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Chapter

Uses of the Response Surface Methodology for the Optimization of Agro-Industrial Processes

José Manuel Pais-Chanfrau, Jimmy Núñez-Pérez, Rosario del Carmen Espin-Valladares, Marco Vinicio Lara-Fiallos and Luis Enrique Trujillo-Toledo

Abstract

Response surface methodology is a tool for the design of experiments, widely used today to optimize industrial processes, including agro-industrial ones. Since its appearance in the last century's fifties, hundreds of articles, chapters of books, and books attest to this. In this work, a general overview of this tool's general practical aspects is made. This statistical tool's usefulness and popularity, used in the optimization of agro-industrial processes and in making them more efficient and sustainable, is described through multiple examples.

Keywords: response surface methodology, agro-industry, central composite design, independent variables, uncontrolled variables, response variables, optimization

1. Introduction

The response surfaces methodology (RSM) is a set of statistical tools for the design of experiments aimed at finding the value or values of the independent variables, which allow developed, improved and optimization (i.e., finding the maximum, minimum, or equal to a certain convenient value) one or more dependent variables or responses [1, 2].

Since the first works reported by Box and coworkers [3–5], RSM has been gaining popularity among researchers, developers, and engineers, and today it has become one of the preferred tools for increasing the productivity and efficiency of R&D processes and the production of goods and services.

The agro-industry, on the other hand, comprises a set of process industries that use agricultural and livestock resources to transform them into products of higher added value. Processed and improved foods, nutraceutical foods and beverages, chemical products and bioactive substances for the chemical, pharmaceutical and cosmetic industries, industrial enzymes and above all, vast and abundant quantities of plant and animal biomass, which could be the primary renewable raw materials with which that will count the industry of the future, are some of the main "outputs" of the agro-Industry.

By their nature, the sources of the raw materials of the agro-industry are renewable and could be a strategical industrial sector for the sustainable development of the whole of humankind, given the constant growth of the human population, Ambiental deterioration, and the evident depletion of the natural sources of raw materials. It is for this reason, that it is required to have well-designed processes that generate a minimum negative impact on the already deteriorated ecosystems, and in which yields, and productivity are maximized.

The objective of this work is to show, through a group of examples, the utility of RSM for the design of efficient, productive agro-industrial processes with a minimum negative impact on agro-ecosystems.

2. Agro-industries: the pillar in sustainable development that the world needs

Agroindustry can be defined as the process industries that use agricultural, livestock and aquaculture products as raw materials, transforming them into valuable, more elaborate products with greater added value. Among the products emerging from agroindustries are processed foods and beverages, dry and canned foods with greater durability, fermented foods and beverages with nutraceutical properties, as well as basic chemicals, precursors of other chemical compounds, biofuels, industrial enzymes, bioactive products, such as antibiotics, probiotics, prebiotics and synbiotics substances, vitamins, organic acids, phytohormones, antioxidant agents, growth factors, etc. (**Figure 1**).

Agro-industries can be subdivided into primary, secondary and tertiary transformation agroindustries, depending on the set of predominant operations carried out in them and the degree of complexity of their output products (**Figure 1**).

In primary transformation, the selection, crushing, separation, isolation, concentration, or drying of the product or products of interest usually predominate. The sugar factories made from sugar cane or sugar beet [6], the traditional dairy industry were powdered, evaporated, or condensed milk is produced (whole, defatted or lactose-free) [7], or the slaughter of cattle meat [8] or industries that produce concentrated juices or condiments and canned foods are examples of industries where these operations of physicochemical transformation of raw materials from agriculture, aquaculture and livestock, into products prevail.

On the other hand, in secondary transformation agro-industries, the products, by-products and residuals of the first transformation are usually used as starting

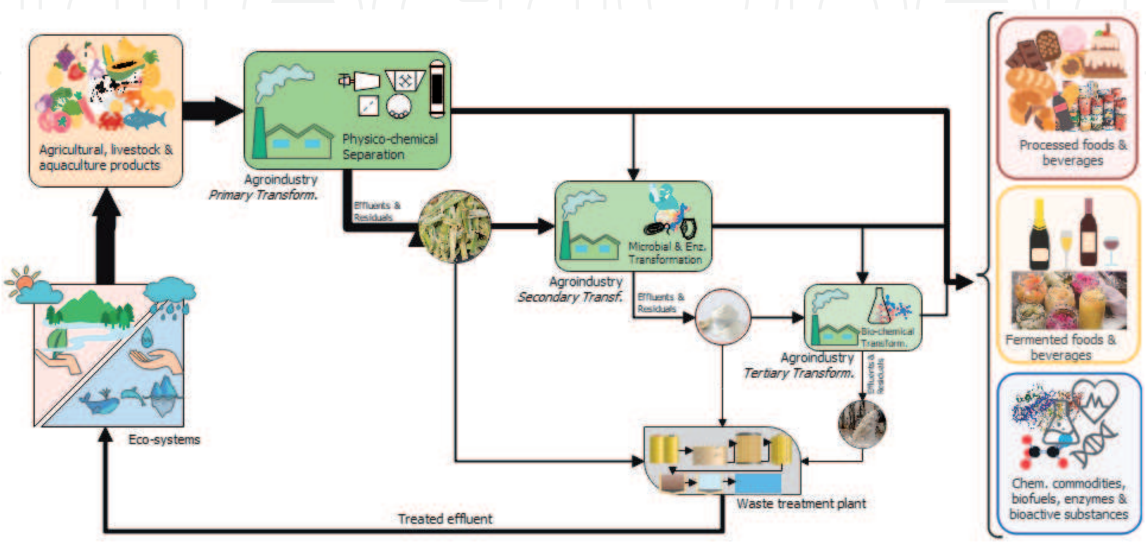

Figure 1.
Agroindustry: Its source of raw materials and main productions.

raw materials, and in their transformation performed by microorganisms, perfectly adapted to grow and develop using these raw materials, obtaining, as a result of their microbial activity, fermented products and beverages, with beneficial nutritional and food properties. Fermented food and beverage production industries [9, 10], such as yoghurt [11, 12], kefir [13, 14] and the manufacturing of beer [15] and wine [16], fermented sauces and condiments, such as soy sauce, as well as the production of bio-ethanol [17, 18], vinegar [19, 20] and some organic acids [21, 22], such as citric acid [23] and lactic acid [24], are practical examples of these agro-industries, where microorganisms and enzymes carry out the transformation of raw materials to product.

Finally, in the tertiary transformation agro-industries, the products, by-products or residues of the primary and secondary transformation agro-industries continue to be transformed chemically and/or biochemically into new chemical compounds, like bioactive compounds, enzymes, polysaccharides, gums, phytohormones, growth factors, etc. These, as a rule, are the products derived from agro-industries that have the highest added value. Some industrial enzymes such as cellulases [25], lipases [26] amylases [27], fructosyltransferases and invertases [28]; macromolecules like fructo- and galactooligosaccharides (FOS and GOS) [29–31], etc., are examples of agro-industries of tertiary transformation.

Currently, the production volumes of tertiary transformation agro-industries are significantly lower than the previous two. However, they should increase in the future, stimulated by the high prices of these products and the depletion of oil, the main raw material from which the traditional chemical industry's precursors are obtained [32].

An agro-industrial process can be considered as a set of operations that allow the gradual transformation of the process inputs (for example, raw materials, material, and energy resources) into the outputs (such as the main product (s), by-products, disposable materials and waste) (**Figure 2**).

As a rule, the added value of the product or products is significantly higher than the value of the inputs and other elements of the outputs.

An agro-industrial process, like any other, is made up of a series of stages of transformation processes. Each stage can be made up of one or more unit operations. In each of the stages of the transformation process of raw materials or intermediate products, a set of factors or variables can influence the efficiency and speed of said transformation. These factors can be subdivided into controllable and non-controllable factors or variables (**Figure 3**). The first ones are all those intensive variables of the process (such as temperature, pH, the concentration of certain analyte, etc.), whose values must be kept within a certain range on any scale and which, besides, are the ones that have the real possibility of being controlled within pre-established ranges in

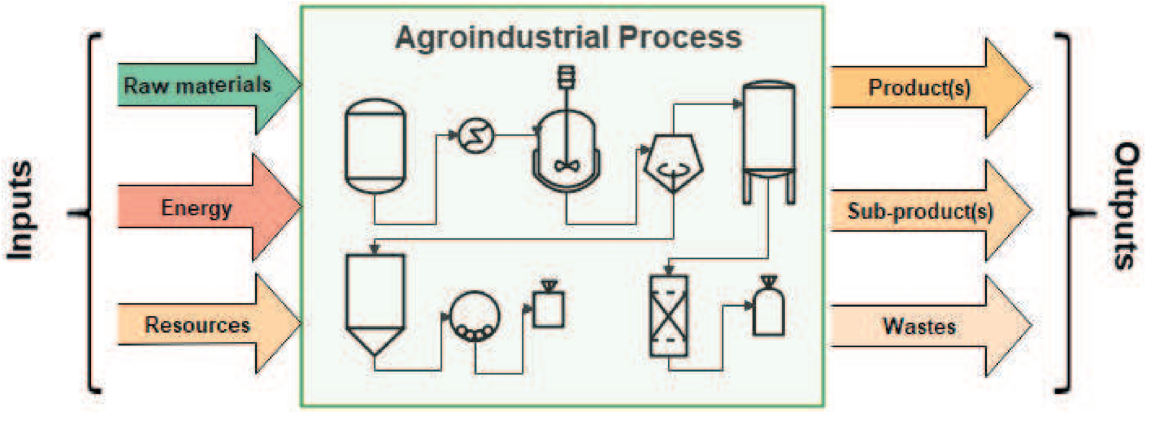

Figure 2.
General scheme of an agro-industrial process.

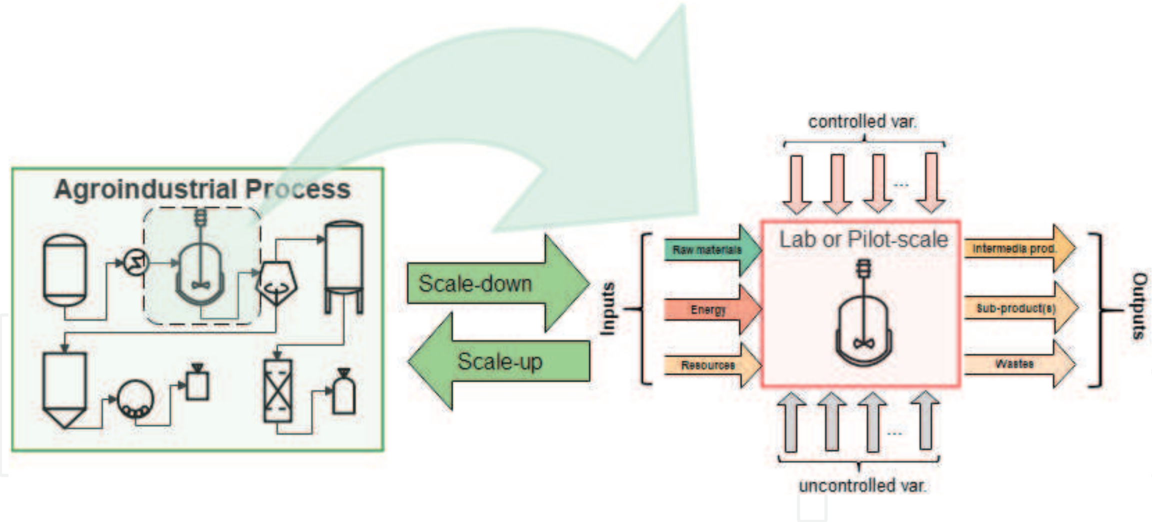

Figure 3.
The two ways to optimise agro-industrial processes: Scale-down of established processes and the Scale-up of new processes.

the different scales. The second, for their part, are all those variables, including those whose existence is still unknown, that may influence the transformation process but are not within reach of the processes and technologies to be controlled. By focusing attention on the intensive controllable variables, not only will it be possible to find the combination of these that allow the development of an optimal transformation process, but it will also allow knowing the values that must be achieved in the productive scale of a certain variable or response factor, commonly associated with some quality attribute of the final or intermediate product within the process.

An efficient and sustainable agro-industrial process will *maximize* the efficiency of the transformation of raw materials to finished products, *minimizing*, at the same time, the use of energy resources and the generation of by-products disposable and residual materials. The latter can be achieved by optimizing each of the stages of the process.

To do this, normally, you can proceed in two ways. If it is intended to optimize an already established large-scale non-optimal process, the established process could be scale-down to a smaller scale, a pilot-scale for example, or later to a laboratory, where all the necessary optimization experiments could be developed (**Figure 3**).

If it is intended to optimize the design of new processes, these can be optimized on a laboratory scale, first and later, these optimized processes would be scaled-up to pilot and further to industrial scale.

Due to the wide range of useful products that emerge from the agro-industry, ranging from products that improve the durability, texture and nutritional composition of natural foods, through simple chemical substances, precursors of other more complex and elaborated, to complex substances like antibiotics, prebiotics, hormones, enzymes, polysaccharides, etc. (**Figure 1**). There are numerous niches where modern techniques of experiment design and process optimization can be used [33, 34].

Among the most popular and effective tools to know the optimal parameters of a process is the response surface methodology (RSM), frequently associated with searching for an extreme value of one or more objective functions. The objective function or response is frequently associated with one or more of the product's attributes of a stage or unit operation of the process (for example, the concentration, the yield, the efficiency, the conversion, the productivity, etc.). Additionally, there may be other objective functions or responses, which can also integrate into the same optimization process, which may be related to other needs of the unit process or stage, such as the reduction of some by-product or residue, the decrease in consumption of energy, cleaning agents, shortening of the processing time, etc. In such cases, we would be in the presence of multi-objective optimization.

3. A short overview of response surface methodology (RSM)

The idea of the RSM is, through the design of experiments, to find the relationship between a certain response variable, commonly associated with one of the attributes of the experimental unit's output product with a few controllable variables. Strictly speaking, any response variable depends on both controllable and non-controllable variables. However, it is necessary to try to find a certain objective function, dependent only on a few controllable variables (usually from two to six), which allows navigating its surface in search of the combination of controlled variables with which an extreme value of the objective function is reached.

The response variable, as mentioned before, will also depend on the contribution of a certain "noise" function that depends on the rest of the controllable variables not taken into account in the objective function, as well as on the non-controllable factors. Still, it is must seek that noise's influence on the response is low enough or not significant. The determining influence on the response can be exerted mainly by the contribution of the objective function (**Figure 4A**).

To find the relationship between the variable response and the independent variables or controllable factors requires careful design of the experiments. These experiments must be carried out randomly and making the necessary replications to have the necessary certainty of their results [35]. In this sense, first of all, there must be solid evidence that the independent variables to be evaluated significantly influence the response variable or variables under study. This is based on our own experiments previously carried out or abundant reports published in the scientific literature. And secondly, must choose a suitable range for the independent variable analyzed, neither too narrow nor too long, so that the different values obtained from the response variable are notable.

The experimental runs must be carried out so that they cover the entire possible range of the independent variables that are being evaluated in the best way. Thus, the influence that each one, separately and combined with other independent variables, exerts on the response variables being analyzed can be evaluated. This can be ensured when the total sum of the products of all the coded independent variables of each run is equal to zero. The latter is known as the *orthogonal* design of experiments.

In addition to randomization and to minimize the influence that uncontrolled factors or variables may exert on the response variables, the different treatments are usually grouped into experimental blocks [36]. The latter can be beneficial, especially when various factors are evaluated, and the experiments must be performed over several days (**Figure 4B**).

In this way, the experiments must be *random*, with *replications* and designed in an *orthogonal* and *block-based* manner [37].

The most common experiment designs used in response surface methodology are the central composite design (CCD) and the Box–Behnken design (BBD). As a rule, in the BBDs, there are fewer experimental runs than in the CCDs (three levels for each factor in BBD, against five levels in CCD, for example). Therefore, it may be the preferred choice when the experiments are costly or when you need to have resulted in a shorter time. However, more robust and reliable models are obtained in CCDs, and they better support the loss or mismeasured response of the runs. The latter makes CCDs the "workhorse" and the first choice of researchers trying to optimize agro-industrial processes [37].

Fortunately, statistical packages accurately plan these experiment designs. Commercial statistical software such as Design-Expert®, JMP®, and Minitab® stand out, which are very useful and popular among scientific researchers and engineers communities. Additionally, there are becoming more popular every day; some free tools, such as the R and Python languages, are somewhat more

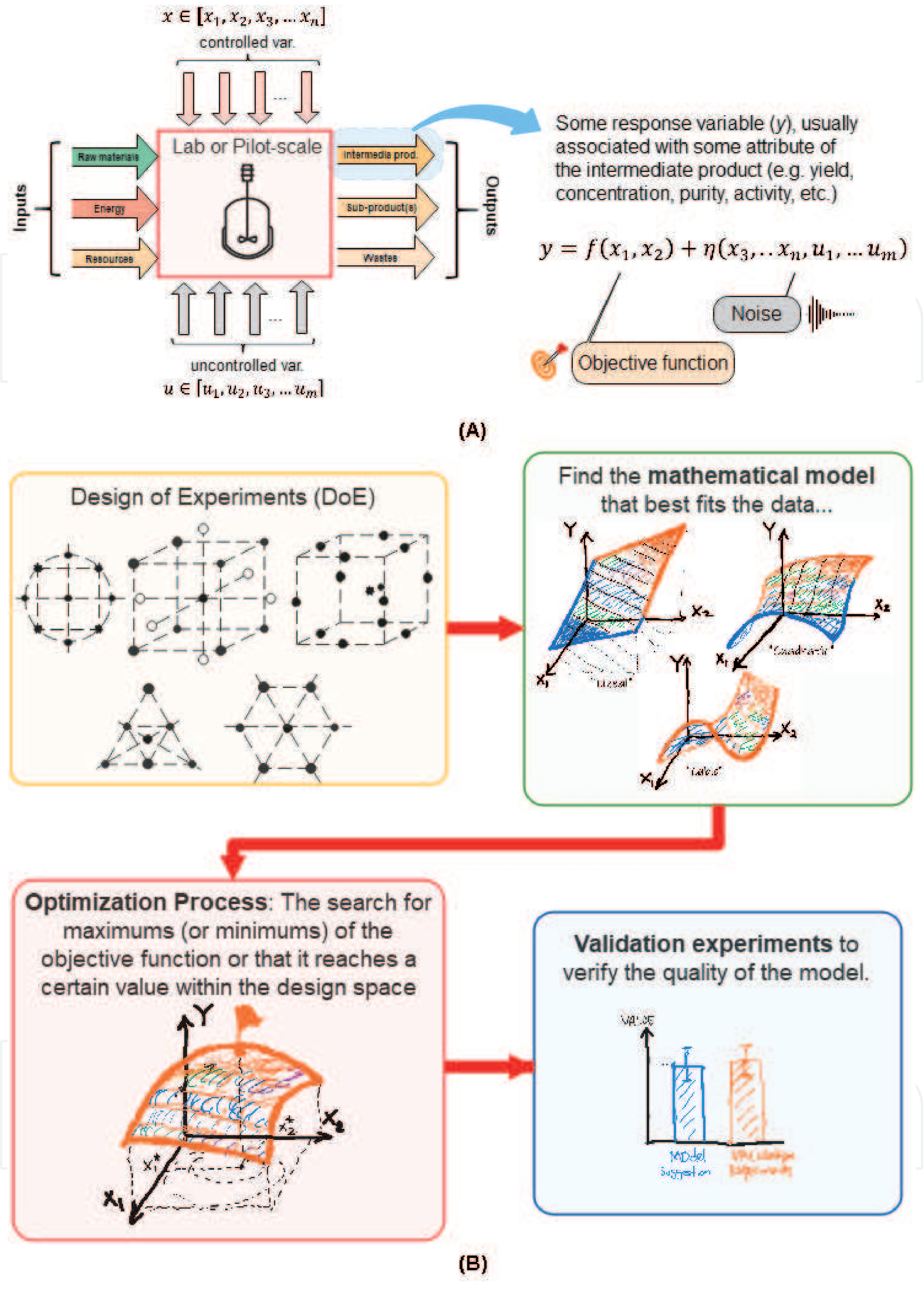

Figure 4.
(A) The response variable and its links with objective functions and noise, (B) general workflow for implementing response surface methodology.

complex to use and require greater statistical and programming knowledge for their successful use.

Once the experiments have been designed and executed, it is necessary to adjust the experimental data to a certain function that represents a close approximation to the response variable or variables obtained to each treatment, depending on the experiments' independent variables or factors (**Figure 4B**).

Depending on the values obtained in the response variable's experiments and if the difference between the maximum and minimum values obtained is huge, it will be necessary to transform the response variable before finding the adjustment function. Frequently the response variable (s), transformed or not, are adjusted to a certain polynomial, depending on the chosen design.

Subsequently, the polynomial that best fits the experimental data will be chosen. An analysis of variance will be carried out to the chosen polynomial. Those coefficients that are not significant for the model will be discarded as long as they do not sacrifice different runs' orthogonality. The quality of the model is evidenced through different statistical parameters, such as the adjusted quadratic coefficient of regression, adequate precision, the graphs of the predicted value versus the real value or through the graphs of the distribution of the residuals; the model may or may not be used, to find, within the design space of the independent variables, the optimal values of the function that adjusts the response variable(s) with the independent variables.

Once the appropriate model has been chosen, it is proceeding to explore the extreme or optimal values of the response function within the design space, that is, to find the combination of independent variables or factors that make the response objective function reach its maximum value, minimum value or equal to a specific value, depending on the response function. During the response function's optimisation process, and depending on the model's precision and variance, one or more extreme values may appear. If the extreme values found are related to variables or independent factors that are not related or are very far from each other, new experiments may be necessary around these points to improve the model's precision (**Figure 4B**).

On the contrary, if within the explored design space there is a single extreme value or only a few within a close region of the independent variables, can choose this solitary extreme value or can select one representative of the set of comparable response values can be chosen to proceed with a group of model confirmation or validation experiments.

There is no hard and fast rule about how many of these validation experiments are necessary, but they are usually between three and five. The model is validated when all the response function values are located within the range predicted by the model. The average weight of these does not differ significantly ($p < 0.05$) from the value predicted by the model. Otherwise, it would be suggesting that the model does not have the necessary accuracy. It is essential to continue exploring the search for extreme values within or outside of the original design space. In the latter case, an additional set of RSM-experiments would need to achieve (**Figure 4B**).

4. Agroindustry: a suitable receptor for the use of the response surface methodology (RSM)

Since Box and Wilson in 1951 [3] proposed this methodology, hundreds of scientific articles have been published [38–41].

Due to the wide range of useful products that emerge from the agro-industry, ranging from products that improve the durability, texture and nutritional composition of natural foods, through simple chemical substances, precursors of other more complex and elaborated, to complex substances like antibiotics, hormones, enzymes, polysaccharides, etc. (**Figure 2**). There are numerous niches where modern techniques of experiment design and process optimization can be used [42, 43].

Among the most popular and effective tools to know the optimal parameters of a process is the response surface methodology, frequently associated with development of new products [44–46] and processes [47, 48], the maximization of the productivity or yield of the process products [49–52], the reduction of their

Title	Clase[1]	Source/Product	RSM DOE	Optimal values	Ref.
Control of selected fermentation indices by statistically designed experiments in industrial scale beer fermentation.	AI PT	Optimization of beer fermentation	Box–Behnken	Pitching rate $6{\cdot}10^6$ cells/mL; fermentation temp. 11.2 °C; aeration level 10.5 mg/L; and CCTs filling time 13.5 h.	[57]
Effect of ohmic heating on quality and storability of sugarcane juice.	AI PT	Sugarcane juice/ sugarcane juice	Box–Behnken	Ohmic heating of sugarcane juice at 70°C for 3 min holding time.	[58]
Extraction of steviol glycosides from dried *Stevia rebaudiana* by pressurized hot water extraction.	AI PT	*Stevia rebaudiana* Bertoni leaves/Stevioside	CCD	2 bars of pressure, 20 min reaction time, and 20% dry leaves to water ratio	[59]
Optimization of spray-drying parameters for the production of 'Cempedak' (*Artocarpus integer*) fruit powder.	AI PT	Fruit juice/fruit powder	CCD	Air temperature of 160°C and maltodextrin conc. of 15% (w/w)	[60]
Optimizing the extraction of bioactive compounds from pu-erh tea (*Camellia sinensis var. assamica*) and evaluation of antioxidant, cytotoxic, antimicrobial, antihemolytic, and inhibition of α-amylase and α-glucosidase activities.	AI PT	Pu-erh tea/Antioxidants	CCD	Temperature of 85.4°C and time of 3 min	[61]
Maize stover as a feedstock for enhanced laccase production by two gammaproteobacteria: A solution to agroindustrial waste stockpiling.	AI PT	Maize stover/laccase	Box–Behnken	pH 5, 0.50 g biomaterial, 100 rpm and 0.10 $NaNO_3$	[62]
Evaluation of textural properties of corn based extruded products.	AI PT	Three corn varieties/ Extruded product	Box–Behnken	Temperature: 127.66°C, 18.96% feed moisture and 92:4:4 feed composition	[63]
Response Surface Methodology approach for optimization of endoglucanase from alkaliphilic *Fusarium oxysporum* VSTPDK and its potential application in pulp and paper industry.	AI PT	Rice straw/CMCase	CCD	pH 8.5, temperature 45°C, ammonium sulphate concentration 3% and 8 day incubation.	[64]
Antioxidant and prebiotic effects of a beverage composed by tropical fruits and yacon in alloxan-induced diabetic rats.	AI PT	Yacon extract + fruit juice/ fructo-oligosaccharides	CCD	Yacon extract: 50% and sweetener: 0.07%	[65]
Optimization of concentrating process using rotary vacuum evaporation for pineapple juice.	AI PT	Pineapple juice/ concentrated juice	CCD	Temp. 60°C and pressure 200 mBar for 75 min.	[66]

Title	Clase[1]	Source/Product	RSM DOE	Optimal values	Ref.
Pre-treatment optimization of barley straw as agro-industrial waste via alkaline peroxide and ultrasound for soluble sugar production and degradation.	AI PT	Barley straw/Sugars	Box–Behnken	US Power: 20 kj/kg DM Particle size: 0.6 mm	[67]
Techno-economic feasibility of bioethanol production via biorefinery of olive tree prunings (OTP): Optimization of the pretreatment stage.	AI PT	OTP/bioethanol	Box–Behnken	Minimum of Total Capital Cost: Temp. 199.98°C, 8 g H_2SO_4/100 g; 35% (w/v)	[68]
Design of experiments for enhanced production of bioactive exopolysaccharides from indigenous probiotic lactic acid bacteria.	AI ST	Lactose/ Exo-polysacharides	Box–Behnken	*Enterococcus faecium* K1: Lactose: 10.07g/L, Ammonium citrate 2.48 g/L, pH 5.4	[69]
Response surface methodology to optimize a bioprocess for kefiran production.	AI ST	WP/kefiran	CCD	Temp.: 25°C and 44.1% (w/w) of WP	[70]
Microwave-assisted extraction of pectin from “Saba” banana peel waste: Optimization, characterization, and rheology study.	AI ST	Banana peel waste/pectin	CCD	195° C, 8% solid–liquid ratio, and pH 3 HCl	[71]
Hydrolysis of orange peel with cellulase and pectinase to produce bacterial cellulose using *Gluconacetobacter xylinus*.	AI ST	Orange peel/cellulose	Box–Behnken	cellulase of 1589.41 U/g, pectinase of 31.75 U/g and a reaction time of 5.28 h	[72]
Valorization of sugarcane bagasse to high value-added xylooligosaccharides and evaluation of their prebiotic function in a synbiotic pomegranate juice	AI ST	Sugarcane bagasse/xylan	CCD	5.63% H_2O_2, 12.91% NaOH, and extraction time of 17.51 h	[50]
Playing with the senses: application of Box–Behnken design to optimize the bukayo formulation.	AI ST	Coconut meat and juice+sugar/bukayo acceptability	Box–Behnken	430 g young coconut meat, 400 g sinakob, and 340 g coconut juice	[73]
Utilization of Atlantic salmon by-product oil for omega-3 fatty acids rich 2-monoacylglycerol production: Optimization of enzymatic reaction parameters.	AI ST	Salmon By-product Oil/ Omega-3	Box–Behnken	Reaction temp. 42.5°C, time 4.15 h, enzyme load 42.81%, & ethanol: oil mol. Ratio 49.82	[74]
Bioconversion of cheese whey permeate into fungal oil by *Mucor circinelloides*.	AI ST	Whey permeate/fungal oil	CCD	Fermentation temp. 33.6°C and pH 4.5	[75]
Olive mill and winery wastes as viable sources of bioactive compounds: A study on polyphenols recovery.	AI ST	olive pomace residues/ polyphenols	Box–Behnken	Olive pomace microwave-extraction: ethanol:water 50:50 (v/v), 90°C, 5 min	[76]

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Title	Clase[1]	Source/Product	RSM DOE	Optimal values	Ref.
Development of a low-temperature and high-performance green extraction process for the recovery of polyphenolic phytochemicals from waste potato peels using hydroxypropyl β-cyclodextrin.	AI ST	Potato peel/polyphenols	Box–Behnken	pH 5.0, ratio solvent-to-dry weigth 80 mL g^{-1} and agitation speed 800 rpm	[77]
Optimized preparation of activated carbon from coconut shell and municipal sludge.	AI ST	Coconut shell/activated carbon	Box–Behnken	Temp.: 800°C, activation time: 60 min, activator concentration: 2.5 mol/L, a 50% coconut shell.	[78]
Response surface methodology as a tool for modeling galacto-oligosaccharide (GOS) production.	AI ST	DWP/GOS	CCD	DWP: 18 g/ml, 0.20 g/L of β-galactosidase	[79]
Optimization of β-galactosidase production by batch cultures of *Lactobacillus leichmannii* 313 (ATCC 7830™).	AI ST	Lactose/β-galactosidase	CCD	pH 7.06 and 15.3 g/L lactose	[80]
An eco-friendly pressure liquid extraction method to recover anthocyanins from broken black bean hulls.	AI ST	Broken black bean hulls/anthocyanins	Box–Behnken	Ratio ethanol and citric acid sol.n 0.1 mol/L of 30:70 (v/v), flow rate: 4 mL/min, 60°C.	[81]
Canola meal as a promising source of fermentable sugars: Potential of the *Penicillium glabrum* crude extract for biomass hydrolysis.	AI ST	Canola meal/β-glucosidase	CCD	Fermentation time: 6.5 days, pH adjusted to 6.0, and substrate concentration of 2%	[82]
Optimization of galacto-oligosacharides (GOS) synthesis using response surface methodology.	AI ST	Lactose/GOS	CCD	Lactose conc. of 400 g/l, enzyme conc. of 13.5 g/l and reaction time of 13 min	[83]
Pre-treatment of sugarcane bagasse with aqueous ammonia–glycerol mixtures to enhance enzymatic saccharification and recovery of ammonia.	AI ST	Sugarcane bagasse/Sugars	Box–Behnken	Conc. of ammonia: 9.25%, pre-treatment time: 1.86 h, pre-treatment temp.: 180°C	[84]
Low-cost production of PHA using cashew apple (*Anacardium occidentale* L.) juice as potential substrate: optimization and characterization.	AI ST	Cashew apple juice/PHA	CCD	Conc. of total reducing sugar of 50 g/L, inoculum of 50 mL/L, and urea of 3 g/L.	[85]
A facile noncatalytic methyl ester production from waste chicken tallow (WCT) using single step subcritical methanol: Optimization study.	AI ST	WCT/biodiesel (FAME)	CCD	167°C, 36.8 min., and 42.7:1 (methanol/WCT, mol/mol)	[86]

Title	Clase[1]	Source/Product	RSM DOE	Optimal values	Ref.
Recovery and bio-potentialities of astaxanthin-rich oil from shrimp (*Peneanus monodon*) waste and mackerel (*Scomberomous niphonius*) skin using concurrent supercritical CO_2 extraction.	AI ST	Astaxanthin-rich oil/shrimp waste & fish skin	CCD	Extraction temp. 45.7°C; pressure 264.09 bar, and shrimp waste-to-fish skin mixing ratio 79.63:20.37.	[87]
Zero-waste biorefinery of oleaginous microalgae as promising sources of biofuels and biochemicals through direct transesterification and acid hydrolysis.	AI ST/ TT	Microalgae (marine *Chlorella* sp.)/biofuels (FAME) & sugars.	Box–Behnken	FAME yield: Temp. 70 °C, ratio of chloroform:methanol 1.35:1 and reaction time 120 min. Sugar yield: 7.5% H_2SO_4, 60 min hydrolysis time, 3% biomass loading, and 100°C hydrolysis temp.	[88]
Sequential production of lignin, fatty acid methyl esters and biogas from spent coffee grounds (SCG) via an integrated physicochemical and biological process.	AI TT	SCG/Lignin/FAME & biogas	CCD	Temp. 161.0°C, sulfuric acid: 3.6% and methanol:SCG ratio: 4.7 mL/g	[89]
Heterogeneous catalytic conversion of rapeseed oil to methyl esters: Optimization and kinetic study.	AI TT	Rapeseed oil/FAME	CCD	Catalyst ratio (bentonite/NaOH): 1:20; catalyst amount: 6%wt.; reaction time: 3.5 h.	[90]

Abbreviations: DWP: demineralised whey powder; WP: whey powder; CMCase: carboxy-methyl-celulase; PHA: poly-hydroxy-alkanoate; FAME: fatty-acid methyl-ester.
[1]*AI PT, ST, TT: Agro-industry (AI) of primary, secondary, or tertiary transformations.*

Table 1.
Some of the recent work on the response surface methodology related to the agro-industry.

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production costs [53], the minimization of risks for the human health [54] or its negative impacts on ecosystems [55, 56].

A summarized sample of some of the recent work in agro-industry related to the response surface methodology is shown in **Table 1**.

Table 1 shows more than thirty selected examples chosen from the last five years (2017–2021) from the multiple reports in the specialized bibliography, using RSM in all areas of agro-industry. In the selected cases, it is confirmed that the BBD and CCD designs are the most widely used and the utility that these experimental design and optimisation tools provide to researchers and engineers working in the agro-industry is demonstrated.

On the other hand, RSM is conveniently intertwined with the concepts of the "circular economy" [91] applied to agro-industry toward a broader framework of a sustainable bioeconomy [92, 93], where it is intended to maximize the efficiency and productivity of the transformation processes of raw materials into products, with a minimal negative impact on the environment and to minimize generation of by-products, wastes, and residuals of the agro-industrial processes, and, at the same time, reuse the latter as sources of raw materials for other products, valuing them.

On some occasions the by-products and wastes of some agro-industrial processes become sources of raw materials for obtaining other valuable products through chemical, enzymatic or biological transformation. Some examples such as whey, a by-product of the cheese industry [94–96], and molasses and bagasse by-products of the sugar cane industry, from which some valuable products are obtained [97–100].

This fact gives rise to the concept of biorefineries and circular economies [91, 93], applicable in certain economic agricultural crops exploited on a large scale, where a group of valuable products could be obtained from abundant and renewable raw materials, in addition to those that have traditionally been obtained previously.

5. Conclusion

Despite an appreciable decrease in publications related to the response surface methodology in agro-industry, in 2020 and so far in 2021, due to the effects of the impact of the SARS-CoV-2 pandemic in the world, everything indicates that RSM is a prevalent tool among researchers and engineers to improve agro-industrial processes, as demonstrated in this work, and that it will continue to be very useful and necessary to achieve efficient, sustainable and friendly agro-industrial processes with the environment. For this reason, once the effects of the pandemic have passed, new reports of applications of the use of this statistical tool will surely continue to appear.

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