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Techno-Economic Analysis of Alternative Designs for Low-pH Lactic Acid Production

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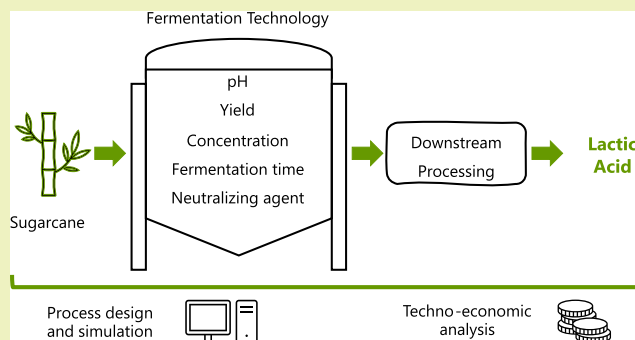
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ABSTRACT: Lactic acid production is highly affected by the fermentation pH. The need for neutralizing agents and the salts produced during fermentation have a significant impact on the overall process performance. Changing the neutralizing agent and allowing lower pH fermentation can improve the process profitability. This work investigates the impact of fermentation parameters and evaluates the process economics of alternative downstream processing designs to produce lactic acid. The results show that low-pH fermentation (pH = 3.86) was profitable (internal rate of return, IRR > 10%) at a fermentation yield of 0.97 g/g sucrose. Decomposing the salt subproduct to reduce the environmental burden associated with gypsum disposal has a significant impact on the economic performance, resulting in a lower IRR than the other designs. Although the salt decomposition process has a high energy demand, it is compensated by the savings obtained in the downstream processing, thus resulting in a similar overall energy demand when compared to conventional reactive distillation. A novel process configuration with ammonium sulfate subproduct shows potential for 3 p.p. higher IRR and up to 30% lower fuel demand in comparison with the conventional process. Therefore, alternative downstream processes could drive low-pH fermentation to outperform the conventional process without any neutralizing agent.

KEYWORDS: lactic acid, fermentation, downstream processing, liquid–liquid extraction, process simulation, techno-economic analysis, gypsum-free



INTRODUCTION

The interest in producing chemicals and materials from renewable sources has pushed the development of biorefineries, in which a variety of products can be obtained through biological or chemical conversion routes from intermediate molecules, the so-called platform chemicals. Among these molecules, lactic acid (LA), produced from the fermentation of refined sugars and starches, has broad applications in food, pharmaceutical, and chemical industries.¹

Most LA-producer microorganisms have an optimum pH close to neutral. Thus, the acid product itself leads to inhibition as fermentation occurs. This limits the initial sugar and final product concentrations besides fermentation productivity, which, in turn, impacts the purification costs due to dilute product streams.² Hence, LA fermentation pH is controlled through the addition of lime (or other base). After biomass filtration, LA is recovered through sulfuric acid addition, producing equivalent amounts of low-value gypsum (calcium sulfate), which represents a problem of its own due to the environmental impact and cost for its disposal.² Alternative strategies have been developed to circumvent low pH inhibition, including product in situ removal through membrane separation, solvent extraction, adsorption, and

electrodialysis.^{2,3} However, these technologies have a high cost and so far are not compatible with the targeted LA cost.

Another approach is to use acid-tolerant microorganisms. One strategy is to improve acid tolerance of natural LA-producer strains⁴ or to turn more robust, acid-tolerant strains such as yeasts into efficient LA producers.^{5,6} Nonetheless, experimental results shown in Table 1 suggest that the engineered microorganisms that withstand lower pHs tend to have lower yields and productivity in comparison to less acid-tolerant strains. This negatively impacts the economic evaluation of such processes and does not discard the need for neutralization and disposal of salt subproducts. For example, low-pH (≤ 3.0) yeast-based fermentation has been applied commercially by Cargill since 2008, with product concentration and productivity of ca. 130 g/L and 3 g/(L h),⁷ respectively. This process, however, only decreases the amount

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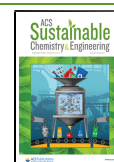


Table 1. Literature Survey of Microorganisms for LA Production at Different pHs^a

ref.	microorganism	pH	substrate
5	<i>Saccharomyces cerevisiae</i> (engineered)		glucose [100 g/L, 0.70 g/g, 0.97 g/(L h), D]
8	<i>Sporolactobacillus terrae</i>	5.10	sucrose [120 g/L, 0.86 g/g, 1.44 g/(L h), D]
9	<i>Lactobacillus delbrueckii</i>	6.00	sugarcane juice [133 g/L, 0.90 g/g, 1.67 g/(L h), D]
10	<i>Saccharomyces cerevisiae</i> (mutant)	2.37	glucose [90 g/L, 0.97 g/g, 0.98 g/(L h), L]
11	<i>Escherichia coli</i> (engineered)	7.00	sucrose [109 g/L, 0.89 g/g, 1.83 g/(L h), L]
12	not informed	6.40	beet juice [278 g/L, 0.97 g/g, 11.22 g/(L h), L]
13	<i>Lactobacillus plantarum</i>	6.00	cane molasse [200 g/L, 0.90 g/g, 5.38 g/(L h), –]

^aProcess conditions are indicated besides the substrate as [initial concentration of substrate, mass yield, productivity, and D or L isomer].

of inorganic salt produced instead of eliminating it. The environmental impact is reduced by using the gypsum subproduct as a soil conditioner.^{2,7} Therefore, while “perfect” high-acid tolerant microorganisms are not available, the pH the microorganisms withstand and the need for neutralization are important aspects that impact the LA production costs.

This work evaluates how different LA production routes impact the final costs employing process simulation and economic analysis. The simulation considers different fermentation pHs and yield to evaluate different neutralizing agents and their adequate downstream processing. Considering that low pH fermentation usually results in lower yields and productivity, the material, energy, and economic requirements for different LA yields and fermentation pH for different downstream processing strategies are estimated in this work. The results show that alternative processes could be

competitive with the conventional design if higher product concentration and yield were obtained in low-pH fermentation. Thus, simulation and economic analysis result in fermentation yield and productivity–profitability trade-off data, thus providing performance targets to the scientific community for future developments in process design and acid-tolerant strains for LA fermentation.

PROCESS DESIGN

The LA production process is simulated from traditional sugarcane feedstocks. The simulations consider a sugarcane supply of 212 ton/h (1 million tons/year) based on an autonomous ethanol distillery.¹⁴ After sugarcane crushing, the juice is clarified and sent to fermentation. During fermentation, the lactic acid product build-up causes inhibition, thus lowering the yield and productivity. Because of that, in this step, a base is added to the fermenter, maintaining the fermentation pH required by the microorganisms. Depending on the neutralizing agent employed, different downstream processing configurations were adopted to obtain an 88 wt % LA product.

Figure 1 shows the overall process representation for all scenarios. Sugarcane composition, conditioning, juice extraction, and juice treatment steps are based on a first-generation ethanol distillery design.¹⁴ The juice obtained after clarification has a sucrose concentration of 125 g/L. For the scenarios with higher sugar concentration, after clarification, the juice is concentrated in a triple-effect evaporator. The evaporation coefficient (*c*) is estimated from eq 1,¹⁵ where *B* represents the Brix (sugar content in g per 100 g of aqueous solution) of the juice leaving the effect and *T* the temperature of the heating vapor, in °C.

$$c \left[\frac{\text{kg of vapor}}{\text{h m}^2 \text{ } ^\circ\text{C}} \right] = 0.001(100 - B)(T - 54) \quad (1)$$

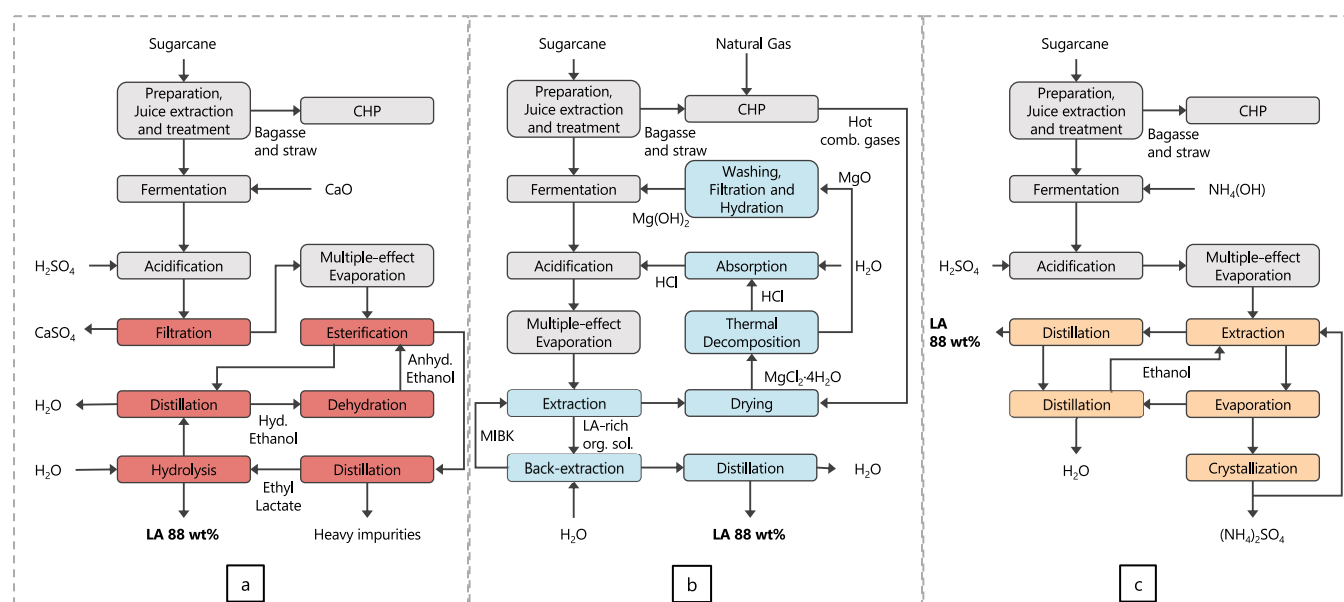


Figure 1. Simplified block flow diagrams of alternative processes for the production of lactic acid according to the neutralizing agent employed during fermentation. The steps in gray are common to all scenarios, and those before fermentation are based on an autonomous ethanol distillery.¹⁴ The steps in different colors vary according to the chosen neutralizing agent. (a) CaO: “business-as-usual” process—gypsum (CaSO₄) subproduct separation and reactive distillation; (b) Mg(OH)₂: “salt-free” process, with Mg(OH)₂ and HCl recovery and recycle; and (c) NH₄OH: salting-out extraction using (NH₄)₂SO₄ and ethanol, with (NH₄)₂SO₄ subproduct.

Fermentation. The design and simulation scenarios were based on different fermentation pHs, yields, batch duration, feed sugar concentrations, and neutralizing agents according to Table 2. Since literature results for modified microorganisms

Table 2. Fermentation Scenarios

parameter	values
fermentation pH	3.86; 7.0
mass yield (g LA/g sucrose)	0.7; 0.97
fermentation time (h)	24; 48; 72
sugar concentration (g/L)	130; 250
neutralizing agents	Mg(OH) ₂ ; NH ₄ OH; CaO

(Table 1) are usually obtained under different conditions, such as temperatures, substrates and/or neutralizing agents, and their concentrations, they would not allow a fair comparison between process designs and neutralizing agents. Therefore, the parameters in Table 2 were defined to represent sugar concentration, yield, and productivity compatible with the literature data. The conditions in Table 2 were assumed at a fixed temperature of 40 °C across all scenarios.

The amount of added neutralizing agents was calculated to neutralize 50 or 100% of the produced lactic acid to achieve a pH of 3.86 or 7.00, respectively. After fermentation, the cells are removed through centrifugation, and the LA solution is sent to the different downstream processing alternatives.

Downstream Processing. Each downstream processing configuration was designed according to the neutralizing agent used during fermentation. In the first scenario (business-as-usual), calcium oxide is used, resulting in a gypsum subproduct. After gypsum removal, the lactic acid product is subjected to esterification with ethanol in the reactive distillation process for separation and purification.

In the second scenario, the salt subproduct is magnesium chloride, which is used to increase the lactic acid product removal through solvent extraction. In this scenario, the neutralizing base, magnesium hydroxide, and the required acid added, hydrochloric acid, are recovered and recycled, so that there is no salt subproduct to be disposed of. In the last scenario, the salt subproduct (ammonium sulfate) also favors solvent extraction. However, in this case, the neutralizing base, ammonium hydroxide, is not recovered and the salt subproduct can be used as a fertilizer. Further description of each scenario is provided in the following subsections.

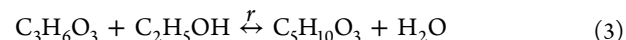
Calcium Oxide—"Business-As-Usual". In the conventional process (Figure 1a), the calcium neutralizer reacts with lactic acid during fermentation, producing a Ca-lactate solution, which is then contacted with H₂SO₄ in an acidulation tank, to produce CaSO₄ (gypsum). The precipitated salt is removed in a system of hydrocyclone and vacuum filter,¹⁶ while the LA recovered will be concentrated and then purified in a series of both reactive and conventional distillation columns (herein referred to as reactive distillation) to achieve the required product specification. The LA solution is concentrated to 50 wt % in a six-effect evaporator and a final evaporation step, where the vapor goes through a six-stage distillation column to achieve a 70 wt % solution.¹⁷

The design pressures in the series of multiple effect evaporators (MEE) were set to obtain a temperature difference of at least 5 °C. The average heat-transfer coefficient for each effect was estimated as a function of the lactic acid mass

fraction in the feed solution (w_{LA}) based on a rigorous Aspen Plus heat exchanger calculation according to eq 2.

$$U \left[\frac{\text{kJ}}{\text{s m}^2 \text{K}} \right] = 1.4094 - 1.9874 w_{LA} \quad (2)$$

This concentration step is important to favor the following esterification step, which is equilibrium-limited (eq 3). Otherwise, larger volumes of ethanol would be required to achieve high LA conversion.¹⁸



The concentrated LA solution then reacts with ethanol in a reactive distillation column at an EtOH/LA molar ratio of 3.5 to produce ethyl-lactate (EtLA), which is recovered in the bottom stream and separated from heavier impurities and unreacted LA by vacuum distillation.¹⁸ The recovered EtLA is hydrolyzed back to LA in another reactive distillation column at an H₂O/EtLA molar ratio of 1.5.¹⁹ The 88 wt % LA product is obtained as the bottom stream of this column. The excess ethanol and water obtained in the distillate streams of both reactive distillation columns are separated by distillation to produce a 93 wt % ethanol solution, which is then dehydrated to 99.2 wt % in a membrane separation system,²⁰ before being recycled to the first column. The main design parameters are listed in Table 3.

Table 3. Main Parameters of the CaO-Based Process

process	specifications
acidification	residence time: 4 h; T: 50 °C
CaSO ₄ separation	25 wt % moisture
MEE	70 wt % LA
	1st effect: 1.8 bar
	6th effect: 0.26 bar
esterification	EtOH/LA molar ratio: 3.5
	LA conversion: 98%
	34 stages; 12 reactive stages;
EtLA distillation	0.015 bar; 25 stages
	99.9% EtLA recovery
hydrolysis	H ₂ O/EtLA molar ratio: 1.5
	42 stages; 34 reactive stages
EtOH distillation	1 bar; 63 stages
	100% EtOH recovery
	93 wt % EtOH
EtOH dehydration	99.2 wt % EtOH

Magnesium Hydroxide—"Salt-free". To produce gypsum-free lactic acid, Purac Biochem patented a process based on the salting-out extraction using an oxygenated solvent, preferably methyl isobutyl ketone (MIBK).²¹ In this process, the neutralizing chemicals (base and acid) are recovered and recycled to the fermentation step, so that there is no undesired gypsum residue. The process configuration adopted in this work (Figure 1b) is based on the Purac Biochem patent^{21,22} and the Aman process²³ used for the production of high-purity MgO from MgCl₂.

When Mg(OH)₂ is used as the neutralizing agent, the Mg-lactate solution obtained from fermentation after biomass removal is contacted with a 20 wt % HCl solution in an acidulation tank to produce MgCl₂. Although LA has a low distribution ratio in MIBK,²⁴ the presence of MgCl₂ salt in the aqueous phase increases the distribution ratio, thus reducing

the number of equilibrium stages and solvent volume required for the liquid–liquid extraction. However, the MgCl_2 concentration in the broth is lower than recommended,²¹ so a six-effect evaporation process is used to achieve a 14–15 wt % MgCl_2 solution, similar to the one described in the previous sections.

After concentration, this solution is contacted with MIBK in a sieve-tray tower at 60 °C. The extract is then fed to a second extraction column, where LA is back-extracted using water at 40 °C. The number of equilibrium stages and solvent amounts were defined based on sensitivity analysis to achieve a 98% LA recovery after both extractions. After extraction, this higher purity solution is concentrated by vacuum distillation.

To recover and recycle the neutralizing $\text{Mg}(\text{OH})_2$ and HCl, the MgCl_2 aqueous solution is subjected to a drying step, where the hydrate $\text{MgCl}_2 \cdot 4\text{H}_2\text{O}$ is obtained, and then fed to a thermal decomposition reactor, where a hot flue gas stream provides the required energy for the decomposition of this salt to HCl and MgO. The gaseous HCl-containing stream is sent to an absorption column, producing an aqueous HCl solution that can be recycled to the acidification reactor, whereas the MgO solid is subjected to a washing step to remove soluble impurities and then sent to a hydration tank to produce $\text{Mg}(\text{OH})_2$ that is used in the fermenter.²⁵ Table 4 shows the main design parameters for the $\text{Mg}(\text{OH})_2$ -based process.

Table 4. Main Parameters of the $\text{Mg}(\text{OH})_2$ -Based Process

process	specifications
acidification	residence time: 4 h; T : 50 °C
MEE	14–15 wt % MgCl_2 1st: 1.8 bar 6th effect: 0.26 bar
extraction	98% LA recovery
distillation	0.2 bar; 10 stages 99.99% LA recovery 88 wt % LA
drying	air; 130 °C
decomposition	natural gas combustion gases T_{in} : 1000 °C; T_{out} : 125 °C
absorption	8 equilibrium stages; 20 wt % HCl
MgO washing	water to MgO mass ratio: 2 100% impurities removed
MgO filtration	40% moisture
MgO hydration	T : 107 °C; 50 wt % $\text{Mg}(\text{OH})_2$ residence time: 2 h

Ammonium Hydroxide. Although calcium or ammonium hydroxides could be used as neutralizing agents and then recovered through electrodialysis without the requirement of acid addition, such a process has high capital and operating costs.⁷ Salts such as phosphates and sulfates have gained attention for the salting-out extraction of bio-derived products such as organic acids using short-chain alcohols as the solvent.^{26,27} In particular, ammonium sulfate, which can be produced during fermentation when NH_4OH is employed as the neutralizing agent, has been studied in single equilibrium-stage extraction experiments with ethanol.²⁶ The intention here is to take advantage of the salting-out effect instead of avoiding the formation of ammonium sulfate.

In this process (Figure 1c), the ammonium lactate solution from fermentation after biomass removal is contacted with a 70 mol % H_2SO_4 solution in an acidulation tank to produce

$(\text{NH}_4)_2\text{SO}_4$. MEE is employed in a similar manner to the one described in the previous section. However, achieving the required salt concentration (18.5 wt %) would result in a too high LA concentration, so the specification here is to achieve a 250 g/L LA solution, while additional salt is recycled from the process before the extraction. The extraction occurs in a sieve-tray tower at 50 °C using hydrous ethanol (93 wt %) as the solvent. The extract is fed to a vacuum distillation column to produce 88 wt % LA and the ethanol and water mixture is distilled for recovery and recycle of ethanol.

The raffinate stream is fed to a double-effect evaporation before crystallization at approximately 45 °C in a continuous evaporative forced circulation crystallizer, which was sized according to Ref 28 based on the $(\text{NH}_4)_2\text{SO}_4$ solubility data from Zapp et al.²⁹ The solid product is then filtered and dried. Table 5 shows the main design parameters for the NH_4OH -based process.

Table 5. Main Parameters of the NH_4OH -Based Process

process	specifications
acidification	residence time: 4 h; T : 50 °C
MEE	250 g/L LA 1st effect: 1.8 bar 6th effect: 0.26 bar
extraction	99% LA recovery 18.5 wt % $(\text{NH}_4)_2\text{SO}_4$ EtOH/sol. of 0.29 g/g 8 stages; 50 °C
LA distillation	0.2 bar; 10 stages 99.99% LA recovery 88 wt % LA
EtOH distillation	1 bar; 63 stages 100% EtOH recovery 93 wt % EtOH
$(\text{NH}_4)_2\text{SO}_4$ crystallization	45 °C
$(\text{NH}_4)_2\text{SO}_4$ filtration	25% moisture
drying	air; 130 °C

METHODS

Simulation. All scenarios were simulated in Aspen Plus 10 (Aspen Tech, Inc., Bedford, USA) using equilibrium (distillation and liquid–liquid extraction) and stoichiometric models (fermentation and acidification). The sugarcane composition and properties, sugarcane crushing, and juice clarification steps were based on the Aspen Plus model from the literature.¹⁴

Calcium Oxide. To model the vapor–liquid equilibrium (VLE), the non-random two-liquid (NRTL) activity coefficient model was used for the liquid phase and the Hayden–O’Connell equation of state was used for the vapor phase. The binary parameters were regressed from VLE data.^{30–32}

The reactive distillation columns were simulated using the kinetic model shown in eqs 4–6 over the Amberlyst-15 catalyst.^{33,34} The Katapak SP-12 packing characteristics and the hydrodynamic models from Ratheesh and Kannan³⁵ were applied in a user model subroutine in the rigorous distillation model (Radfrac) to estimate the column diameter and liquid holdup in the catalyst bags.

$$r = k_e \left(a_{\text{LA}} a_{\text{EtOH}} - \frac{a_{\text{EtLA}} a_{\text{H}_2\text{O}}}{K_{\text{eq}}} \right) \quad (4)$$

where

$$k_e = 1.188 \times 10^8 \left[\frac{\text{kmol}}{\text{s m}^3 \text{ holdup}} \right] \exp \left(\frac{-58.47 \left[\frac{\text{kJ}}{\text{mol}} \right]}{RT} \right) \quad (5)$$

and

$$K_{eq} = \exp \left(2.9625 - \frac{515.13}{T} \right) \quad (6)$$

Magnesium Hydroxide. To model the salting-out extraction, the electrolyte NRTL (ELECNRTL) model was employed. The binary parameters for the H₂O + LA + MIBK system were regressed from experimental data^{24,36} and the liquid–liquid equilibrium (LLE) model was validated based on the Purac Biochem patent data.²¹ The HCl absorption process was also modeled using ELECNRTL with binary parameters from Ref 37. The extraction columns were sized as tray columns,³⁸ while absorption and distillation columns were sized in Aspen Plus using the Radfrac model.

Ammonium Hydroxide. To model the VLE, the NRTL activity coefficient model was used. In salting-out extraction, the electrolyte NRTL (ELECNRTL) model was employed, and the LLE model was validated based on the experimental data from Refs 26 39 40. The extraction column was sized as a tray column,³⁸ and the distillation columns were sized using the Radfrac model in Aspen Plus.

The binary interaction parameters and the comparison between the regressed models and the experimental data are listed in the Supporting Information of this paper.

Economic Analysis. The economic analysis was based on the material and energy balances by estimating the capital and operating costs for all scenarios and determining the LA minimum selling price (MSP, in \$/t) from a discounted cash-flow analysis according to the economic assumptions in Table 6. The free on board purchase cost of

Table 6. Main Assumptions of the Economic Analysis

parameter	value
Discounted Cash Flow Analysis	
production lifetime (y)	30
construction period (y)	2
nominal capacity in the first year of production	100%
operating factor (d/y)	200
project financing	no debt, 100% equity
initial royalty fee (% CAPEX)	2%
income tax (Brazil)	34%
working capital (% CAPEX)	10%
depreciation method	10 year straight line
minimum acceptable rate of return (MARR)	10%
exchange rate	USD 1.00 = BRL 3.9451
Annual Fixed Operating Costs	
labor (% CAPEX)	1%
maintenance (% CAPEX)	2%
Annual Variable Operating Costs	
royalty fee (% product sales)	3%
location factor	1.46

conventional equipment (heat exchangers, pumps, evaporators, distillation columns, tanks, filters, etc.) was estimated from cost equations from Refs 38 44 49 50. The material of construction assumed was Stainless steel 316 (material factor = 2.9⁵¹), except for equipment in contact with HCl, for which Nickel was considered (material factor = 2.5⁴⁹). The cost of non-conventional units (sugarcane reception and juice extraction, fermenter, and cogeneration of heat and power–CHP) was calculated based on the literature data.^{14,20,52} All purchase costs were updated to December 2019 values using the Chemical Engineering Plant Cost Index (CEPCI). The fixed capital investment was estimated by using a Lang factor of 4.28.⁴⁹ In all scenarios, the CHP unit was sized to satisfy the steam required by

the process, and bagasse surplus was considered as an income in the cash flow analysis.

Uncertainty analysis of the internal rate of return (IRR) of different scenarios was carried out using Monte Carlo simulations in @RISK v.8.1.1 (Palisade Company, LLC, Ithaca, USA) with 10,000 iterations based on the prices of inputs and outputs shown in Table 7. For the

Table 7. Prices of Inputs and Outputs of LA Production Scenarios

parameter	price
electricity (\$/MW h)	47.31 ± 20% ^{a,f}
process water (\$/t)	0.56 ⁴¹
H ₂ SO ₄ (\$/t)	44.69 ± 19.03 ^{b,g}
lactic acid (\$/t)	1374.25 ± 123.64 ^{b,g}
juice treatment (\$/t _{sugarcane})	0.71 ⁴²
sugarcane stalks (\$/t)	17.97 ± 20% ^{f,42}
sugarcane straw (\$/t)	16.11 ± 20% ^{f,42}
catalyst (\$/kg)	50 ⁴³
cooling water (\$/t)	0.14 ⁴⁴
ethanol dehydration (\$/t _{EtOH})	2.66 ²⁰
sugarcane bagasse (\$/t)	33.08 ± 20% ^{f,45}
Mg(OH) ₂ (\$/t)	300 ± 20% ^{f,1}
HCl (\$/t)	145.06 ± 79.89 ^{b,g}
CaO (\$/t)	163.32 ± 8.15 ^{b,g}
NH ₄ OH (\$/t)	502.41 ± 62.90 ^{b,g}
MIBK (\$/t)	944 ± 20% ^{f,46}
hydrous ethanol (\$/t)	590.33 ± 81.01 ^{47,c,g}
(NH ₄) ₂ SO ₄ (\$/t)	134.59 ± 12.22 ^{b,d,g}
CaSO ₄ (\$/t)	12.89 ± 0.69 ^{b,c,g}
natural gas (\$/t)	369.83 ± 20% ^{f,48}

^aAverage price in Brazilian energy auctions from 2018 to 2019 (epe.gov.br/en). ^bWeighted average values from Brazilian Exports and Imports from 2015 to 2019 (comexstat.mdic.gov.br/en/home). ^cAverage values from 2015 to 2019. ^d80% of the average values. ^eValues for Limestone. ^fTriangular distribution. ^gNormal distribution.

prices based on the Brazilian historic price series, the ranges were defined based on a normal distribution within ± 1 standard deviation, while those based on literature values were set as a triangular distribution within a variation range of ± 20%.

RESULTS AND DISCUSSION

The production capacity evaluated in all scenarios is based on a sugarcane crushing capacity of 1 million t/year, which corresponds to the LA annual production ranging from 92,000 to 140,000 t, depending on the process scenario. The different LA production scenarios were simulated in Aspen Plus to obtain their material and energy requirements.

Technical and Sustainability Aspects. Table 8 shows the main material (neutralizing agents and solvents) and energy (expressed in terms of specific fuel demand) inputs, as well as product outputs (LA, salt subproducts, and electricity exported to the grid). The specific fuel demand is calculated based on the lower heating value of the fuels to account for the natural gas used in the MgCl₂ decomposition and the sugarcane bagasse and straw burned in the CHP unit. All technical results are shown for the different neutralizing agents (CaO, Mg(OH)₂, and NH₄OH) at a fixed fermentation time of 24 h.

When comparing the energy requirements for the different neutralizing agents, salting-out extraction in the process using Mg(OH)₂ has fuel demand similar to the conventional RD process (CaO). Although the salting-out extraction offers

Table 8. Technical and Environmental Performance: Neutralizing Agents and Solvent Inputs, Energy Demand, and Product Outputs for Different LA Production Scenarios

parameter	scenarios							
sucrose concentration (g/L)	130	130	130	130	250	250	250	250
pH	3.86	3.86	7.00	7.00	3.86	3.86	7.00	7.00
LA yield (g/g)	0.70	0.97	0.70	0.97	0.70	0.97	0.70	0.97
neutralizing agent	CaO							
CaO (kg/kg _{LA})	0.95	0.68	0.96	0.68	2.90	2.05	2.97	1.93
H ₂ SO ₄ (kg/kg _{LA})	0.28	0.28	0.56	0.56	0.27	0.27	0.56	0.56
ethanol (kg/kg _{LA})	0.004	0.014	0.012	0.014	0.011	0.014	0.014	0.013
electricity exported to the grid (MW h/y)	63.39	85.35	61.78	83.38	77.07	101.88	73.60	99.12
specific fuel demand (MJ/kg _{LA})	29.74	26.41	29.77	26.42	31.94	21.89	31.79	28.43
lactic acid (kg/t _{sugarcane})	92.17	129.23	91.00	127.79	93.02	131.60	90.84	128.75
calcium sulfate (kg/kg _{LA})	0.45	0.45	0.92	0.91	0.45	0.45	0.91	0.91
neutralizing agent	Mg(OH) ₂							
Mg(OH) ₂ (kg/kg _{LA})	0.08	0.10	0.03	0.02	0.22	0.20	0.03	0.02
HCl (kg/kg _{LA})	0.22	0.28	< 0.01	< 0.01	0.22	0.29	< 0.01	< 0.01
MIBK (kg/kg _{LA})	0.17	0.17	0.16	0.15	0.18	0.17	0.13	0.15
electricity exported to the grid (MWh/y)	71.24	76.42	82.87	110.48	67.44	94.63	79.58	107.52
specific fuel demand (MJ/kg _{LA})	29.11	21.93	33.55	30.35	27.38	25.00	26.05	29.67
lactic acid (kg/t _{sugarcane})	96.82	135.98	98.24	137.58	96.87	137.20	119.58	138.32
neutralizing agent	NH ₄ OH							
H ₂ SO ₄ (kg/kg _{LA})	0.26	0.26	0.52	0.52	0.26	0.26	0.52	0.52
NH ₄ OH (kg/kg _{LA})	0.61	0.60	1.21	1.19	0.61	0.59	1.21	1.18
Ethanol (kg/kg _{LA})	0.011	0.003	0.008	0.011	0.023	0.011	0.014	0.011
electricity exported to the grid (MWh/y)	50.75	67.89	49.63	65.07	59.65	79.39	57.70	75.12
specific fuel demand (MJ/kg _{LA})	22.08	19.16	22.02	18.55	24.05	20.51	23.47	19.76
lactic acid (kg/t _{sugarcane})	98.83	138.85	99.00	139.52	98.71	140.46	99.23	140.94
ammonium sulfate (kg/kg _{LA})	0.39	0.33	0.78	0.72	0.34	0.31	0.78	0.72

savings in product concentration and distillation, these savings are offset by the high energy demand of MgCl₂ drying and decomposition processes. On the other hand, the NH₄OH-based process has the lowest energy requirement because the extract product has a higher LA mass fraction than the Mg(OH)₂ alternative, thus reducing the final distillation energy demand. These results demonstrate that decomposing the salt to avoid producing an undesired, low-value gypsum subproduct that has to be disposed of has a high energy cost. Meanwhile, replacing the gypsum subproduct with a more attractive salt, such as (NH₄)₂SO₄, reduces the environmental impact in terms of the specific fuel demand by 6–30%, as shown in Table 8. Such a difference in fuel demand between the two salting-out extraction processes shows the importance of finding a good combination of solvent and salt to achieve high LA recovery and concentration in the extract to reduce the energy demand.

The business-as-usual process options using CaO as the neutralizing agent have an average global yield of 113 kg *t*_{LA}/*t*_{sugarcane}, 5% lower than the process options using Mg(OH)₂ and 7% lower than in the process options using NH₄OH. This difference can be explained by some product loss in the CaSO₄ removal step. Despite losses in the process, this result reflects the better atom economy of lactic acid fermentation because the product yield is much higher than that observed for ethanol fermentation, which is 67.2 kg/*t*_{sugarcane}.¹⁴ In terms of solvent input in the salting-out extraction processes, the ethanol recovery by distillation results in lower solvent loss when compared with MIBK back-extraction [Mg(OH)₂] because of solvent loss in the final extract product.

Different combinations of salts and solvents have been studied for the LA salting-out extraction, such as NaSO₄ and

1,4-dioxane.⁵³ However, effort should be made to explore greener solvents. The CHEM21 initiative,⁵⁴ for example, provides a simplified evaluation of common solvents. Although solvents such as MIBK and 2-propanol⁴⁰ have been classified as recommended solvents, ethanol is also safe and has the advantage of being widely produced from renewable sources. Another bio-derived solvent is butanol, which, alone, showed a low partition coefficient in LA extraction.⁵⁵ Nonetheless, the addition of salts increases the size of the biphasic area,^{56,57} which could improve LA partition, as in the case of MIBK.

K₂HPO₄ has shown a slightly higher LA recovery than (NH₄)₂SO₄.⁴⁰ However, the salt selection should consider the neutralization requirements during fermentation for a complete integration between fermentation and downstream processing and a suitable process design. Other salts that could be produced as fermentation and neutralization subproducts and have been studied in the formation of aqueous two-phase systems include Na₂SO₄,^{58,59} NaNO₃,⁵⁹ and MgSO₄.^{58,60} Even so, the salt selection should also consider the impact of their respective neutralizing base on the fermentation performance. Liu et al.⁶¹ reported that using Ca(OH)₂ as the neutralizing agent resulted in 3 times higher LA volumetric productivity than with KOH and NH₄OH for a genetically engineered *Escherichia coli* strain. Finally, another important factor is the market price and size of the neutralizing chemicals and the salt subproduct destination, whether decomposition or sale.

Economic Assessment. Figure 2 shows the total investment cost breakdown at a fixed fermentation time of 24 h. In this figure, the solvent recovery and final distillation steps are included in the RD and LLE areas. These results show that the energy-intensive steps (product concentration and distillation)

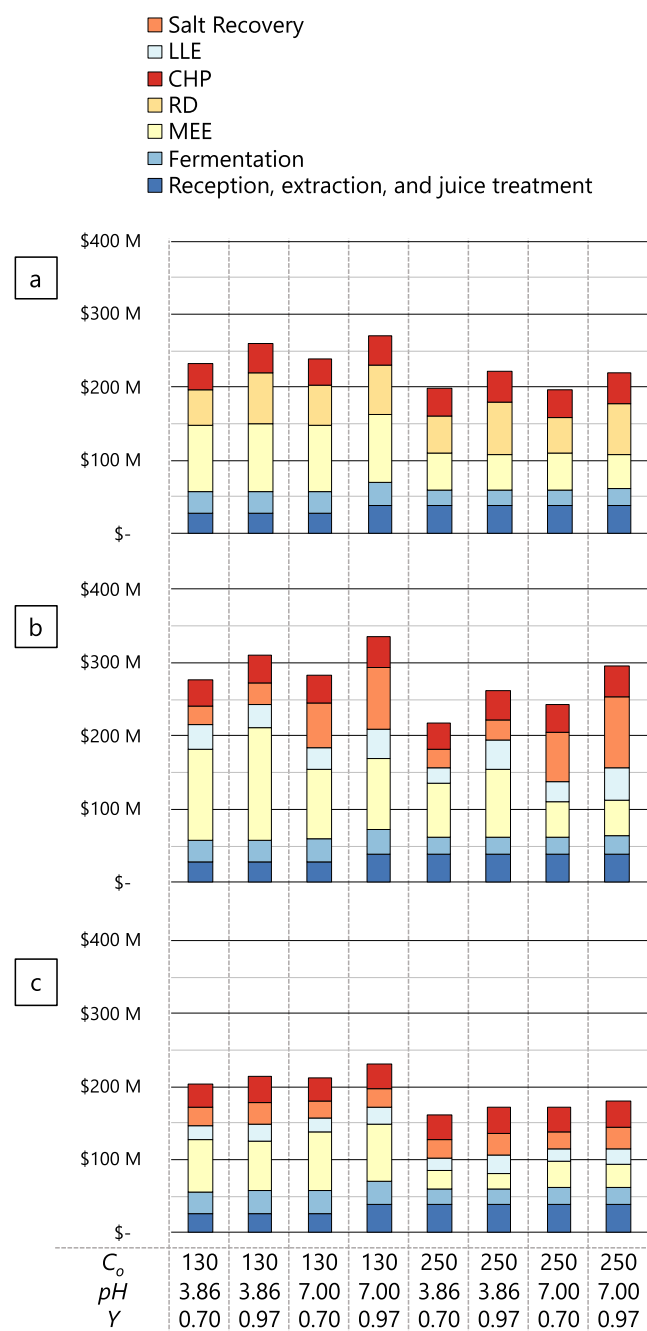


Figure 2. Total investment cost breakdown according to the neutralizing agent: (a) CaO; (b) Mg(OH)₂; and (c) NH₄OH.

have a high contribution to the total investment. Even though salting-out extraction reduces the required investment in concentration and distillation, the recovery and decomposition of the salt subproduct back to the neutralizing agents [Mg(OH)₂ and HCl] have a significant impact on these costs. Thus, the process based on NH₄OH has the lowest investment cost.

The fermentation area has a small contribution to the total investment cost (ca. 11%) in comparison with other process areas for all downstream processing scenarios. Therefore, the productivity parameter has a small effect on the production costs. This effect can be observed in Figure 3, which shows the LA MSP as a function of fermentation time. There is a linear, consistent relationship between these two variables, while the

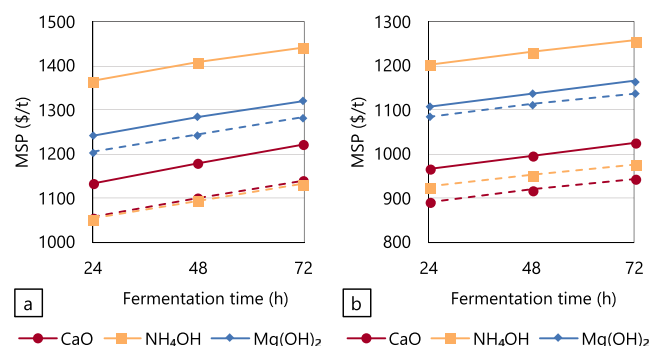


Figure 3. Effect of fermentation time on lactic acid minimum selling price for a fixed yield of 0.97 and different initial sugar concentrations: (a) 130 g/L and (b) 250 g/L. Solid and dashed lines represent fermentation pHs of 7.00 and 3.86, respectively.

other variables have a more evident impact on the MSP. Therefore, from this point on, the results will be shown for the scenarios at a fixed fermentation time of 24 h.

Figure 4 shows the MSP distribution for the three downstream processing scenarios, which varies from \$891/t to \$1726/t. The business-as-usual case has the lowest MSP in

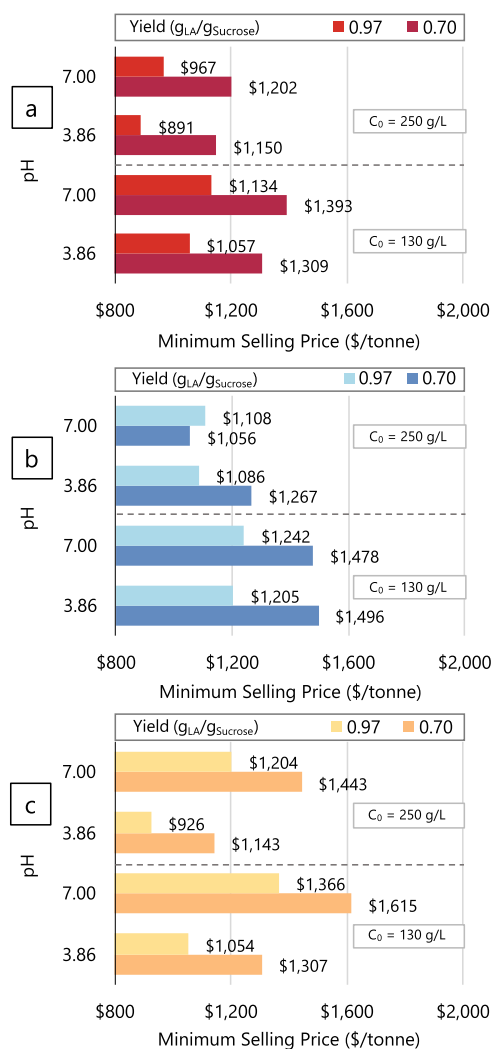


Figure 4. Lactic acid minimum selling price according to the neutralizing agent: (a) CaO; (b) Mg(OH)₂; and (c) NH₄OH.

the scenarios with neutral pH and high sugar concentration. In general, both lower pH and higher sucrose feed concentrations result in lower MSP, but the NH_4OH process is the most sensitive to changes in the fermentation pH. This difference can be explained by the differences in the price of the neutralizing agents and their percentage in the total operating cost. Figure 5 shows the operating cost breakdown at a fixed LA selling price. Nonetheless, for the low pH scenarios, the process based on NH_4OH shows MSP results similar to those based on CaO .

Li et al.⁶² evaluated the impact of fermentation parameters on the LA MSP obtained from lignocellulosic feedstocks. Their design is based on the business-as-usual process, but the authors obtained higher MSP (\$1380/t–1910/t) for neutral pH fermentation scenarios. This difference can be explained by the higher price of neutralizing agents and the low conversion in the esterification step (20%), which had a significant impact on the production costs. For higher LA yield and esterification conversion (90%), their MSP is reduced to \$1020/t, closer to the results of this work. The authors also evaluated the low-pH fermentation scenario, but their design is based on the assumption that no neutralizing agent is employed. In this scenario, the MSP varies from \$930/t to \$2660/t. This difference can be explained by the wider yield and concentration range evaluated by the authors in their study. Although such a scenario would be ideal, current fermentation results have lower yields under no pH control than those controlled at low values.⁵ Furthermore, given that the concentration and distillation steps have a much higher capital cost than the other areas (Figure 2) and the neutralizing agents have a small impact on the LA operating costs in the CaO scenarios (Figure 5), the IRR of a scenario under no pH control would reduce the MSP in this study by ca. 5%. Thus, improving product concentration and yield in low-pH fermentation would reduce the LA production more markedly than operating under no pH control.

Given the significant role of the input and product prices in the economic performance, four scenarios were selected based on current fermentation results: one pessimistic, two realistic, and one optimistic, as shown in Table 9. These scenarios were chosen to perform an uncertainty analysis of the IRR to compare the economic robustness of the three downstream processing designs. The pessimistic scenario has a low product yield at low pH. The first realistic scenario (low pH) was defined to evaluate the impact of yield improvement alone for low pH fermentation, compatible with previously reported experimental results.¹⁰ The second realistic scenario (neutral pH) was defined to evaluate the impact of using current fermentation technology (similar to the results from ref 12) in the alternative process configurations. Finally, the optimistic scenario was defined based on hypothetical fermentation results at low pH (performance equal to the neutral pH results). The results of probability distribution for all scenarios and tornado charts for the realistic (low-pH) scenario are shown in Figure 6.

The results in Figure 6 demonstrate that improving the fermentation yield (i.e., moving to a more realistic scenario) is mandatory to increase the probability of achieving an IRR greater than the MARR of 10%. Nonetheless, the realistic (low-pH) scenario demonstrates that reducing the salt subproduct by employing low-pH fermentation, although profitable with an average IRR in the range of 11–14%, would result in a decreased probability of IRR > MARR in comparison with the

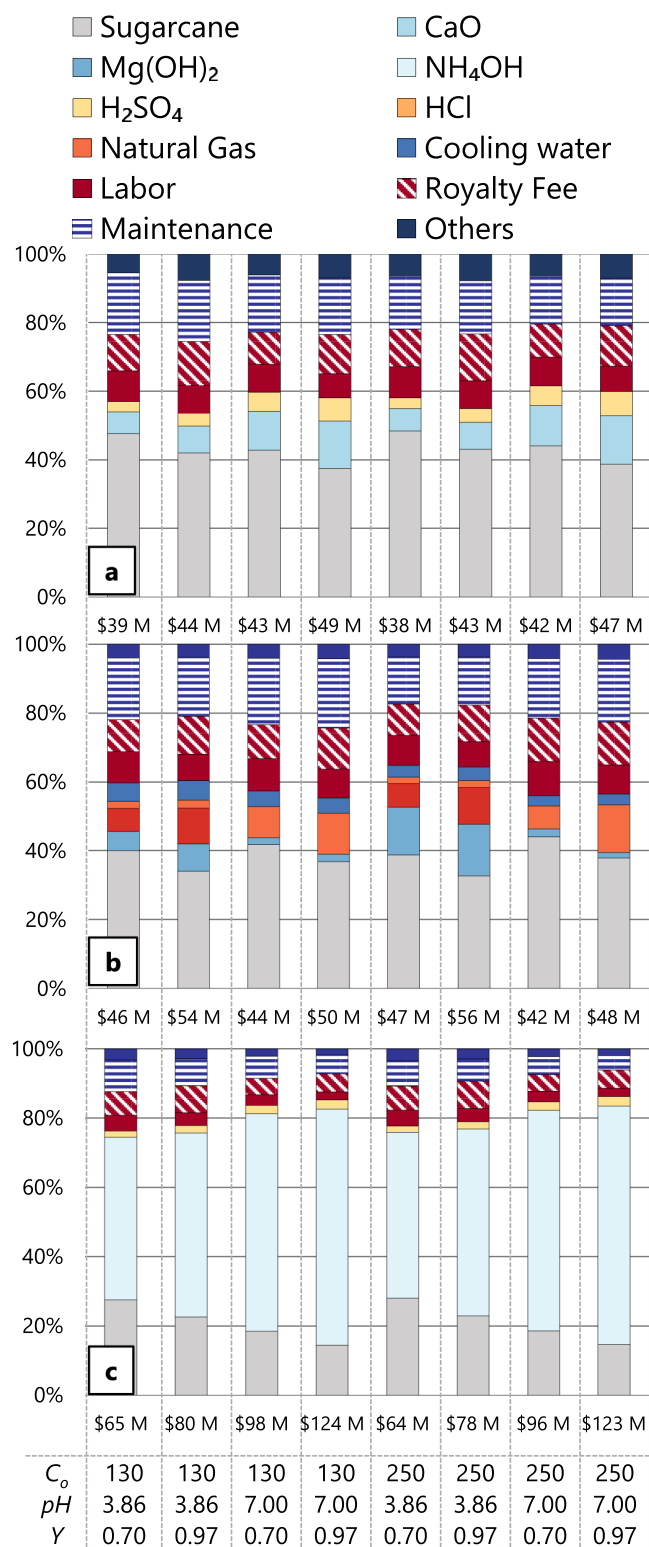


Figure 5. Operating cost breakdown for a lactic acid selling price of \$1375.24/t according to the neutralizing agent: (a) CaO ; (b) $\text{Mg}(\text{OH})_2$; and (c) NH_4OH .

current neutral pH technology, especially for the $\text{Mg}(\text{OH})_2$ -based process. The IRR of the realistic–neutral pH scenario shows a great change in the probability distribution when comparing results for the NH_4OH technology (Figure 6c) with the other two technologies (Figure 6a,b) because of the high

Table 9. Scenarios Employed in the Uncertainty Analysis

scenario	characteristics of each scenario			
	pH	yield (g/g)	duration (h)	concentration (g/L)
pessimistic	3.86	0.7	72	130
realistic—low pH	3.86	0.97	72	130
realistic—neutral pH	7.00	0.97	24	250
optimistic	3.86	0.97	24	250

requirement of the neutralizing agent associated with its higher price and spread.

Market uncertainties regarding the LA price is by far the variable affecting the most the IRR of the realistic (low-pH) scenarios according to Figure 6c–f, although the probability distribution shows that the realistic and optimistic scenarios have a high probability of achieving $IRR > MARR$. Portfolio diversification could be used to mitigate this risk by integrating the production of lactic acid to the production of ethanol and/or crystal sugar. For comparison, a 1G standalone ethanol distillery has an IRR of 13.1% (2014 values)¹⁴ and a 1G2G ethanol facility has an average IRR of ca. 12% (2018 values),⁴² which are values compatible with the results presented in this work for realistic scenarios. Therefore, the techno-economic results indicate that the Brazilian sugarcane industry could benefit from exploring LA to expand its product portfolio.

Daful and Görgens¹ evaluated the economic performance of another gypsum-free process, which also uses $Mg(OH)_2$ as the neutralizing agent. In their configuration, the base is recovered by contacting the Mg-lactate solution with triethylamine, where an amine–lactate complex is produced, and the base is recovered in the form of crystals. The complex has to be subject to a thermal decomposition step to recover the LA product and the amine—the latter being recycled. However, such decomposition may be a risky process from technical point of view due to energy- and mass-transfer complications.²

Daful and Görgens¹ obtained IRR values of 14.72 and 21.28% for this process configuration using lignocellulosic sugars as the feedstock but for a LA selling price of \$3000/t and an annual production 10 times lower. In this study, for $Mg(OH)_2$ as the neutralizing agent and the \$3000/t LA price, the estimated IRR is 22.9 and 36.8% in the pessimistic and optimistic scenarios, respectively.

Improving fermentation technology in terms of all variables here evaluated (pH, sugar concentration, yield, and productivity) would offer incremental improvement in the IRR for the CaO-based process but would greatly reduce the environmental impact associated with the gypsum subproduct. These conditions would certainly make the alternative downstream processing designs a safer investment and even offer higher IRR for the $(NH_4)_2SO_4$ -based process. Nevertheless, the salting-out extraction process requires technological development for scale-up.

Such difference in the IRR for different process designs shows that the development of alternative downstream processes could benefit the LA industry, even if the ideal scenario of efficient fermentation under no pH control has not been achieved yet. The results of this study demonstrate that taking advantage of the salt subproduct in alternative separation designs has the potential to improve the economic performance, which is necessary to decrease the market price of LA and create opportunities for new applications. Therefore, these results should stimulate further research and development in the area, in particular, to investigate pilot-scale production because the models considered here for the alternative designs are based on limited lab-scale data.

CONCLUSIONS

The sustainable production of lactic acid is challenging because of the aspects related to the high energy demand for its downstream processing and the production of an undesired gypsum subproduct. In this work, a comparison of process

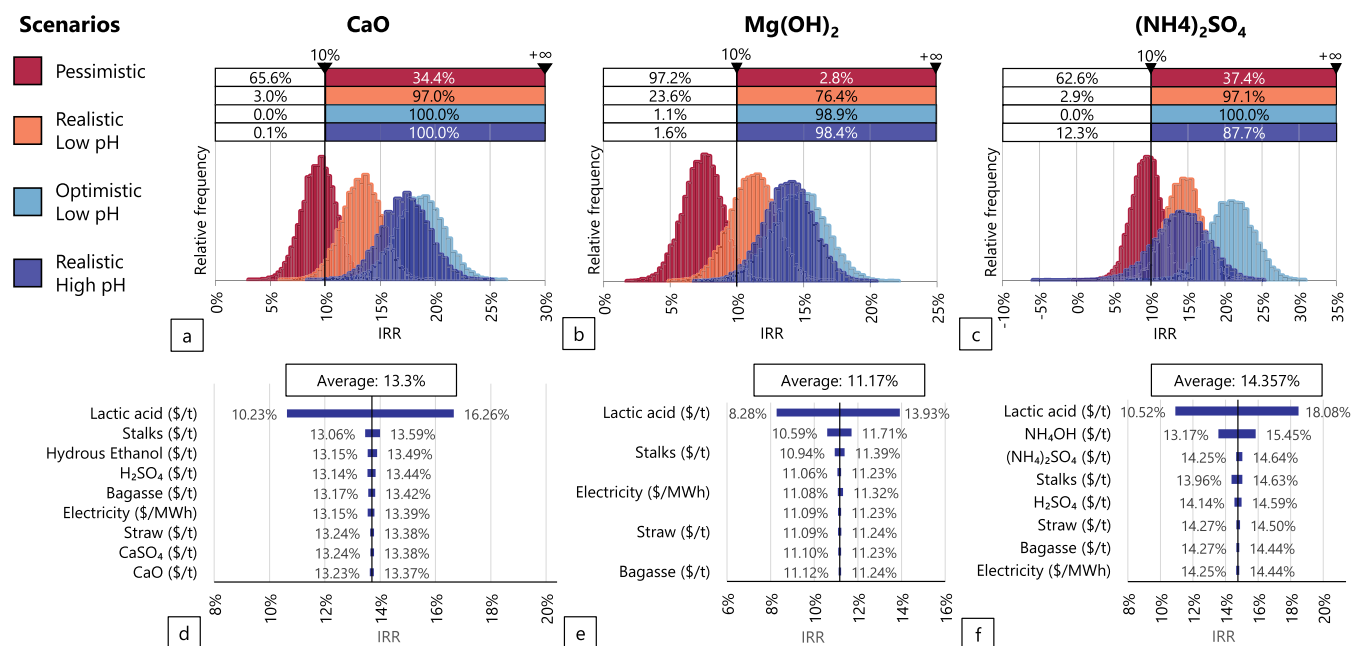


Figure 6. Probability distribution (a–c) and Tornado charts for the realistic (low pH) scenario (d–f) for the IRR according to the neutralizing agent: (a,d) CaO; (b,e) $Mg(OH)_2$; and (c,f) NH_4OH .

options considering different fermentation parameters combined with different downstream processing options indicates the economic outcomes of these technologies integrated into a complete sugarcane-based biorefinery design. Alternative salting-out extraction can become economically attractive to produce lactic acid from sugarcane juice provided that high fermentation yields (0.97 g/g) are obtained.

In this case, besides the impact of the salt and solvent on the recovery cost of lactic acid, special attention should be given to the choice of the salt because of the impact of the related base on fermentation performance. Salting-out extraction is economically feasible but has lower IRR (14–15%) and similar fuel demand when compared with the conventional process (IRR = 17%) for neutral pH fermentation. On the other hand, if a similar yield becomes technically feasible in low-pH fermentation, using salting-out extraction with $(\text{NH}_4)_2\text{SO}_4$ would result in an IRR of 20.71 and a 30% lower fuel demand. Therefore, though some separation processes are economically infeasible or unsuitable for traditional fermentation processes, they can become viable for newly developed fermentation processes if specific conditions are met. These results demonstrate the importance of the parallel development of fermentation and downstream processing and should motivate their further development beyond laboratory scale and process simulation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acssuschemeng.1c03447>.

Binary interaction parameters and model validation (PDF)

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Notes

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■ REFERENCES

- (1) Gezae Daful, A.; Görgens, J. F. Techno-economic analysis and environmental impact assessment of lignocellulosic lactic acid production. *Chem. Eng. Sci.* **2017**, *162*, 53–65.
- (2) López-Garzón, C. S.; Straathof, A. J. J. Recovery of carboxylic acids produced by fermentation. *Biotechnol. Adv.* **2014**, *32*, 873–904.
- (3) Zhang, Y.; Chen, X.; Qi, B.; Luo, J.; Shen, F.; Su, Y.; Khan, R.; Wan, Y. Improving lactic acid productivity from wheat straw hydrolysates by membrane integrated repeated batch fermentation under non-sterilized conditions. *Bioresour. Technol.* **2014**, *163*, 160–166.
- (4) Ye, L.; Zhao, H.; Li, Z.; Wu, J. C. Improved acid tolerance of *Lactobacillus pentosus* by error-prone whole genome amplification. *Bioresour. Technol.* **2013**, *135*, 459–463.
- (5) Baek, S. H.; Kwon, E. Y.; Bae, S. J.; Cho, B. R.; Kim, S. Y.; Hahn, J. S. Improvement of d -Lactic Acid Production in *Saccharomyces cerevisiae* Under Acidic Conditions by Evolutionary and Rational Metabolic Engineering. *Biotechnol. J.* **2017**, *12*, 1700015.
- (6) Yamada, R.; Wakita, K.; Mitsui, R.; Ogino, H. Enhanced d -lactic acid production by recombinant *Saccharomyces cerevisiae* following optimization of the global metabolic pathway. *Biotechnol. Bioeng.* **2017**, *114*, 2075–2084.
- (7) Miller, C.; Fosmer, A.; Rush, B.; McMullin, T.; Beacom, D.; Suominen, P. Industrial Production of Lactic Acid. *Comprehensive Biotechnology*, 2nd ed.; Elsevier B.V., 2011; Chapter 3.17, Vol. 3, pp 179–188.
- (8) Han, X.; Huang, K.; Tang, H.; Ni, J.; Liu, J.; Xu, P.; Tao, F. Steps Toward High-Performance PLA: Economical Production of d -Lactate Enabled by a Newly Isolated *Sporolactobacillus terrae* Strain. *Biotechnol. J.* **2019**, *14*, 1800656.
- (9) Calabria, B. P.; Tokiwa, Y. Production of D-lactic acid from sugarcane molasses, sugarcane juice and sugar beet juice by *Lactobacillus delbrueckii*. *Biotechnol. Lett.* **2007**, *29*, 1329–1332.
- (10) Valli, M.; Sauer, M.; Porro, D.; Branduardi, P.; Mattanovich, D. Methods for Selecting a Yeast Population for the Production of an Organic Acid and Producing an Organic Acid. U.S. Patent 7,473,540 B2, 2007.
- (11) Wang, Y.; Li, K.; Huang, F.; Wang, J.; Zhao, J.; Zhao, X.; Garza, E.; Manow, R.; Grayburn, S.; Zhou, S. Engineering and adaptive evolution of *Escherichia coli* W for l-lactic acid fermentation from molasses and corn steep liquor without additional nutrients. *Bioresour. Technol.* **2013**, *148*, 394–400.
- (12) Visser, D.; Van Breugel, J.; de Bruijn, J. M.; A'Campo, P. Lactic Acid from Concentrated Raw Sugar Beet Juice. EP 1870474 A1, 2007.
- (13) Alves De Oliveira, R.; Vaz Rossell, C. E.; Lunelli, B. H.; Schichi, P. O. M.; Venus, J.; Filho, R. M. Different Strategies to Improve Lactic Acid Productivity Based on Microorganism Physiology and Optimum Operating Conditions. *Ind. Eng. Chem. Res.* **2018**, *57*, 10118–10125.
- (14) *Virtual Biorefinery*; Bonomi, A., Cavalet, O., da Cunha, M. P., Lima, M. A. P., Eds.; Springer, 2016; pp 1–285.
- (15) Hugot, E. *Handbook of Cane Sugar Engineering*, 3rd Ed.; Elsevier Science Publishers B.V.: Amsterdam, The Netherlands, 1986; pp 1–1166.
- (16) Aden, A.; Ruth, M.; Ibsen, K.; Jechura, J.; Neeves, K.; Sheehan, J.; Wallace, B.; Montague, L.; Slayton, A.; Lukas, J. *Lignocellulosic Biomass to Ethanol Process Design and Economics Utilizing Co-current Dilute Acid Prehydrolysis and Enzymatic Hydrolysis for Corn Stover*; National Renewable Energy Laboratory, 2002; pp 1–88.
- (17) Van Breugel, J.; Van Krieken, J.; Cerdà Baró, A.; Vidal Lancis, J. M.; Caprubi Vila, M. Method of Industrial-Scale Purification of Lactic Acid. U.S. Patent 6,630,603 B1, 2008.
- (18) Asthana, N.; Kolah, A.; Vu, D. T.; Lira, C. T.; Miller, D. J. A continuous reactive separation process for ethyl lactate formation. *Org. Process Res. Dev.* **2005**, *9*, 599–607.
- (19) Su, C.-Y.; Yu, C.-C.; Chien, I.-L.; Ward, J. D. Plant-wide economic comparison of lactic acid recovery processes by reactive

distillation with different alcohols. *Ind. Eng. Chem. Res.* **2013**, *52*, 11070–11083.

(20) Kang, Q.; Huybrechts, J.; Van Der Bruggen, B.; Baeyens, J.; Tan, T.; Dewil, R. Hydrophilic membranes to replace molecular sieves in dewatering the bio-ethanol/water azeotropic mixture. *Sep. Purif. Technol.* **2014**, *136*, 144–149.

(21) de Haan, A. B.; Van Krieken, J.; Dekic Zivkovic, T. Method for Isolating a Carboxylic Acid from an Aqueous Solution. EA 024143 B1, 2013.

(22) de Haan, A. B.; Bokhove, J.; Laksmanna, F. L. Thermal Decomposition of Magnesium Chloride. WO 2015150325 A1, 2015.

(23) Aman, J. J. Improvements in or Relating to the Thermal Decomposition of certain Chlorides and Sulphates. GB 793700 A, 1956.

(24) Laiadi, D.; Hasseine, A.; Merzougui, A. Homotopy method to predict liquid-liquid equilibria for ternary mixtures of (water + carboxylic acid + organic solvent). *Fluid Phase Equilib.* **2012**, *313*, 114–120.

(25) Shand, M. A. *The Chemistry and Technology of Magnesia*; John Wiley & Sons, Inc.: Hoboken, New Jersey, 2006; pp 1–262.

(26) Fu, H.; Sun, Y.; Teng, H.; Zhang, D.; Xiu, Z. Salting-out extraction of carboxylic acids. *Sep. Purif. Technol.* **2015**, *139*, 36–42.

(27) Fu, H.; Sun, Y.; Xiu, Z. Continuous countercurrent salting-out extraction of 1,3-propanediol from fermentation broth in a packed column. *Process Biochem.* **2013**, *48*, 1381–1386.

(28) Kramer, H. J. M.; Lakerveld, R. Selection and Design of Industrial Crystallizers. In *Handbook of Industrial Crystallization*, 3rd ed.; Myerson, A. S., Erdemir, D., Lee, A. Y., Eds.; Cambridge University Press, 2019; p 197–215.

(29) Zapp, K.-H.; Wostbrock, K.-H.; Schäfer, M.; Sato, K.; Seiter, H.; Zwick, W.; Creutziger, R.; Leiter, H. *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH, 2000; pp 1–26.

(30) Vu, D. T.; Lira, C. T.; Asthana, N. S.; Kolah, A. K.; Miller, D. J. Vapor–Liquid Equilibria in the Systems Ethyl Lactate + Ethanol and Ethyl Lactate + Water. *J. Chem. Eng. Data* **2006**, *51*, 1220–1225.

(31) Peña-Tejedor, S.; Murga, R.; Sanz, M. T.; Beltrán, S. Vapor-liquid equilibria and excess volumes of the binary systems ethanol + ethyl lactate, isopropanol + isopropyl lactate and n-butanol + n-butyl lactate at 101.325 kPa. *Fluid Phase Equilib.* **2005**, *230*, 197–203.

(32) Delgado, P.; Sanz, M. T.; Beltrán, S. Isobaric vapor-liquid equilibria for the quaternary reactive system: Ethanol + water + ethyl lactate + lactic acid at 101.33 kPa. *Fluid Phase Equilib.* **2007**, *255*, 17–23.

(33) Delgado, P.; Sanz, M. T.; Beltrán, S. Kinetic study for esterification of lactic acid with ethanol and hydrolysis of ethyl lactate using an ion-exchange resin catalyst. *Chem. Eng. J.* **2007**, *126*, 111–118.

(34) Pereira, C. S. M.; Pinho, S. P.; Silva, V. M. T. M.; Rodrigues, A. E. Thermodynamic equilibrium and reaction kinetics for the esterification of lactic acid with ethanol catalyzed by acid ion-exchange resin. *Ind. Eng. Chem. Res.* **2008**, *47*, 1453–1463.

(35) Ratheesh, S.; Kannan, A. Holdup and pressure drop studies in structured packings with catalysts. *Chem. Eng. J.* **2004**, *104*, 45–54.

(36) Stephenson, R. M. Mutual Solubilities: Water-Ketones, Water-Ethers, and Water-Gasoline-Alcohols. *J. Chem. Eng. Data* **1992**, *37*, 80–95.

(37) Saravi, S. H.; Honarparvar, S.; Chen, C.-C. Thermodynamic modeling of HCl-H₂O binary system with symmetric electrolyte NRTL model. *J. Chem. Thermodyn.* **2018**, *125*, 159–171.

(38) Couper, J. R.; Penney, W. R.; Fair, J. R.; Walas, S. M. *Chemical Process Equipment*, 3rd ed.; Butterworth-Heinemann, 2012; pp 1–864.

(39) Wang, Y.; Yan, Y.; Hu, S.; Han, J.; Xu, X. Phase Diagrams of Ammonium Sulfate + Ethanol/1-Propanol/2-Propanol + Water Aqueous Two-Phase Systems at 298.15 K and Correlation. *J. Chem. Eng. Data* **2010**, *55*, 876–881.

(40) Aydoğan, Ö.; Bayraktar, E.; Mehmetoğlu, Ü. Aqueous two-phase extraction of lactic acid: Optimization by response surface methodology. *Sep. Sci. Technol.* **2011**, *46*, 1164–1171.

(41) Macrelli, S.; Mogensen, J.; Zacchi, G. Techno-economic evaluation of 2nd generation bioethanol production from sugar cane bagasse and leaves integrated with the sugar-based ethanol process. *Biotechnol. Biofuels* **2012**, *5*, 22.

(42) Vasconcelos, M. H.; Mendes, F. M.; Ramos, L.; Dias, M. O. S.; Bonomi, A.; Jesus, C. D. F.; Watanabe, M. D. B.; Junqueira, T. L.; Milagres, A. M. F.; Ferraz, A.; Santos, J. C. d. Techno-economic assessment of bioenergy and biofuel production in integrated sugarcane biorefinery: Identification of technological bottlenecks and economic feasibility of dilute acid pretreatment. *Energy* **2020**, *199*, 117422.

(43) Bildea, C. S.; György, R.; Sánchez-Ramírez, E.; Quiroz-Ramírez, J. J.; Segovia-Hernandez, J. G.; Kiss, A. A. Optimal design and plantwide control of novel processes for di-n-pentyl ether production. *J. Chem. Technol. Biotechnol.* **2015**, *90*, 992–1001.

(44) Turton, R.; Shaeiwitz, J. A.; Bhattacharyya, D.; Whiting, W. B. *Analysis, Synthesis, and Design of Chemical Processes*, 5th ed.; Prentice Hall, 2018; pp 1–1520.

(45) Leal Silva, J. F.; Grekin, R.; Mariano, A. P.; Maciel Filho, R. Making Levulinic Acid and Ethyl Levulinate Economically Viable: A Worldwide Technoeconomic and Environmental Assessment of Possible Routes. *Energy Technol.* **2017**, *6*, 613.

(46) Zang, G.; Shah, A.; Wan, C. Techno-economic analysis of an integrated biorefinery strategy based on one-pot biomass fractionation and furfural production. *J. Cleaner Prod.* **2020**, *260*, 120837.

(47) CEPEA. Center for Advanced Studies on Applied Economics. <http://www.cepea.esalq.usp.br>. (accessed Dec 01, 2020).

(48) Leal Silva, J. F.; Mariano, A. P.; Maciel Filho, R. Economic potential of 2-methyltetrahydrofuran (MTHF) and ethyl levulinate (EL) produced from hemicelluloses-derived furfural. *Biomass Bioenergy* **2018**, *119*, 492–502.

(49) Seider, W. D.; Seader, J. D.; Lewin, D. R.; Widagdo, S. *Product and Process Design Principles*, 3rd ed.; John Wiley & Sons, Inc., 2009; pp 1–768.

(50) Towler, G.; Sinnott, R. *Chemical Engineering Design—Principles Practice and Economics of Plant and Process Design*; Butterworth-Heinemann, 2007; pp 1–1245.

(51) Holland, F. A.; Wilkinson, J. K. *Perry's Chemical Engineers Handbook*, 7th ed.; Perry, R. H., Green, D. W., Eds.; McGraw-Hill, 1997; pp 1–80.

(52) Humbird, D.; Davis, R.; Tao, L.; Kinchin, C.; Hsu, D.; Aden, A.; Schoen, P.; Lukas, J.; Olthof, B.; Worley, M.; Sexton, D.; Dudgeon, D. *Process Design and Economics for Biochemical Conversion of Lignocellulosic Biomass to Ethanol: Dilute-Acid Pretreatment and Enzymatic Hydrolysis of Corn Stover*; NREL, 2011; pp 1–147.

(53) Xu, S.; Lan, K.; Li, J.; He, T.; Hu, C. Separation of lactic acid from synthetic solutions and the mixture directly derived from corn stover by aqueous two phase extraction. *Sep. Purif. Technol.* **2018**, *204*, 281–289.

(54) Prat, D.; Wells, A.; Hayler, J.; Sneddon, H.; McElroy, C. R.; Abou-Shehadeh, S.; Dunn, P. J. CHEM21 selection guide of classical- and less classical-solvents. *Green Chem.* **2016**, *18*, 288–296.

(55) Domingues, L.; Cussolin, P. A.; da Silva, J. L.; de Oliveira, L. H.; Aznar, M. Liquid-liquid equilibrium data for ternary systems of water + lactic acid + C₄–C₇ alcohols at 298.2 K and atmospheric pressure. *Fluid Phase Equilib.* **2013**, *354*, 12–18.

(56) Aznar, M.; Araújo, R. N.; Romanato, J. F.; Santos, G. R.; d'Ávila, S. G. Effects on Liquid–Liquid Equilibrium in Water + Ethanol + Alcohol + Salt Systems. *J. Chem. Eng. Data* **2000**, *45*, 1055–1059.

(57) Feng, Z.; Li, J. Q.; Sun, X.; Sun, L.; Chen, J. Liquid-liquid equilibria of aqueous systems containing alcohol and ammonium sulfate. *Fluid Phase Equilib.* **2012**, *317*, 1–8.

(58) Pimentel, J. G.; Bicalho, S. F.; Gandolfi, O. R. R.; Verissimo, L. A. A.; Castro, S. d. S.; Souza, E. A.; Veloso, C. M.; Fontan, R. d. C. I.; Sampaio, V. S.; Bonomo, R. C. F. Evaluation of salting-out effect in the liquid-liquid equilibrium of aqueous two-phase systems composed of 2-propanol and Na₂SO₄/MgSO₄ at different temperatures. *Fluid Phase Equilib.* **2017**, *450*, 184–193.

(59) Souza, P. P. A.; Julião, I. B.; Mendes, M. F. Liquid-Liquid Equilibrium Data of 2-Propanol + Sodium Sulfate/Nitrate/Acetate + Water Systems. *J. Chem. Eng. Data* **2020**, *65*, 1369–1378.

(60) Guo, W.; Ma, J.; Wang, Y.; Han, J.; Li, Y.; Song, S. Liquid-liquid equilibrium of aqueous two-phase systems composed of hydrophilic alcohols (ethanol/2-propanol/1-propanol) and $\text{MgSO}_4/\text{ZnSO}_4$ at (303.15 and 313.15)K and correlation. *Thermochim. Acta* **2012**, *546*, 8–15.

(61) Liu, Y.; Gao, W.; Zhao, X.; Wang, J.; Garza, E.; Manow, R.; Zhou, S. Pilot scale demonstration of d -lactic acid fermentation facilitated by $\text{Ca}(\text{OH})_2$ using a metabolically engineered *Escherichia coli*. *Bioresour. Technol.* **2014**, *169*, 559–565.

(62) Li, Y.; Bhagwat, S. S.; Cortés-Peña, Y. R.; Ki, D.; Rao, C. V.; Jin, Y.-S.; Guest, J. S. Sustainable Lactic Acid Production from Lignocellulosic Biomass. *ACS Sustainable Chem. Eng.* **2021**, *9*, 1341–1351.