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# Discrete Event Simulation Modelling for Dynamic Decision Making in Biopharmaceutical Manufacturing

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#### Abstract

With the increase in demand for biopharmaceutical products, industries have realised the need to scale up their manufacturing from laboratorybased processes to financially viable production processes. In this context, biopharmaceutical manufacturers are increasingly using simulationbased approaches to gain transparency of their current production system and to assist with designing improved systems. This paper discusses the application of Discrete Event Simulation (DES) and its ability to model the various scenarios for dynamic decision making in biopharmaceutical manufacturing sector. This paper further illustrates a methodology used to develop a simulation model for a biopharmaceutical company, which is considering several capital investments to improve its manufacturing processes. A simulation model for a subset of manufacturing activities was developed that facilitated 'what-if' scenario planning for a proposed process in terms of throughout time reduction, better resource utilisation, operating cost reduction, reduced bottlenecks etc. This visibility of the existing and proposed production system assisted the company in identifying the potential capital and efficiency gains from the investments therefore demonstrating that DES can be an effective tool for making more informed decisions. Furthermore, the paper also discusses the utilisation of DES models to develop a number of bespoke productivity improvement tools for the company.

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# 1. Introduction

EvaluatePharma World Preview consensus forecasts the prescription drug sale to be \$895 billion of which biological products account to about 50%. [1]. With this increasing demand, biopharmaceutical manufacturers are now looking at scaling up their manufacturing processes to mass produce biological products, especially Gene Therapy (GT) products. GT is a new generation of biopharmaceutical drugs that are targeted at treating genetic disorders as well as life threatening conditions such as cancer. FDA (2013) defines GT as a 'treatment process that introduces genetic material into a DNA to replace faulty or missing genetic material, thus treating a disease or abnormal medical condition' [2]. Despite their increasing popularity and promising nature, most of GT products have long remained in clinical trial phases. With the

completion of clinical trials nearing the end, there is a definite possibility for these drugs to be developed into commercially available and effective GT products. However, unlike conventional drugs that are mass produced, GT products are novel/complex and hence offer unique challenges in product development. Complex manufacturing processes [3], high cost of production [4], high risk of clinical failure [5], strict regulatory policies [6] are likely to affect the manufacturing processes. GT companies considering expansion need to make investment decisions under these uncertain conditions and have to realise that the key to their commercial success lies in optimal planning, efficient manufacturing and early assessment of cost/benefits. Therefore, computer-aided simulation tools are increasingly being used to capture the dynamic behaviour of the current process and to experiment with various process alternatives.

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This paper presents a Discrete Event Simulation (DES) model developed in Witness 13 visualising a subset of the GT manufacturing processes in order to assess the impact of the proposed investment decision involving a process alternative. The model evaluates the alternatives in terms of manufacturing time, cost, resources utilisation, bottlenecks, and throughput. Section 2 & 3 of this paper provides a brief overview of various modelling approaches and their relevance to biopharmaceutical process modelling along with the challenges in their adoption in GT industries. Section 3 outlines the methodology employed to develop a DES model to support 'what-if' scenario planning along with a case study from a biopharmaceutical company (Section 4).

# 2. Approaches in Biopharmaceutical process and business modelling

Decision-making in drug development is increasingly relying on tools that capture dynamic process data and facilitate representation of technical/business aspects of drug development. Fig. 1 illustrates the application of such tools in various stages of biopharmaceutical drug development as depicted by Ashouri (2001) [7]. Despite the range of application, their utilisation is not as seamless in process industries as it is in mature manufacturing industries such as Automobile/Aerospace. This may be because the GT industries are still developing their core technology and the use of computer-aided tools in process planning and optimising is a novelty [8]. Furthermore, Saraph (2001) [9] regards biopharmaceutical as complex manufacturing characterised by:

- Lack of well-defined processes with a mix of discrete and continuous flows
- Intermediate quality control and assurance processes between production stages
- Non-uniform batch sizes and buffer sizes that vary significantly from stage to stage
- Highly uncertain production output due to shorter shelflife of products and higher rejection rates
- Limited standardisation/automation with manual handling of materials
- Stringent regulations, adherence to Good Manufacturing Practices (GMPs) creating further operational constraints

# 2.1. State of the art methodologies and tools

Despite the challenges, many researches have considered computer-aided process design, simulation, and scheduling tools to enhance the understanding of bioprocesses and to develop test cases for evaluation [10, 11]. Usage of these computer-aided tools in the biopharmaceutical industry falls broadly into four categories as depicted in Fig. 2. Although this classification distinguishes one methodology from another, in practice, most of the tools developed for industries are a combination of one or more of these methods.

Mathematical programming is the oldest and traditional method involves building mathematical relationships between variables to technically represent the unit operations. For example, mass balance equations created using spreadsheets or general-purpose simulators such as SPEEDUP by Aspen Technology (12), Matlab (13), and Labview by National Instruments (14) are used to model unit operations in biopharmaceutical manufacturing. These methodologies do not have the capability to visualise unit operations in real time. Therefore, mathematical modelling methods have slowly evolved to use graphical user interfaces. Hierarchical modelling approaches developed by Farid et al [15] uses Object Oriented Programming (OOP) implemented in a graphical simulation tool (ReThink) to simulate the key activities in manufacturing such as resource utilisation and cost. This method combines both process modelling using mass balance methods for plant design and capacity management, and business modelling using techniques such as investment appraisal, risk evaluation, and production planning.

Karri et al [16] has also applied the OOP methodology to model not just the key tasks but also other activities in the manufacturing stage. Furthermore, in another study, Lim et al. [17] extends this hierarchical approach to include additional tasks such as QA/QC and documentation using a DES based tool (ExtendSim). Whilst, mathematical programming and DES methods are deterministic, Rajapakse et al. [18] has developed a tool to model the uncertainties in biopharmaceutical product portfolio management to predict the outcome of various development strategies using techniques such as Monte Carlo Simulation and Sensitivity Analysis. It quantifies the outputs in the form of economic metrics such as Net Present Value (NPV) to support decisionmaking. Application of stand-alone DES packages also allow stochastic and dynamic modelling of biopharmaceutical processes/systems aimed for capacity planning, scheduling, debottlenecking, and water minimisation [8, 9]. Another tool developed by Sharda and Bury [19] has shown the potential application of DES model (built in ExtendSim) in the maintenance stage. On the other hand, optimisation methodologies employed by Petries [20] uses SuperPro Designer simulation package to account for batch process simulation rather than unit operation simulation.



Fig. 1. Computer-aided tools in biopharmaceutical product development (adapted from Ashouri (2001) [7])



Fig. 2. Classification of Simulation Methodologies

The tool developed can be used to evaluate resource utilisation, material balances, environmental emissions, cycle time analysis, and scheduling problems to debottleneck and optimise batch processes. Additionally, several bespoke spreadsheet-based tools are widely developed and used in industries to address specific needs. One tool of relevance is BioSolve [21] by Biopharm Services Ltd. It is a stand-alone Microsoft-Excel Spreadsheet based analytical tool particularly targeted at modelling the manufacturing processes to estimate the performance and costs of the existing system to compare it with a future system.

#### 3. Scope for Research Work

Given the range and capacity of these modelling methodologies/tools, the selection of a particular or a combination of these techniques is based on the type of solution required and also the application area (whether modelling a unit process or overall business operation). Although very comprehensive, mathematical programming methods are most likely to be used for mass balancing of chemical processes in unit operations, and on the other hand DES is more suitable for modelling discrete and dynamic systems to visualise the flow of entities and resources (activity scheduling and resource utilisation). Also, the mass balancing methodologies have shown limited applications when considering parallel processing or when there are too many input parameters [22].

Alternatively spreadsheet-based tools/solutions are very simplistic and do not score well in the areas of dynamic modelling and visualisation of processes which is a prerequisite for most simulation modelling. A spreadsheetbased model may not consider complex aspects of simulation such as: parameters that change over time, restrictions on various resources, queuing of products, variability in arrival/processing etc. In order to account for such variability and discrepancies, average values are used in spreadsheet models which are most likely to result in deterministic outcomes that are again averaged out. Therefore the final data or results are far from the actual outcome. On the other hand, DES offers flexibility to model various system constraints and their interaction with each other in greater detail. In addition DES software accounts for various restraints on the resources (setups, equipment breakdown, skill levels of a worker, shift patterns etc.) to be modelled in order to visualise the knock-on effect it may have on other downstream processes. Therefore, as highlighted in the review:

- 1. There is a need for a simplistic approach to dynamically model the biopharmaceutical manufacturing unit operations and to utilise the simulation output to support business decisions.
- DES based tools provide the flexibility to model nonlinearity, uncertainties that would have been time consuming and inaccurate if any other approaches were considered.

In light of this, a methodology for the development of a DES model is presented in this paper along with a proposed framework for an investment appraisal decision support tool.

# 4. DES Modelling Approach

As established in the previous section, simulation in biopharmaceutical industry, although not significantly developed, is very crucial since the effects of very small process variations having much greater impacts on the system can be visualised. Also modelling for biopharmaceutical presents its own challenges because of lack of standardisation (variable time, variable titre, variable rejection etc.) and high uncertainties. Hence simulation approaches based on discrete events offer flexibility to capture the dynamic (where model changes over time) stochastic (include the impact of uncertainty) processes of GT manufacturing. Witness 13 simulation package was used to develop the model. Witness was chosen because of its ability to simulate both discrete and continuous flows which is the characteristic of many process industries including biopharmaceutical.

#### 4.1. Modelling methodology

The challenges presented in simulating (see section 2) biopharmaceutical manufacturing process required a specific methodology to be defined for the DES model development and is as shown in Fig. 3. Mapping the processes and understanding the scope of the project is fundamental in model development. A model can represent an individual manufacturing stage/activity in the entire system or include a range of activities within a system therefore it is essential to define the modelling boundaries prior to model development. Models at a higher level of abstraction only require information related to the primary processes whereas a model with a lower level of abstractness requires detailed information that includes secondary processes information. For example, costing, energy and water usage, waste generation etc.).



Fig. 3. Discrete Event Simulation Methodology

The next step in model development is to identify the elements in the simulation engine that represent the manufacturing system under study. Modelling elements such as entities (elements that flow through the system), variables (elements that change over time), attributes (the characteristics of elements), resources (system assets, machines, conveyors, labour, buffers) are determined. These are essential to build the simulation logic and to establish product and resource flows.

The data input into the model development determines the accuracy of the simulation results. Therefore, the model is built in several modules representing various unit operations (illustrated in Fig. 4) to facilitate easier data collection organization, and validation. Given the uncertain environment characterized by both market and technical risks in GT manufacturing, variables are defined to input data. Additionally the flexibility to connect with an external file enables dynamic import and export of simulation data to and from the simulation software. Within the simulation engine, input data can be categorised into three types: (i) Product Flow data (ii) Process Schedule data (iii) System Capacity data. The continuous and discrete flow of products require product flows represented as moving parts/entities per unit time as well as flowrates/volumes for fluids. Process specific data includes data pertaining to activities such as process times, batch process consideration, input and output rules, resource schedules, clean in place schedules etc. whilst the system capacity data includes data pertaining to the capacity of the system such as, buffer capacity, number of runs, run length, costing data etc. In order to address the objectives defined in the initial stages of model development, a number of performance parameters were defined at the overall process and unit operation level (see Table 1).

# 4.2. Cost Benefit Analysis

Integral to this study was the development of an Investment Appraisal tool for Cost Benefit Analysis. The efficiency benefits in terms of time saving, better operator utilization, reduced waste achieved in the new process (visualized in the simulation model) can be utilized in evaluating the benefits of the new process. The open architecture of the Witness simulation model permits assessment of various production alternatives by comparing their performance parameters.

Level	Performance Parameter	
Project	Campaign/Subrun throughput time	
	Rejections	
	Resource Cost	
Process	Process Time	
	Number of Operators	
	Operator Utilization	
	MSC Utilization	
Operation	Queuing Times	
	Operation Time	
	Reagents Used (vol)	
	Reagents Wasted (vol)	
	Cost of Reagents	

# 5. Case Study

The case study details a DES model developed for a subset of the GT manufacturing process at a biopharmaceutical company. The process considered in this cases study is preparing the media used in cell culture. Media is used in various stages of production (growing cells and viral vectors, recovering viral vectors/harvesting, purification) and is prepared by measuring and adding four types of reagents to it in batches. The current process and a future state is modelled using the methodology discussed in Section 4.

#### 5.1. Problem Definition

Some of the critical issues noted in the current manufacturing process are as listed:



Fig. 4. DES framework with Excel integration

- Longer processing times (batch production leading to multiple grade transitions in the production plant)
- Labour intensive & manual handling leading to increased risk of unwanted errors and occasional microbial contamination
- Increased number of pharma containers requiring more storage space
- Risk of inconsistent cell distribution and concentration within unit operations
- Bottlenecks in terms of personnel and equipment

In order to address these issues, the company proposed a new technology to prepare media in bulk instead of multiple small batches which requires significant changes in the way of working within the existing manufacturing facility. In order to visualize the proposed process change a simulation model was developed that enabled what-if scenario planning.

#### 5.2. Simulation Objectives

Based on the current and proposed manufacturing processes, the following objectives were defined:

- Model current state (batch process with aliquots and pharma containers)
- Estimate current process time /cost for media preparation
- Model proposed state (pallet tanks with bags reagent addition without dividing into pharma containers)
- Compare the key performance parameters for current and proposed state (as identified in Table 1)
- Quantify the impact of capital investment
- Identify further improvement opportunities

# 5.3. Data Collection

As highlighted in section 3, the data collection was for three levels: product, processes, and system. A range of sources such as manufacturing records, historical data, literature, etc. were used to obtain default values. Three workshops, each with duration of 3 hrs, with the project management team were held to understand the initial requirements. Additionally, the visit to the clean rooms gave an insight into the actual media manufacturing process. Senior biotechnologists and process improvement experts were consulted to gather process/cost data and validate the modelling assumptions at every stage.

#### 5.4. Simulation Model Development

The model for the entire media preparation process was built in modules consisting of five unit operations: (1) Media division, (2) Reagent 1 addition, (3) Reagent 2 addition, (4) Reagent 3 addition, and (4) Reagent 4 addition as depicted in Fig. 5. These modules were developed and validated independently prior to their integration. In the current manufacturing process, the pharma containers move from one safety cabinet to another in batches where the reagents are manually added into the pharma containers. Fig. 5 also illustrates the key variables and constraints defined to develop the simulation model in Witness 13. In the proposed manufacturing process, the reagents are sequentially added to the media contained in a large pallet tank which substantially reduced the number of processing steps thereby significantly reducing the need for manual handling. Fig. 6 illustrates the conceptual simulation model of the proposed process.

#### 6. Simulation Results

The simulation models developed in Witness indicated considerable improvements in the proposed process over the existing process. The proposed system requires transfer of reagents directly into the tanks and eliminates repetitive processes such as pipetting each reagents, handling multiple pharma containers, and sterilization. The three main performance parameters that were of interest to the company were (1) Process time (2) No. of Operators (3) Operator Utilisation (summarized in Table 2). The existing process took about 95 minutes to prepare a batch of media whilst the proposed process required only 45 mins. The proposed process showed about 50% reduction in throughput time releasing the safety cabinets and other shared resources.



Fig. 5. Conceptual model of the current process



Fig. 6. Conceptual model of the proposed process

Table 2. Key Performance Parameters for current and proposed media preparation  $\operatorname{process}$ 

Key Process Parameter	Current Media Preparation	Proposed Media Preparation
Process Time	95 mins per subrun	45 mins per subrun
No. of Operators	3 per subrun	2 per subrun
Operator Utilisation	60% per subrun	85% per subrun

Furthermore, the operators required in the proposed process were reduced from three to one along with a 25% increase in operator utilization. The model developed and the result obtained for the current process is reflective of the real system and was verified by comparing simulation outputs with the manufacturing records. The simulation results for the proposed process were utilized in an Investment Appraisal tool to quantify the efficiency benefits. The validation process included workshops with suppliers and project management teams to evaluate costs/benefits of the proposed process. The figures obtained were very close to the initial estimates provided by the project management.

# 7. Conclusion

The study has highlighted the value of applying computeraided tools in decision-making for biopharmaceutical (and other) manufacturing. Whilst simulation techniques are widely utilized to address various operational issues, there is an opportunity for their increased and targeted application in biopharmaceutical process modelling.

This paper has presented a Discrete Event Simulation (DES) model for a subset of GT manufacturing process that was developed in Witness. The systematic methodology adopted in this paper allowed modelling of both discrete and continuous flow of elements which is intrinsic to GT manufacturing. Moreover, the modular approach and the integration of the simulation engine with an external .csv file confer maximum flexibility for 'what-if' scenario planning and allow dynamic assessment of various process alternatives.

The DES model developed for the company provided a sense of reality into the existing and proposed process flow enabling focus groups to easily map the specific areas of improvement and potential benefits in terms of cost, risk, time, material, manpower etc. Additionally the results from the simulation model were used as support material in explaining and defending decisions to various stakeholders, which has demonstrated a streamlined approach to business decision-making. The quantification of parameters in DES model has also been utilized in an investment appraisal tool to facilitate rational and objective evaluation of the proposed investment decisions.

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