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Broader Context

Succinic acid is a naturally occurring chemical. It is one of the top 12 most widely used platform chemicals with application in food, pharmaceutical, and household chemical formulations. Succinic acid can be produced from both chemical and biological routes. Biological production of succinic acid is of particular interest in view of the challenges faced by the petrochemical industry in terms of significant environmental impact, volatile raw material prices, and the economic effects of a dwindling raw material supply. Consequently, numerous bio-succinic acid production strategies using several renewable feedstocks, including corn stover, seaweed, glycerol, and glucose etc. have been studied. However, the biological production route poses several technological challenges (insecure biomass supply, low product yield and titer, energy-intensive purification, and high production cost), limiting its potential to reach commercial scale. Thus, this work aims to identify sustainable bio-succinic acid production processes on a commercial scale. The problem solved in this article integrates several fields, including superstructure optimization, profitability and risk assessment, environmental assessment, and worldwide bio-SA production assessment, thus, making this investigation truly interdisciplinary in nature.
Sustainable bio-succinic acid production: Superstructure optimization, techno-economic, and lifecycle assessment

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Introduction

A major engineering challenge today is the required transition from non-renewable to renewable resources for the production of chemicals and materials. The transition is needed to help reduce greenhouse gas emissions. In this regard, bio-succinic acid (bio-SA) has potential to capture carbon dioxide and provide a cleaner environment by managing waste streams. This study evaluates the economics, environmental impact, risk assessment, and optimal processing route of bio-SA production from multiple feedstocks (first, second, and third-generation), including (1) glucose, (2) corn stover, (3) glycerol, and (4) seaweed. A superstructure-based optimization model consisting of 39 processing alternatives with a technology readiness level of 7–9 is developed, and the optimal topology for bio-SA production by maximization of the net present value under deterministic and stochastic conditions is identified. Once optimization is completed, the framework provides clear guidance for multi-criteria analysis, including the technical, economical, and environmental aspects of the biorefinery. The results indicate that glycerol is the best feedstock and corn stover is the second to best, producing bio-SA at selling prices of 1.6–1.9 USD/kg and 1.7–2.0 USD/kg, respectively, through their optimal processing pathways. Saccharina japonica (seaweed) is less suitable for large-scale bio-SA production due to the high cost of seaweed and the inability of enzymes to hydrolyze alginate, which is one of the major carbohydrate fractions (25–30 wt%) of this feedstock. The environmental results indicate that the optimal pathway from glycerol is the most environmentally friendly process, followed by optimal processing pathways from substrates such as corn stover, glucose, and S. japonica.

Feedstock challenges. Bio-SA from sugar fermentation can be produced from numerous feedstocks, including first-glucose, second- (bio-glycerol, corn stover), third-generation (S. japonica or seaweed) biomass. For example, bio-SA derived from first-generation feedstock, such as glucose, are attractive due to a well-established infrastructure for the cultivation and harvesting of crops, followed by relatively simple conversion of feedstock to bio-SA. However, this type of feedstock is not sustainable because of competition with food production, land, and irrigation requirements. Hence, a good alternative is to produce bio-SA from second- or third-generation feedstocks. Corn stover, a second-generation feedstock, is considered a future feedstock for bio-SA production since it is not in competition with food and its global production is constantly increasing, which reached approximately 1.1 billion t in 2019. However, the structural
complexity and high lignin content in the chemical composition of corn stover makes it nearly impossible for direct conversion of carbohydrates into sugars by microbes without an additional expensive pretreatment. From these arguments, it can be seen that many renewable feedstock sources have inherent challenges. Likewise, each feedstock needs to be pretreated for use in bio-SA production. This is necessary to maximize the bio-SA yield and remove toxic compounds naturally present in the feedstock or synthesized in some pretreatment steps. Potential methods for biomass pretreatment are acid thermal hydrolysis, alkaline thermal hydrolysis, deacetylation, hot water washing, and enzymatic hydrolysis. Finding an optimal technology for biomass pretreatment is challenging, because each method has a different effectiveness, selectivity, and expense, including capital and operating costs.

**Fermentation challenges.** After identifying appropriate biomass feedstock and its subsequent pretreatment, the next step is fermentation, which is considered to be the heart of bio-SA processing. Fermentation determines the economic viability of the whole process based on three metrics: yield, titer, and productivity (g/L.h). To achieve high values for these metrics, selection of an appropriate production host, pH control reagents (buffering agents), fermenter configuration, and operation are essential. For instance, several host microorganisms have shown to have high bio-SA yields; some important examples for commercial bio-SA production are *Actinobacillus succinogenes* and engineered *Escherichia coli*. Likewise, there are several pH control reagents and numerous fermenter configurations that affect the economics of the entire process. Considering the number of fermentation technologies to be chosen, it is challenging to determine the optimal technology to achieve maximum efficiency in yield, titer, and productivity.

**Downstream challenges.** Highly pure (>99 wt% purity) bio-SA is required to make a marketable product, but every technology currently available shows advantages and disadvantages and no single specific technology or method has been identified as the best technique for bio-SA separation from the fermentation broth. Table 2 presents the advantages and disadvantages of the main downstream technologies used for bio-SA separation. Selecting the best technology from the perspective of economics and the environment (byproduct formation) is challenging due to the large number of purification alternatives. In addition, the downstream technology sequence is highly correlated with the feedstock, pretreatment, and pH control reagent used, which significantly increases the complexity of finding the optimal purification technology.

As there are several feedstock sources and many alternative technologies both in upstream and downstream of bio-SA production, this creates many potential process design configurations. Therefore, the process design of bio-SA production is a challenging task that cannot be solved optimally using a standard process design approach, such as a sequential hierarchical decomposition strategy. This challenge requires mathematical programming approaches capable of systematically evaluating all alternatives based on a rigorous economic objective function such as net present value to guarantee the economically optimal processing route for bio-SA production. In addition, identified optimal processing routes should be evaluated based on risk assessment and environmental sustainability to design a sustainable bio-SA production process. However, there have been few analyses based on multi-criteria analysis that can answer all of the following questions: (1) what feedstock should be used to produce bio-SA; (2) what upstream and downstream technologies should be used for a specific feedstock to decrease the production cost of bio-SA; (3) what is the economic and environmental impact of bio-SA production over the whole supply chain; (4) what are the limiting factors hindering the economics; and (5) what is the economic risk of bio-SA production.

To address these questions, a multi-stage framework is applied. As shown in Figure S1, the framework starts with the problem statement definition (step 1), through which the scope of the study is defined by selecting an appropriate objective function. In step 2, the superstructure is developed, followed by its mathematical formulation. Step 3a deals with deterministic analysis, whereby the optimal processing pathway(s) of the biorefinery, along with suitable process indicators, are determined by maximization of the net present value (NPV). In step 3b, post-hoc local sensitivity analysis is performed on the optimal topologies obtained from step 3a to identify the main critical parameters affecting process economics. These parameters are then used in step 4, whereby stochastic optimization of the superstructure is performed to study the impact of uncertainties on biorefinery topology and process indicators. The main objective of this step is to find robust topologies that maximally remained profitable under uncertain scenarios. Finally, a sustainable bio-SA production route is identified by performing two post-hoc analyses (risk assessment and environmental assessment) on the robust topologies obtained from step 4. In step 5a, risk assessment is performed, whereby economic risk is quantified based on the minimum product-selling price (MPSP) using Monte Carlo simulation. Finally, in step 5b, the lifecycle inventory data for the robust optimal processing pathways are obtained from step 4 to perform cradle-to-grave lifecycle assessment (LCA) of bio-SA production. Finally yet importantly, the analysis is further widened by (1) demonstrating how the developed model can be helpful in the decision-making process of secure investment and (2) carefully investigating the number of bio-SA plants and feedstock needed to meet the forecasted global demand for SA by 2025. Afterward, detailed profitability and comparative environmental assessments of bio-based and fossil-based SA are performed to investigate bio-SA production effectiveness at the worldwide level.

**Methodology**

**Problem statement**
This study aims to identify the optimal processing pathway, economic factors, risk assessment, and environmental impact...
of commercial-scale bio-SA production. In addition, this study performs multi-criteria assessment of bio-SA plants based on global demand. To this end, the most relevant first-, second-, and third-generation feedstocks have been explored, including glucose, glycerol, corn stover, and *S. japonica*. A superstructure is developed to find the economically optimal processing route by maximizing NPV, while risk assessment is performed through Monte Carlo simulation to quantify economic risk. Finally, LCA is conducted to evaluate and compare the life cycles of bio-SA production, as well as to identify environmental bottlenecks through cradle-to-grave analysis.

**Superstructure development: conceptual design and mathematical modeling**

This section outlines the design and modeling of key sections of the bio-SA biorefinery superstructure shown in Figure 1. The novelty of the proposed process synthesis superstructure features a comprehensive network of 39 process alternatives with technology readiness level of 7–9 as the basis for optimal design identification. This ensures that the resulting superstructure optimization solution is appealing from an implementation viewpoint. Ten major sections or processing intervals are included in the superstructure, namely, feedstock, pretreatment, fermentation, cell mass removal, concentration pre-isolation, isolation, concentration post-isolation, color impurities removal, purification, and drying. Each section (except for drying) is embedded with multiple alternatives for performing the specific task. Bypassing is included in some processing intervals to avoid certain steps, which are modeled using an empty box. In the superstructure, each alternative is represented by two indices, the first of which refers to the alternative, and the second refers to the processing stage. For example, “1, 3” refers to alternative 1 in processing stage 3. The nomenclature for the superstructure is listed in Table S1 of the supplementary material. Note that even though different processing alternatives/technologies are shown in the superstructure as a block, the economic and technical evaluation of each alternative technology is performed in detail. The complete information from each section regarding process flow diagrams (Figures S2–S10), process descriptions, experimental data (Table S2–S3) concerning the operating conditions and yields, technological constraints, and feasibility rules are detailed in Section 1 of the supplementary material.

The proposed biorefinery process starts with biomass handling and storage (the feedstock section in the superstructure), in which multiple biomass sources, including glucose (first-generation), glycerol and corn stover (second-generation), and *S. japonica* (third-generation) can be used to produce bio-SA. For effective utilization of biomass in fermentation, five pretreatment technologies are included in the superstructure. These include acid thermal hydrolysis of corn stover, deacetylation followed by acid thermal hydrolysis, alkaline (sodium hydroxide) hydrolysis, acid thermal hydrolysis of *S. japonica*, and hot water washing hydrolysis. All of these technologies can break up the cell walls of the biomass to convert hemicellulose into sugar monomers such as xylose and mannitol. To further increase the yield of sugar monomers, biomass is pretreated again using enzymatic hydrolysis to convert cellulose to glucose using cellulase enzymes. Once biomass is pretreated, the fermentation of sugars can be carried out using a batch or fed-batch fermenter to produce bio-SA along with byproducts. Nine fermentation technologies are included in the superstructure, which correspond to different microorganisms (bacteria), pH control agents, titers, yields, and productivities of bio-SA. All fermentation included use carbon dioxide as an additional carbon source; this will provide additional environmental credits due to biological sequestration of carbon dioxide. As indicated before, the choice of a pH control reagent is important in terms of economics; therefore, five pH control agents, including magnesium hydroxide, magnesium carbonate, sodium hydroxide, sodium carbonate, and ammonia are included in the superstructure. The choice of an appropriate pH control reagent will be made on the basis of its cost and the cost of downstream purification technology.

After fermentation, the dead cell mass is removed from the fermentation broth by microfiltration or centrifugation. The clean broth can then be concentrated either before or after isolation of the SA using evaporation or vacuum distillation. Afterward, depending upon the isolation technology, acidification can be performed to produce free acid and salt. Isolation is a separation task that recovers or separates SA from its salt. Since this task is energy-intensive, six processing alternatives—electrodialysis, direct crystallization, reactive extraction, an ion-exchange column, reactive crystallization, and membrane technology (a combination of ultra- and nanofiltration)—are included in the superstructure. The color impurities, pigments, and protein can be removed from the succinate broth using activated carbon or nanofiltration. The isolated SA broth free from cells and color impurities can then be purified via solvent-based or crystallization techniques and is finally dried to remove moisture until the desired purity is reached.

**Mathematical modeling and the objective function of the superstructure**

The mathematical model of the superstructure represents a large-scale mixed-integer linear-programming model that considers mass- and energy-balance constraints, capital and operating-cost constraints, and an objective function. Note that energy-balance equations and design constraints are non-convex, which may cause difficulties for solution convergence and the computation of a global optimal solution due to the size of this large combinatorial problem involving more than 125 binary decision variables, 85,000 continuous decision variables, and 35,000 constraints. Therefore, piecewise linearization using 25,000 special-order-set of type 2 variables is employed by approximating the initial mixed-integer non-linear programming problem as a linear one. The complete mathematical model of the superstructure is detailed in Section 2 of the supplementary material. The model was implemented in GAMS (25.0.2), and its solution was computed using the CPLEX solver. To find an optimal topology, the objective...
function chosen for this study is NPV, which should be maximized and is defined as:

\[ NPV = \sum_{n=0}^{20} \frac{NCF_n}{(1 + r)^n} \]

where \( NCF_n \) is the non-discounted cash flow for year \( n \).

To systematically compare optimal topology with suboptimal topologies, an integer cut algorithm is used.\(^{40}\) The objective of this algorithm is to exclude the topology obtained through the previous iterations (K). In this way, the algorithm will always find a unique topology at each iteration. The termination of the algorithm occurs as soon as (1) the absolute number of iterations is reached or (2) \( Z^k \) is equal to zero. The assumptions in the techno-economic model include a discount rate of 10%, a straight-line depreciation method over 7 years, a tax rate of 30%, a 2-year construction time, plant start-up during the 3rd year, a financing equity of 100%, and 8,000 hours of operation per year.

The total capital investment includes total direct and indirect costs, land costs, and working capital. Note that the total direct and indirect costs include many subdivisions, which are reported in Table S6 (see supplementary material), and their sum corresponds to the fixed capital investment. A factor methodology is used by which suitable multipliers reported in Table S6 are applied to the installation costs of equipment to estimate the total capital investment. However, in this study, the installation costs are scaled to the new capacity on the basis of vendor-quoted equipment costs and capacity using an installation factor and scaling factors specific to the equipment. Later, the installation equipment costs are updated to the year of analysis (i.e., 2019-dollar value) using the Chemical Engineering Plant Cost Index. Table S7 summarizes the main equipment costs along with the scaling exponent, the installation factors, the scaling variable value, the equipment capacities, and the cost year.

The total manufacturing costs consist of direct (variable), fixed, and general manufacturing costs. Direct manufacturing costs include raw material, operating labor, and utility costs. Fixed manufacturing costs include maintenance and repairs, depreciation, local taxes, insurance, and plant overhead. General costs are related to administration and research-and-development costs. A factor methodology proposed by Turton et al.\(^{41}\) is used to calculate the total manufacturing cost (\( T_{\text{COM}} \)) as:

\[ T_{\text{COM}} = f_1 C_{\text{OL}} + f_2 C_{\text{UT}} + f_3 (C_{\text{RM}} + C_{\text{OL}}) \]

where \( f_1, f_2, \) and \( f_3 \) are multipliers given in Table S6, \( C_{\text{OL}} \) is the cost of operating labor, \( C_{\text{UT}} \) is the fixed capital investment, \( C_{\text{RM}} \) is the utility cost, and \( C_{\text{OL}} \) is the raw materials cost. The costs of utilities and raw materials such as biomass, processing water, enzymes, and chemicals are estimated by mass- and energy-balance constraints. The cost of labor is calculated as 1.6% of the total installation costs. The unit prices of chemicals, utilities, and wastewater treatment are summarized in Tables S8 and S9.

**LCA methodology**

LCA is a holistic and systematic environmental-management tool for assessing the environmental impact associated with all stages of a product’s lifecycle according to ISO 14040 and 14044 guidelines. The goal of LCA in this study is to evaluate and compare the environmental impacts of bio-SA production from the optimal processing pathways of 1st-3rd generation feedstocks. A cradle-to-grave analysis that considers (1) raw material extraction and transportation, (2) conversion at the biorefinery, (3) transportation of products, and (4) end use will be considered in the assessment. One kilogram of bio-SA was selected as a functional unit. For each processing pathway, the unit-specific inventory is shown in Table S10. The environmental impacts from maleic anhydride (petroleum)-based SA were considered as benchmark to evaluate and compare environmental effectiveness of bio-SA production. The unit-specific inventory of SA production from maleic anhydride is shown in Table S11.\(^{42}\) Characterization data are extracted from the Ecoinvent 3.6 and USLCI databases (Table S12) and characterized for lifecycle impact assessment using the CML-IA V3.06 method in SimaPro 9.1.0.7. Eleven environmental indicators are considered in this assessment: abiotic fossil fuel depletion potential, abiotic depletion potential, global warming potential over 100 years, ozone-layer-depletion potential, human toxicity potential, freshwater-aquatic ecotoxicity potential, marine aquatic ecotoxicity potential, terrestrial ecotoxicity potential, photochemical oxidation potential, acidification potential, and eutrophication potential. The definitions of all aforementioned indicators are provided in Table S13.

**Methodology for finding robust bio-SA production process through superstructure optimization**

To investigate robust topologies for bio-SA production three analyses were performed: deterministic, sensitivity (post-hoc), and stochastic analysis. The main reason for performing these three analyses is that it is possible that deterministic topologies only perform well in certain (perfect) conditions and may become suboptimal under uncertainties. Hence, for robust decision-making, the superstructure should be optimized under deterministic and stochastic conditions.

In deterministic analysis, the optimal feedstock and the associated processing route for producing bio-SA are investigated by maximizing the NPV with the nominal parameters reported in Tables S2, S3, and S7–S9. Note that all uncertainties in the parameters are disregarded here.

Once the optimal topologies were found through deterministic analysis, local sensitivity analysis was performed for the optimal topologies to evaluate the parameters most critically influencing the NPV. The evaluated variables include the cost of feed, the price of products, the utility cost, the total capital investment, income-tax rate, discount rate, operating hours, plant capacity, pretreatment yield, fermentation yield, titer, and purification efficiency. The variation (i.e., maxima and minima) pertaining to these variables are
based on literature review, process experts, and market analysis, and reported in Tables S14–S16.

Finally, stochastic optimization was performed to determine the most promising feedstock and its processing pathway. Our main objective was to determine the processing pathway that remains maximally viable in an economic sense under uncertain conditions. Therefore, the most influential sources of uncertainties, as determined by local sensitivity analysis, are now characterized using a random value generated from a uniform distribution function. Therefore, for further analysis, the scenario to be analyzed was setup based on historical cost data for the raw materials and the uncertainty ranges suggested in the literature for process indicators. Complete information regarding the uncertainty parameters included in stochastic optimization and their ranges are given in Tables S14–S16 of the supplementary materials. To identify an optimal feedstock and processing route under uncertainty, 5000 scenarios were generated, and the results are mapped and analyzed statistically.

Methodology for sustainable bio-SA production through post-hoc analyses

Economic and environmental sustainability is the key for the stable growth of economy without damaging the environment. Therefore, the robust topologies were subjected to two post-hoc analyses to investigate economic risk and LCA in order to find sustainable bio-SA production route.

Risk is evaluated based on the MPSP by comparing the current market selling price of fossil-based SA with that of bio-based SA. In this study, risk is defined as the probability that the manufacturing process will produce bio-SA at a price greater than the target petrochemical-based SA price. To evaluate the risk, we assumed that the price of petrochemical-derived SA lies between 1.6 and 2.0 USD/kg. Monte Carlo simulation was performed to compute economic risk. In this analysis, the binary variables corresponding to the robust optimal pathways of all feedstocks are fixed, and total 10000 simulations were performed using a random value generated from a uniform distribution for all uncertainty parameters listed in Tables S14–S16. Finally, LCA of robust topologies were performed according to the strategy detailed in the Section “LCA methodology” to investigate environmental impact of bio-SA production.

Results and discussion

Robust bio-SA production

Optimal feedstock and its processing route: Deterministic analysis

A summary of the process indicators, including NPV, total capital investment, total cost of manufacturing, and MPSP is presented in Figure 2A, while the total capital cost breakdown is presented in Figure 2B. The process flow diagram of the optimal processing route is shown in Figure 3. The results shown in Figure 2A indicate that utilizing corn stover via the processing pathway presented in Figure 3A leads to the highest NPV (57.2 million USD) of all remaining feedstock candidates for a plant scale of 30,000 t/y and a project life of 20 years. The optimal corn stover-processing route consists of acid thermal hydrolysis for biomass pretreatment, separate hydrolysis and fermentation using Actinobacillus succinogenes and sodium hydroxide (pH control reagent) for bio-SA production, centrifugation for cell mass removal, and the use of an ion-exchange column, crystallization, and drying for bio-SA purification to 99.2 wt% purity. The yield, titer, and productivity achieved in fermentation are 56.40 g/L, 0.73 g/g of sugars, and 1.08 g/(Lh), respectively.

The main reason for a large upstream investment is the expensive pretreatment of biomass and the large anaerobic fermentation volume of up to 5,260 m³, which requires 7 fermenters. The total manufacturing cost of the biorefinery is 39 million USD, with 56% of the investment being upstream and 44% downstream, as shown in Figure 2A and Figure 2B, respectively. For bio-SA purification, the downstream-processing pathway is based on historical cost data for the raw materials and the centrifugation for cell mass removal, and the use of an ion-exchange column, crystallization, and drying. The main reason for this difference is the high cost of glucose, which makes membranes the optimal purification technology in this case compared with the ion-exchange column. This is due to the low recovery rate of the ion-exchange column (71%) compared with the membranes (86.5%). It is also noteworthy that the impact of the corn stover-processing pathway in terms of total capital investment is higher than those of either the glycerol- or...
glucose-processing pathways by 1.53- and 1.55- times, respectively. However, the high cost of glycerol and glucose overcomes the savings achieved in the total capital investment, making them the second and third optimal feedstocks for producing bio-SA through optimal processing pathways. For *S. japonica*, hot water washing was found to be the optimal pretreatment compared with acid thermal hydrolysis in the case of corn stover. It is also important to note that although the yield from acid thermal hydrolysis is higher than that from hot water washing, the high capital and operating costs of acid thermal hydrolysis make this pretreatment technology economically unviable. Implementing acid thermal hydrolysis when utilizing *S. japonica* leads to a negative NPV. Under the optimal topology for *S. japonica*, the fermenter type, bacterial strain, pH control reagent, and downstream-processing pathway are similar to those of corn stover. The yield, titer, and productivity achieved by fermentation of different carbon sources obtained from glycerol, glucose, and *S. japonica* are presented in Table S3.

Overall, the economic results shown in Figure 2 indicate a large variability in the bio-SA selling price from 1.60 to 1.90 USD/kg just based on feedstock. Likewise, the total investment cost varies between 32 and 89 million USD, being lowest for the glucose-processing pathway and highest for the *S. japonica*-processing pathway. The total capital cost breakdown shows that in the processing pathway for all feedstocks, fermentation and purification are the most expensive areas, comprising 30%–51% and 43%–62% contributions to the total capital cost, respectively.

Clearly, different biomass sources lead to significantly different process indicators when producing bio-SA. Therefore, an integer cut algorithm was used to systematically rank the top hundred topologies by screening all potential alternatives to give more insight into various configurations for producing bio-SA. The complete results for the top 100 processing pathways and process economic indicators are given in Table S17 of the supplementary material. The results in Table S17 show that corn stover is the top-recommended feedstock, as it was most frequently selected within top 10 topologies. Of the top 10 topologies, six use corn stover and four use glycerol. For the downstream-processing steps, nine of the top ten use an ion-exchange column, and membrane technology consisting of microfiltration and nanofiltration is selected once to purify the bio-SA. *S. japonica* is only selected eight times in the top 100 topologies, indicating that it is less suitable for standalone production of bio-SA at an industrial scale. Figure 4 shows that glycerol and corn stover are important precursors for producing bio-SA at a lower selling price. As the minimum selling price increases, the selection of corn stover and glycerol decreases while the selection of glucose and *S. japonica* increases, indicating that corn stover and glycerol rank highly as feedstocks.

**Sensitivity analysis**

Sensitivity analysis results in Figure 5 indicate that the optimal topologies for different feedstocks have different critical parameters affecting process economics. For instance, Figure 5 shows that the bio-SA selling price is the most influential parameter affecting NPV in all cases. Unlike the processing pathways of glycerol and glucose, the installation cost is the dominant parameter affecting NPV in the corn stover- and *S. japonica*-based topologies because of two additional processing steps (i.e., biomass pretreatment and DDS purification). The feedstock cost was a very crucial parameter for all processing pathways, but most sensitive in that for glucose, which can increase the NPV by up to 87 million USD when the glucose cost is 0.58 USD/kg, or can decrease the NPV to −0.18 million USD when the glucose cost is 15% more than the current market price of 0.99 USD/kg. Likewise, increasing plant capacity was found to be economically favorable for all processing pathways. In the processing pathway of *S. japonica*, the variations in purification efficiency, fermentation yield, and pretreatment yield can vary base case NPV by −165%–136%, −31%–29%, 102%–84%, respectively. The abovementioned sources of uncertainty clearly indicate that it is unreliable to recommend an optimal feedstock and its processing route on the sole basis of deterministic conditions. It is quite likely that the determined optimal pathways only perform well under nominal scenarios and do not yield a robust solution when uncertainties are considered. Thus, the abovementioned sources of uncertainty are considered and analyzed further to find the optimal feedstock and processing pathway under uncertainty.

**Optimal feedstock and processing route under uncertainty**

Stochastic optimization results in Table S18 indicate that the selection frequencies of glycerol, corn stover, and glucose are 2654/5000 (53.1%), 1367/5000 (27.3%), and 979/5000 (19.6%), respectively. The results of the feedstock ranking by stochastic optimization can be seen to differ from the ranking obtained through deterministic optimization, indicating that the uncertainty in the dataset indeed has a significant impact on optimal feedstock selection. *S. japonica* was not selected a single time out of the 5000 scenarios, indicating that its use for this purpose is not economically viable at the current technology level and feedstock cost.

Regarding the topologies of the selected feedstock, 39 unique pathways are found, as shown in Table S18. Of these, 12 are for glycerol, 16 for corn stover, and 11 for glucose. Here, only the pathway occurring with the highest frequency can be considered a robust optimal processing pathway for further analysis. The results presented in Table S18 and Figure 6 show that the highest frequency processing pathways for almost all feedstocks are similar to the deterministic pathway. The exceptions are the processing pathways of corn stover and glycerol, for which different pH control reagents are selected (i.e., ammonia and magnesium hydroxide, respectively, instead of sodium hydroxide). The similarity of the stochastic-optimization-based biorefinery structures to those achieved through deterministic optimization indicates the robustness of the deterministic processing pathways. Even though *S. japonica* is not selected even once out of 5000 scenarios, the optimal processing route of *S. japonica*, as obtained from the deterministic calculation, was also included in further calculations for a rigorous comparative analysis between all feedstocks and their processing pathways.

**Process-indicator distributions**
The highest frequency optimal topologies listed in Table S18 of the supplementary material i.e., pathway 1 for glycerol, corn stover, and glucose as well as a deterministic optimal pathway for *S. japonica* presented in Figure 3D are further analyzed to evaluate the distribution of process indicators under uncertainty. Here, the binary variables corresponding to the aforementioned optimal pathways of all feedstocks are fixed, and Monte Carlo simulation is performed for 10000 samples using a random value generated from a uniform distribution for all uncertainty parameters listed in Tables S14–S16 to evaluate the distribution of the process indicators. The results in Figure 7A and 7C indicate that bio-SA production from the optimal processing pathway for glycerol has the maximum average NPV (21.3 million USD) and the minimum average bio-SA selling price (1.8 USD/kg). The variation in NPV and MPSP is maximal for optimal processing of glucose, which is actually in accordance with the results of local sensitivity analysis whereby glucose was found to be most sensitive to feedstock cost. Results in Figure 7B show that the average total capital investment is lowest for the optimal processing pathways of glucose and glycerol. Despite the comparable capital investment, bio-SA production from the glycerol topology is much more promising due to its higher NPV and lower MPSP, with a minimum standard deviation for both indicators. The optimal processing pathway for corn stover is the second to best option for producing bio-SA at a 4.0% higher MPSP than the optimal processing route for glycerol. Significant changes in the average NPV (73.4% decrease) and MPSP (6.2% increase) were observed in the processing pathway of glucose compared with glycerol-based bio-SA. *S. japonica* had the worst process economics with a negative NPV corresponding to an average of –38.2 million USD and an MPSP of 2.2 USD/kg, which are respectively 266.1% lower and 23.7% higher than the corresponding values for the optimal pathway of glycerol.

**Sustainable bio-SA production**

**Risk assessment**

The results in Figure 7C show that bio-SA production through the optimal pathway of glycerol is potentially the best investment alternative since it has the lowest risk. The risks associated with bio-SA production via the optimal processing pathways for glycerol, corn stover, glucose, and *S. japonica* at the market selling price of 2 USD/kg are 5%, 17%, 32%, and 85%, respectively. It was of interest to calculate the market selling price of bio-SA at a 4.0% higher MPSP than the optimal processing route for glycerol. Significant changes in the average NPV (73.4% decrease) and MPSP (6.2% increase) were observed in the processing pathway of glucose compared with glycerol-based bio-SA. *S. japonica* had the worst process economics with a negative NPV corresponding to an average of –38.2 million USD and an MPSP of 2.2 USD/kg, which are respectively 266.1% lower and 23.7% higher than the corresponding values for the optimal pathway of glycerol.

**Lifecycle assessment**

The characterization scores and indicators results for the optimal processing pathways of glycerol, corn stover, glucose, and *S. japonica* are shown in Figure 8 and Table S19, in which a positive value shows an environmental burden, while a negative value shows environmental savings. The environmental burdens of bio-SA production can occur in four stages: feedstock, transportation, conversion at the biorefinery (pretreatment, fermentation, and purification), and product transportation. However, environmental savings can be achieved by producing bio-SA and digestate to displace maleic anhydride-based SA and dried distillers’ grains with solubles (DDGS) as a high-protein animal feed, respectively. A system-expansion approach was used to avoid co-product allocation based upon the consequential LCA.

The overall lifecycle impact-assessment results shown in Figure 8 indicate that the environmental indicators (except abiotic depletion potential, human toxicity potential, fresh water aquatic ecotoxicity potential, terrestrial ecotoxicity potential, and eutrophication potential) have much smaller values for the processing pathway of glycerol. Therefore, the glycerol-processing pathway is the most environmentally friendly option.

To evaluate the critical parameters of the environmental profile, Figure S11 presents lifecycle profiles of bio-SA production through the optimal processing pathways of glycerol, corn stover, glucose, and *S. japonica*. The results in Figure S11 indicate that in all processing pathways, abiotic depletion potential is most significantly affected by the emissions from the purification area, of which the main cause is the use of a large amount of sulfuric acid, which is used to regenerate free SA from its salts. About 0.92–1.15 kg of sulfuric acid is consumed to produce 1 kg of SA. The high agitation power needed in the fermenter and the large consumption of heating utility in the purification area are the main contributors to fossil fuel depletion potential in all topologies. In the processing pathway of *S. japonica*, sea field cultivation is found to be another major contributor to fossil fuel depletion potential, mainly due to the high consumption of polymeric materials used during cultivation and harvesting of seaweed, as well as the fuel consumed to transport seaweed to the biorefinery. The greenhouse gases released (1) during the consumption of fossil fuels to power the biorefinery, (2) from the processing to the atmosphere, and (3) from the extraction, preprocessing, and transportation of raw materials to the biorefinery gates have significant impacts on the global warming potential indicator. The heating utility in the purification area is the main driver of global warming potential; indeed, 60.6%, 71.7%, 78.7%, and 89.3% of the total process energy is consumed in the downstream-processing pathways for glycerol, *S. japonica*, corn stover, and glucose, respectively. Consequently, 50%–85% of greenhouse gas emissions are generated by utility consumption in downstream operations where phase change operations such as evaporation or drying or both occur. In the upstream, power consumption by agitation in the fermenter and the pretreatment reactor is found to be the main contributor to global warming potential. Utilities, as well as large amounts of pH control reagent in the fermenter and acid utilization in downstream operations are the main contributors to ozone depletion potential, human toxicity potential, fresh water aquatic ecotoxicity potential, marine aquatic ecotoxicity potential, terrestrial ecotoxicity potential, photo chemical oxidation potential, and acidification potential.

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*J. Name.*, **2013**, *00*, 1-3 | 7
in the optimal processing pathways of glucose, glycerol, and corn stover. By contrast, the aforementioned environmental indicators are primarily affected by sea field cultivation and harvesting in the processing pathway of S. japonica. The emissions from the wastewater treatment area are the key drivers for eutrophication potential in all processing pathways. Environmental savings are achieved by displacing petroleum-based SA in topologies of glucose and glycerol. Interestingly, the processing pathways for corn stover and S. japonica achieve environmental savings by displacing both petroleum-based SA and DDGS.

The operating costs of the process are estimated to be 87 million USD, whereas the revenue from the product sale is estimated to be operating at only 17.5% capacity, at which the revenue generated from SA sale was only 12 million USD, with all debts the same and more losses. Over time, these losses accumulated and the company went bankrupt. The techno-economic results further revealed that the NPV and MPSP of bio-SA obtained from the BioAmber process are −143.5 million USD and 3.5 USD/kg, respectively. The cash flow diagram shown in Figure S13 indicates that the plant would not make any profit throughout the project life, which is why the NPV is −143.5 million USD. In addition, the cash flow diagram further demonstrates that the process would not even pay out the initial investment (payback period). Owing to continuously increasing loans and under capacity production, BioAmber quickly ran out of funding and cash, and the company was bankrupt after two years of operation. The MPSP suggests that BioAmber’s process would make money only if the SA market price was above 3.5 USD/kg.

Suggestions to improve the process economics of the BioAmber Plant

1) The first target should be improving the upstream technology. More efficient and robust metabolic engineered strains are needed to resist acidic pH levels and generate a high yield of products to decrease production costs. In case of a 90% yield in the fermentation, an NPV of −8.6 million USD and an MPSP of 2.6 USD/kg are estimated. This represents a 16.5-fold improvement in NPV and 1.3-fold improvement in MPSP.

2) Using cost-effective feedstock, such as corn stover or bakery waste, would further improve the economics. The techno-economic results indicate that raw material costs (corn syrup) account for 66.7% of the total manufacturing costs. To this end, decreasing the feedstock cost by 25% compared to the base case costs (0.78 USD/kg) and integrating this goal with the previous target generates an NPV of 27.2 million USD and an MPSP of 2.3 USD/kg.

3) Developing efficient downstream processing can further improve the economics. In the base case, utility costs contribute 16.2% toward the total manufacturing costs, of which 77% of the utility costs are utilized in downstream. Therefore, the downstream of BioAmber’s process should be optimized. The optimization results suggest that replacing the phase change distillation process with an ion-exchange column can dramatically decrease the utility costs from 10.1 million USD to 1.5 million USD due to the elimination of phase change operations such as distillation. Consequently, an NPV of 37.8 million USD and an MPSP of 2.2 USD/kg are achieved after implementing all three suggestions in the model. The cash flow diagram (Figure S14) indicates that the newly suggested plant would have a payback period of ~9 years.

To this end, this analysis highlights several factors that may have contributed to the bankruptcy of the BioAmber plant. The most significant factors are 1) high production costs of up to 3.5 USD/kg, (2) inefficient upstream and downstream technologies, (3) the inability of management and skilled staff to operate the plant at full or even half capacity, and (4) an overestimation of the SA market and its price. Certainly, the real case is more complicated than simulating the process since BioAmber’s management had to minimize various risks such as stochastic
conditions related to funds, foreign exchange rate, and company reputation, all of which required knowledge and support services for risk mitigation. Nevertheless, the developed model could be useful for investment decisions related to bio-SA production at a commercial scale.

**Multi-criteria assessment of bio-SA plants based on global demand**

The goal of this analysis is to estimate the total number of bio-SA plants needed to meet the forecasted global demand for SA (94,000 t) by 2025. Based on the determined number of bio-SA plants, multi-criteria analysis is performed on (1) feedstock requirements and availability, (2) profitability assessment, and (3) global warming potential compared with petrochemical-based SA. Since the forecasted demand for SA may change due to unforeseen market conditions, three cases were considered for conducting a realistic multi-criteria analysis. These were the conservative, base, and optimistic cases, which were respectively defined as being 50% lower than, equal to, and 50% higher than the forecasted demand for SA in 2025. Furthermore, various biorefinery sizes based on commercial-scale bio-SA plants (Table 1) and historical feedstock prices (Table S14) were investigated to determine the scale of future biorefineries and feedstock price ranges with ultimate MPSP targets of 1.5 and 1.6 USD/kg for SA. Bio-SA production from first-generation-based glucose is excluded from the analysis due to food security issues.

Considering the BioAmber plant’s capacity (i.e., 30,000 t/y), the number of bio-SA plants required for the conservative, base, and optimistic cases are 2, 4, and 5, respectively. Taking an optimistic scenario as a reference for estimating feedstock requirements and availability, 0.16 million t of glycerol, 0.61 million t of corn stover, and 9.78 million t (wet basis) of *S. japonica* are required. As of 2019, the global production of glycerol, corn stover, and *S. japonica* were 4–5 million t, respectively. Clearly, bio-SA plants using glycerol and corn stover as a feedstock would have a secure biomass supply; by contrast, plants using *S. japonica* as a feedstock would be at considerable risk, as 86% of total global production would be required to meet the bio-SA demand. Based on the calculated numbers of bio-SA plants, the results in Figure 9A indicate that, for all scenarios, the total capital investment required to build the nth-scale bio-SA plant is minimal for glycerol (70–170 million USD) and maximal for *S. japonica* (180–450 million USD). When compared based on MPSP, the glycerol-based bio-SA plant performs better economically. The results in Figure 9A show that the TCI required to build nth corn stover-based bio-SA plant is 111% higher than that for glycerol-based bio-SA plants. Nevertheless, the MPSP achieved in corn stover-based bio-SA plants is comparable to that in glycerol-based bio-SA plants because corn stover is an 89% less expensive feedstock than glycerol. This clearly indicates that bio-SA should be produced from glycerol and corn stover. It is important to note that if multi-criteria analysis is conducted considering the Myriant plant’s capacity (i.e., ~15,000 t/y), the TCI increases by 10%–20%, and the MPSP of SA decreases by 4%–10% compared with the results obtained considering the BioAmber plant capacity. These results show that careful consideration of the biorefinery scale and feedstock price is required to capture the lowest possible MPSP for SA. The results in Figure 9B–9C demonstrate that, to achieve an MPSP of 1.5 USD/kg, the plant scale should be between 30,000 and 45,000 t/y for glycerol and between 27,000 and 45,000 t/y for corn stover, whereas the feedstock price should be below 700 USD/t for glycerol and below 75 USD/t for corn stover. LCA results in Table S20 shows that the global warming potential of bio-SA production from the optimal processing pathway of glycerol is 2.9 kg CO2-eq, which is 24% lower than the SA production from maleic anhydride. However, if environmental credit is considered by displacing an equivalent amount of maleic anhydride-based SA, the global warming potential of glycerol-based bio-SA becomes ~0.94 kg CO2-eq (Table S19). These results indicate that bio-SA production from glycerol is more environmentally friendly than petroleum-based SA production.

**Conclusion**

One of the biggest challenges facing green projects from the investors’ viewpoint is to ensure a secure investment that will generate profits with minimum risk while still abiding by strict environmental legislation. In addition, securing a long-term supply of biomass for producing green chemicals is a major bottleneck threatening the commercial success of biorefineries. In this study, we evaluated the economic factors and lifecycle profiles of bio-SA production from glucose (first-generation feedstock), corn stover and bio-glycerol (second-generation feedstock), and seaweed (third-generation feedstock) by investigating their optimal processing pathways under deterministic and stochastic conditions. Overall, the results indicate that uncertainties may have a significant impact on process economics, as well as on the topology of the optimal process required to produce bio-SA. Therefore, stochastic optimization was performed to cope with all potential challenges arising from uncertainties. The results of stochastic optimization indicate that glycerol is the best feedstock for producing bio-SA at the lowest selling price of 1.6–1.9 USD/kg, while corn stover is the second best to 1.7–2.0 USD/kg. An optimal pathway for glycerol is found to be a very attractive option from the investors’ viewpoint for producing bio-SA at the lowest possible selling price with a minimum investment of 34–44 million USD. Corn stover can be an excellent feedstock for producing bio-SA; however, major technological breakthroughs are needed to avoid expensive pretreatment and high capital investment of up to 75–94 million USD, which is about twice the capital investment needed for the optimal processing pathway of glycerol. *S. japonica* is not suitable for large-scale bio-SA production due to the high cost of seaweed, as well as the inability of enzymes to process alginate, which is a major carbohydrate representing 25–30 wt% of this feedstock. By implementing an integrated strategy in which bioethanol is first produced by fermenting algin and bio-SA is then produced by fermenting the remaining carbohydrates such as laminaria and mannitol, it may be possible to enhance the economic potential of the project.
viability. Risk assessment shows that bio-SA production from an optimal pathway of glycerol is the best alternative due to its lower associated risk. The overall environmental profile indicates that the optimal pathway of glycerol is also the most environmentally friendly process, followed by that using corn stover, glucose, and S. japonica. In all processing pathways, utility, pH control reagent, and acidification are found to be the main contributors to all environmental indicators. Fermentation at acidic pH should be used to avoid using high quantities of pH control reagent in fermentation and acid in the regeneration of SA from its salts. Additionally, purification technologies that require phase change operations should also be avoided to enhance environmental sustainability by decreasing the utility consumption. An ion-exchange column is found to be the optimal purification technology in terms of environmental indicators compared with technologies in which phase change operations are involved. Bearing in mind the need for a secure long-time supply of biomass and minimal investment, glycerol from a bio-diesel biorefinery is highly recommended as feedstock to produce bio-SA through its optimal processing pathway due to the low associated risk and superior environmental profile. Another attractive business option for future biorefineries would be an SA through its optimal processing pathway due to the low market value of SA and its good environmental performance due to its utilization of carbon dioxide to produce bio-SA. Considering the forecasted global demand for bio-SA (94,000 t/y) by 2025, four bio-SA plants corresponding to BioAmber’s plant capacity (30,000 t/y) would be needed to meet this demand. The total capital investment required for these plants would be 135 million USD for glycerol-based plants and 285 million USD for corn stover-based plants. Decreasing the fermentation time, increasing the product titer, and improving bacterial resistance to lower pH values have been highlighted as future bench-scale research targets to further improve the economic prospects of bio-SA production compared with petrochemical SA production.

Conflicts of interest
There are no conflicts to declare.

Acknowledgements
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Abbreviations

<table>
<thead>
<tr>
<th>Units</th>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metric ton</td>
<td>t</td>
<td></td>
</tr>
<tr>
<td>US dollar</td>
<td>USD</td>
<td></td>
</tr>
<tr>
<td>kilo-ton/year</td>
<td>kt/year</td>
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</table>

Notes and references


Figure 1 Biorefinery superstructure for the production of bio-SA from multiple feedstocks including corn stover, *S. japonica*, glycerol, and glucose.
Figure 2 Process economic indicators of optimal topologies [A]. Total capital investment breakdown of optimal topologies [B]. Abbreviations: NPV = Net present value; TCI = Total capital investment; COM = Cost of manufacturing; MPSP = Minimum product selling price; and DDS = Dry distiller solids.
Figure 3 Optimal processing pathway for corn stover (A), glycerol (B), glucose (C), and S. japonica (D) through deterministic optimization (red solid arrows) and stochastic optimization (blue dashed arrows). Black solid lines are common unit operations in both the deterministic and the stochastic optimization.
Figure 4 Feedstock selection and minimum product selling price variation in the top 10 to 100 topologies. Each bar indicates the number of times (frequency) certain feedstock appears in the top 10 to 100 topologies. The line chart shows the average minimum product selling price in each bar.
Figure 5 Local sensitivity analysis on net present value for bio-SA production from corn stover (A), glycerol (B), glucose (C), and S. japonica (D). In local sensitivity analysis, the impact of each variable on economics was estimated by varying its maxima and minima while keeping all other variables constant (single point sensitivity analysis). Variations in uncertain parameters of all processing pathways are shown on the right-hand side of each figure. Maximum variation in in the fermentation of glycerol (B) and glucose (C) is varied to 2% as base case experimental value is already close to the theoretical yield.
Figure 6 Frequency of selection of pathways for glycerol, corn stover, and glucose using stochastic optimization for 5000 scenarios. The processing pathway with the highest frequency would be considered robust for each feedstock.
Figure 7 Net present value range (A), total capital investment range (B), and minimum product selling price range based on 10000 Monte Carlo simulations (C). Y-axis in Figure 7C shows variation in minimum product selling, whereas bars with vertical patterns in Figure 7C indicate economic risk considering the market price of bio-SA at 2 USD/kg. The risk of any processing pathways of feedstock can be estimated by dividing the summation of vertical bars’ frequency by the total frequency (10000) of simulation.
Figure 8 Comparative life cycle impact assessment of bio-SA production through the optimal processing pathway (OPP) of glycerol, corn stover, glucose, and S. japonica. Abbreviations: ADP = Abiotic depletion potential; AFFDP = Fossil fuel depletion potential; GWP = Global warming potential 100 years; ODP = Ozone depletion potential; HTP = Human toxicity potential; FWAE = Fresh water aquatic ecotoxicity potential; MAETP = Marine aquatic ecotoxicity potential; TEP = Terrestrial ecotoxicity potential; PCOP = Photochemical oxidation potential; AP = Acidification potential; EP = Eutrophication potential.
Figure 9 Profitability analysis of nth bio-SA plants to satisfy forecasted demand of SA by considering conservation, base, and optimistic cases (A). Minimum product selling price (MPSP) for SA in optimal processing pathways (OPP) of glycerol (B) and corn stover (C) as a function of biorefinery plant scale and feedstock price. The area under the line in Figure 9B-9C represents a feasible combination of plant scales and feedstock prices to achieve the target MPSP.
Table 1 Commercial-scale succinic acid biorefineries in the world including their capacity, start-up year, the biomass source, major upstream and downstream technologies, and challenges.

<table>
<thead>
<tr>
<th>Company</th>
<th>Capacity (kt/year)</th>
<th>Operative Year</th>
<th>Raw material</th>
<th>Fermentation/ Microorganism</th>
<th>Downstream recovery</th>
<th>Potential challenges</th>
<th>Location</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>BioAmber(^{a}) Mitsui &amp; Co</td>
<td>30-50</td>
<td>2015</td>
<td>Corn glucose</td>
<td>Candida krusei /pH 3, aerobic batch</td>
<td>DAS(^{b}) + reactive evaporation</td>
<td>Effect of low pH on fermentation performance.</td>
<td>Sarnia, Canada</td>
<td>7</td>
</tr>
<tr>
<td>Reverdia(^{c}) (Roquette)</td>
<td>10</td>
<td>2012</td>
<td>Starch/Sugar</td>
<td>pH 3, dual phase fed-batch/ Recombinant S. cerevisiae (by DSM)(^{1})</td>
<td>Direct separation of SA</td>
<td></td>
<td>Cassano, Spinola, Italy</td>
<td>7,50–52</td>
</tr>
<tr>
<td>Myriant(^{d})</td>
<td>14</td>
<td>2013</td>
<td>Glucose/Sugars</td>
<td>E. coli</td>
<td>Ammonia precipitation</td>
<td></td>
<td>Lake Providence, Louisiana, USA</td>
<td>7,53</td>
</tr>
<tr>
<td>Succinity(^{e}) (joint venture BASF &amp; Corbion-Purac)</td>
<td>10</td>
<td>2014</td>
<td>Glycerol/Sugar/CO(_2)</td>
<td>Anaerobic fed-batch/B. succiniciproducens</td>
<td>Mg(OH)(_2) as neutralizer followed by recycling</td>
<td>Dependency on two recycles in process Cost and performance of MgCl(_2) cracking SA recovery in MgCl(_2)-stream</td>
<td>Montmel, Spain</td>
<td>7,53,54</td>
</tr>
</tbody>
</table>

\(^{a}\) BioAmber went bankrupt.\(^{55}\)  
\(^{b}\) DAS: diammonium succinate  
\(^{c}\) Formerly a joint venture between DSM and Roquette: From April 2019 Roquette has all the rights and obligations related to Reverdia’s Biosuccinium plant in Cassano, Italy.\(^{56}\)  
\(^{d}\) Myriant became GC Innovation America in August 2018, restructuring its operations in 2017 from bio-SA production to R&D.\(^{57}\)
Table 2 Advantages and disadvantages of main downstream technologies for bio-SA recovery: electrodialysis bipolar membrane (EDBM), microfiltration (MF), ultrafiltration (UF), nanofiltration (NF), centrifugation, extraction, precipitation, absorption, and crystallization.

<table>
<thead>
<tr>
<th>Technology</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membranes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDBM</td>
<td>High degree of SA separation from the fermentation broth: removal of uncharged molecule e.g. microbial cell, proteins, pigments and water; Microbial cell recycle applicable;</td>
<td>High capital and operative costs; Limited lifetime;</td>
</tr>
<tr>
<td>MF</td>
<td>Complete separation of microbial cells; easily scalable; Continuous operation; Complete cell recycle; No bio-SA losses;</td>
<td>High sensitivity to broth condition: cell viability, feedstock quality; Membrane fouling;</td>
</tr>
<tr>
<td>UF</td>
<td>High protein removal efficiency (&gt;75%); Easily scalable; Continues operation</td>
<td>Severe membrane fouling is typically reported; Reduced durability if frequent cleanings;</td>
</tr>
<tr>
<td>NF</td>
<td>Organic acid separation and concentration of bio-SA (&gt;80%); Complete pigments removal can be achieved; Easily scalable; Continues operation;</td>
<td>Membrane fouling; Low selectivity: bio-SA cannot be efficiently separated from the other organic acids and ions in the fermentation broth</td>
</tr>
<tr>
<td>Extraction</td>
<td>Removal of host microbial cells and proteins in one step;</td>
<td>Large use of chemicals; High loss of bio-SA</td>
</tr>
<tr>
<td>Centrifugation</td>
<td>Well known technology for industrial application; Efficiently used for complete cell removal from fermentation broth; High throughput up to 96 m^3/h;</td>
<td>Different design and performance between lab and industrial; High losses for low concentrated bio-SA broths; Not continuous; Sterilization required at every batch;</td>
</tr>
<tr>
<td>Chromatography</td>
<td>Conversion/separation of bio-SA salt into/from the free acid form;</td>
<td>Limited selectivity; Low yield</td>
</tr>
<tr>
<td>Activated carbon</td>
<td>Efficient pigment and protein fragments removal;</td>
<td>High carbon quantity may be required; Loss of bio-SA</td>
</tr>
<tr>
<td>Precipitation</td>
<td>Reduced waste formation; Nearly complete recycle of reagents; Both BioAmber, Myriant used a form of precipitation in their process;</td>
<td>High energy consumption to regenerate reagents; Corrosion of equipment due to low pH;</td>
</tr>
<tr>
<td>Crystallization</td>
<td>Very high bio-SA purity (&gt;99%) when applied in the last steps of the downstream purification; Fundamental technology to produce marketable bio-SA crystals;</td>
<td>Low pH (&lt; 3.0) required; Impurities can crystallize with bio-SA if impurities not previously removed;</td>
</tr>
</tbody>
</table>