

**DECISION SUPPORT SYSTEM FOR IMPROVED  
SCHEDULING, MAINTENANCE, AND ASSESSMENT  
OF BIOPHARMACEUTICAL PROCESSES**

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SCHEDULING, MAINTENANCE, AND ASSESSMENT  
OF BIOPHARMACEUTICAL PROCESSES**

*by*

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*submitted*

*in fulfilment of the requirements of the degree of Doctor of Philosophy*

*to the*



**Indian Institute of Technology Delhi**

**OCTOBER 2021**

*Dedicated to my family*

## Certificate

I am satisfied that the thesis presented by **Mr. Vaibhav Kumar** on “*Decision Support System for Improved Scheduling, Maintenance, and Assessment of Biopharmaceutical Processes*” is worthy of consideration for the award of the degree of Doctor of Philosophy and is a record of the original bonafide research work carried out under my guidance and supervision and that the results contained in it have not been submitted in part or full to any other university or institute for award of any degree/diploma.

I certify that he has pursued the prescribed course of research.



11 Oct 2021

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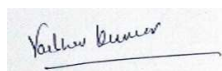
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A handwritten signature in cursive script, reading "Vaibhav Kumar", is enclosed in a light gray rectangular box. A horizontal line is drawn beneath the signature.

(Vaibhav Kumar)

## **Abstract**

Biopharmaceuticals are therapeutic drugs that successfully cure autoimmune diseases by manipulating patient genetics with fewer side effects than traditional chemical drugs. Under the risk of high clinical failure linked to drug development coupled with more significant process variability, designing a decision support system for multiproduct facilities in biopharmaceuticals remains a challenge. Computer-aided decision support systems have been used to assist decision-making in the past for biopharmaceutical processes using heuristic approaches for production planning and scheduling, facility design, debottlenecking, and capacity analysis. Much work has been done towards planning, scheduling, and optimization in process systems engineering (PSE), and recently increasing efforts are being made to understand process design and optimization in the biopharmaceutical industry. More work is required to get a more precise, deeper, and better understanding of process design and optimization in this field. Therefore, the purpose of the present study is to conduct research and develop novel models to fill the gap between computer-aided process design tools and mathematical optimization and scheduling.

The first objective in this thesis is to propose an extension of the earlier unit-specific event-based literature model to address the observed model inconsistencies such as early product delivery, no initial setup time, no proper mapping of upstream and downstream tasks, and storage sequencing. Then in the second part, an improved model is proposed with features such as minimum campaign length and shelf-life occurring over consecutive multiple events, modified material balances, sales and penalty constraints, and new initial setup sequencing constraints. Then it is extended for handling the early product delivery case by providing new material balance and sales and penalty constraints. The improved model gave better results compared to the literature.

Chromatography has a significant impact on the purity attributes of the final product in the bio-pharmaceutical industry. Limited lifetime and higher cost of chromatography resins make it necessary to get the maximum yield from the process step, due to which the resins are reused multiple times. Therefore, maintenance (i.e. restoring resin capability and performance to its initial level) is one of the most critical decisions for such processes. So, when to plan the maintenance operation subject to performance decay is crucial in the bioprocess facility design and scheduling. In the second objective, a state task network (STN) framework-based, unit-specific event-based model is proposed for performance decay of chromatography resin for optimum resin utilization, which shows improvement in profit and capacity utilization over the literature models that used discrete events and global events.

The third objective is to conduct research and develop novel mathematical models to fill the gap between computer-aided process design tools such as SchedulePro® and mathematical optimization and scheduling. To explore techno-economic benefits, if any, some examples adopted from the SchedulePro® library on a microbial biopharmaceutical process are modeled and validated using mathematical programming-based approaches. Two unit-specific event-based models are proposed with and without utility constraints, which shows improvement over the heuristic approaches. In the fourth objective, the proposed mathematical model for batch processing is demonstrated on available experimental data for production of Lethal Toxin Neutralizing Factor (LTNF) and Granulocyte Colony-Stimulating Factor (GCSF).

*Keywords:* Optimization, Scheduling, Mathematical programming, Biopharmaceuticals, Shelf life, Storage.

## सार

बायोफार्मास्युटिकल्स चिकित्सीय दवाएं हैं जो पारंपरिक रासायनिक दवाओं की तुलना में कम साइड इफेक्ट वाले रोगी आनुवंशिकी में हेरफेर करके ऑटोइम्यून बीमारियों का सफलतापूर्वक इलाज करती हैं। अधिक महत्वपूर्ण प्रक्रिया परिवर्तनशीलता के साथ दवा विकास से जुड़ी उच्च नैदानिक विफलता के जोखिम के तहत, बायोफार्मास्युटिकल्स में बहु-उत्पाद सुविधाओं के लिए निर्णय समर्थन प्रणाली को डिजाइन करना एक चुनौती बनी हुई है। उत्पादन योजना और शेड्यूलिंग, फैसिलिटी डिज़ाइन, डिबॉटलनेकिंग और क्षमता विश्लेषण के लिए अनुमानी दृष्टिकोण का उपयोग करके बायोफार्मास्युटिकल प्रक्रियाओं के लिए अतीत में निर्णय लेने में सहायता के लिए कंप्यूटर सहायता प्राप्त निर्णय समर्थन प्रणालियों का उपयोग किया गया है। प्रोसेस सिस्टम इंजीनियरिंग (पीएसई) में योजना, शेड्यूलिंग और ऑप्टिमाइजेशन की दिशा में बहुत काम किया गया है, और हाल ही में बायोफार्मास्युटिकल उद्योग में प्रक्रिया डिजाइन और अनुकूलन को समझने के लिए बढ़ते प्रयास किए जा रहे हैं। इस क्षेत्र में प्रक्रिया डिजाइन और अनुकूलन की अधिक सटीक, गहरी और बेहतर समझ प्राप्त करने के लिए और अधिक काम करने की आवश्यकता है। इसलिए, वर्तमान अध्ययन का उद्देश्य कंप्यूटर सहायता प्राप्त प्रक्रिया डिजाइन उपकरण और गणितीय अनुकूलन और शेड्यूलिंग के बीच की खाई को भरने के लिए अनुसंधान करना और उपन्यास मॉडल विकसित करना है।

इस थीसिस में पहला उद्देश्य मनाया गया मॉडल विसंगतियों जैसे प्रारंभिक उत्पाद वितरण, कोई प्रारंभिक सेटअप समय, अपस्ट्रीम और डाउनस्ट्रीम कार्यों का कोई उचित मानचित्रण नहीं, और भंडारण को संबोधित करने के लिए पहले इकाई-विशिष्ट घटना-आधारित साहित्य मॉडल के विस्तार का प्रस्ताव करना है। अनुक्रमण फिर दूसरे भाग में, एक बेहतर मॉडल प्रस्तावित किया गया है जिसमें न्यूनतम अभियान लंबाई और लगातार कई घटनाओं में होने वाली शेल्फ-लाइफ, संशोधित सामग्री संतुलन, बिक्री और दंड की कमी, और नई प्रारंभिक सेटअप अनुक्रमण बाधाएं शामिल हैं। फिर इसे नई सामग्री संतुलन और बिक्री और दंड की कमी प्रदान करके प्रारंभिक उत्पाद वितरण मामले को संभालने के लिए बढ़ाया जाता है। बेहतर मॉडल ने साहित्य की तुलना में बेहतर परिणाम दिए।

जैव-फार्मास्युटिकल उद्योग में अंतिम उत्पाद की शुद्धता विशेषताओं पर क्रोमैटोग्राफी का महत्वपूर्ण प्रभाव पड़ता है। सीमित जीवनकाल और क्रोमैटोग्राफी रेजिन की उच्च लागत प्रक्रिया चरण से अधिकतम उपज प्राप्त करना आवश्यक बनाती है, जिसके कारण रेजिन को कई बार पुनः उपयोग किया जाता है। इसलिए, रखरखाव (यानी राल क्षमता और उसके प्रारंभिक स्तर पर प्रदर्शन को बहाल करना) ऐसी प्रक्रियाओं के लिए सबसे महत्वपूर्ण निर्णयों में से एक है। इसलिए, बायोप्रोसेस सुविधा

डिजाइन और शेड्यूलिंग में प्रदर्शन क्षय के अधीन रखरखाव संचालन की योजना कब बनाई जाए। दूसरे उद्देश्य में, इष्टतम राल उपयोग के लिए क्रोमेटोग्राफी राल के प्रदर्शन क्षय के लिए एक राज्य कार्य नेटवर्क (एसटीएन) ढांचा-आधारित, इकाई-विशिष्ट घटना-आधारित मॉडल प्रस्तावित है, जो उपयोग किए गए साहित्य मॉडल पर लाभ और क्षमता उपयोग में सुधार दर्शाता है, असतत घटनाओं और वैश्विक घटनाओं।

तीसरा उद्देश्य कंप्यूटर एडेड प्रोसेस डिज़ाइन टूल्स जैसे शेड्यूलप्रो® और गणितीय अनुकूलन और शेड्यूलिंग के बीच की खाई को भरने के लिए अनुसंधान करना और उपन्यास गणितीय मॉडल विकसित करना है। तकनीकी-आर्थिक लाभों का पता लगाने के लिए, यदि कोई हो, माइक्रोबियल बायोफार्मास्यूटिकल प्रक्रिया पर शेड्यूलप्रो® लाइब्रेरी से अपनाए गए कुछ उदाहरणों को गणितीय प्रोग्रामिंग-आधारित दृष्टिकोणों का उपयोग करके मॉडलिंग और मान्य किया जाता है। उपयोगिता बाधाओं के साथ और बिना दो इकाई-विशिष्ट घटना-आधारित मॉडल प्रस्तावित हैं, जो अनुमानी दृष्टिकोणों में सुधार दर्शाता है। चौथे उद्देश्य में, बैच प्रोसेसिंग के लिए प्रस्तावित गणितीय मॉडल को लेथल टॉक्सिन न्यूट्रलाइजिंग फैक्टर और ग्रैनुलोसाइट कॉलोनी-स्टिमुलेटिंग फैक्टर के उत्पादन के लिए उपलब्ध प्रायोगिक डेटा पर प्रदर्शित किया जाता है।

**कीवर्ड:** ऑप्टिमाइज़ेशन, शेड्यूलिंग, गणितीय प्रोग्रामिंग, बायोफार्मास्यूटिकल्स, शेल्फ लाइफ, स्टोरेज।

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## ABBREVIATIONS

USP	<i>Upstream processing</i>
DSP	<i>Downstream processing</i>
STN	<i>State-task-network</i>
RTN	<i>Resource-task-network</i>
SSN	<i>State-sequence-network</i>
RD	<i>Recipe diagrams</i>
LP	<i>Linear programming</i>
MILP	<i>Mixed integer linear programming</i>
NLP	<i>Non-linear programming</i>
MINLP	<i>Mixed integer non-linear programming</i>
RMIP	<i>Relaxed mixed integer programming</i>
MILFP	<i>Mixed integer linear fractional programming</i>
FFIS	<i>Flexible finite intermediate storage</i>
RTSV	<i>Real-time storage violation</i>
RTSLV	<i>Real-time shelf-life violation</i>
FIS	<i>Finite intermediate storage</i>
GA	<i>Genetic algorithm</i>
GCSF	<i>Granulocyte Colony-Stimulating Factor</i>
LTNF	<i>Lethal Toxin Neutralizing Factor</i>