Scheduling Strategies for Continuous Processes

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Summary

- Discrete-event simulation framework to simulate a single-product perfusion process prone to failure events.
- Highlighted the scheduling inefficiencies when a process fails.
- Demonstrated that selecting the run time of the cell culture operation based on the expected process economics of a singular batch is inferior to decision-making that considers the expected annual demand or utilisation.

Introduction & Goal(s)

The run time of a continuous operation is determined by consideration of several factors (including cell line stability, culture productivity, product quality among others) but usually without accounting for the consequences of failure events on scheduling and capacity planning.

The goal is therefore to determine the optimal process duration(s) for a perfusion process given technical, economic and scheduling constraints as well as the scheduling strategies that cope best with process failure and stochastic demand.

The Trade-off of Perfusion Process Duration

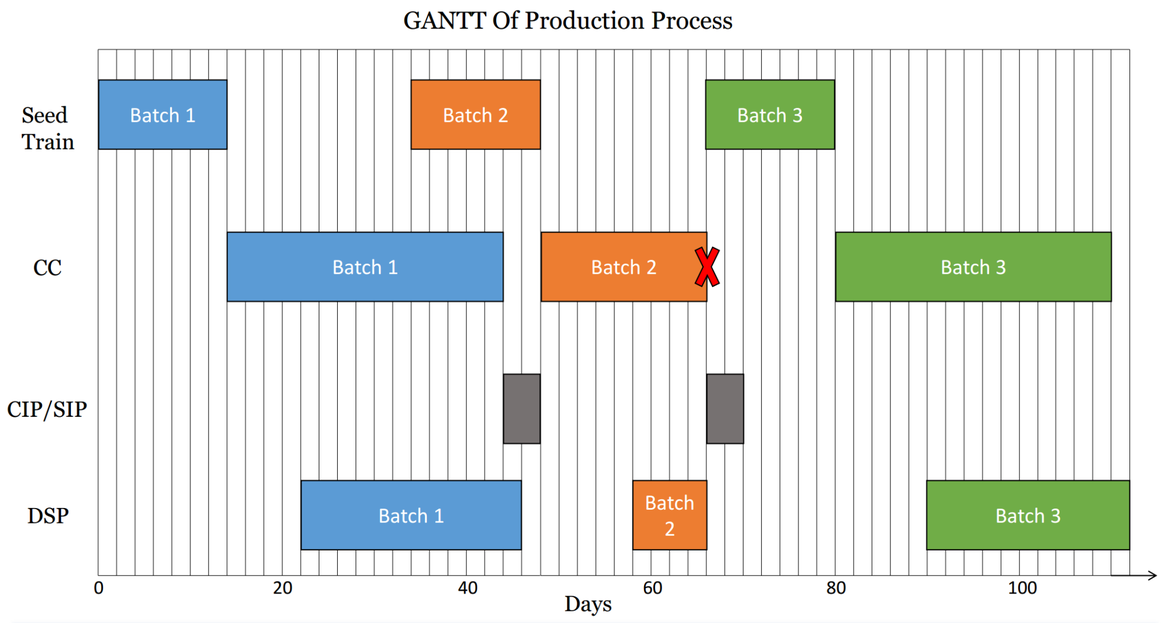

Figure: Mini GANTT of continuous process over three batches. CC = Cell Culture; CIP/SIP = Cleaning/Sterilisation-in-place; DSP = Downstream processing

- The longer the process, the greater the probability of failure, which has associated costs, clean-up, and long lead-times to restart the process.
- If the process is too short, not enough material is delivered before the process is ended and restarted.
- Batches 1 and 3 run to completion but Batch 2 fails on Day 18 of its cell culture operation.

Results

Simulation results based on a mAb process capable of c.a. 500 kg/year output (if failure is not accounted for). Process economic parameters and failure consequences are based on Pollock et al. (2013). Probability of cell culture contamination and ATF filter failure is 10% and 2% respectively within 60 days and increases exponentially with run time.

Cell culture contamination/failure rate (%)	Optimal processing duration (days)
6	98
8	89
10	86
12.5	80
15	76
20	68
25	61

Table: Optimal processing durations with respect to Cost of Goods (COGs) without capacity or demand constraints.

Capacity Utilisation	Optimal process duration (days)	
	Highest Profit	Lowest COG
6%	49	49
15%	75	75
30%	64	63
50%	64	88
61%	83	79
91%	114	114

Table: Optimal process durations with respect to COGs and profit with capacity constraints and demand targets.

Process Configuration and Multiple Bioreactors

- Assuming that all reactors share a common seed train, the trade-off between a large single reactor and multiple smaller reactors with the same failure profiles is such that with more reactors the probability of achieving a low output is minimised but at the cost of also reducing the likelihood of achieving maximum output from the process.
- In the case of multiple bioreactors, where one reactor fails:
  - **Normal seed restart** - Allow any reactors that haven't failed to run to its planned end.
  - **Immediate/early seed restart** – Start a new seed train and restart the cell culture as soon as the seed is ready.
- Process configurations that utilise only one bioreactor are able to manufacture more than the other process configurations that comprise multiple bioreactors regardless of failure response.
- Early seed restart is the superior response to failure and the difference in productivity between configurations is relatively small.

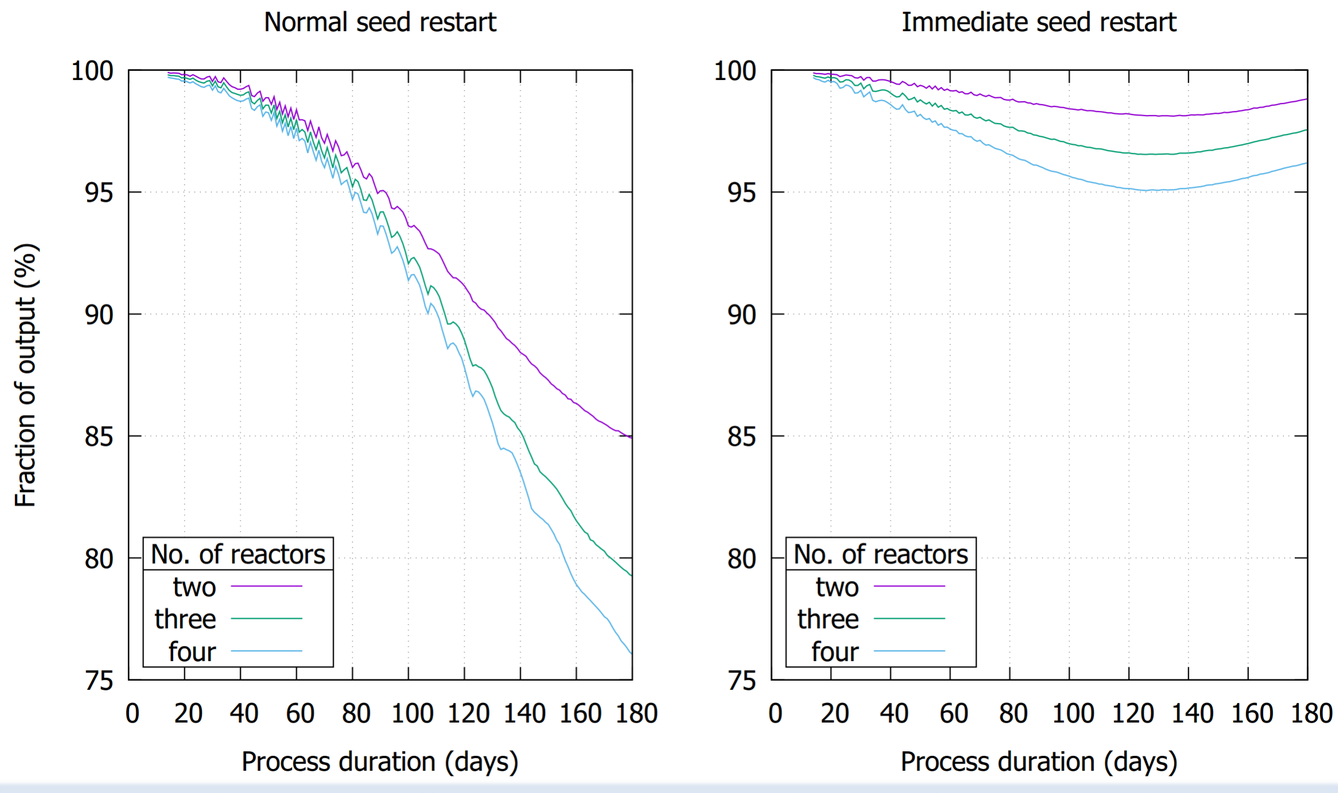

Figure: Evaluating the difference in productivity of USP configurations with the two responses to failure.

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References:
Pollock, J., Ho, S. V, & Farid, S. S. (2013). Fed-batch and perfusion culture processes: Economic, environmental, and operational feasibility under uncertainty. *Biotechnology and Bioengineering*, *110*(1), 206–219.

Future Work

- Determining optimal strategies in a capacity planning scenario involving multiple products.
  - Dynamically react to changes in state
  - Simultaneously optimise process duration(s)