Production of Biobased Itaconic Acid

Modeling and Evaluation with

SuperPro Designer®

by

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This is the ReadMe file of a SuperPro Designer example that deals with process modeling, cost analysis and optimization of Itaconic Acid production via fermentation. The flowsheet of the process is appended to the bottom of this document. You may test-drive the model by downloading the functional evaluation edition of SuperPro Designer from the downloads page of our website (**www.intelligen.com**). The files of this example can be found in the **Examples \ Bio-Materials \ ItaconicAcid** folder. The default installation path of the SuperPro Designer Examples folder follows below.

C:\ Users \ Public \ Public Documents \ Intelligen \ SuperPro Designer \ v11 \ Process Library \ Examples

If you have any questions about this example and SuperPro Designer in general, please send an email message to dpetrides@intelligen.com

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Introduction

Itaconic acid (IA) was discovered in 1837 as a thermal decomposition product of citric acid. It was only in 1932, however, that IA was found to be synthesized by certain microorganisms. The first microorganism known to produce IA was a filamentous fungus, aptly named *Aspergillus itaconicus*. In 1939, another species of *Aspergillus*, *A. terreus*, was shown to produce even higher levels of IA; this species remains the best producer of IA to date. Nowadays, approximately 40,000 MT of IA are produced per year, and all of it is obtained by microbial culture [1].
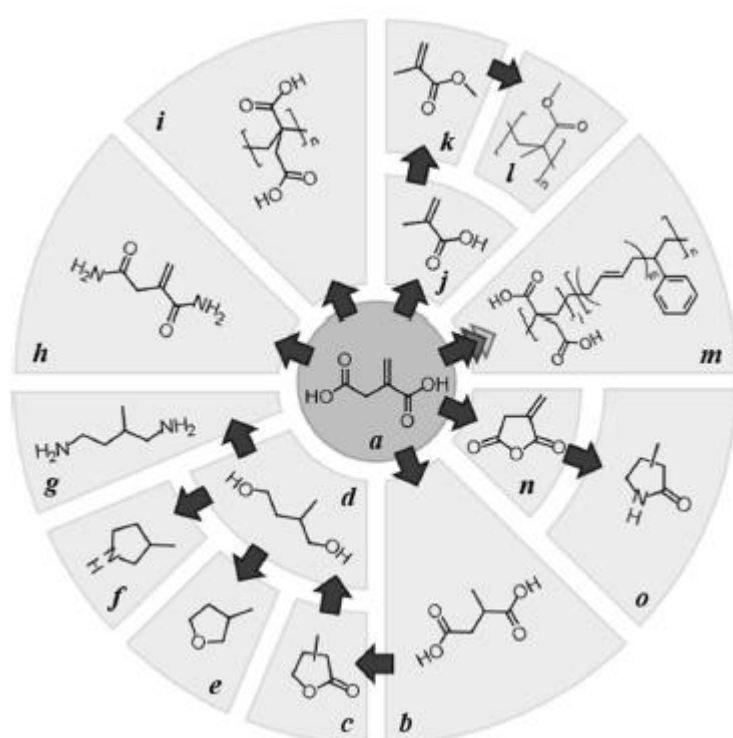

Figure 1: Molecular structure of itaconic acid and routes to itaconic acid-based products. **(a)** itaconic acid; **(b)** methyl succinic acid; **(c)** 3 and 4-methyl-γ-butyrolactone; **(d)** 2-methyl-1,4-butanediol; **(e)** 3-methyltetrahydrofuran; **(f)** 3-methylpyrrolidine; **(g)** 2-methylbutane-1,4-diamine; **(h)** itaconic diamide; **(i)** poly-itaconic acid; **(j)** methacrylic acid; **(k)** methyl methacrylate; **(l)** polymethyl methacrylate; **(m)** styrene-butadiene-itaconic acid; **(n)** itaconic anhydride; and **(o)** 3 and 4-methyl-2-pyrrolidone. Source: [2].

In terms of molecular structure, IA is a mono-unsaturated dicarboxylic acid (cf. Error! Reference source not found.**a**, at the center). The presence of three functional groups (one double bond and two carboxyl groups) allows various types of reactions; as such, IA can be used to produce a large number of

derivatives, e.g. itaconic acid anhydride, methyl succinic acid, 3-methyltetrahydrofuran, 3-methylpyrrolidine, methacrylic acid and methyl methacrylate (cf. **Figure 1**). Moreover, itaconic acid and some of these derivatives may be used as monomers or co-monomers for the production of numerous polymers, such as poly-IA, styrene-butadiene-IA latex, polyacrylonitrile, poly methyl methacrylate, unsaturated polyester resins, and polyamides [1–3]. These diverse compounds, in turn, can be employed in a wide range of applications, from paints and detergents through hygiene and medical products to the construction [1] and agriculture [3] sectors. Currently, IA is mostly used in the production of synthetic fibers, ion-exchange resins, paper making and water treatment [3]. In addition, a large market potential for IA exists in the production of plastics, as a substitute for acrylic acid and methyl acrylic acid [3,4]. However, a substantial price reduction from the current 1.8-2 US$/kg would have to be achieved for such applications. If the price of IA dropped to 1.5 $/kg, for instance, the market for IA could reach over 400,000 MT/year [1,4]. Due to its extraordinary potential, IA was included among the 12 most promising biobased chemical building blocks in the list put together by the U. S. Department of Energy in 2004 [4,5].

With respect to its physicochemical properties, IA is a white crystalline solid at room temperature, with a melting point near 165 °C (cf. **Table 1**). IA is soluble in water up to 83 g/L at 20 °C, and it is even more soluble in ethanol and methanol at ambient temperature, as shown in **Figure 2**. The presence of two carboxylic acid groups confers IA two ionizable protons and therefore two pK_a values: 3.84 and 5.55. Consequently, IA fermentation tends to acidify the medium. It is worth noting that, for proper crystallization, IA must be in the fully protonated form (i.e. under low pH).

Table 1: Physicochemical properties of itaconic acid.

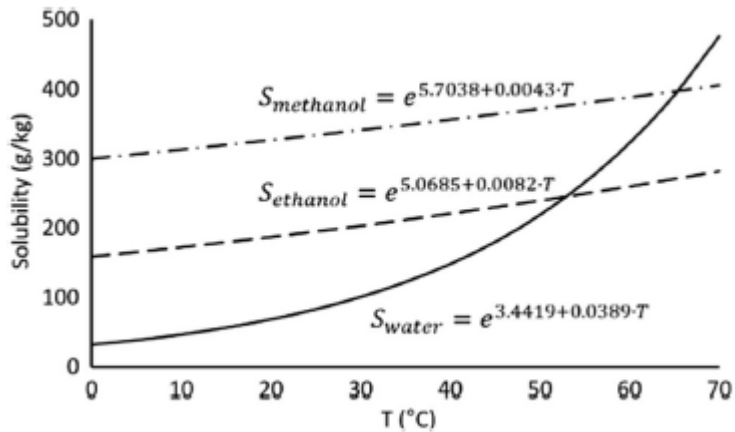|	
Chemical Formula	$C_5H_6O_4$
Molar Mass	130.1 g/mol [1]
Appearance	white and crystalline [1]
Density	1.63 g/cm^3 [1]
Melting Point	163-169 °C (decomposes) [6]
pK_a	3.84 and 5.55 [1]
Solubility in H_2O (at 20 °C)	83 g/L [1]

Figure 2: Solubility of itaconic acid (*S*) *versus* temperature (*T*) for water, methanol and ethanol; the curves are valid between 10 °C and 60 °C. Source: [2]**.**

Microorganisms

As mentioned earlier, certain species of *Aspergillus*, and particularly *A. terreus*, are able to produce IA. Other fungi, such as those from genera *Ustilago*, *Pseudozyma*, *Candida*, *Rhodotorula* and *Helicobasidium* are also capable of natively synthesizing IA. In addition, IA has been successfully produced through recombinant technology in more traditional biotechnology workhorses, such as *A. niger*, *Escherichia coli* and *Corynebacterium glutamicum* [1]. Nevertheless, *A. terreus* remains by far the best IA producer in terms of acid titer and volumetric productivity, achieving up to 160 g/L of IA, and a volumetric productivity close to 1 g/L/h, as shown in **Table 2**. For that reason, *A. terreus* is currently the main microorganism employed in industrial production of IA [3].

Table 2: Titer, yield and productivity of itaconic acid production in the literature. Source: [1].

Table 2 Itaconic acid production of wild-type strains and strains generated by random mutagenesis

Microorganism	Substrate	Itaconic acid [g/L]	Yield [g/g][b]	Productivity [g/L/h]	Reference
Aspergillus terreus DSM 23081	Glucose	129	0.58	1.15	(Hevekerl et al. 2014b)
Aspergillus terreus NRRL 1960	Glucose	130	–	–	(Karaffa et al. 2015)
Aspergillus terreus DSM 23081	Glucose	160	0.46	1	(Krull et al. 2017b)
A. terreus SKR10 N45[a]	Hydrolyzed corn starch	50	0.42	0.35	(Reddy and Singh 2002)
Aspergillus terreus R104[a]	Glucose	52.7	0.72	0.55	(Shin et al. 2013)
Aspergillus terreus IFO-6365 TN-484[a]	Glucose	82.3	0.54	0.57	(Yahiro et al. 1995)
Candidia sp.strain B-1[a]	Glucose	35	–	0.29	(Tabuchi et al. 1981)
Helicobasidium sp.	–	–	–	–	(Sayama et al. 1994)
Pseudozyma antarctica NRRL Y-7808	Glucose	30	0.38	–	(Levinson et al. 2006)
Pseudozyma tsukubaensis H488	Glucose	74.7	0.49	0.36	(Specht et al. 2014)
Ustilago cynodontis K470	Glucose	28.4	–	–	(Guevara and Tabuchi 1990)
Ustilago maydis DSM 17144	Glucose	44.5	0.24	0.31	(Maassen et al. 2014)
Ustilago rabenhorstina IFO 8995	Glucose	15.7	–	–	(Guevara and Tabuchi 1990)

[a] Strains generated by random mutagenesis
[b] Itaconate per consumed glucose

Biosynthesis of Itaconic Acid and Culture Conditions

The metabolic pathway for production of IA has been investigated in *A. terreus* and *Ustilago maydis*. In both cases, IA is produced from *cis*-aconitic acid, an intermediate from the citric acid cycle. In *A. terreus*, IA is synthesized from *cis*-aconitic acid in a single step by enzyme *cis*-aconitic acid decarboxylase (CAD), as shown in **Figure 3**. In *U. maydis*, however, *cis*-aconitic acid is first isomerized to *trans*-aconitic acid, and only then converted into IA. In any case, the fact that IA originates from an intermediate of the citric acid cycle means that a variety of carbohydrate sources can be used to produce IA, including glucose, sucrose, corn starch, xylose, glycerol and agricultural residues [1,3–5]. Although the maximum theoretical yield of IA on xylose is higher than that on glucose (87% vs 72%, respectively), in practice the best results have been obtained using glucose as the main substrate [7]. Adequate levels of oxygen are also crucial for the production of IA, so much so that interrupting aeration for just a few minutes can fully stop the production of IA for a whole day of cultivation [1,3]. When cultivating *A. terreus* in stirred tank fermentors, however, there is a tradeoff between aeration and preservation of fungal morphology, given that filamentous fungi develop structures that are susceptible to shear stress. For that reason, air lift fermentors have also been employed for IA production [3–5].
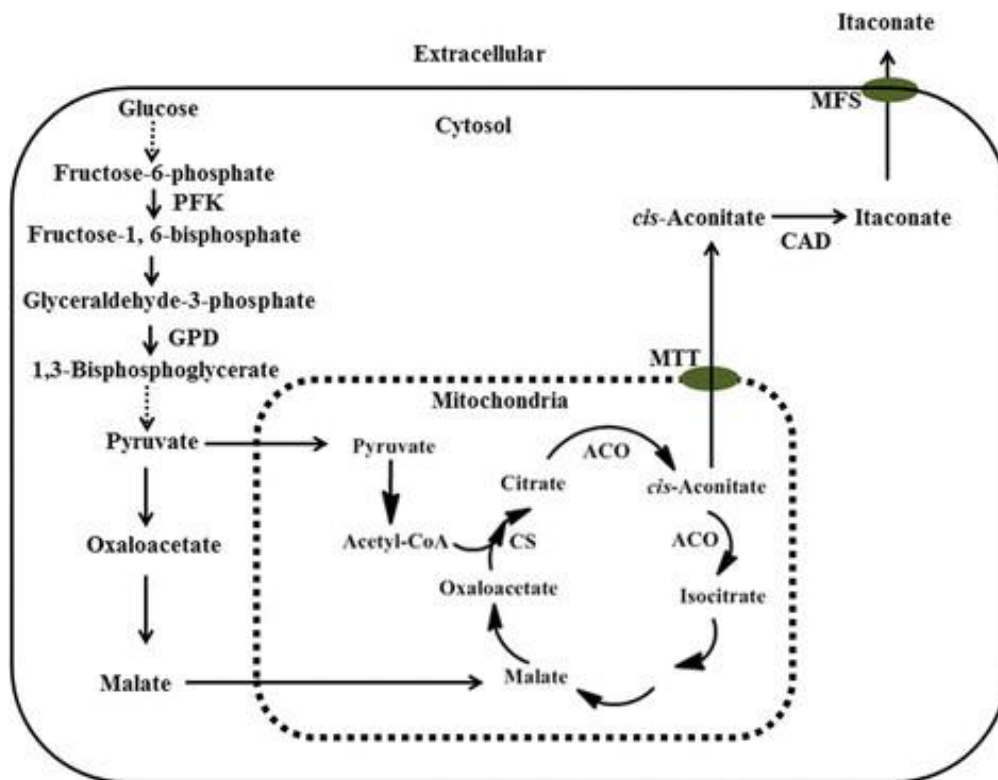
Figure 3: Metabolic pathway leading to itaconic acid production in *Aspergillus terreus*, under the form of itaconate. Source: [3].

The concentrations of glucose and manganese ions also significantly affect IA production by *A. terreus*, mirroring their effect on the production of citric acid by *A. niger*. In fact, it has been verified that maximum IA yields are obtained when the concentration of glucose is in the range of 12-20% w/v and that of manganese is lower than 3 ppm [8].

It is worth noting that the best IA production results have been achieved in batch cultivations. These are typically composed of two phases: in the first phase, the spores germinate, and the fungal cells grow consuming ammonium ions present in the medium, thereby acidifying it. Once a certain pH threshold is surpassed, the fungus enters the stationary phase and starts producing IA, which characterizes the second phase [1].

The literature shows a variety of approaches for pH management during *A. terreus* culture for IA production. The initial medium pH ranges from 2.0 to 5.9, although pH values below 3.0 slow the germination of spores and therefore retard the growth phase. After germination, cell mass grows and the pH is allowed to drop. Eventually the production phase begins; in this phase, the pH may be either controlled at a fixed value, subjected to a single pH upward shift or left free to vary. The first two strategies have led to the best IA titer results [1].

Recovery and Purification

The current industrial process of recovery and purification of IA is similar to that of citric acid and other carboxylic acids obtained by fermentation. As such, after fermentation the broth is first clarified and then subjected to evaporation, cooling, crystallization, liquid-solid separation (filtration or centrifugation), decolorization and drying operations [5,9]. Crystallization is typically employed multiple times, e.g. to recover the product at an earlier process stage and to polish the purification process at a later stage [2,9]. This kind of downstream process, however, requires a large amount of energy as well as costly equipment [2,4]. For those reasons, alternative downstream strategies have been evaluated in the literature. Promising approaches include reactive extraction, adsorption and electrodialysis [2,9].

Reactive extraction is a combination of liquid-liquid extraction with a reaction or complexation step. Typically, an aqueous solution containing IA is mixed with an organic solvent containing an organophosphate or aliphatic amine, which complexes with the acid and thus greatly improves its partition to the organic phase. Adsorption exploits the differential affinity of a solid phase (the adsorbent) for the product and its impurities. In the case of IA, anion-exchange resins may be used to adsorb the acid, while impurities flow through. Subsequently, the product can be eluted with an acidic solution that will compete with IA for the adsorption sites. Electrodialysis is a process that utilizes an electric field and special membranes to separate electrolytes. In conventional electrodialysis (CED), a number of membranes that only allow the passage of cations and an equal number of membranes that only allow the passage of anions, named cation-exchange membranes (CM) and anion-exchange membranes (AM), respectively, are arranged in an alternate fashion inside the product solution, forming a stack. In addition, two electrodes (a cathode and an anode) are introduced into the system, in order to generate an electrostatic potential over the membrane stack. As a consequence, ion-rich and ion-depleted streams will develop, as shown in **Figure 4a.** Thus, this process can be used to concentrate carboxylic acids such as IA (under the carboxylate form, which is electrically charged). Another kind of electrodialysis, called Bipolar Membrane Electrodialysis (BPMED), may be used to convert a carboxylate (such as itaconate) into its corresponding carboxylic acid. As its name implies, BPMED utilizes bipolar membranes (BPMs), which are bilayer membranes consisting of one CM and one AM juxtaposed. To produce the desired effect, BPMs are used together with monolayer membranes (AMs and/or CMs), laid out in an alternate fashion, as shown **Figure 4b** [2,10].
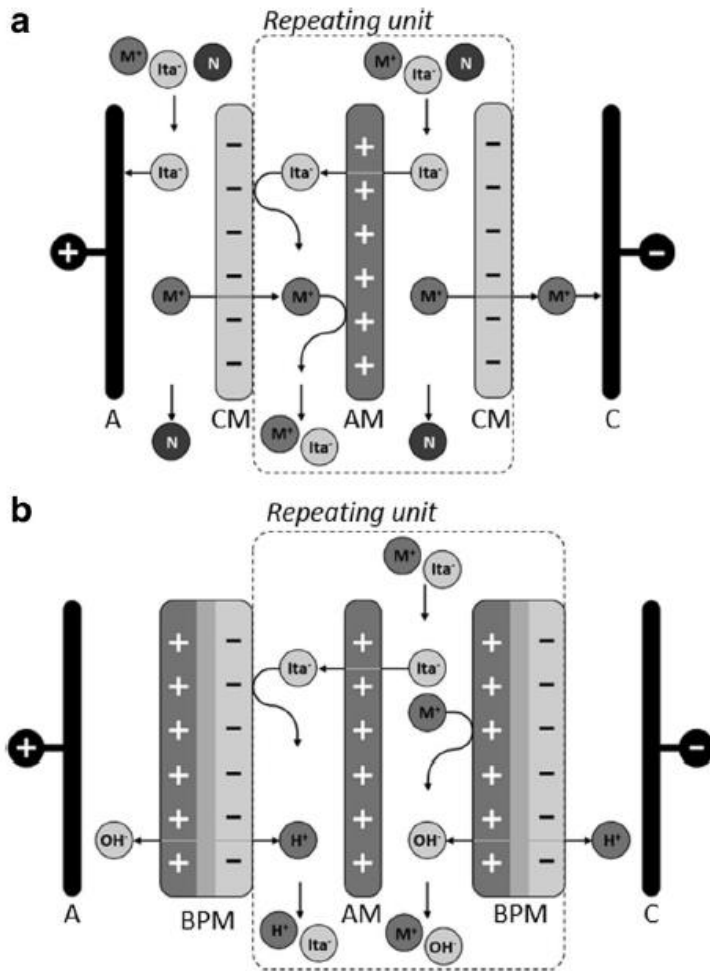
Figure 4: Schematic representation of electrodialysis applied to the production of itaconic acid. **(a)** Conventional Electrodialysis; **(b)** Bipolar Membrane Electrodialysis. Label: **M⁺** stands for any cation (such as Na⁺); **Ita⁻** stands for itaconate; **N** stands for any neutral species; **A** stands for anode; **C** stands for cathode; **AM** stands for anion-exchange membrane; **CM** stands for cation-exchange membrane; and **BPM** stands for bipolar membrane. Source: [2]**.**

Process Description

The model of this example is based on the conventional process technology to produce IA through microbial culture, described in the literature [1–5,9,10]. The flowsheet of the process is appended to the bottom of this document. Briefly, filamentous fungus *Aspergillus terreus* is cultivated in submerged culture, in batch mode, using glucose as the main carbon source to produce IA. After the end of microbial culture, the broth is first clarified by centrifugation; then subjected to evaporation, crystallization and filtration twice; decolorized with activated carbon; recrystallized and filtered once again; and finally dried to generate 99%-pure IA crystals. Considering that IA demand may reach over 400,000 MT/year in the future [1], in this example the production target was set to 40,000 MT of IA/year, which translates to approximately 5.3 MT/h. As it will be shown later, each production batch generates approximately 126 MT of IA in crystal form.

For reporting and analysis purposes, the IA production process has been divided into three sections:

- **Fermentation**
- **Recovery**
- **Purification**

Flowsheet sections in SuperPro are simply sets of related unit procedures (processing steps). In this example, the unit procedure icons of each section are displayed in a unique color (blue for fermentation, purple for recovery and green for purification). For more information on how to specify flowsheet sections and edit their properties, please consult Chapter 8.1 of the SuperPro manual. The contents of each of this example's flowsheet sections are described in greater detail below.

Fermentation Section

The fermentation section comprises the media preparation and microbial culture steps. Microbial culture occurs in two seed fermentation procedures (P-17/SFR-101 and P-19/SFR-102) and one production fermentation procedure (P-21/FR-101). The culture medium comprises 3 major components: glucose (the carbon source), ammonia (the nitrogen source), and "salts", which represent a mixture of minerals necessary for microbial growth and buffering. Each major component is mixed with water in a blending tank (P-1/BT-101 for glucose, P-5/BT-102 for salts and P-12/BT-103 for ammonia) to obtain appropriate stock solutions: glucose 50% w/w; salts 16% w/w; and ammonia 30% w/w. After charging the components and water into the appropriate tanks, the liquid is thoroughly agitated for 15 mins. In addition, the solutions of glucose and salts subsequently pass through a heat sterilizer (P-2/ST-101 and P-6/ST-102, respectively). Each solution is then divided into three separate streams using a 3-way flow splitter (P-3/FSP-101 for glucose; P-7/FSP-103 for salts; and P-13/FSP-104 for ammonia). Each stream feeds a fermentation unit procedure (either a seed fermentation or a production fermentation step). To dilute the medium to appropriate concentrations, additional water is also sterilized through heat

sterilization (P-10/ST-103) and distributed to the fermentors using a flow-distribution procedure (P-11/FDIS-101). Most of this water (14.6 MT/h) is recycled from downstream procedures, while the remaining fraction (0.8 MT/h) is fresh; both sources are combined through a flow-adjusting procedure (P-9/FAD-101), which is further explained at the end of this document.

Given that *Aspergillus* fungi are obligate aerobes, during fermentation ambient air is sterilized through an air filter (P-14/AF-101), compressed to increase its pressure by 2 bar using a centrifugal compressor (P-15/G-101); and finally distributed to the fermentation procedures using a flow-distribution procedure (P-16/FDIS-102).

After the addition of all the medium components (glucose, salts, ammonia and water) to the first seed fermentor (SFR-101), the filamentous fungi grow for 54 h at 35 °C. The microbial growth is described by the following fermentation reaction:

12 Ammonia + 180 Glucose + 76 Oxygen + 2 Salts → 85 Biomass + 112 Carb. Dioxide + 73 Water
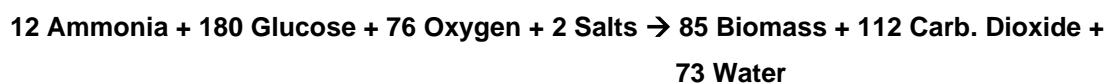
where the coefficients are mass-based. Note that it is assumed that no organic acid is produced in this step.

The whole broth produced in seed fermentor SFR-101 is then transferred to the second seed fermentor, SFR-102, which is 10✕ larger. All the operations in SFR-102 are the same as those in SFR-101, except that microbial growth starts after inoculation by the broth from SFR-101.

Finally, the inoculum produced in SFR-102 is transferred to the production fermentors (FR-101; at the present scale, two fermentors of 466 m^3 running in parallel are required), which operate in fed-batch mode, so that glucose is continuously introduced into the fermentors. This prevents cell growth inhibition and makes it possible to achieve higher product titers. The fermentation process in the production fermentor is also carried out at 35 °C, but it takes a whole week (168 h) to accomplish. It is described by the following reaction:

1.5 Ammonia + 180 Glucose + 50 Oxygen + 1 Salts → 13 Biomass + 40 Carb. Dioxide + 126 Itaconic Acid + 4 Organic Acids + 49.5 Water
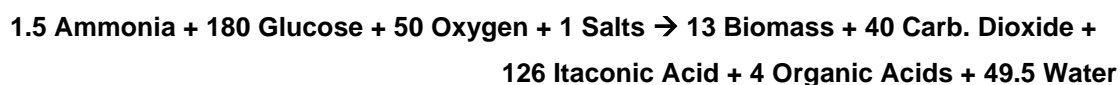
where the coefficients are also mass-based. The component "Organic Acids" encompasses by-products such as malic acid and fumaric acid.

In contrast with the medium components, the amount of air fed to the fermentors was determined by the fermentation procedures, by setting an aeration rate of 0.5 VVM (volume of gas per volume of liquid per minute) to each FERMENT operation. Besides, the aeration-related procedures (Air Filtration AF-101, Gas Compression G-101 and Flow Distribution FDIS-102) were all set to continuous mode, by right-clicking on the unit procedure, selecting **Procedure Data** and then switching the operating mode to **Continuous**. For more details on how to use Flow Distribution procedures or Continuous procedures in batch flowsheets, please consult the PDO example or the Help tool.

The production fermentors deliver 793 MT of broth per batch. The broth contains around 176 g/L of IA and 20 g/L of biomass (dry cell weight).

Recovery Section

The broth produced by the main fermentors is first transferred to a holding tank (P-23/HT-201) that acts as a buffer element between the Fermentation Section, which operates in batch/fed-batch mode, and the Recovery and Purification sections, which operate almost entirely in continuous mode. From tank HT-201, the broth is pumped at a rate of 33 MT/h to a disk-stack centrifuge (P-24/DS-201) for clarification (biomass removal). 99% of the biomass is removed through continuous centrifugation, with a particulate concentration of 500 g/L in the centrifuge sludge. Although most IA ends up in the supernatant (5.1 MT of IA/h), the centrifuge sludge contains a significant amount of IA as well (0.4 MT of IA/h). As such, the sludge is subsequently diluted with water using a custom mixer (P-25/MX-201; for more information on how to use Custom Mixing procedures, please consult the PDO example or the Help tool) and then re-centrifuged in a second disk-stack centrifuge (P-26/DS-202), under the same conditions as the first centrifugation.

Next, the supernatants from both centrifuges are combined using a flow mixer (P-27/MX-202) and sent to a triple-stage evaporator (P-28/EV-201), where the solution is concentrated from 152 g/L to 350 g/L of IA. The concentrated solution is then sent to a continuous crystallizer (P-29/CR-201). Crystals are formed by cooling the solution to 15 ˚C, and the crystallization yield is assumed to be 80%. A new component, named IA Crystal, was created to represent the crystalline form of IA. In addition, the condensed steam generated by the evaporation step is recycled to the Fermentation Section; more specifically, the condensate is sent to holding tank P-8/HT-101.

The slurry produced by the crystallizer CR-201 is then filtered using a Rotary Vacuum Filtration procedure (P-30/RVF-201), which retains 99% of the IA crystals in the filtration cake. Nevertheless, the filtrate of RVF-201 contains a considerable amount of uncrystallized IA; therefore, the filtrate goes through a second round of evaporation (P-31/EV-202), crystallization (P-32/CR-202) and filtration (P-33/RVF-202). The second evaporation and filtration steps are carried out under the same conditions as the first evaporation and filtration steps, respectively. The second crystallization procedure, however, generates IA crystals with a higher yield (99%).
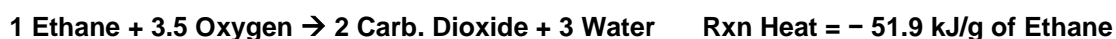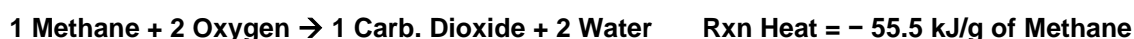
Purification Section

The filter cakes from both rotary vacuum filters (RVF-201 and RVF-202) are then combined using a flow mixing procedure (P-34/MX-301). The condensed steam produced by the second evaporation procedure (EV-202), which has a temperature of 79 °C, is also mixed with the filter cakes in this flow mixer. Next, the material is mixed with fresh water so as to produce a suspension with 350 g/L of crystals, using a custom mixer (P-35/MX-302). The suspension is then heated to 80 °C in a stirred tank

(P-36/R-301), in order to re-dissolve the IA crystals. The dissolution process in the tank is represented by the simple stochiometric reaction below.

1 IA Crystal → 1 Itaconic Acid
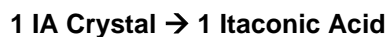
The IA solution resulting from R-301 is then sent to a granular activated carbon column (P-37/GAC-301) to remove residual organic acids and other impurities that alter the color of the product. After that, the decolorized solution is transferred to a crystallization step (P-38/CR-301) in which IA is recrystallized at 15 °C. Subsequently, the IA crystals are recovered using another rotary vacuum filter (P-39/RVF-301) and, finally, the crystals are sent to a rotary dryer (P-42/RDR-301) which removes the residual moisture with hot air. In the drying procedure, a final loss on drying (LOD) of 1% was specified, so that the final product contains approximately 99% of IA crystals and 1% of moisture. Note that the hot drying air is generated by burning natural gas; the fuel is first mixed with ambient air using a custom mixer (P-40/MX-303) and then passes through a burner, represented by a continuous generic box (P-41/GBX-301) where the combustion of the hydrocarbons occurs. Natural gas was considered as a mixture of methane (75%), ethane (8%), carbon dioxide (12%) and nitrogen (5%); and the combustion process was described by the following stoichiometric equations:

1 Methane + 2 Oxygen → 1 Carb. Dioxide + 2 Water   Rxn Heat = − 55.5 kJ/g of Methane

1 Ethane + 3.5 Oxygen → 2 Carb. Dioxide + 3 Water   Rxn Heat = − 51.9 kJ/g of Ethane

All the procedures in the Recovery and Purification sections operate in continuous mode, except for the activated carbon column (GAC-301), which operates in a cyclical fashion (more precisely, with 8 cycles per batch). To set a procedure to operate in multiple cycles per batch, the user must right-click on the unit procedure icon, select **Procedure Data**, keep the operating mode as **Batch / Semi-Continuous** and finally specify the **Number of Cycles per Batch** as desired. For more information on that subject, please consult the PDO example or the Help tool.

Process Scheduling and Cycle Time Reduction

Key process scheduling data can be found in the Recipe Scheduling Information dialog (cf. **Figure 5**); to access it, select the **Tasks** menu and click on **Recipe Scheduling Information…** This dialog shows that the overall Batch Time (a.k.a. Recipe Time) for this process is 314.75 h (about 13 days). This is the time elapsed from the beginning of a given batch (i.e., the preparation of fermentation media) to the end of that batch (generation of the pure product). It also indicates that the longest unit procedure is the Main Fermentation P-21, which takes 177.5 h (this number can be found by right-clicking on P-21 and selecting Procedure Data). However, the overall Process Cycle Time (a.k.a. Recipe Cycle Time), which is the time between consecutive batches, is only 24 h. This is accomplished by having multiple fermentors operating in staggered mode (alternating from batch to batch). More specifically, the process utilizes a total of 16 production fermentors operating in staggered mode as eight sets of two. A batch of two production fermentors is initiated every 24 hours. The inoculum preparation steps utilize multiple vessels in staggered mode as well. For information on how to reduce the overall cycle time of a process by utilizing equipment operating in Stagger Mode, please consult the ReadMe files of the PDO and Farnesene examples in the Examples \ Bio-Materials folder.

Figure 5: Recipe Scheduling Information dialog

The staggered fermentors can be visualized through the **Equipment Occupancy Chart** (EOC), which can be generated by selecting **Charts➲ Equipment Occupancy➲ Multiple Batches**. A picture of the EOC, showing 24 consecutive batches of this process, is displayed in **Figure 6**. Each batch has its own color. Each single-colored bar in the EOC represents the execution of a procedure over time in a certain piece of equipment, for a given batch. The 16 production fermentors operating in staggered mode (in sets of two fermentors) are represented by the following lines on the Y-axis of the chart: FR-101, FR-101b, …. FR-101h. Each of those lines represents two fermentors of equal size operating in parallel. The procedures of the Recovery and Purification sections operate in continuous mode, which is specified by right-clicking on a procedure icon, selecting Procedure Data and then clicking on the **Continuous** radio button on the lower part of that window. As explained on that window, when a procedure operates in continuous mode in a batch flowsheet, the duration of its single operation is set equal to the Process (Recipe) Cycle Time, which is 24 hours for this process. That is why there is no

idle time (white space) between consecutive batches for the equipment of the Recovery and Purification sections.
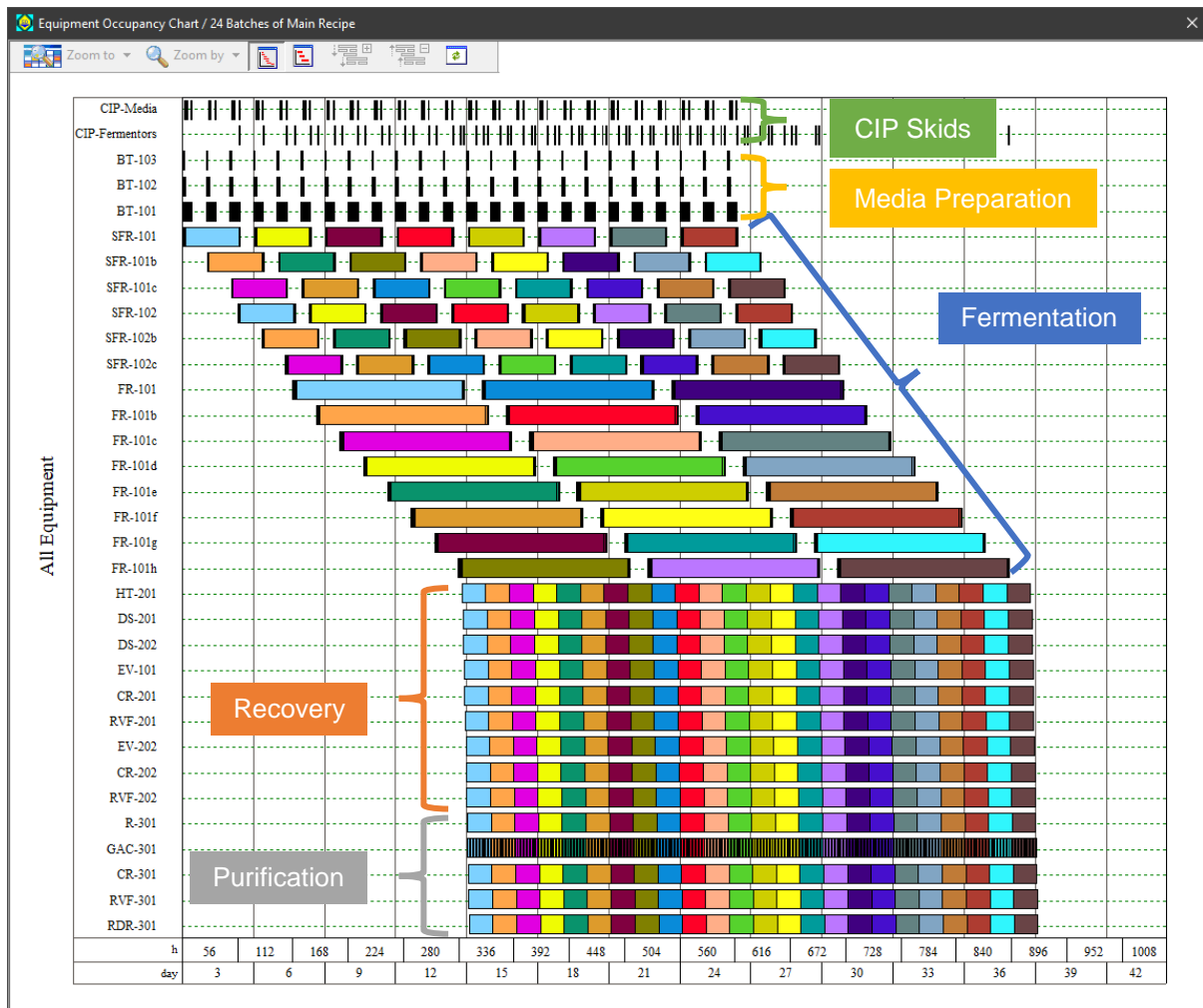

Figure 6: Equipment Occupancy Chart for 24 batches

The scheduling of a batch process can be visualized in greater detail with the **Operations Gantt chart** which is generated by selecting **Charts➲ Gantt Charts➲ Operations GC.** Figure 7 displays a portion of that chart for a single batch of this process. The style of the chart is similar to the style of MS Project. The dark blue bars represent procedures and the cyan bars represent the operations of the corresponding procedures. The table on the left displays the duration, start time and end time of the various activities.

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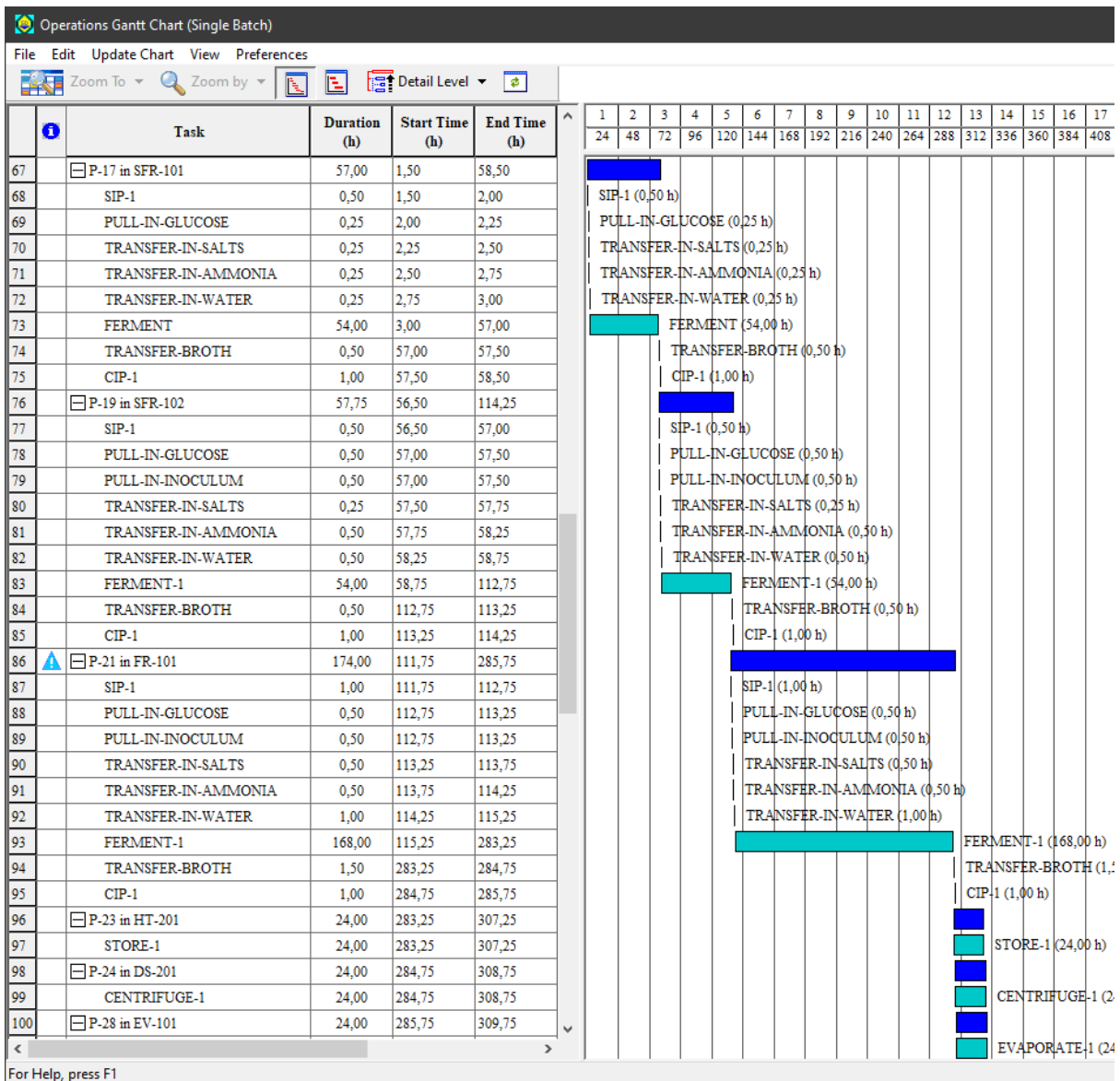
Figure 7: Portion of the Gantt chart for a single batch of itaconic acid production

Much like the EOC, the Gantt chart facilitates editing of batch processes. Double-clicking on any of its bars brings up the dialog of the corresponding entity (operation or procedure), which can be edited by user. Then, just like in the EOC, the simulation can be redone and the chart can be updated by clicking on the refresh button (⟳).

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Material Requirements

Table 3 displays overall process data, such as the batch size and the annual production rate, while **Table 4** lists the raw material requirements for IA production in kg/year, kg/batch, and kg/MT MP ("MP" = main product) for this process. **Table 3** shows that each batch produces approximately 126 MT of IA, and that 317 batches are carried out per year, totaling 40,000 MT of IA per year. According to **Table 4**, the main materials used to produce IA (other than air and water) include the glucose solution (Glucose 70%) and the cleaning/regeneration solutions (NaOH 2% and NaOH 1 M).

Both tables were extracted from the RTF version of the **Materials & Streams** report, which can be generated by selecting **Reports� Materials & Streams** from the main menu bar of SuperPro Designer. Reports can be generated in various formats (e.g., PDF, RTF, XLS, etc.,) specified through **Reports➥ Options**.

Table 3: Overall Process Data for the Itaconic Acid Production Process

OVERALL PROCESS DATA

Annual Operating Time	7,898.75 h
Unit Production Ref. Rate	40,000.00 MT
Batch Size	126.18 MT
Recipe Batch Time	314.75 h
Recipe Cycle Time	24.00 h
Number of Batches per Year	317.00

MP = Total Flow of Stream 'S-319'

Table 4: Material Requirements for the Itaconic Acid Production Process

BULK MATERIALS (Entire Process)

Material	kg/yr	kg/batch	kg/MT MP
Air	1,172,318,420	3,698,165.36	29,307.96
Ammonia	676,440	2,133.88	16.91
Glucose 70%	86,719,617	273,563.46	2,167.99
NaOH (1 M)	8,334,107	26,290.56	208.35
NaOH (2%)	5,478,075	17,280.99	136.95
Natural Gas	719,454	2,269.57	17.99
Salts	1,256,663	3,964.24	31.42
Water	192,488,491	607,219.21	4,812.21
TOTAL	1,467,991,267	4,630,887.28	36,699.78

Cost Analysis

SuperPro Designer performs thorough cost analysis, estimating capital (CAPEX) as well as operating (OPEX) costs, and generates the following three pertinent reports (through the **Reports** menu): the *Economic Evaluation Report (EER),* the *Cash Flow Analysis Report (CFR),* and the *Itemized Cost Report (ICR).* **Table 5** displays the **Executive Summary** of the EER. It shows that the total capital investment required for this project is estimated in approximately $113 million, while the annual operating cost is calculated to be $56 million. The resulting unit production cost is $1.4/kg of IA.

Assuming a selling price of $1.7/kg of IA, the gross margin would be 18.2 %; the return on investment would be 17.6 %; and the payback period would be 5.7 years. These metrics suggest that this process for IA production would be highly competitive. Moreover, the unit cost achieved by this process is lower than $ 1.5/kg, which is considered as the threshold for the use of IA in the production of plastics [4].

Table 5: Executive Summary for the Itaconic Acid Process

EXECUTIVE SUMMARY (2019 prices)

Total Capital Investment	112,757,000 $
Capital Investment Charged to This Project	112,757,000 $
Operating Cost	55,635,000 $/yr
Revenues	68,000,000 $/yr
Batch Size	126.18 MT MP
Cost Basis Annual Rate	40,000 MT MP/yr
Unit Production Cost	1,390.89 $/MT MP
Unit Production Revenue	1,700.00 $/MT MP
Gross Margin	18.18 %
Return On Investment	17.57 %
Payback Time	5.69 years
IRR (After Taxes)	13.89 %
NPV (at 3,0% Interest)	173,996,000 $

MP = Total Flow of Stream 'S-319'

Figure 8 displays the breakdown of the annual operating cost (AOC), which is also part of the EER. This type of chart can be included in the report by selecting **Reports➲ Options** and activating the **Include Charts** option in the lower right corner of the dialog. This chart shows that the facility-dependent cost is the most important OPEX component, accounting for 37% of the total operating expenses, closely followed by raw materials (35%) and utilities (19%). The facility-dependent cost encompasses maintenance costs, depreciation costs and overhead expenses; as such, it is highly dependent on the equipment purchase cost. The use of a long downstream process involving a great deal of expensive equipment (such as evaporators and crystallizers) explains why the facility-dependent cost is so high for this process (you may check the purchase cost of each piece of equipment in the EER too). The

relatively large contribution of utilities to the OPEX is due to the multiple evaporation and cooling steps employed in the downstream scheme of this process.
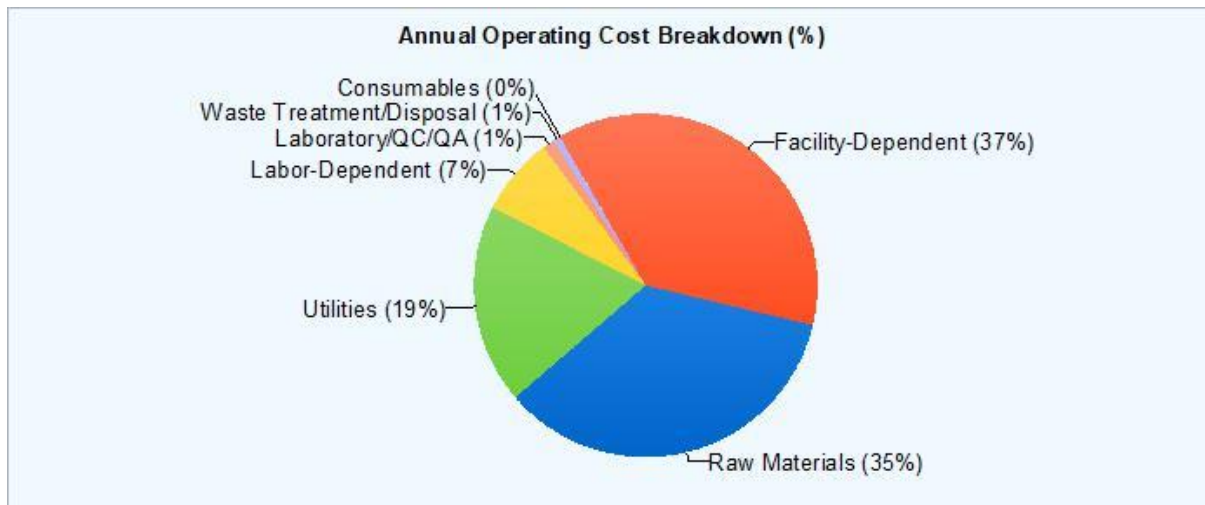

Figure 8: Annual Operating Cost Breakdown for the Itaconic Acid Process

A potential strategy to further reduce the unit production cost and, in particular, the facility-dependent cost and the utilities cost, would be to replace the current downstream process based on repeated evaporation and crystallization steps with an alternative downstream process based on modern separative methods such as electrodialysis, adsorption or reactive extraction. Electrodialysis and adsorption have already been applied to the industrial production of succinic acid, for example, while reactive extraction has been applied to the industrial production of citric acid and lactic acid [10].

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Miscellaneous Modeling Tips

Flow Adjusting Procedure

In this example, a flow adjusting procedure (P-9/FAD-101) is used in the Fermentation Section to adjust the amount of water that is sterilized and sent to the seed fermentors and production fermentors. The flow adjusting procedure can act either as a custom flow mixing procedure or as a custom flow splitting procedure depending on the flow specification of its main outlet stream (which can be either set by the user or by a downstream process). If the flow of the main outlet stream is greater than that of the process stream, then this procedure will act as a custom flow mixing procedure used to mix two bulk flow streams, where one of the two streams (the adjustable inlet stream) is of known composition, but adjustable flow, and is allowed to assume any value in order to meet the flow specification of the main outlet stream. If the flow of the main outlet stream is lower than that of the process stream, then this procedure will act as a custom flow splitting procedure used to split a stream into two, in a way that the split percentage is not fixed a priori, but it is determined by the program to meet the flow specification of the main outlet stream.

In the present example, the flow of the main outlet stream of FAD-101 (S-165) is determined by a downstream procedure, the 3-way bulk flow distribution procedure P-11/FDIS-101. In the Flow Distribution operation dialog of FDIS-101, the flowrates of its 3 output streams were set by the user, by checking the appropriate boxes as shown in **Figure 9**. Then, in the Flow Adjusting operation dialog of FAD-101, the Main Outlet Stream Flow was defined as "Set by Process", as shown in **Figure 10**.

The main inlet stream of FAD-101 (S-119), on the other hand, comes from P-8/HT-101, the Recycled Water tank that stores the condensate produced by evaporation procedure P-28/EV-201. Finally, the adjustable inlet stream of FAD-101 (S-164 / Makeup Water) was specified within the Flow Adjusting operation dialog of FAD-101 (cf. **Figure 10**). In the bottom of this dialog, the "essay tubes" button (🧪) was clicked, bringing up the S-164 stream dialog. In this window, the composition of the adjustable inlet stream was specified as 100% Water. This series of steps ensures that the fermentors are supplied with the exact amount of water they require, and, at the same time, that the recycled water from EV-201 is adequately used.
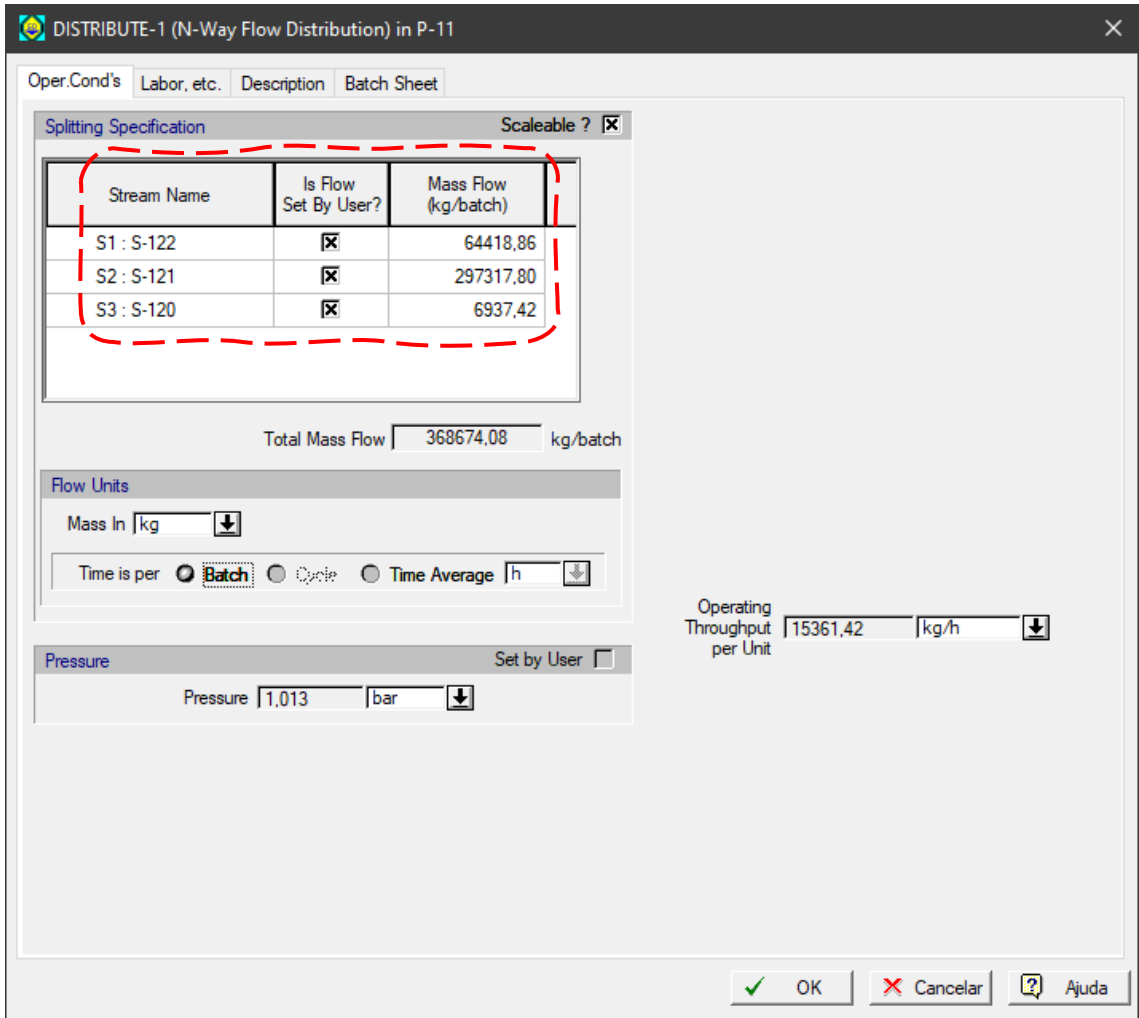
Figure 9: Operation Data dialog for the Flow Distribution operation in procedure P-11/FDIS-101
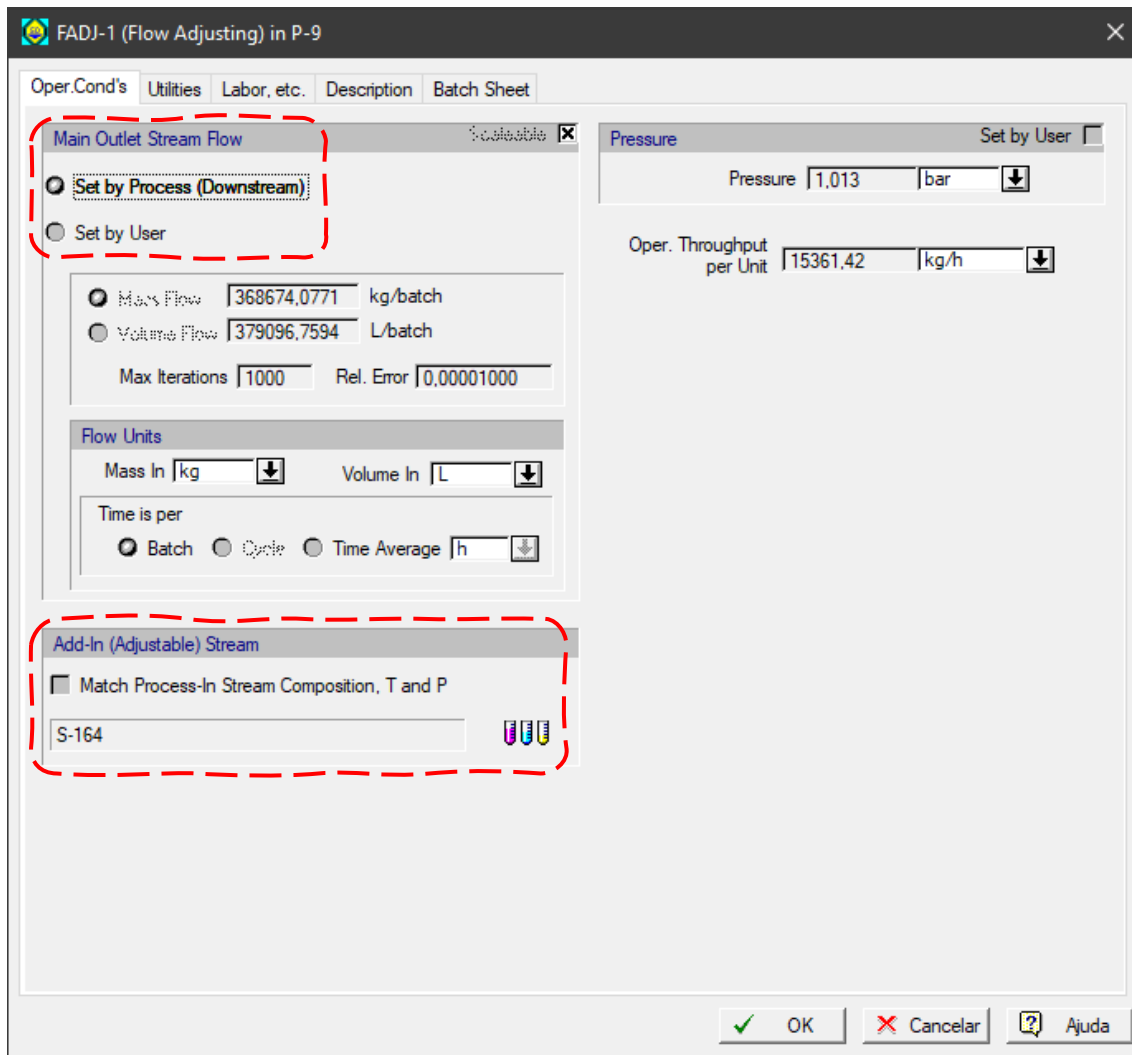
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Figure 10: Operation Data dialog for the Flow Adjusting operation in procedure P-9/FAD-101

Cell Water Content

When modeling a process that involves biological cells, the user can specify the average water content of the cells and track the amount of extracellular water in every process stream. To that purpose, the user must first define the primary biomass component of the process, by clicking on **Tasks➲ Pure Components➲ Register, Edit/View Properties…**and, in the bottom of the dialog that pops up, specifying the (main) cellular component. In the current example, the "Biomass" component was selected as the primary biomass, as shown in **Figure 11**.
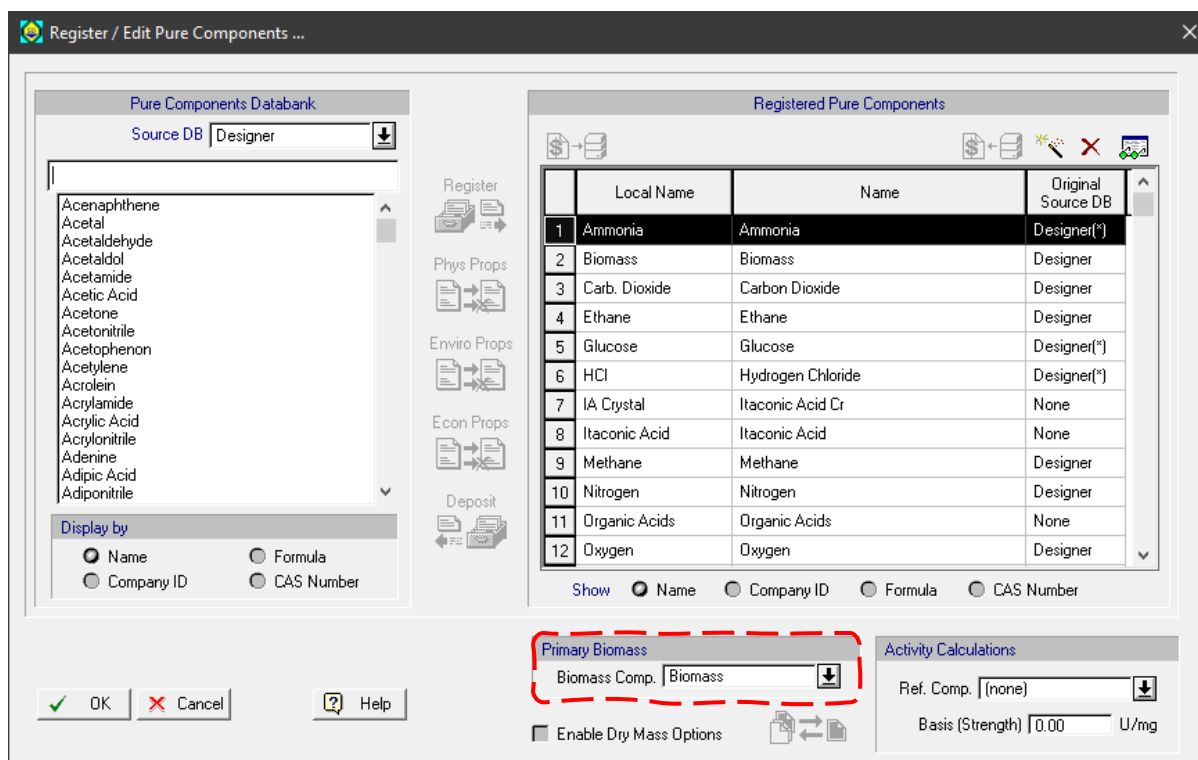
Figure 11: Pure Component Registration dialog, highlighting the Primary Biomass frame

Next, the user must access the Fermentation operation within the cell culture or fermentation procedure in the process. This is done by right-clicking on the procedure icon, choosing **Operation Data** and then the appropriate FERMENT operation. Subsequently, the user must switch to the **Reactions** tab, shown in **Figure 12**; a new frame named "Primary Biomass Water Content" will have appeared below the Reaction Sequence box. There, the user must select the component that represents intracellular water (in this example, the "Water" component) and specify the average water content of cell mass in weight % (in this example, 70%). Typically, the water content of cells ranges between 60% and 80%.
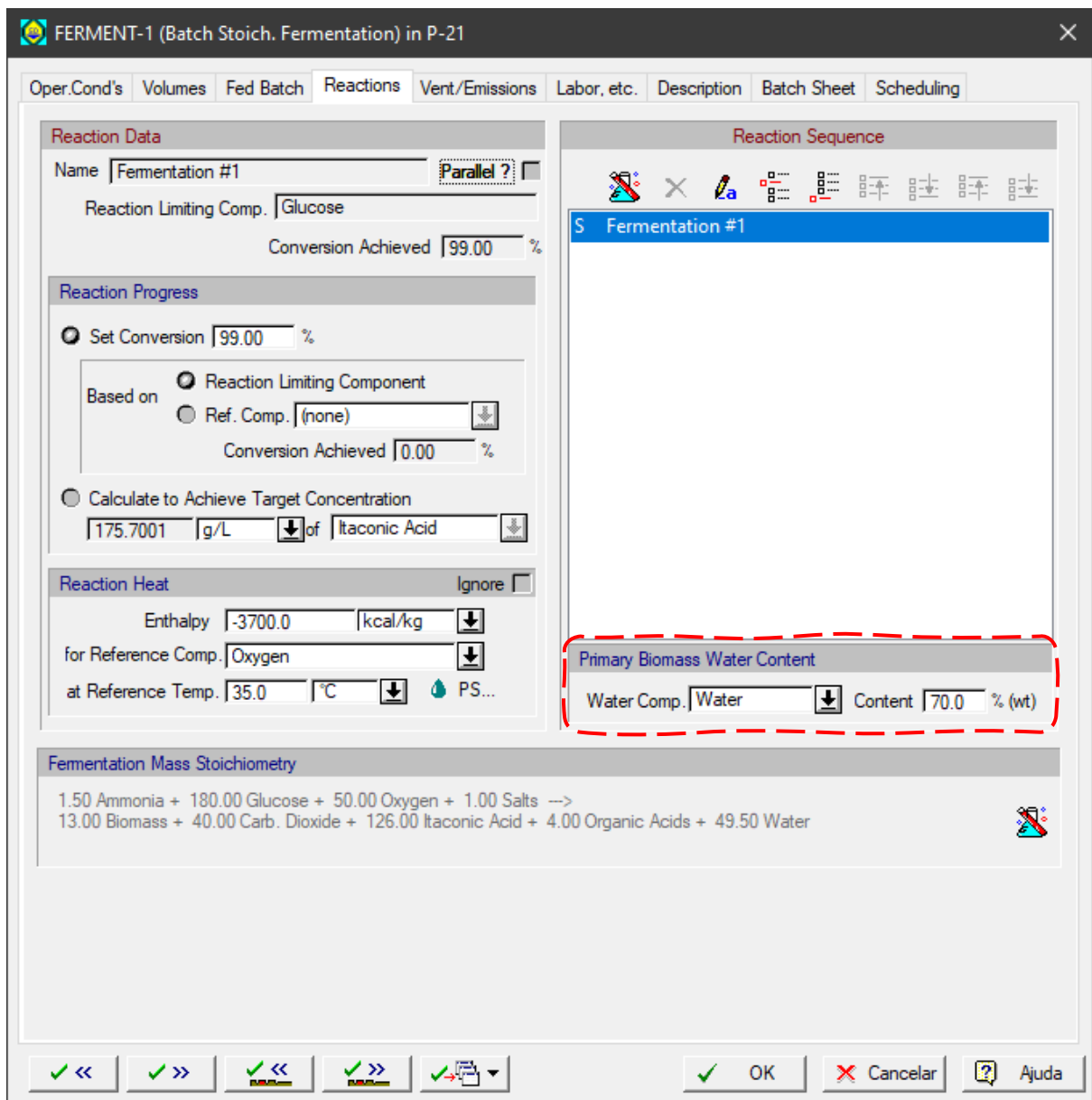
Figure 12: Reactions tab of a FERMENT operation, highlighting the Primary Biomass Water Content frame

After you do the M&E Balances (simulation calculations), SuperPro will display the amount of extracellular water in any process stream by inspecting the "Extra-Cell (%)" column for the water component. For instance, **Figure 13** indicates that 55.61% of the water in the centrifuge sludge S-153 is extracellular; it follows that 44.39% of the water is intracellular.
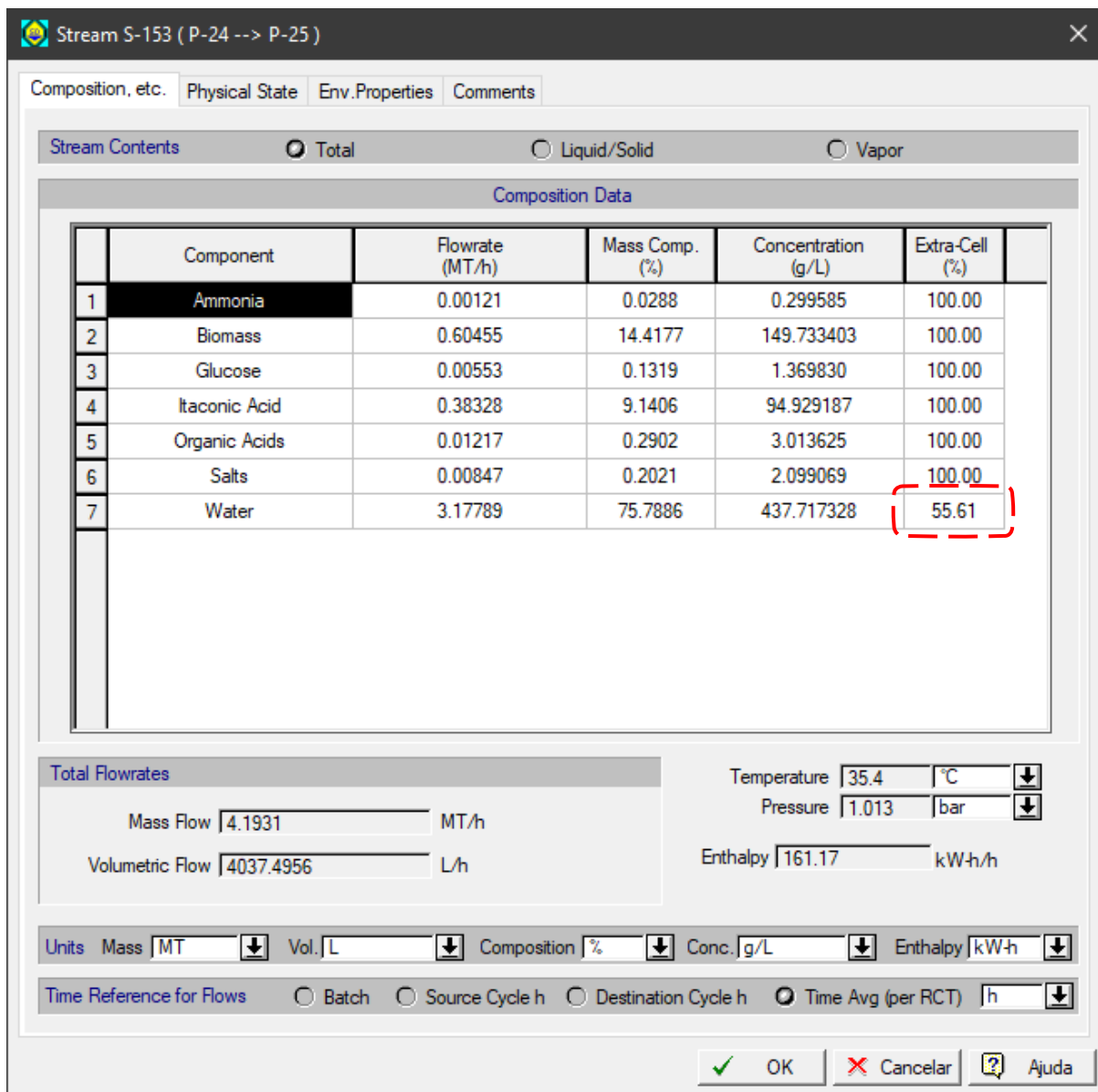
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Figure 13: Simulation Data dialog for stream S-153, highlighting the amount (%) of extracellular water

It is important to consider the cell water content when the process involves cell harvesting procedures such as disk-stack centrifugation or rotary vacuum filtration, given that the intracellular water will affect the material balances and the product yield. For instance, in the centrifugation procedure P-24/DS-201 of this example, 99% of the biomass is removed as a particulate solid, as shown in **Figure 14**. The 99% removal also applies to the Intracellular Water that follows the path of Biomass. The amount of extracellular solution that ends up in the solids stream of the centrifuge depends of the concentration of the solids stream. A Particulate Concentration of 500 g/L was specified for the Solids Stream of this centrifuge (see bottom of Figure 14). In this case, the value of 500 g/L represents the concentration of wet cell mass. In other words, approximately half of the mass of the solids stream consists of cell (whole

cells) and the rest is the extracellular liquid in which product is dissolved and potentially lost. If the intracellular water content had not been defined in the fermentation procedure, a lower Particulate Concentration should be specified representing Dry Cell Mass (the default value is 150 g/L). However, under those conditions, the extracellular liquid that contains dissolved product is considerably larger and results in higher product loss (lower product yield) during centrifugation.
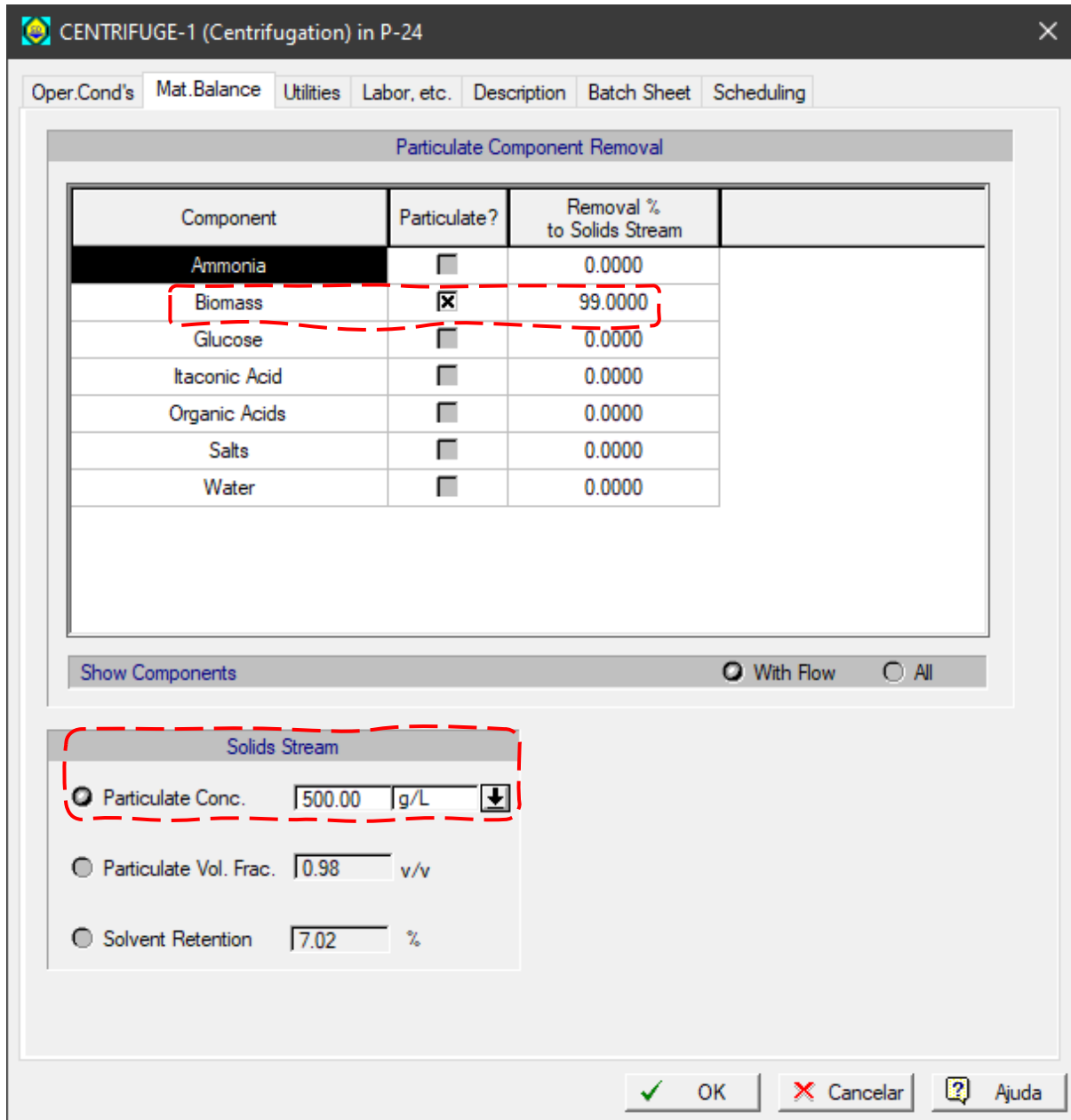

Figure 14: Material Balance tab of a CENTRIFUGE operation, highlighting the particulate component removal (%) and the particulate concentration in the solids stream

To reduce the product loss during cell removal in this example, two centrifuges are utilized in sequence. The solids stream of the first (S-153) is diluted with water at a ratio of 2:1 in P-25 / MX-201 and flows

through a second centrifuge (P-26 / DS-202). That increases the product yield by 0.31 MT/h (flow of Itaconic Acid in stream S-163).

CIP Sequence Templates

Starting from version 11 of SuperPro Designer, it is possible to create, edit and re-use CIP steps through CIP Sequence Templates. This functionality saves modeling time when similar CIP protocols must be applied to various equipment items.

Figure 15: Operation Data dialog for a CIP operation.

In the present example, blending tanks and fermentors use the same CIP sequence consisting of 3 steps, including a caustic wash. First, a CIP operation was added to the appropriate procedures. Next, the CIP operation dialog of one of these CIP operations was accessed, as shown in **Figure 15**. The 3-step cleaning sequence was then properly defined. After that, the CIP sequence was registered as a template in the program database by clicking on the **Magic Wand** ( ) button within the "Cleaning Step Sequence" frame, located on the right side of **Figure 15**. This prompts a new window where the user must name the CIP sequence to deposit it into the software database (in this example, the template was named "Caustic Protocol"). Once this step is completed, if the user wants to specify the same CIP sequence to another CIP operation, they can simply access the CIP operation dialog, check the box "Link to Template" on the right side of the window (cf. **Figure 15** again) and then choose one of the templates stored in the database. If necessary, the user can also freely modify the CIP details imported from the template.

CIP Sequence Templates can also be created outside of the CIP operation dialog, by accessing the menu **Databanks➲ CIP Templates…**

Summary

The current example analyzes a process to produce itaconic acid by fungal fermentation. Itaconic acid is a versatile chemical that can serve as a building block for a myriad of compounds, including plastics. The process modeled here is based on the fed-batch culture of *Aspergillus terreus*, using glucose as the main carbon source. The recovery and purification scheme relies on two rounds of evaporation, crystallization and filtration of the carboxylic acid. The plant produces 40,000 MT/year of itaconic acid at a unit cost of $1.4/kg. The CAPEX required is estimated in $113 million and the annual OPEX, in $57 million. Assuming a selling price of $1.7/kg, the gross margin, return on investment, and payback time would be 18.2%, 17.6% and 5.7 years, respectively.

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Itaconic Acid Production

Fermentation Section

Recovery Section

Purification Section