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"Process Systems Engineering for Pharmaceutical Manufacturing"

Edited by Ravendra Singh (Rutgers, The State University of New Jersey, USA) and Zhinhong Yuan (Tsinghua University, Beijing, China), Computer Aided Chemical Engineering, Volume 41, Elsevier, Amsterdam, The Netherlands, 2018, 674 pages, ISBN: 978-0-444-63963-9, US$187.50, £150.00, €184.57

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Introduction

"Process Systems Engineering for Pharmaceutical Manufacturing" is an ambitious reference comprising 24 chapters covering process systems engineering (PSE) methods and case studies of interest to engineers working in pharmaceutical process development, model development, process simulation, process optimisation and supply-chain or enterprise optimisation. Business model optimisation, including optimisation of clinical trials and supply chain, are topics covered in Chapters 1 and 21–24. Continuous manufacturing of drug product (downstream) is a key theme covered in Chapters 6 and 16–20, while process control, flowsheet modelling and key unit operation modelling are covered in Chapters 5, 7, 8–11 and 13–15. Of particular interest is the topic of small molecule upstream development and workup solvent selection and optimisation discussed in Chapters 3–4, with case studies involving separation solvent selection presented for ibuprofen, artemisinin and diphenhydramine in Chapter 4.

Chapter 2, 'The Development of a Pharmaceutical Oral Solid Dosage Forms' submitted by Rahamatullah Shaikh, Dónal P. O'Brien, Denise M. Croker and Gavin M. Walker (University of Limerick, Ireland), provides a summary of solid oral dosage form development, covering solubility and dissolution kinetics, pKa, excipient types and the standard formulation processes of direct compression as well as wet and dry granulation and capsule filling. This chapter is recommended reading for anyone not familiar with formulation of drug tablets as it provides a well-organised summary helpful in understanding the types of processes modelled in the chapters on continuous manufacturing, flowsheet and unit operation modelling as it relates to drug product.

I have organised this review according to general topics covered rather than by sequential order of the chapters.

Business Model and Optimisation

Chapter 1, 'New Product Development and Supply Chains in the Pharmaceutical Industry', contributed by Catherine Azzaro-Pantel (Université de Toulouse, France), introduces the pharmaceutical supply chain and summarises the product life cycle of a drug starting from discovery through clinical trials, registration and commercialisation. This chapter provides a concise summary of clinal trial phases, pre-launch and launch activities and is recommended reading for those not familiar with the pharmaceutical business model and drug development process (**Figure 1**).

Chapter 21, contributed by Brianna Christian and Selen Cremaschi (Auburn University, USA), covers 'Planning of Pharmaceutical Clinical Trials Under Outcome Uncertainty'. The authors reference an increase in attrition rates in clinical trials and

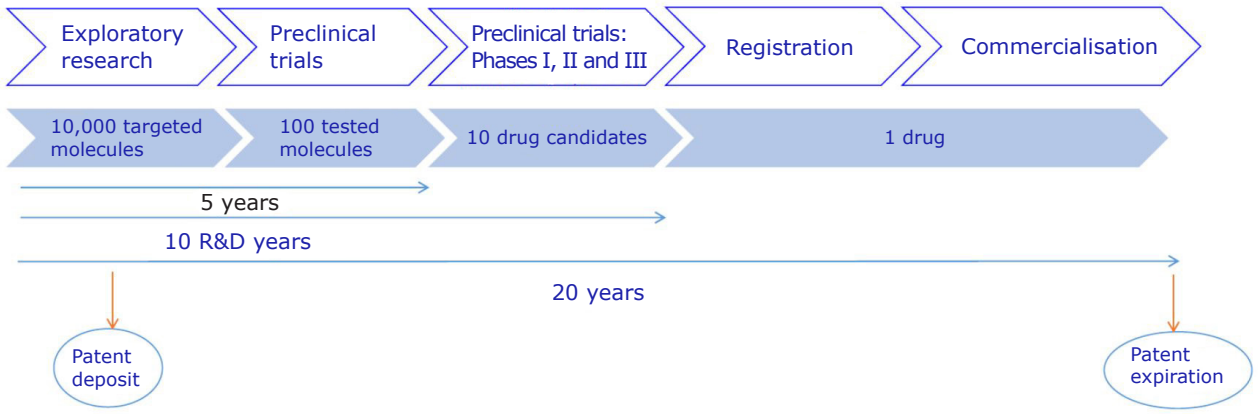


Fig. 1. Drug development process. Copyright (2018). Reprinted with permission from Elsevier

state "the time from discovery to product launch of a drug is around 10–15 years with an average research and development (R&D) cost of about $2.6 billion per drug" as motivating factors driving the need for better clinical trial optimisation. This chapter provides details of a "perfect information" deterministic mixed-integer linear programming model (MILP) problem including constraints. By using an innovative heuristic modification to the stochastic programming model a five order of magnitude improvement is reported.

Chapter 22, 'Integrated Production Planning and Inventory Management in a Multinational Pharmaceutical Supply Chain' contributed by Naresh Susarla and Iftekhar A. Karimi (National University of Singapore) presents a MILP model for a complex supply chain and provides a strategy to optimise inventory, resources and production schedules in the supply chain to maximise profit. The intent of the model is as a tool for decision making for "production planning and scenario analysis in a multinational pharmaceutical enterprise". To mitigate risk associated with the complex, multinational network of supply, drug inventories of 180 days are not atypical. However, high levels of inventory come at a cost. A change introduced in the supply network may have impact on inventories, lead-times and dependencies as impacted by other portions of the supply network. In this chapter the authors describe their approach to this optimisation problem. While looking at the authors' formulation of their case study problem, the value of working with fewer strategic suppliers in a vertically integrated supply network is evident in that it will minimise the complexity, delay and cost associated with a complex network. A takeaway from this chapter is that pharmaceutical companies can anticipate improved access to software tools to compare the impact of supply chain alternatives as research is translated into commercial software offerings.

Process Analytical Technology

Chapter 12, 'PAT for Pharmaceutical Manufacturing Process Involving Solid Dosages Forms' contributed by Andrés D. Román-Ospino and Ravendra Singh (Rutgers, The State University of New Jersey, USA), Vanessa Cárdenas and Carlos Ortega-Zuñiga (University of Puerto Rico, USA), presents near-infrared (NIR) calibration models and chemometrics. For those not skilled in process analytical technology (PAT) and analytical determination, this chapter is very informative and provides comparison of various methods for analytical data fitting to determine blend uniformity for real-time control of continuous pharmaceutical processes. Principal component analysis (PCA), partial least squares (PLS) and multivariate curve resolution alternating least squares (MCR-ALS) are presented as suitable techniques for multiple parameter determination where linear regression or classical least squares methods are not suitable. Layering of talc and lactose as a specific case study in non-homogeneity is discussed in this chapter. Finally, a process example utilising Unscrambler® X Process Pulse II (Camo Analytics AS, Norway) and NIR (Viavi Solutions Inc, USA) is presented where Unscrambler® X software is utilised to generate and upload a calibration model generated *via* methods presented in the chapter. In the example the NIR data processing system is

interfaced to a DeltaV™ distributed control system (Emerson Electric Co, USA) to provide real time process control of a tableting process.

Chapter 19, 'Monitoring and Control of a Continuous Tumble Mixer' contributed by Carlos Velázquez, Miguel Florían and Leonel Quiñones, (University of Puerto Rico, USA), presents a case study for the mixing of naproxen sodium with excipient using a continuous mixer designed by Velázquez. The PAT technology implemented for this case study employed the use of NIR in conjunction with Unscrambler® X in a PAT implementation similar to that described in Chapter 12. The closed-loop control dynamics for the experimental mixer are evaluated. A finding from the study is that a different control scheme is required for very low dosage active pharmaceutical ingredient (API) *vs*. higher dosages. The authors identified flowrate control of API addition at very low dosage as variable due to poor powder flow properties as well as limitations of the NIR methods employed in low dosage applications.

Chapter 9, 'Crystallization Process Monitoring and Control Using Process Analytical Technology' contributed by Levente L. Simon (Syngenta Crop Protection AG, Switzerland), Elena Simone (University of Leeds, UK) and Kaoutar Abbou Oucherif (Eli Lilly and Co, USA), introduces quality by design (QbD) and reviews online analytical techniques available for crystallisation monitoring and control which include attenuated total reflectance Fourier-transform infrared (ATR-FTIR), Raman spectroscopy, acoustic spectroscopy, conductivity measurement, refractive index measurement, turbidity measurement, focused beam reflectance measurement (FBRM) and particle vision and measurement (PVM).

Automated direct nucleation control (ADNC) along with polymorph determination and control *via* Raman and attenuated total reflectance ultraviolet (ATR-UV) spectroscopy are presented for batch and continuous crystallisation processes. The ADNC method involves heating and cooling cycles to control crystal count as measured by FBRM to a specified target. In the batch implementation, after initial nucleation, the system automatically heats to dissolve fines and heating and cooling cycles proceed until the crystallisation endpoint (low solution concentration). An advantage of this method is that from PAT data collected, the metastable zone width (MSZW) and solubility curves may be constructed. Since solubility curves are not required prior to running ADNC experiments, this method is useful for process development. An interesting adaptation of the ADNC method to a two-stage continuous mixed-suspension mixed-product removal (MSMPR) crystalliser system is an innovation by Yang *et al*. (1) where heating and cooling is performed on the jacket of a wet mill while the MSMPR crystalliser is maintained at constant temperature. The MSMPR with wet mill achieves both form control and FBRM particle count control under continuous flow operation.

Continuous Drug Product Manufacturing (Downstream)

Chapter 5, 'Flowsheet Modeling of a Continuous Direct Compression Process' contributed by Seongkyu Yoon, Shaun Galbraith, Bumjoon Cha and Huolong Liu (The University of Massachusetts Lowell, USA), summarises the scope of individual unit operation models for continuous powder blending, powder feeding (and potency control), tablet press, feed frame and tablet compaction. The authors highlight both a population balance model (PBM) as well as a stirred-tanks-in-series modelling approach to blending. The value of the modelling is in being able to accurately predict the response of perturbations on key quality attributes of finished tablets. An accurate system-wide process model allows implementation of both feedback and feedforward (predictive) control methodologies which can be developed and tested offline, provided that the underlying unit operation models are accurate. Modelling will facilitate development of continuous direct compression (CDC) processes and control schemes for CDC, where elimination of granulation results in simpler, less expensive processes.

Chapter 6, 'Applications of a Plant-Wide Dynamic Model of an Integrated Continuous Pharmaceutical Plant: Design of the Recycle in the Case of Multiple Impurities' submitted by Brahim Benyahia (Loughborough University, UK), takes the continuous methodology described in Chapter 5 a step further by integrating the chemical synthesis steps (upstream) with the formulation and tabletting steps (downstream) into a single continuous flowsheet. Of interest is the impact of wash-factor (i.e. wash volumes) and recycle (purge ratio) on the quantity of in-specification product produced. The recycle of wash streams is not often performed in batch API but in continuous processing this recycle provides potential for optimisation and cost savings. The evaluation of

wash factors and their limits as potential critical process parameters (CPP) is performed following a model-driven QbD approach. In the case study presented, plant dynamics are compared for both full purge and full recycle purge ratios.

Process Control

Chapter 11 'Process Dynamics and Control of API Manufacturing and Purification Processes' submitted by Maitraye Sen, Ravendra Singh and Rohit Ramachandran (Rutgers, The State University of New Jersey, USA) introduces a hybrid model predictive control/proportional-integral-derivative (MPC-PID) controller in which a single model based controller coupled with one PID temperature controller replaced four separate PID controllers in a continuous API/pharmaceutical intermediate process comprised of crystallisation, filtration, drying and excipient blending operations. PBM and discrete element method (DEM) methods were utilised to model the process while PCA was used to generate a reduced-order model for use by the model predictive controller. Various control schemes can be tested and optimised entirely *in silico* allowing investigations of system or controller response to transient conditions and process upsets to be investigated. The authors used MATLAB® (MathWorks Inc, USA) to fit data resulting from process simulations to transfer functions useful for model predictive control. gPROMS® (Process Systems Enterprise Ltd, UK) was utilised for PBM calculations and EDEM® (DEM Solutions Ltd, UK) was used to simulate the mixer where a PCA method was fit to six components from the DEM model.

Chapter 13, 'Model-Based Control System Design and Evaluation for Continuous Tablet Manufacturing Processes (via Direct Compaction, via Roller Compaction, via Wet Granulation)' contributed by one of the editors of the volume, Ravendra Singh (Rutgers, The State University of New Jersey, USA), is a review of model-based control for a formulation process which includes blending, granulation, roller compaction, milling and tableting. For the case study in Chapter 13, a PBM is employed in gPROMS®, but this time for the roller compactor. Unlike the example in Chapter 11, the API crystallisation, isolation and drying steps are not included as API is taken as the input and blended with excipients prior to granulation.

Chapter 7, 'Advanced Multiphase Hybrid Model Development of Fluidized Bed Wet Granulation Processes' submitted by Ashutosh Tamrakar, Dheeraj R. Devarampally and Rohit Ramachandran (Rutgers, The State University of New Jersey, USA), implements a hybrid computational fluid dynamics (CFD)/DEM approach to model the coupled behaviour of fluid flow and collisions. The authors transfer data from their CFD-DEM model to a PBM to provide resulting distributions from the granulation process. The DEM-CFD-PBM approach considers residence time in the spray zone, particle collision frequency, aggregation, attrition, particle temperatures and fluid/particle velocities. Residence time in the two zones (spray zone and drying zone) is impacted by fluid flow within the zones and the passing of particles between zones as modelled *via* CFD-DEM. Results from the CFD-DEM runs are exported to the PBM to investigate sensitivity to inlet gas temperature and gas flow rate. Excellent fit of experimental data from the fluid bed granulator is achieved.

Chapter 15, 'Advanced Control for the Continuous Dropwise Additive Manufacturing of Pharmaceutical Products' was contributed by Elçin Içten (Amgen Inc, USA), Gintaras V. Reklaitis and Zoltan K. Nagy (Purdue University, USA). In this chapter the authors describe a system and control methodology for the generation of solid oral dosage forms *via* a drop on demand (DoD) additive manufacturing technique involving dropwise deposition of API as solvent solution or as solvent/polymer melt (see **Figure 2**).

The DoD system is particularly useful for generation of personalised medicine for highly potent (low dosage) products. The authors present a control scheme based on image analysis of each drop and investigate various cooling profiles for the substrate (tablets). The authors present a polynomial chaos expansion (PCE) surrogate model for prediction of crystallisation, total dosage and product attributes as a function of drop attributes and cooling profile. The PCE model provides a QbD approach for predictive performance of the tablets' release profile.

Chapters 16–18 present case studies for automation of continuous pharmaceutical process plants where process control is the focus. Chapters 17 and 18 have a bit of redundancy with Chapter 13 as all three chapters are based on a series of published articles by one of the editors of the volume, Ravendra Singh. Chapter 18 is focused on formulation without granulation but with a control scheme to control tablet hardness by controlling tablet press punch depth and real-time measurement of bulk density is used in a feedforward control scheme. Detailed discussion of the control hardware, sensors and control algorithms for the pilot plant is presented

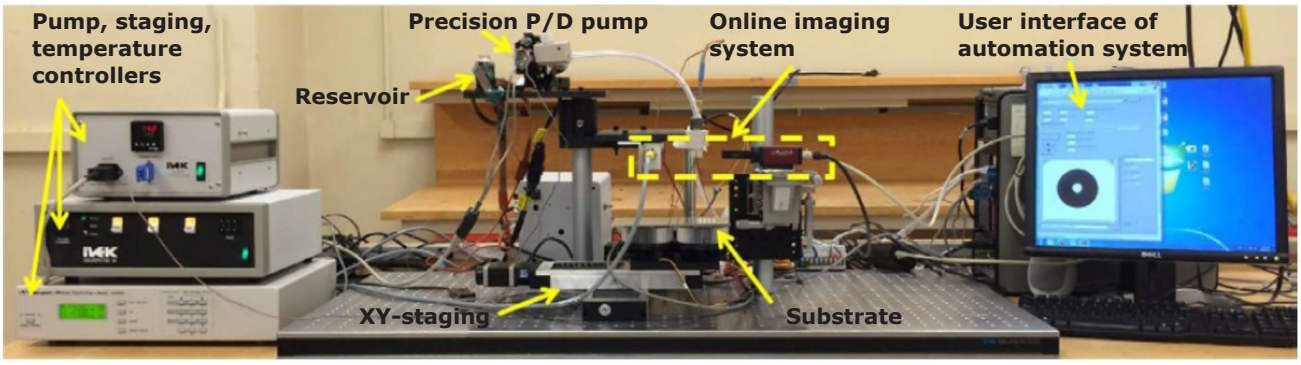


Fig. 2. Dropwise additive manufacturing system. Copyright (2018). Reprinted with permission from Elsevier

in Chapter 17. Process modelling allows complex system dynamics, interactions and control schemes to be investigated and optimised *in silico*, as enabling technology in the development of robust continuous drug manufacturing processes.

Small Molecule Upstream

Chapter 3, 'Innovative Process Development and Production Concepts for Small-Molecule API Manufacturing', contributed by John M. Woodley (Technical University of Denmark), summarises innovations in process systems engineering used to facilitate process development and optimisation. After a viable process model is developed, 'virtual experimentation' may be used to better focus benchtop experiments. Alternative routes and separation schemes can be evaluated if physical property data is available. The CAPEC-PROCESS Industrial Consortium (now the Process and Systems Engineering Centre (PROSYS)) at the Technical University of Denmark has contributed to the generation of physical property estimation methods to address this need.

The author describes use of template processes in which processes under development are fit to a template scheme based on conditions known to work for similar processes. For instance, a reaction step is evaluated against a process template for which simulation and laboratory models already exist (**Figure 3**). The sufficiency of the template is tested and then the process is optimised using modelling tools already developed for the template process. The author notes that while the template process approach may only be adaptable to 80% of process candidates, for those processes which are adapted, existing knowledge may be leveraged in the development of the new process. Process templating is a powerful tool in the application of PSE models for process integration and intensification and may be useful in evaluating process scheme alternatives

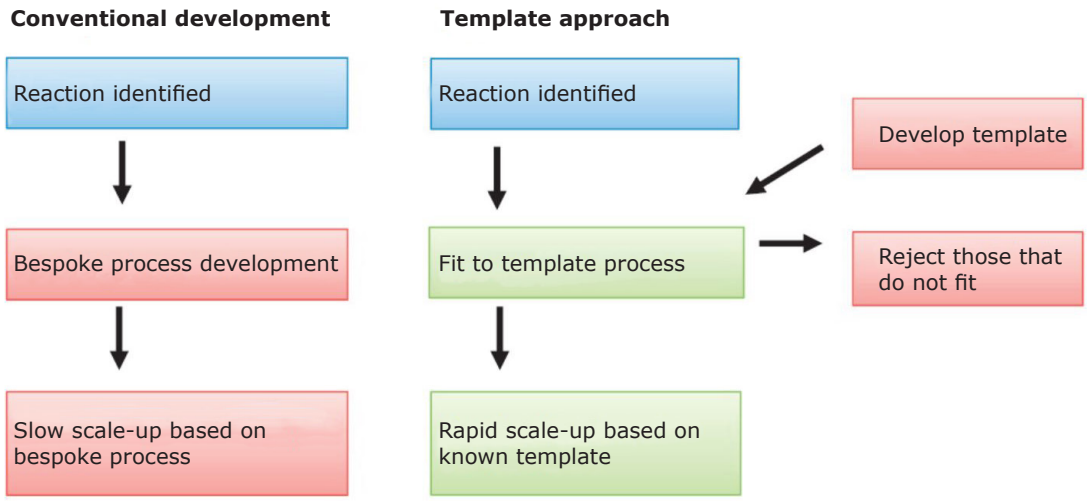


Fig. 3. Concept of template process to accelerate process development. Copyright (2018). Reprinted with permission from Elsevier

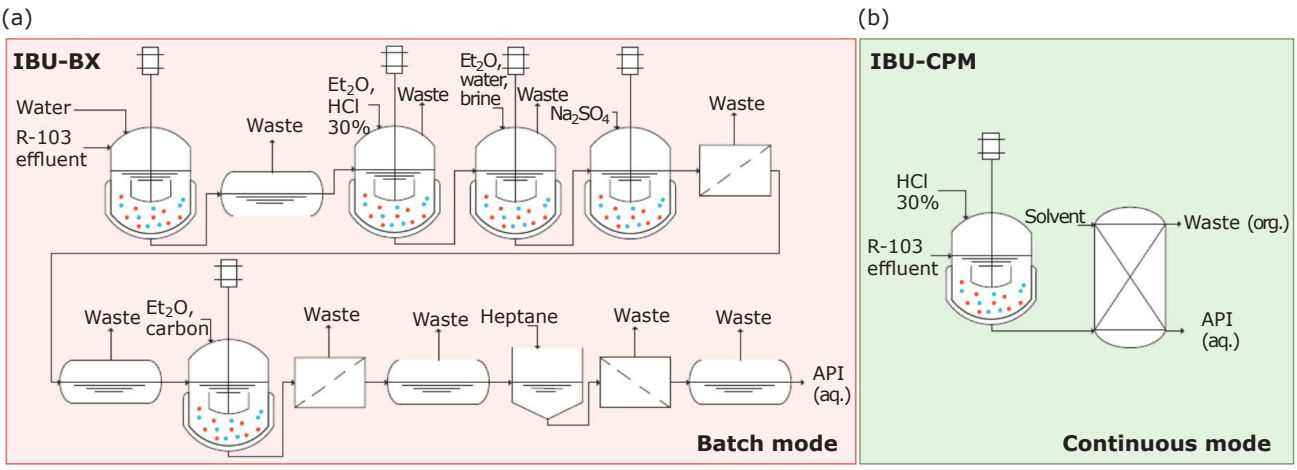


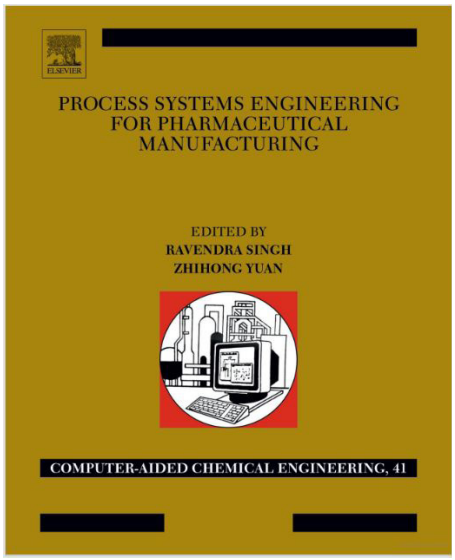
Fig. 4. (a) Batch (2); and (b) conceptual continuous (3, 4) separation schemes for ibuprofen (IBU). Copyright (2018). Reprinted with permission from Elsevier

when an API synthetic scheme involves multiple transformations.

Chapter 4, 'Plantwide Technoeconomic Analysis and Separation Solvent Selection for Continuous Pharmaceutical Manufacturing: Ibuprofen, Artemisinin, and Diphenhydramine' contributed by Samir A. Diab, Hikaru G. Jolliffe and Dimitrios I. Gerogiorgis (University of Edinburgh, UK), provides an evaluation of continuous separation steps *vs*. their batch separation counterparts. The authors noted that for the three continuous API processes evaluated by others, the evaluations had focused on performing the chemistry steps continuously and had not implemented continuous separation steps. As shown in **Figure 4**, the authors present a continuous liquid-liquid extraction (LLE) separation scheme as a replacement for the batch scheme found in the literature for ibuprofen (IBU). In addition, the authors evaluated additional solvents including *n*-heptane, cyclohexane, methylcyclohexane and isooctane and found many of the solvent choices to be suitable when a continuous LLE process is used *vs*. a continuous process. Using process modelling, the efficiencies of separation, the quantities of solvent and an economic comparison of alternative solvents are presented. For a continuous IBU extraction using heptane, the authors project capital savings of 58% and operating savings greater than 50% *vs*. the batch process utilising diethylether. The case studies presented in this chapter are based on process simulations performed by the authors and not on actual laboratory data. While it does not validate a final solvent choice, the use and conclusions based on simulation data highlight the value of a modelling-based approach to selecting workup or extraction solvents with environmental, flammability and regulatory suitability.

Conclusions

"Process Systems Engineering for Pharmaceutical Manufacturing" is a diverse collection of reviews and case studies, most of which were published previously. While this book provides an excellent summary of process modelling and computing with a view to the increased importance of robust simulation tools in pharmaceutical process development and manufacturing, more recent



"Process Systems Engineering for Pharmaceutical Manufacturing"

journal publications may provide additional or more in-depth information on the current state of specific technologies or algorithms described in the book. It is also evident that much of the key work in these areas has yet to be done. One topic missing from discussion in the book is the advent of quantum computing and the potential quantum computing presents in solving optimisation problems in process systems engineering. I would look forward to seeing an additional volume added to the series as the technology develops.

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The Reviewer

Michael Hamlin joined Johnson Matthey in November 2016 as Assistant Director, Processes Engineering at Johnson Matthey's Devens Research Centre in Devens, MA, USA where he leads the engineering group working to establish a particle engineering capability in Devens. Prior to joining Johnson Matthey, Mike worked in engineering roles in both fine chemicals and contract pharmaceuticals for more than 20 years. Mike received a BS degree in Chemical Engineering from Bucknell University in Lewisburg, PA, USA.