

---

## CONTENTS

---

LIST OF FIGURES	vii
LIST OF TABLES	xi
ABSTRACT	xiii
KURZFASSUNG	xv
PREFACE	xvii
<b>1 INTRODUCTION</b>	<b>1</b>
1.1 Pharmaceutical manufacturing . . . . .	2
1.2 Chemical reaction engineering for API synthesis . . . . .	5
1.3 Research hypothesis and objectives . . . . .	6
1.4 Thesis structure . . . . .	6
<b>2 METHODOLOGY</b>	<b>9</b>
2.1 Elementary process functions . . . . .	9
2.2 Dynamic optimization: mathematical formulation . . . . .	13
2.3 Dynamic optimization solution strategy . . . . .	13
<b>3 A SYSTEMATIC REACTOR DESIGN APPROACH FOR THE SYNTHESIS OF ACTIVE PHARMACEUTICAL INGREDIENTS</b>	<b>17</b>
3.1 Optimal reactor design for the S <sub>N</sub> Ar reaction of 2,4-difluoronitrobenzene . . . . .	17
3.2 Level 1: Applying integration and enhancement concepts . . . . .	19
3.3 Implementation . . . . .	24
3.4 Level 2: Limited fluxes and control variable selection . . . . .	26
3.5 Level 3: Technical Approximation . . . . .	33
3.6 Summary . . . . .	36
<b>4 MODEL-BASED DESIGN OF AN OPTIMAL REACTOR FOR ENZYME CATALYZED CROSS-CARBOYLATION</b>	<b>39</b>
4.1 Background . . . . .	39
4.2 Methodology . . . . .	42
4.3 Results and Discussion . . . . .	50

4.4 Summary . . . . .	58
<b>5 ROBUST DYNAMIC OPTIMIZATION OF ENZYME-CATALYZED CARBOLIGATION . . . . .</b>	<b>61</b>
5.1 Background . . . . .	61
5.2 Problem description . . . . .	65
5.3 Methodology . . . . .	66
5.4 Optimization strategies for <i>PfBAL</i> -catalyzed carboligation without uncertainties . . . . .	73
5.5 Optimization of <i>PfBAL</i> -catalyzed carboligation under uncertainties . . . . .	77
5.6 Summary . . . . .	84
<b>6 MULTISCALE BIOREACTOR DESIGN BASED ON DYNAMIC FLUX BALANCE ANALYSIS . . . . .</b>	<b>87</b>
6.1 Background . . . . .	87
6.2 Preliminaries . . . . .	91
6.3 Solution strategy . . . . .	96
6.4 Case study: Recombinant protein production in <i>Pichia pastoris</i> . . . . .	100
6.5 Results and Discussion . . . . .	104
6.6 Summary . . . . .	115
<b>7 CONCLUSIONS AND FUTURE DIRECTIONS . . . . .</b>	<b>117</b>
7.1 Conclusions . . . . .	117
7.2 Future research directions . . . . .	119
<b>A APPENDIX TO CHAPTER 3 . . . . .</b>	<b>121</b>
A.1 Further results for level 1 . . . . .	121
A.2 Model assumptions for level 2 . . . . .	123
A.3 Heat capacity . . . . .	123
A.4 Detailed model development for level 3 . . . . .	126
<b>B APPENDIX TO CHAPTER 5 . . . . .</b>	<b>129</b>
B.1 Results for the reference case: Batch reactor . . . . .	129
B.2 Results for Case 1: Dosing of propanal . . . . .	130
B.3 Results for Case 2: Dosing of benzaldehyde . . . . .	132
B.4 Time-varying forward propagation of uncertainty with the nominal control . . . . .	132
B.5 Sparsity patterns . . . . .	135
<b>BIBLIOGRAPHY . . . . .</b>	<b>137</b>
<b>INDEX . . . . .</b>	<b>167</b>