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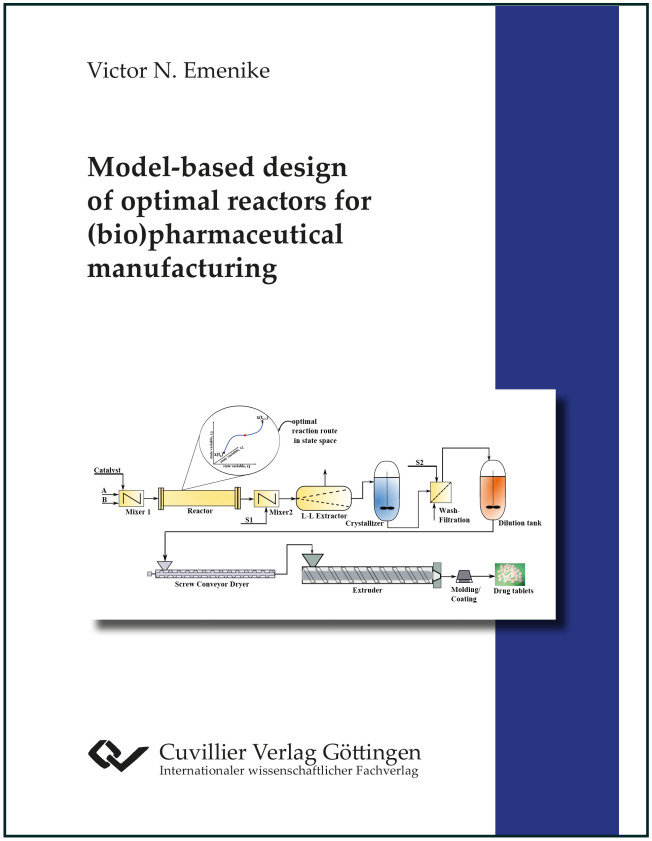
Model-based design of optimal reactors for (bio)pharmaceutical manufacturing



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ABSTRACT

The pharmaceutical industry is on the cusp of a technological revolution especially with regards to its manufacturing practices. At the center of this advancement, is the Quality by Design paradigm—which was initiated by the U.S. Food and Drug Administration—to guide the development of future manufacturing processes for small and large molecule drugs.

Moreover, it has been identified by academia and industry alike that process systems engineering will play a crucial role in making Quality by Design possible. A focal point of process systems engineering is a systems-oriented framework that is based on chemical engineering unit operations. While the unit operations approach has served the chemical industries, there are recent ideas for designing manufacturing processes by leveraging ideas from process intensification. A recent idea in process intensification is the concept of elementary process functions (EPF) which proposes designing processes by considering their inherent functionalities instead of already prescribed unit operations. By so doing, the optimal route in thermodynamic state space can be obtained and then technically approximated by either an appropriate off-the-shelf unit operation or could lead to the design of novel processes. So far the, EPF approach has found success specifically in the area of reactor design for the production of bulk chemicals. Therefore, the major goal of this thesis is to extend the EPF approach to design optimal reactors for pharmaceutical process development and manufacturing.

There are four main contributions in this thesis. First, it is shown how the EPF concept can be adapted to design reactors for the synthesis of active pharmaceutical ingredients—small molecule drugs—and organic intermediates. By considering the nucleophilic aromatic substitution as a case study, it is demonstrated that the residence time in comparison to results from the literature could be reduced by 33% by only exploiting the heating flux and that dosing strategies have no benefits in this case.

Second, the EPF approach was extended to enzyme-catalyzed reactions specifically benzaldehyde lyase (BAL)-catalyzed carboligation. In contrast to the preceding case study, it was shown that dosing strategies could lead to a 13% improvement of the final product concentration in comparison to a reference batch reactor. Moreover, this result was experimentally validated.

Based on this improvement, a robust optimal reactor for the BAL-catalyzed carboligation was designed as the third contribution of this thesis. In doing so, a systematic reactor design approach that combines the EPF conceptual framework, global sensitivity analysis, and a novel point estimate method-based back-off strategy was proposed. It was shown

that this back-off approach could lead to the design of robust optimal reactors, while being at least 10 times faster than the conventional Monte Carlo-based back-off approach.

Lastly, the EPF approach was extended to multi-scale bioreactor design for the manufacture of biologics—large molecule drugs. As a case study, the recombinant production of erythropoietin in *Pichia pastoris* using glucose as a substrate was considered, and the dynamic flux balance analysis approach was cast into the EPF framework. Moroever, a novel solution strategy for solving such optimization problems was proposed. The approach combines ideas from simultaneous dynamic optimization, bilevel optimization and the exact ℓ_1-penalization scheme. By using this approach it was shown that both optimal extracellular and intracellular fluxes leading to a 66% improvement in productivity could be resolved efficiently in less than one second. It was shown that this improvement could be obtained by implementing an almost constant optimal feeding strategy, which is different from typical exponential feeding strategies; and the engineering of a *P. pastoris* strain with high activity of most pathways in the central carbon metabolism.

Ultimately, this thesis has shown that the EPF approach is a viable approach for designing optimal and robust reactors for the synthesis of active pharmaceutical ingredients and organic intermediates, and for manufacturing biologics.

KURZFASSUNG

Die Pharmaindustrie durchläuft einen tiefgreifenden Wandel, der durch eine technologische Revolution der Herstellungsverfahren getrieben wird. Im Mittelpunkt des Umbruches steht das Quality-by-Design, das von der amerikanischen Food and Drug Administration initiiert wurde, um die Entwicklung zukünftiger Fertigungsprozesse für nieder- und hochmolekulare Medikamente zu steuern. Basierend auf den Anforderungen der Industrie und unter Berücksichtigung der aktuellen Fachliteratur spielen systemverfahrenstechnische Konzepte (engl. Process Systems Engineering) bei der Implementierung von Quality-by-Design-Methoden eine entscheidende Rolle.

Die systemorientierte Betrachtung von verfahrenstechnischen Prozessen des „Process Systems Engineering" basiert gewöhnlich auf verfahrenstechnischen Grundoperationen (engl. Unit Operations) und deren technischen Realisierungen. Während der Unit-Operations-Ansatz in der Chemieindustrie heute bereits weit verbreitet ist, nimmt die Bedeutung von innovativen Prozessintensivierungstrategien bei der Gestaltung von Herstellungsprozessen im Bereich von Forschung und Entwicklung stetig zu. Ein vielversprechendes Prozessintensivierungskonzept ist das der Elementaren Prozessfunktionen (EPF), das als Gegenpol zum traditionellen Unit-Operations-Ansatz die verfahrenstechnische Prozessgestaltung unter Berücksichtigung von thermodynamischen Zustandsgrößen beschreibt. Auf diese Weise kann zunächst die optimale Prozess-/Syntheseroute im thermodynamischen Zustandsraum ohne technische Vorprägung und Einschränkung bestimmt werden. Erst anschließend erfolgt der Schritt der technischen Realisierung bzw. dient die berechnete optimale Syntheseroute als Grundlage für das Design von neuen verfahrenstechnischen Prozesseinheiten. Insbesondere bei der Gestaltung von Reaktoren für die Produktion von Grundchemikalien führte die erstmalig angewandte EPF-Methodik zu signifikanten Prozessverbesserungen. Basierend auf den bisher erreichten Erfolgen steht im Fokus der vorliegenden Arbeit die Erweiterung des EPF-Ansatzes auf die optimale Reaktorauslegung für die Wirkstoffherstellung.

Die erzielten Ergebnisse lassen sich in vier wesentliche wissenschaftliche Beiträge einordnen. Zunächst wird das EPF-Konzept für das Reaktordesign zur Synthese von pharmazeutischen Wirkstoffen (engl. Active Pharmaceutical Ingredients, APIs) und organischen (niedermolekularen) Zwischenprodukten angewandt. Als erste Fallstudie wird eine nukleophile aromatische Substitution betrachtet, bei der allein durch die Optimierung des Thermo-Managements die Verweilzeit um 33% reduziert werden konnte. Gleichermaßen wird gezeigt, dass eine dynamische Anregung anhand von Dosierungsstrategien keine weitere Prozessverbesserung erzielt.

Darauf aufbauend wird der EPF-Ansatz auf enzymatische Reaktionen, speziell auf Benzaldehyd-Lyase- (BAL)-katalysierte Carboligationen, ausgeweitet. Im Gegensatz zur vorangehenden Fallstudie führen hier optimierte Dosierungsstrategien zu einer Erhöhung der Produktkonzentration um 13% im Vergleich zu Versuchen im Batch-Reaktor. Eine anschließende experimentelle Validierung konnte die simulativ errechneten Ergebnisse bestätigen.

Ergänzend beinhaltet der dritte Beitrag dieser Arbeit ein robustes optimales Reaktordesign für das BAL-katalysierte Reaktionssystem. Hauptmerkmal des robusten Designkonzepts ist ein systematischer Ansatz, der die EPF-Theorie, die Analyse von globalen Sensitivitäten und eine neuartige Backoff-Strategie auf Basis der Point Estimate Method (PEM) vereint. Mit der PEM-basierten Strategie können robuste, optimale Reaktorauslegungen erzielt werden, bei denen die Rechnersimulationen zehnmal schneller konvergieren als konventionelle Monte-Carlo-basierte Ansätze.

Im letzten Beitrag wird ein Multiskalen-Ansatz erstmalig mit der EPF-Theorie verknüpft, um Herstellungsprozesse von hochmolekularen Biopharmazeutika für die Reaktorauslegung abbilden zu können. Als Fallbeispiel dient die rekombinante Produktion von Erythropoetin aus *Pichia pastoris*, bei der die dynamische Flussbilanzanalyse (dFBA) in eine EPF-basierte Optimierung eingebettet wurde. Der neue Ansatz kombiniert Lösungsstrategien aus der Bilevel- und dynamischen Optimierung mittels exaktem l_1-Penalisierungsschemas. Durch die Optimierung der inner- und außerzellularen Flussraten wird eine Produktivitätssteigerung um 66% berechnet – bei weniger als eine Sekunde Rechnerlaufzeit. Diese Verbesserung kann durch die Implementierung eines nahezu konstanten Zuflusses von Glucose-Substrat erreicht werden. Bemerkenswert dabei ist, dass das Ergebnis in starkem Kontrast zu vorherrschenden Dosierungsstrategien steht, bei denen typischerweise exponentiell dosiert wird.

Zusammenfassend zeigt diese Arbeit, dass der EPF-Ansatz ein praktikables und zielführendes Werkzeug für die Entwicklung optimaler und robuster Reaktoren zur Synthese von niedermolekularen APIs, organischen Zwischenprodukten und zur Herstellung von höhermolekularen Biopharmazeutika darstellt.

PREFACE

This work was conducted during my employment as a research associate ("Wissenschaftlicher Mitarbeiter") at the Institute of Energy and Process Systems Engineering (InES), TU Braunschweig between June 2014 and June 2018. Besides my primary affiliation with InES, I also held joint affiliations at the International Max Planck Research School for Advanced Methods in Process Systems Engineering (IMPRS ProEng) and the Center for Pharmaceutical Engineering (PVZ) at TU Braunschweig.

Moreover, the research in this thesis has been published/submitted in peer-reviewed scientific journals and presented at conferences. These journal publications and conference proceedings are listed below.

JOURNAL PUBLICATIONS

1. Emenike, V.N., Krewer, U., Model-based optimal design of continuous flow reactors for the synthesis of active pharmaceutical ingredients. Chemie Ingenieur Technik, 88(9), pp. 1215-1216, 2016.

2. Emenike, V.N., Schulze, M., Schenkendorf, R., Krewer, U., Model-based optimization of the recombinant protein production in *Pichia pastoris* based on dynamic flux balance analysis and elementary process functions. Computer Aided Chemical Engineering, 40, pp. 2815-2820, 2017.

3. Emenike, V.N., Schenkendorf, R., Krewer, U., A systematic reactor design approach for the synthesis of active pharmaceutical ingredients. European Journal of Pharmaceutics and Biopharmaceutics, 126, pp. 75 - 88, 2018.

4. Emenike, V.N., Schenkendorf, R., Krewer, U., Model-based optimization of biopharmaceutical manufacturing in *Pichia pastoris* based on dynamic flux balance analysis. Computers & Chemical Engineering, 118, pp. 1 - 13, 2018.

5. Emenike, V.N., Xie, X., Schenkendorf, R.,Spiess, A.C., Krewer, U., Robust dynamic optimization of enzyme-catalyzed carboligation: a point estimate-based back-off approach. Computers & Chemical Engineering, 121, pp. 232 - 247, 2019.

6. Emenike, V.N., Xie, X., Schenkendorf, R., Krewer, U., A point estimate method-based back-off approach to robust optimization: application to pharmaceutical processes. Computer Aided Chemical Engineering, 46, pp. 223 - 228, 2019.

7. Emenike, V.N., Hertwig, D., Schenkendorf, R., Spiess, A.C., Krewer, U., A rigorous model-driven approach for the optimal design of reaction strategies for enzyme catalysis. *In Preparation* 2019.

CONFERENCE PROCEEDINGS

1. Emenike, V.N., Krewer, U., Model-based optimal design of continuous flow reactors for the synthesis of active pharmaceutical ingredients. ProcessNet-Jahrestagung und 32. DECHEMA-Jahrestagung der Biotechnologen 2016, Aachen, Germany, 12 - 15 September, 2016.

2. Emenike, V.N., Schulze, M., Schenkendorf, R., Krewer, U., Model-based optimal design of reactors for biopharmaceutical manufacturing of recombinant proteins in *Pichia pastoris*. 15th International Conference on Molecular Systems Biology (ICMSB2017), Raitenhaslach, Munich, Germany, 26 - 28 July, 2017.

3. Emenike, V.N., Schenkendorf, R., Krewer, U., Advances in model-assisted process design for (bio)pharmaceutical manufacturing. 2nd International Symposium on Pharmaceutical Engineering Research (SPhERe), Braunschweig, Germany, 6 - 8 September, 2017.

4. Emenike, V.N., Schulze, M., Schenkendorf, R., Krewer, U., Model-based optimization of the recombinant protein production in *Pichia pastoris* based on dynamic flux balance analysis and elementary process functions. 10th World Congress of Chemical Engineering (WCCE10)/ 27th European Symposium on Computer Aided Process Engineering (ESCAPE-27), Barcelona, Spain, 1 - 5 October, 2017.

5. Emenike, V.N., Hertwig, D., Schenkendorf, R., Krewer, U., Spiess, A. Out-of-the-box process intensification for enzyme-catalyzed cross-carboligation. 12th Symposium of the European Society of Biochemical Engineering Sciences (ESBES2018), Lisbon, Portugal, 9 - 12 September, 2018.

6. Emenike, V.N., Xie, X., Schenkendorf, R., Krewer, U., A point estimate method-based back-off approach to robust optimization: application to pharmaceutical processes. 29th European Symposium on Computer Aided Process Engineering (ESCAPE-29), Eindhoven, Netherlands, 16 - 19 June, 2019.

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INTRODUCTION

The pharmaceutical industry has for centuries served as a vanguard for producing high quality medicines for the well-being of humanity. Traditionally, the quality of these medicines have been ensured by using procedural guidelines [37]. These guidelines have been set-up by regulatory bodies such as the United State's Food and Drug Administration (FDA) and the European Medicines Agency. The major driver for these guidelines as set by both institutions stems from historical issues regarding the toxicity of drugs and manufacturing failures in the 1960s and 1970s [37]. A classical example is an incident in 1932, where diethylene glycol which is toxic to humans, was used to produce the elixir of sulfanilamide [77]. Another classical example was the sulfathiazole disaster in 1941 which was found to be due to poor manufacturing practises as documented in [179].

Due to these issues, the FDA established a forerunner of the current Good Manufacturing Practices (cGMPs) in the early 1960s and later finalized it in 1978. From then on, pharmaceutical companies have endeavoured to meet these cGMPs by following procedural regulatory control measures which are based on quality by testing [37, 144].

Due to economic constraints, it has been agreed by industry leaders and regulatory bodies alike that areas of pharmaceutical manufacturing ranging from clinical trials to actual drug production have to be modernized. Due to this, the International Conference on Harmonization introduced the process analytical technology (PAT) and Quality by Design (QbD) initiatives about 15 years ago [37]. QbD entails using PAT tools such as sensors

to ensure and monitor critical quality attributes and quality target product profiles by manipulating critical process parameters [98].

Even though QbD is relatively new to the pharmaceutical industry, the inherent technologies in QbD have already been widely applied in the chemical and petrochemical industries. As such, there is a rising campaign for the pharmaceutical manufacturers to adopt QbD. Nevertheless, a successful implementation of QbD involves the implementation of technologies such as PAT [167], continuous manufacturing [37] and process systems engineering [59].

Moreover, it is envisioned that process systems engineering—a subdomain of chemical engineering—will play a pivotal role in designing future pharmaceutical processes [182, 59]. A key goal of this thesis is to cross-fertilize the domains of process systems engineering and pharmaceutical manufacturing.

Based on this short background on the history of pharmaceutical manufacturing, the motivation for the specific research conducted in this thesis will be presented in the subsequent sections. By doing so, the aim is to give the reader a background knowledge in pharmaceutical manufacturing and the role of chemical engineering in pharmaceutical manufacturing. Ultimately, the research hypothesis, objectives and structure of the thesis will be presented in the final sections of this chapter.

1.1 PHARMACEUTICAL MANUFACTURING

Traditionally,[1] batch processing is the standard in the fine chemicals and pharmaceutical industry because of its simplicity and flexibility [150]. However, batch manufacturing has some well-known disadvantages such as scale-up difficulties, mass and heat transfer bottlenecks, long production times and possible supply chain disruptions [153, 149]. As shown in Fig. 1.1, the multiple disconnected steps involved in batch pharmaceutical manufacturing are the major causes of the long production times and possible supply chain disruptions.

[1] This section has been published in Emenike *et al.*, Eur. J. Pharm. Biopharm. 2018, 126, 75-88 [50].

Continuous pharmaceutical manufacturing (CPM) , in turn, is a process intensification strategy that enables the reduction of the number of synthesis steps and units, which can lead to significant cost savings [158, 85]. Furthermore, CPM enables safer operation [149, 63, 60], better scalability, enhanced process automation, smaller process footprint, enhanced mass and heat transfer, and higher throughput [98]. As a result, CPM is considered by both academia and industry as the most viable alternative to batch manufacturing [81]. To demonstrate the merits of CPM, Mascia *et al.* [110] developed an end-to-end continuous pharmaceutical manufacturing plant that produces drug products in final tablet form from chemical intermediates. The illustration of this end-to-end CPM plant can be seen in Fig. 1.2.

At the heart of the shift from batch to CPM technology are continuous flow reactors (or simply flow reactors), which serve as the key driver of highly-intensified flow processes; and they can be intensified by using elevated temperatures and pressures, light or immobilization agents [197, 10]. Hence, flow reactors are currently being used to synthesize APIs [20, 61] and organic intermediates quite frequently [170]. Based on the advantages of flow reactors, Hessel proposed the concept of novel process windows, i.e. operating under extreme process conditions to improve API production [68].

However, Valera *et al.* [184] argued that the advantages cited for flow reactors might not always be the case and that the decision to operate a reaction continuously or batch-wise should be done on a case-by-case basis. Hence, the question arises: *how do we systematically choose the best reactor type for a particular API synthesis?*

In an attempt to answer this question, Plouffe *et al.* [136] proposed a tool box approach for the selection of the best reactor for a particular reaction based on reaction classes, reacting phase (single or multiphase), and the reaction network. However, the authors admitted that this heuristic-based approach might not encompass all reaction types [136]. Model-based approaches such as attainable region methods [72] and superstructure-reactor optimization [1] could be used, but these methods are still dependent on existing reactor types, i.e. following a component off-the-shelf philosophy.

Inspired by this challenge, this thesis proposes the use of an apparatus-independent methodology called elementary process functions (EPF) developed by Freund and Sundmacher [56, 132]. A model-based approach such as the EPF methodology can guide the optimal design of intensified flow reactors and complement synthesis experiments. This can lead to novel process windows [68]; thereby, accelerating the pharmaceutical process development phase.

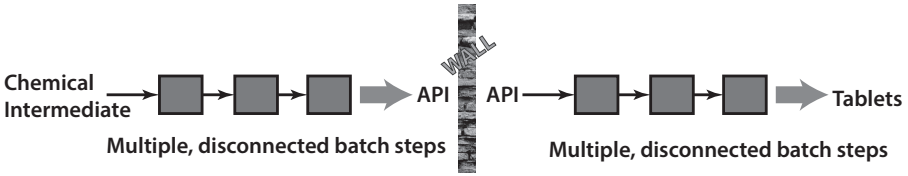

Figure 1.1: Batch pharmaceutical manufacturing.

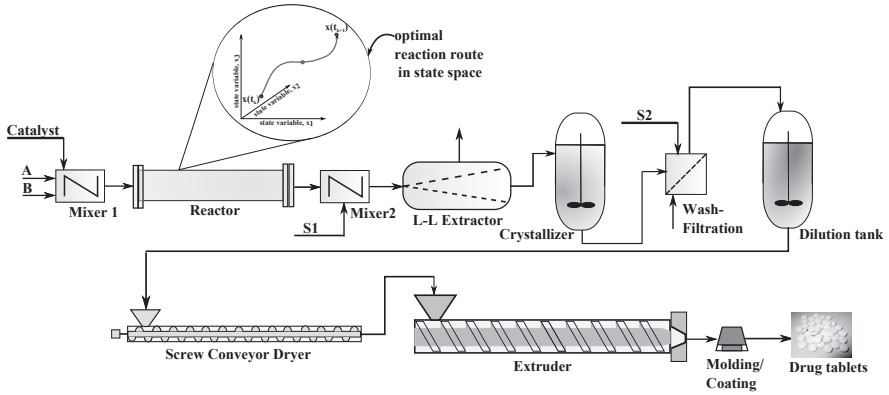

Figure 1.2: Continuous pharmaceutical manufacturing.