upon a DCS (Emerson's DeltaV in this case) and an ontological informatics infrastructure (developed in-house at Purdue), and their interactions. DeltaV has

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Arun Giridhar is a post-doctoral researcher in Chemical Engineering at Purdue University. `agiridha@ecn.purdue.edu`

G.V. Reklaitis is the Edward W. Comings Distinguished Professor of Chemical Engineering, Purdue University, and also the Deputy Director of the ERC-SOPS. `reklaiti@purdue.edu`

V. Venkatasubramanian is a Professor of Chemical Engineering, Purdue University, and also a Thrust Leader of the ERC-SOPS. `venkat@ecn.purdue.edu`

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been installed at Purdue and is being used to support the roller compaction process. DeltaV is also being installed at Rutgers to support the direct compression process.

Process measurements are read from sensors by DeltaV and stored in the process historian. Control is distributed in various places: some low-level control (PID) is implemented in DeltaV itself. The process history is also read by a real-time process management system, which implements two main tasks: real-time optimization (RTO) and exceptional events management (EEM).

In RTO, the process history is read in and reconciled using one of several standard least-squares minimization techniques. The reconciled data is then subjected to several standard statistical tests to detect a gross error. If no gross error is detected, normal regulatory and supervisory control is performed, based upon PID or model predictive control (MPC) or any cascaded combination. The control outputs are sent back to DeltaV through an OPC interface, and also stored in the informatics framework. The set points may also be optimized periodically to improve process economy.

The informatics framework also stores knowledge of several things that can go wrong with the process (faults) and the effect of each fault on various process variables. For instance, a powder flow increase may result in an increased roll gap, increased ribbon density with brittleness, and increased surface burning of the ribbon. The last two quantities can be detected with a suitable sensor, such as a near IR sensor placed over the ribbon. Thus each fault has a distinct signature among several process variables depending on whether each variable is increased, decreased, or unaffected.

Given enough process variables, their local trends can be extracted and matched against a table of known fault signatures. This is what the EEM module does. Knowing the precise fault enables the operator to know the root cause and take remedial action instead of having to deal with several alarms, or (worse), a cascade of alarms. If the fault can be remedied automatically, the EEM system should handle it as well. The RTO and EEM systems effectively pass control to each other based on whether a gross error is detected or not.

Pharmaceutical processes that have traditionally relied on batch control: material (powders, blends, granules etc) is fed into a process unit's hopper, and the output is collected and transported en masse to the next unit. Based on quality assurance tests of partially processed material and final product, an entire batch of product may be discarded. The hope is that continuous process management reduces material waste due to product variability, and consequently brings down the manufacturing cost.

III. EXAMPLE: MODEL PREDICTIVE CONTROL

A schematic of the roller compactor is shown in Fig. 2. The material is fed down from the hopper through a screw feeder to the rollers. The bottom roller is fixed and the top is movable. The powder is compacted by the rollers into a ribbon. From a process perspective, it is important to control the ribbon density ($kg \cdot m^{-3}$) and the production rate ($kg \cdot s^{-1}$). The ribbon cross section can be modeled as being essentially rectangular, with the ribbon width equal to the roller width (a fixed parameter), the ribbon height equal to the roll gap (variable). The ribbon cross section area, linear speed (which can be obtained from the roller rotation speed and diameter), and density (measured externally with a sensor) together give the throughput, which should be the same as the mass flow rate of the powder fed through the screw feeder. Thus the equipment variables are the roll gap, the roller rpm, and the screw feeder rpm.

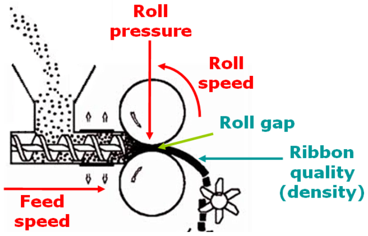

Fig. 2. Schematic of the roller compactor, showing variables of interest.

It is required to control the ribbon density and the ribbon throughput, by changing one or more of the screw feeder rpm, roller rpm, and roll gap. The roll gap cannot be directly manipulated, and also controlling throughput and density is equivalent to controlling roll gap and density. However the roll gap can be changed by changing the hydraulic pressure on the movable roller: more pressure decreases the roll gap. Thus the ribbon density and roll gap are controlled by manipulating the screw feeder rpm and hydraulic pressure. Roller rpm is treated as an uncontrolled and unmanipulated disturbance variable in this model.

Traditional control schemes typically decomposed the problem into two independent control loops, one linking the hydraulic pressure with the roll gap, and another linking the screw feeder with the ribbon density, using PID for each loop. However it was shown [1], [2] that tuning the controllers for such a decomposed approach becomes highly problematic, as shown in Figs. 3 and 4. Indeed, it was found that both Ziegler-Nichols and BLT tuning were unstable for disturbance rejection. Additionally, Ziegler-Nichols was unstable for setpoint changes as well, while BLT tuning caused a very slow response to setpoint changes.

As a result, single-input single-output (SISO) approaches were found to be unsuitable for roller compaction, and an MPC approach is required to simultaneously manipulate screw feeder and hydraulic pressure to control roll gap and ribbon density. Such a model-predictive approach was developed using a version based

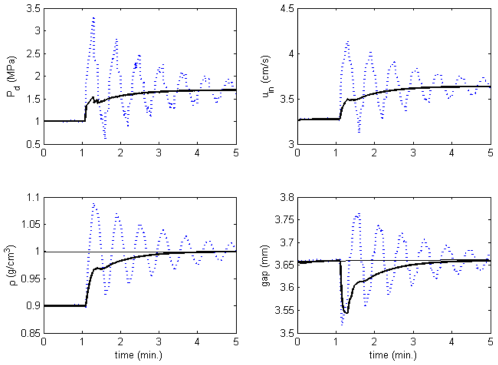

Fig. 3. Closed-loop response of the multi-loop PID control to setpoint changes (dotted lines: Ziegler-Nichols tuning; solid line: BLT tuning)

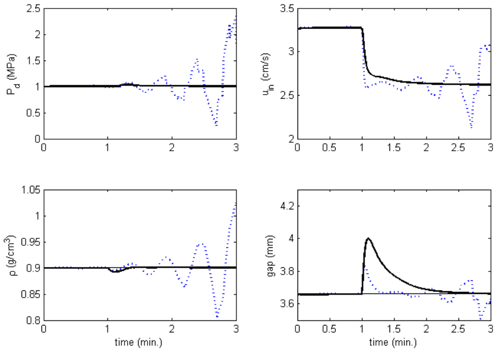

Fig. 4. Closed-loop response of the multi-loop PID control to disturbance rejection (dotted lines: Ziegler-Nichols tuning; solid line: BLT tuning)

on Johanson's model for roller compaction [3]. The MPC control was found to respond quickly and stably to both setpoint changes as well as disturbance changes, as shown in Figs. 5 and 6. This shows the benefit of using more sophisticated control schemes on particulate systems.

IV. CONCLUSIONS AND FUTURE WORK

A. *Conclusions*

There is tremendous opportunity for automation and real-time process management in particulate systems. Particularly in the pharmaceutical industry, the benefits are reduced wastage of material due to failed quality assurance checks, and lower operational costs. These benefits are enabled by a streamlined OPC interface in DeltaV that allows process models to reside as Matlab programs or Java applications while communicating with real-time process data from DeltaV's process historian.

Key challenges remain the availability of suitable sensors, including soft sensors. For the sensors commonly used in particulate systems, it would be useful if commercial control systems can handle spectra and image data natively instead of breaking them into scalars.

B. *Future Work*

The Center is continuing work on microwave sensors for density and moisture measurement. For RTO, dynamic RTO is being considered, which would change the setpoint from the old value smoothly and steadily to the new value without making a step change. Such dynamic RTO has tremendous benefits in startup and shutdown of processes, and also in preventing cyclic transients or instability associated with large step changes. Nonlinear reconciliation techniques may be examined as well.

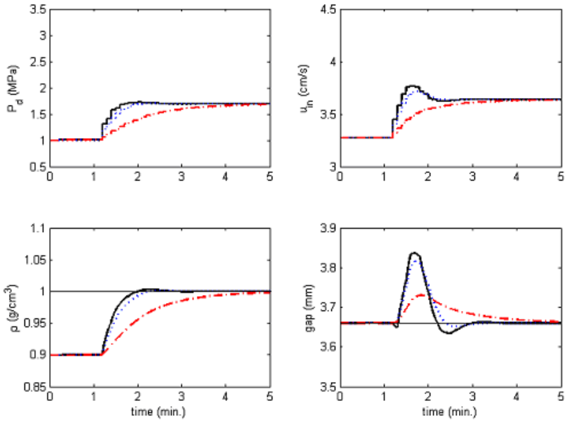

Fig. 5. Closed-loop response of the MPC control to setpoint changes

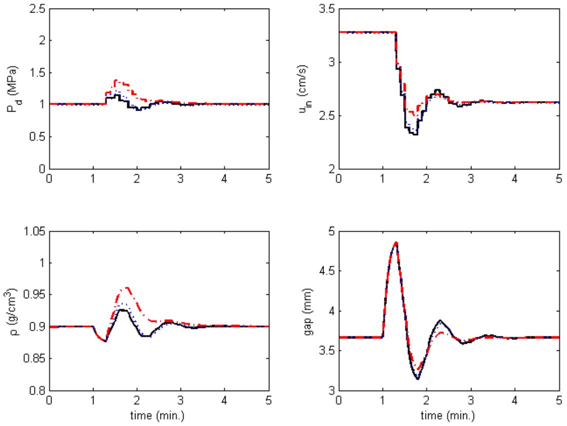

Fig. 6. Closed-loop response of the MPC control to disturbance rejection

V. ACKNOWLEDGMENTS

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