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Unit-specific continuous-time formulation for the scheduling of biopharmaceutical batch and continuous processes

Miguel Vieira[a], Tânia Pinto-Varela[a*] and Ana Paula Barbosa-Póvoa[a]
[a]*CEG-IST, Instituto Superior Técnico, Universidade de Lisboa, Portugal*
[*] Corresponding author: tania.pinto.varela@tecnico.ulisboa.pt

INTRODUCTION

BACKGROUND

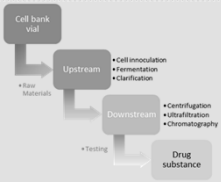
Scheduling optimization has become an essential aspect in the management of most industrial processes and the challenge to provide efficient scheduling tools has motivated the research community for the past years.[1] The case of the biopharmaceutical industry, where a set of highly effective bioengineered drugs treatments are being developed for diseases such as cancer, diabetes or growth disturbances, have identified new optimization problems in the process scheduling due their strict manufacturing specifications and expected market growth.
Regarding the modeling challenge, the general formulation approach based on a unified framework for process representation, as the case of the Resource-Task Network (RTN)[2], has proven to be effective in most classes of scheduling problems. Comparative studies have also been performed concerning time representations, with either discrete or continuous timelines, attesting the various approaches for the wide diversity of scheduling problems.

MOTIVATION

This work aims to develop a mixed integer linear programing (MILP) model applied to the scheduling of biopharmaceutical manufacturing, addressing the specific process constraints and exploring new modelling approaches suitable for the optimization problem.

PROBLEM STATEMENT

The manufacturing process of biopharmaceuticals is characterized by an upstream step, which includes all tasks associated with cell culture and maintenance, and a downstream steps, comprising the chemical/physical operations in the isolation and purification of the drug components. Each step, in particular on downstream, is normally composed by a series of processing tasks performed in either batch or continuous mode. The developed model addresses the implementation of these process constraints, considering a unit-specific continuous-time formulation:



- ***Given:*** the product recipes in terms of their respective RTN framework; the product demands; the characteristics of the processing units, processing times and the task-unit suitability; the shelf-life storage of batch intermediaries (unlimited intermediate storage and wait policies are assumed)
- ***To determine:*** the optimal task-unit assignment and sequencing, sequence dependent changeovers, campaign lots number and size and temporary storage allocation of batch lots,
- ***So as to:*** minimize makespan.

MODEL FORMULATION

The proposed MILP model is based on the optimal short-term scheduling of multistage multiproduct plants proposed by Castro et al.[3]. The formulation is extended to address the features of hybrid batch and continuous processing tasks, shelf-life storage constrains of intermediaries batch products and the traceability control of campaign lots for regulatory policies (e.g. trace proportions of different lots of products allowed to be mixed/split)[4]:

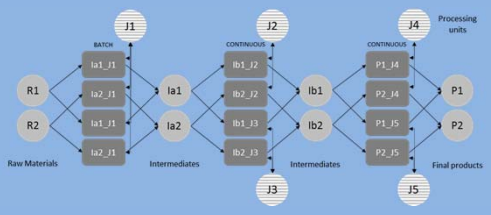
- binary variables $N_{i,i',l,m,t}$ accounts for the processing of product i of lot l in unit m at event time point t, followed by product i' which assess the required changeover task duration;
- continuous extent variables $\xi_{i,l,m,t}$ verifies the amount produced;
- timing variables $T_{m,t}$ hold the absolute time event point t in unit m, while the processing time of tasks can be given by a constant $\alpha_{i,m}$ and/or a term proportional $\beta_{i,m}$ to the amount of material being processed.

Regarding the objective function, the goal is to minimize the total production time for a certain product demand. In its general form, the constraint below ensures that all tasks end before the makespan variable MS in each processing unit:

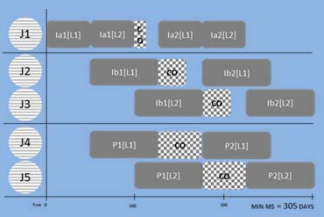
$$MS|_{t=|T|} + T_{t+1,m}|_{t\neq|T|} - T_{t,m} \geq \{tasks\ duration\} \quad \forall m \in M, t \in T$$

EXAMPLE

Based on a biopharmaceutical industrial layout, this example considers one upstream fermentation stage [J1] and two downstream stages with two purification suites [J2, J3, J4, J5] per stage, to produce a predefined demand of products P1 and P2 for a given horizon H. The upstream stage is processed in batch while the downstream stages are continuous.



RTN standard process representation



Optimal Schedule (4 event points)

CONCLUSIONS AND FUTURE WORK

The model effectively addresses the identified scheduling constrains of biopharmaceutical processes, concerning the optimal sequence of tasks, the time storage restrictions, and the track-record of the campaign lots for regulatory policies.
Further research work should address improved modelling constraints concerning material storage and comparisons with alternative time-grid formulations.

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