Throughput Analysis of Biochemical and Pharmaceutical Batch Processes with Simulation and Scheduling Tools

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Abstract
Throughput analysis of batch processes aims at identifying opportunities for increasing annual production by identifying and eliminating size and scheduling bottlenecks. Batch size and cycle time are identified as the key parameters in throughput analysis and the relationship between them is analytically investigated in the context of a single-product batch plant. A framework for performing throughput analysis is developed and demonstrated with the use of a synthetic pharmaceutical production example.

Keywords: batch process simulation, cycle time reduction, debottlenecking

1. Introduction
Following the lead of more traditional chemical industries, biochemical and pharmaceutical processing is quickly embracing computer-aided simulation tools to improve process operation characteristics, reduce operating cost, assess environmental impact, safety, flexibility, and operability and reduce time-to-market (Petrides, et al., 1999). The most important advantage of process simulation is that it allows quick and easy screening of process alternatives and evaluation of different ‘what-if’ scenarios. A model of a batch process encapsulates all the information needed to capture the interplay between batch size and process cycle time. This relationship is instrumental in performing throughput analysis. Understanding this relationship allows the identification of opportunities for throughput increase either by exploiting the benefits of bigger batch sizes or by reducing cycle times. In this paper, we will attempt to develop a systematic way to extract from a model batch size and cycle time information and use it to evaluate the throughput potential of a batch process.

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2. Basic Throughput Concepts

In a single-product batch plant, throughput, $P$, within any period of time, $T$, (which, without loss of generality, will be assumed to be a year) is simply equal to the amount of product produced per batch (BS: batch size) multiplied by the number of batches, $N$, executed during this period:

$$P = N \times BS$$  \hspace{1cm} (1)

How many batches can fit within $T$ depends on how often a new batch is initiated, a quantity captured by the cycle time (CT). Assuming that $T \gg CT$ and all batches are identical, throughput is then equal to:

$$P = \frac{T}{CT} BS$$  \hspace{1cm} (2)

To increase throughput within given $T$, one has to devise ways to increase batch size or reduce cycle time or both. The two quantities are not, however, independent. In general, as we increase batch size, cycle time also increases because certain operations will take longer to complete. It is therefore necessary that the relationship between these two quantities be revealed in a rigorous way.

The execution time, $t_o$, for every elementary task or operation that is part of a batch recipe can be abstracted, in general, to the following simple linear expression:

$$t_o = c_o + \frac{BS}{q_o}$$  \hspace{1cm} (3)

where, $c_o$ represents the contribution of subtasks whose completion time is independent of $BS$ and $q_o$ is the rate of subtasks that scale proportionally to batch size. For example, for a ‘charge’ operation, $c_o$ represents the set-up time needed to establish the physical connection between the two vessels involved in the transfer, while $q_o$ is the flow rate at which the material is transferred. There exist operations whose completion is independent of $BS$. Reaction and vessel cleaning are examples of such operations. On the other extreme, these exist operations, such as filtering, whose completion time is strictly proportional to the amount of material processed. Most operations fall somewhere in between. The values of $c_o$ and $q_o$ can be easily calculated from historical process data or obtained from a simulation where physicochemical models are employed to represent operations in the recipe. Although in this analysis they will be assumed constant, parameters $c_o$ and $q_o$ could themselves be functions of batch size.

The execution time, $t_p$, for a unit procedure (defined as the set of operations that occur sequentially in a given piece of equipment), is simply the sum of the execution times of all contained operations and, thus, can be formulated as in Eq. 3. The only complication is that, for equipment with limited capacity, it might be necessary to execute the hosted procedure in multiple cycles, in which case, $t_p$ is given by:


where \( n_p \) is the number of procedure cycles, \( a_p \) represents the contribution of subtasks with constant duration that have to be repeated in every cycle and \( c_p \) subtasks that occur only once (such as vessel cleaning). The proportional term is independent of the number of cycles because the duration of the corresponding tasks depends only on the amount of material processed irrespectively of whether that processing is done in a single or multiple stages. In general, the number of cycles \( n_p \) is directly proportional to \( BS \) through a capacity factor, \( 1/F_p \), where \( F_p \) represents the maximum amount of material that can be processed per cycle (expressed in the same basis as the batch size.)

Implicit is the assumption that all material flows scale linearly in the process, i.e. if \( BS \) is doubled all material flows in the recipe will be doubled. Under these assumptions:

\[
\begin{align*}
    n_p &= \frac{BS}{F_p}, \quad \text{or,} \quad n_p = \text{int}\left(\frac{BS}{F_p}\right) + 1
\end{align*}
\]  

with the latter expression being true when only integer number of cycles are allowed. It should be noted that \( F_p \) is a property of the procedure/equipment pair and not of just the equipment because it represents the extent to which a procedure makes use of the capacity of the hosting equipment. For equipment with no size limitations, e.g. ‘continuous-type’ equipment that can handle any batch size at the expense of increasing process time, there is always only one cycle and the term \( n_p a_p \) is absent from Eq. 4.

The occupancy time, \( t_e \), of equipment that host a single procedure only is simply equal to that procedure’s execution time. If there are multiple procedures hosted by that equipment then \( t_e \) is the sum over all hosted procedures and all procedures that need to be executed in other equipment in the in-between time intervals, i.e.,

\[
\begin{align*}
    t_e &= c_e + \left(\frac{1}{q_e} + f_e\right)BS, \quad \text{where,} \quad c_e = \sum_j c_{p,j}, \quad \frac{1}{q_e} = \sum_j \frac{1}{q_{p,j}}, \quad f_e = \sum_j \frac{a_{p,j}}{F_{p,j}}
\end{align*}
\]  

In summing up the contribution of procedures in \( t_e \), special care should be taken to avoid double-counting procedures or operations that occur simultaneously or have overlapping execution times. It should also be noted that in this setting, \( t_e \), does not represent the actual equipment usage time but, instead, the period through which equipment is exclusively reserved for a given batch. Implicit is the assumption that, in order to avoid cross-contamination of batches, any equipment cannot be used for a subsequent batch before all operations associated with the present batch and assigned to that equipment have been carried out. This restriction puts a toll on cycle time, but it is both realistic and necessary in order to ensure normal operation and minimize waste of product.
3. Cycle Time Analysis

Based on the above framework, the cycle time of a process cannot be less than the maximum occupancy time over all equipment, \( k \), involved in the recipe, i.e.,

\[
CT = \max_k (t_{e,k}) \tag{7}
\]

The equipment with the maximum occupancy is called the time or scheduling bottleneck because this is the one defining how often a new batch can start. Although as Eq. 6 suggests, \( CT \) increases as \( BS \) increases, most of the times, it is advantageous to increase \( BS \). Mathematically, that can be verified by taking the first derivative of Eq. 2 with respect to \( BS \) to find out that it is always positive (when the number of cycles is allowed to take non-integer values), so \( P \) is an increasing function of \( BS \). Intuitively, one can reach the same conclusion by realizing that there are constant terms in the cycle time expression that cause the cycle time to increase in a less than proportional way to \( BS \). Those terms represent contributions from operations with constant execution times.

Even when benefits are to be expected by an increase in \( BS \), there are always limitations on the batch size introduced by size or throughput bottlenecks such as equipment with limited storing capacity. One way to remove size bottlenecks is to process the material in multiple cycles assuming that in-process inventory is available and the material is stable to be stored. Theoretically speaking, one can continue increasing \( BS \) indefinitely by continuously adding procedure cycles to remove size bottlenecks. Even in this theoretical setting, however, there is a limit in the production that can be achieved:

\[
P_u = \max_k \left( \frac{T}{\frac{1}{d_{e,k}} + f_{e,k}} \right) \tag{8}
\]

Intuitively, Eq. 8 suggests that the plant can do no better than the ‘slowest’ equipment working at full capacity all the time.

Increasing \( BS \) is not always a desirable option because it results in larger inventories, longer material queues and increased cycle times throughout the supply chain. In these cases, increasing throughput can result from the introduction of new equipment to remove time bottlenecks and reduce cycle times. A typical example is the staggering of multiple fermentors in biochemical processes to improve the use of downstream purification equipment. Opportunities for cycle time reduction also exist, whenever possible, through targeted recipe modifications such as the combination or elimination of steps or reassignment of operations from bottleneck to secondary equipment. In Minnich (2000), for example, it is described how cycle time was reduced by removing a heating operation from a vessel to an external heat exchanger. A methodological analysis of the process can reveal such opportunities on a case-by-case basis.
4. Example

The objective of this example is to illustrate how the above concepts can be used to improve throughput in a process that produces a synthetic pharmaceutical intermediate. SuperPro Designer™ (from Intelligen, Inc.) is the simulator used to model the process and retrieve all the throughput-related information. Interested readers can obtain a demo copy of the software and information on this example from www.intelligen.com.

The formation of the intermediate involves 12 steps, 6 of which are vessel procedures, 5 Nutsche filtration procedures and one drying procedure. This process, developed at the pilot-plant with a BS of 55.7 kg, is to be scaled-up to full-scale production of 30000 kg/year. The objective of this exercise is to investigate the throughput potential in a plant initially equipped with two 3.78 m³ reactors (R-101 and R-102), one 4 m² Nutsche filter (NFD-101), and one 10 m² tray dryer (TDR-101).

Figure 1 shows how annual production varies with BS based on the above theoretical analysis. The positive slope is interrupted by discontinuous drops that represent instances where we have to resort to multiple cycles to overcome a size bottleneck (it is assumed that \( n_p \) takes only integer values). For given BS, the introduction of new cycles makes CT longer and results momentarily in a production decline. On the other hand, however, it allows a further increase in BS which, in turn, results in higher production.

The annual throughput at the pilot-plant level of BS is 10874 kg. It is safe to increase BS up to 171.48 kg until the first size bottleneck is reached; this corresponds to an annual production of 23541 kg. The bottleneck in this case is one of the reactors (R-102). To be able to increase BS we need to increase the number of cycles for the offending procedure (P-11) and process the material in two halves. To achieve an even higher throughput, one would have to go through consecutive increases in the number of cycles and that would render processing of large batches practically infeasible.

Figure 1. Annual throughput as a function of batch size.
Further throughput increases will have to result from a decrease in $CT$. As shown in Fig. 2, the equipment that determines $CT$ is R-101. A third reactor (R-103) needs to be introduced and take over some of the tasks that R-101 and R-102 currently host. However, the cycle times NFD-101 is quite close to that of R-101 and R-102 so even if we remove the current time bottlenecks, NFD-101 will trim the prospects for reducing $CT$ by very quickly becoming the next bottleneck. By introducing a new filter and sizing R-103 to be big enough to host the most demanding step (P-11), we can reduce $CT$ without resorting to multiple cycles and increase $P$ to 35185kg well above the target.

5. Conclusions

In the effort to increase plant throughput, the relationship between cycle time and batch size has to be revealed. Increasing batch size is in general beneficial because it reduces the impact of tasks that have fixed process times. Reducing cycle times can be accomplished by reassigning tasks from the time bottleneck to other equipment or by introducing new equipment. Knowing the relationship between batch time and batch size allows for easier and more efficient detection of the best option in every situation. Throughput and cycle time analysis can be formulated as model-based tasks and benefit from the use of process simulation. A process model can be used to judiciously extract the information needed for the analysis and provide the framework where alternative scenarios can be investigated and evaluated. Even more importantly, a simulation-based approach allows all aspects of the process, from engineering to economics and scheduling, to be tackled in an integrated way so that the impact of throughput-related decisions can be evaluated in a thorough and comprehensive way.

References

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