Book Chapter

Novel Applications, Sensory and Sensor Techniques in Beverage and Food Fragrance Biotechnology

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Abstract

Fragrances are important for the beverage and food industries and the search for new compounds is challenging for academic and industrial investigation. Fragrance and flavor compounds present many different chemical structures and can be obtained by biosynthesis (*de novo* synthesis), or extraction, or using enzymatic precursor. Recent innovations have been made concerning “fragrances construction” as also in their application products. Moreover, novel sensory and sensor methodologies, primarily used for fragrances quality evaluation have been developed, as also statistical techniques for sensory and sensors data treatments, allowing a rapid and objective analysis. This overview aims to present the current state of the art of beverage fragrance and flavor biotechnology, including the latest advances

in sensory methodologies and sensor techniques , and also, statistical techniques for data analysis.

Keywords

Natural Flavors; *de novo* Synthesis; Ligand-Receptor Interaction; e-nose; e-tongue; Sensory Analysis

Introduction

The increased consumer preference for natural and sustainable products increased the production of natural flavors, which define the sensory perception of beverages and other food products, which is an ever-challenging purpose for the academic and industrial investigation [1]. The understanding of olfactory perception goes through huge advances in recent years, particularly regarding new mechanisms of olfactory signaling and new principles of olfactory processing [2-4]. It is already known that a family of 400 olfactory receptors (ORs) are used by humans, however, it remains to be clearly explained how the combinatorial activation of these ORs encodes odor perception [5]. The olfactory signaling initiates when odorant molecules contact the olfactory sensory neurons which express proteins that convert chemical signals into neuronal impulses. Consequently, neurochemical effects occur, in several regions of the brain, generating the smell sense. The discovery that each olfactory neuron expressed one special kind of odorant receptor, allowed the researchers Linda Buck and Richard Axel to be distinguished with the Nobel Prize in Medicine in 2004.

The structure of the nasal cavity in humans comprises three regions namely the vestibule, respiratory, and olfactory regions. The ORs, or odorant, is in the olfactory epithelium. However, several studies in recent years had shown the existence of the “ectopic olfactory receptors” in mammals i.e. receptors of the same type spread in many diverse organs and systems [6] such as in tissues as the testes [7, 8] and heart [7]. ORs and related signaling molecules can also be present in non-olfactory areas of the nervous system and may trigger his vulnerability to neurodegenerative diseases, and drugs [6].

It is known that the quantity of functional OR genes is less, in Humans, when compared to other species, leading to the conclusion that, throughout the process of development, the sense of smell may have lost importance for primates. Still, Humans have an extremely sensitive sense of smell, essential for the discovery of odors that are necessary for maintaining a healthy life, such as the smell of smoke (detection of fire) and the smell of rotten food (to avoid its ingestion) [9], and for the discovery and development of new aromas and fragrances.

The food, pharmacy, cosmetics, tissues, agriculture (pheromones), etc. industries have always used volatile and non-volatile compounds in the formulation of its products. The extraction of these products is an activity that is recognized in ancient civilizations. Currently, the flavors used as additives in food and beverages are natural or synthetic [10-12].

The increased consumer preference for natural and sustainable products has led to novel techniques and ideas are emerging, namely methodologies for obtaining aromatic compounds, such as microbial, and enzymatic biotransformation, de *novo* synthesis, and the use of natural and environmentally friendly genetic engineering tools [11-14]. Some examples are plant cell, tissue, and organ cultures (PCTOC), an alternative for the production of high molecular weight flavoring molecules, as well as food and beverage additives [15] and, metabolically engineered microorganisms and enzymatic biocatalysis [15].

Even more, C_{13}-apocarotenoids, derived from the oxidative cleavage of carotenoids, are volatile compounds that contribute to the aromas of diverse flowers and fruits. They are used in the flavor industry and are chemically synthesized, but now, they can be synthesized by bioprocess engineering [16], particularly by *in situ* product removal (ISPR), considered a necessary technology for the development of industrial-scale bioprocesses [17]. According to Sá and co-workers [18], enzyme-catalyzed reactions are the most cost-effective strategy, from the industrial point of view, to reach final green products.

Linking biology to mathematical models and computer science, microbial cell factories, such as *Saccharomyces cerevisiae*, can be engineered using synthetic biological tools, to express synthetic pathways for the manufacturing of food and beverage flavors [19].

Encapsulation processes have been developed to protect the most active aromatic compounds, due to their fragility and specific purpose. Encapsulation technologies have been developed to protect the most active aromatic compounds, due to their fragility and specific purpose. Thus, the encapsulation provides protection, on the one hand against loss of assets, spreading outside the target and subsequent pollution, and on the other hand protection against air, temperature, light, pH, masking or revealing the sensory properties of the molecule, release during the process, etc. [2]. Still, to be able to use the label "natural flavors" and "natural fragrances", it's required the production of natural capsules from natural materials. Among biological structures, yeast-cells offer good protection for active-fragrances. Microbial spores can also be used, they can fully protect actives that do not interact with each other or with the environment. Pollen grains are also able to disseminate actives in the environment [20].

Biosynthesis, Functional Characterization and Metabolic Engineering of Plant-derived Flavor Compounds

Several hundred volatile compounds that are released from leaves, flowers, and fruits into the atmosphere and from roots into the soil have been isolated from more than 90 plant families. These volatile compounds act as a language that plants use for their interaction with the surrounding environment, from attracting pollinators and seed dispersers to protecting themselves from pathogens, parasites, and herbivores [21,22]. Some of those compounds were identified as part of fresh and processed fruits and vegetables causing varied sensory experiences during consumption [23] that can affect consumer's choices [24-27].

Fruit and vegetable-specific aroma depend on species, cultivar, growing conditions, and developmental and maturity stage [21]. Even if some fruits and vegetables present the same volatile compounds, what gives its specific flavor is the combination of volatile and nonvolatile compounds and other water-soluble and insoluble compounds.

Multiple biochemical pathways are responsible for the volatile compounds' composition of fruits and vegetables [28]. Ripeness, temperature, and day/night variations play a fundamental role in volatile compounds biosynthesis, being these compounds often missing in immature fruits [29]. Another factor that can also influence the fruit volatile compounds concentration is postharvest management [31]. Suboptimal conditions experienced during transportation, storage, and postharvest ripening may cause alterations in flavor development [32].

Volatile compounds from fruits and vegetables are lipophilic, mainly terpenoids, phenylpropanoids/benzenoids, fatty acid derivatives, and amino acid derivatives, and represent around 1% of plant secondary metabolites [25]. Among all volatile compounds, esters are produced by fleshy fruit species during ripening and are the major aroma compounds in apples (*Malus domestica*), pears (*Pyrus communis*), and bananas (*Musa sapientum*). However, in soft fruits like strawberries (*Fragaria* × *ananassa*), volatile esters are present in a lower concentration [33].

Fruit volatile compounds present in intact tissues are classified as primary metabolites and can be classified as secondary metabolites if are produced because of tissue disruption due to fruit injury [34]. Therefore, the final fruit aroma profile depends on the sample preparation, namely, if it is used as an intact fruit, slices, or homogenized fruit samples. According to Valero and Serrano [35], volatile compounds determined in intact fruits are related to the consumer smelling perception and the fruit ripening signals, while volatile compounds determined after tissue disruption are more related to the flavor perception during fruit-eating.

According to Pott et al. [36], it is important to understand the connection and regulation of the carbon flow [36] between primary and secondary metabolism, which is a key factor for the development of fruit and vegetable cultivars with enhanced organoleptic and nutritional traits [36]. The biosynthesis of volatile compounds begins from primary metabolic routes. The formed compounds can be classified as terpenes, fatty acid derivatives, polysaccharide derivatives, and amino acid derivatives [27]. The volatile compounds in plants are mostly synthesized from the following pathways, according to Croteau and Karp [37]: (i) short-chain aldehydes and alcohols (like *cis*-3-hexenol and hexanaldehyde) that are synthesized by the action of lipases on lipids, followed by the action of the alcohol dehydrogenases [38], (ii) eugenol, 2-phenylethanol, and guaiacol, resulting from the shikimic acid pathway [37], (iii) nor-isoprenoids (like β-ionone and geranylacetone) that result from the degradation of terpenoids [39], while terpenoids can be produced by two independent pathways: the mevalonate pathway in the cytoplasm and the 2-*C*-methyl-*D*-erythritol-4-phosphate (MEP) pathway in the plastid [40].

Many studies aim the improve the aroma without affecting other fruit or vegetable attributes. Indeed, several strategies have been developed to enhance fruits and vegetables aroma volatile compounds, either eliminating or increasing their emission. Those strategies include a wide range of targets including the metabolic pathways, hormones, and transcription factors, and mechanisms involved in the storage or sequestration of volatile precursors [26, 41]. The production of volatile compounds can also be influenced by lower pectin degradation in transgenic fruits by down-regulation of polygalacturonase (PG), pectin methylesterase (PME), and polygalacturonase + pectin methylesterase [26].

Metabolic engineering of Aromatic Amino Acids, AAA-derived pathways, is an exciting research topic and has been used to improve the aroma and flavor of fruits, either by overexpressing an existing enzyme or by blocking a competing pathway. Manipulation of transcriptional regulation can also be used to change the metabolic profile of AAA-derived volatiles [42]. In

the Fatty Acid Metabolism Engineering for fruit aroma, the lipoxygenases gene (LOX) family catalyzes the oxidation of polyunsaturated fatty acids to form fatty acid hydroperoxides, intermediates in the formation of physiologically active compounds such as oxylipins. Few LOX have been described to be involved in aroma formation, such as, MdLOX1a and MdLOX5e, which were associated with the production of green leaf volatiles by a QTL mapping [43].

Finally, the engineering of terpenoids in plants is also a hot topic that includes enhanced disease resistance, the use of allelopathic compounds in weed control, and increased value of ornamentals by the production of medicinal compounds [44, 45]. The fundamental factors in terpenoid engineering experiments are the phytotoxicity of the introduced terpenoids, the subcellular localization of both the precursor pool and the introduced enzymes, the activity of enzymes that modify the introduced terpenoids, and the impacts on other pathways sharing the same precursor pool [44,45].

Metabolic Engineering of microorganisms for Flavor Compounds Biosynthesis

The increasing demand for natural products in the food and beverage industry around the world has encouraged remarkable efforts towards the development of biotechnological processes to produce natural flavor compounds [46]. Traditionally flavor compounds have been extracted from several plant sources. Nevertheless, the production of natural flavor compounds from plant extract is associated with severe problems for the environmental, ecological, and extent of agricultural soil use [47]. Also, the extraction of flavor compounds from plants is problematic, since most of them are secondary metabolites and generally produced in small amounts, which is further affected by weather and environmental conditions [48]. Additionally, the isolation and purification of natural flavor compounds from plant extracts are also difficult since the plant materials contain a very low concentration of the desired compounds, which makes the extraction process of natural flavor compounds expensive, time-consuming, and environmentally unfriendly as it requires

relatively large quantities of solvents [49]. In this way, most of the flavor compounds employed in the beverages and food industry are commonly produced by chemical synthesis causing a decrease in consumer acceptance due to the additions of a synthesized chemical compound to the food. The chemical synthesis of flavor compounds also results often in environmentally unfriendly production processes and lacks substrate selectivity, which may result in the formation of unwanted racemic mixtures, thus reducing process efficiency and increasing downstream costs [46]. Due to the health awareness, the flavor companies focused their study on the biological flavor compounds, the so-called "natural flavors" or "bio-flavors" [46, 50]. For these reasons, an alternative means of overproducing valuable natural products using microorganisms has emerged. Microorganisms are engineered for the biosynthesis of natural flavor compounds, linked to the advantages such as safety and enough source of precursors [47]. So, a novel promising alternative path for natural flavor synthesis is based on microorganism cell processes, i.e., fermentation (secondary metabolites) or bioconversion of suitable natural precursors using microorganism cells or enzymes (biocatalysis) [44,50-52]. Microorganisms could be used in two different ways to produce natural flavor compounds for the food industry. Namely by the flavor generation as an integral part of food or beverage products such as in wine, beer or in yogurt the flavor compound is part of the product or using specific designed microbial cultures to produce flavor compounds that will be isolated and purified, and will be used as an additive in the food industry. The flavor compounds produced in this way allows being labeled as natural [46]. Enzyme technology is also an option for natural flavor biosynthesis. Several enzymes such as lipases, proteases, and glucosidases can catalyze the production of aroma-related compounds from precursor molecules. Besides, the products thus obtained may also possess the legal status of natural substances [46]. According to the European regulations (EEC 1334/2008), compounds isolated from natural resources or obtained by microbial or enzymatic processes involving precursors isolated from nature are classified as "natural". Furthermore, the biotechnological approach could also ensure a continuous product supply through a well-standardized process with high

productivity [53]. Examples of commercial "natural" flavors produced biotechnologically are ethyl butanoate, 2-heptanone, β-ionone, nootkatone, 1-octen-3-ol, 4-undecalactone, and vanillin [53, 54]. Microorganisms also present several benefits when compared with plants, such as fast-growing, soil saving, and controllable. The similar intracellular structure of yeast especially *Saccharomyces cerevisiae* with plant cells led to a widely used host for producing flavor compounds [55]. There are two ways to produce biotechnologically flavor compounds, through *de novo* synthesis or by biotransformation. *De novo* synthesis is related to the production of substances using molecules such as sugars, amino acids among others which will be metabolized by microorganisms, normally produces a mixture of compounds in low concentration [56]. Biotransformations are related to single reactions catalyzed enzymatically, so the substrate is metabolized by the microorganism, has a higher potential to produce flavor compounds at a commercial scale [56]. Flavor compounds produced by *de novo* synthesis uses the whole metabolism of the microorganism to produce a combination of flavor compounds, in opposite to the biotransformation, where a specific reaction(s) produced a major flavor compound [15].

The development of innovative metabolic engineering gave the start for incredibly significant progress in the metabolic engineering of microorganism's cell factories [57]. For example, for increased, terpenoids synthesis, as they are widely used as natural flavoring compounds [53], and in this way, they could be produced at an industrial scale [57]. Terpenoids (also called terpenes or isoprenoids) are obtained via the mevalonate biosynthesis pathway or the 2-*C*-methyl-*D*-erythritol-4-phosphate pathway with the former being found in yeast and constitute the two main targets of cell engineering approaches to improve terpenoid production [58,59]. Terpenoids are composed of five-carbon building blocks (isoprene) and are modified by the addition or removal of functional groups such as methyl and hydroxyl groups. One of the most promising attempts was overproducing target molecules from simple carbon sources using fast-growing and cost-effective microbes and optimizing the production yield by employing metabolic engineering

strategies [60]. To produce monoterpenes, which are produced directly by terpenoid synthase, *Escherichia coli* is widely used for enzyme identification and their great activity and easy expression of these terpenoid synthases in *E. coli*, as it has a simplicity genetic manipulation [61-63]. Yeasts are also becoming attractive to be used, for example in engineered yeast expressing of geraniol synthase [64-66]. However, the use of yeast cells as an efficient biosynthetic pathway presented some limitations, such as the biosynthetic pathways are not completely explained associated with the reduced or even missing the activity of plant enzymes when expressed in yeast. Besides, reduced cell growth and reduced final product quantity could be related to declines in the native metabolic flux affected by heterogeneous pathways [67,68]. Also, the cytotoxicity of some natural products could be a limitation to use microorganism cells for producing natural flavor compounds. The identification of new microorganism hosts that can reach greater production and the development of existing strategies to identify regulatory effects in the central metabolic pathways are essential questions about the microorganism biosynthesis [46]. Numerous strategies and bio-tools to accelerate the microorganism natural products biosynthesis in yeast cells have been developed based on omics, metabolic engineering, and protein engineering [69-71]. For example, metabolic engineering has allowed the production of good yields of relevant prenyl alcohols, such as nerolidol [72], geranylgeraniol [72], geraniol [73], and cubeb oil in yeasts [74,75].

Approaches to redesign natural biosynthetic pathways are studied by analyzing the genome and transcriptome data to forecast the genes involved in the targeted compound biosynthesis, by comparing the transcriptome data between plants with high- and low-production of the target flavor compounds, several key genes could be forecast [70]. The little final concentration of the synthesized flavor compounds is commonly related to the reduced enzyme activity on the unnatural substrate, so strategies to improve plant enzyme activity and to enhance metabolic flux must be studied [76-78]. As the plant natural products, biosynthetic pathways contain numerous steps, when hosted in the yeast cells, the

heterogeneous pathways would interact with the native metabolic, by competing substrates and co-factors. Therefore, this trouble will limit the targeted flavor compound production, by balancing metabolic flux distribution between heterologous pathways and native metabolic shows essential in improving the production of targeted flavor compound. Also, strategies to decrease toxicity to the hosts are needed [55,79].

Natural products frequently show cytotoxicity to the microorganism hosts, with the consequence to reduce cell growth and prejudice the flavor compounds production. Therefore, several strategies were studied including two-stage fermentation, pathway separation and transporters mediated compound secretion [55,79]. To lessen the negative effects on cell growth separated into two stages, in the first fermentation stage, the heterogeneous pathway retains calm and cells grow fast with precursor accumulated, in the second stage, the target pathway would be induced to produce the target flavor compounds. Consequently, the subcellular separation was a new strategy to decrease products cytotoxicity to the microorganism hosts. An alternative strategy to decrease the internal cytotoxicity of natural products is to secrete these compounds external to the cell automatically. To attain this objective, transporters were considered, for transporting the products to the extracellular space. Transporter engineering has been developed to improve the transports, due to the scarcity of transporters that can transport the flavor natural products [55,79].

Microorganisms can synthesize flavors as secondary metabolites during fermentation (Figure 1) using compounds such as amino acids and sugars. This ability may be employed as an entire part of food or beverage production processes (some examples include fermented beverages like beer and wine, and fermented foods such as vinegar, yogurt, and cheese) which defines the sensory attributes of the resulting product [80,81].

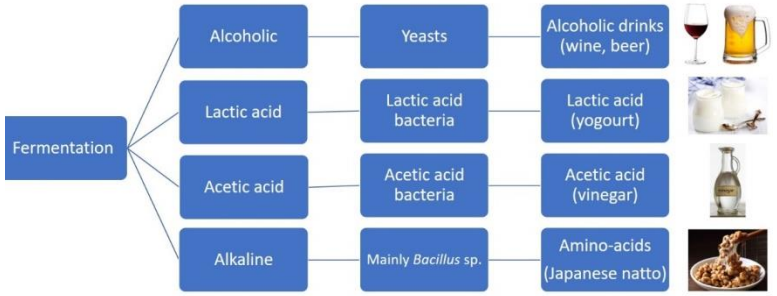


Figure 1: Schematic representation of the common types of fermentation, the microorganisms involved, and the end food products [81]. Alkaline-fermented foods constitute a group of less-known food products that are widely consumed in Southeast Asia and African countries. In alkaline-fermented foods, the protein of the raw materials is broken down into amino acids and peptides, ammonia is released during the fermentation, raising the pH of the final products, and giving the food a strong ammoniacal smell. They can be made from different raw ingredients. For instance, Japanese natto is inoculated with a pure culture of *Bacillus subtilis* var. natto [82].

Saccharomyces cerevisiae yeast act as a microbial cell factory to produce flavor and aroma compounds, according to Kutyna and Borneman [83]. The heterologous production of natural aroma and flavor compounds such as nootkatone, valencene, vanillin, and cinnamaldehyde, is only possible due to synthetic biology. Of the thousands of flavor and aroma compounds that have been identified, only a few amounts have been effectively performed by heterologous means [83]. *S. cerevisiae* and *Escherichia coli* are engaged for the microbial synthesis of almost all-natural products of interest, although new microorganisms are emerging [84].

Lactic acid bacteria (LAB) are used worldwide in the industrial manufacture of fermented foods and can produce high-value metabolites associated with flavor, such as diacetyl and acetaldehyde [85]. Citrate-utilizing LAB produces diacetyl during the manufacture of butter, buttermilk, and several kinds of cheese, diacetyl is the characteristic butter aroma and widely used in the imitation of butter and other dairy flavors when desirable in food or beverages [86]. Because of its value as a flavor compound, the efficient production of diacetyl from lactose rather than citrate has been the aim of numerous

metabolic engineering strategies. Mixed cultures of LAB are also described to produce butyric acid, lactic acid, and diacetyl [87]. Acetaldehyde is another important flavor compound in dairy products, formed by LAB through various pathways. A key metabolic precursor for acetaldehyde synthesis by LAB is glucose through the pyruvate and acetyl coenzyme A (acetyl-CoA) intermediates of glycolysis [88]. Amino acids and other metabolites that are transformed into pyruvate can also contribute to acetaldehyde biosynthesis. The key pathway is through the conversion of threonine into acetaldehyde and glycine, a reaction catalyzed by threonine aldolase [89,90]. LAB possesses a small genome size (~2–3 Mb) and simple carbon metabolism [91]. These physiological and biochemistry features make these bacteria a key candidate for metabolic engineering strategies. These strategies have mainly focused on the redirecting of pyruvate metabolism to produce important fermentation end-product flavor compounds such as diacetyl from lactose rather than citrate has been the purpose of many metabolic engineering strategies [92-94].

Mechanisms of Olfaction and Ligand-Receptor Interaction

Santiago Cajal first described the peripheral olfactory system in 1891. Currently, we continue to observe remarkable discoveries of new olfactory signaling mechanisms and new principles of olfactory processing [95-99], however, much remains to be explained. In 1995, Richard Axel's publication “The molecular logic of smell” was important, which summarized the advances in research on the molecular processes of olfactory translation that occurs in the olfactory epithelium of the nose, from the late 1980s to the early 1990s [100]. Notable advances in our understanding of olfactory perception have been made in recent years, including the discovery of new mechanisms of olfactory signaling and new principles of olfactory processing. Indeed, some authors say that “The next generation of rich media services will be immersive and multisensory, with olfaction playing a key role (…) for enhancing user quality of experience “[101].

According to Mazzatenta et al. [102], the olfaction "(…) is a chemosensory processing system that can detect potentially infinite numbers of low molecular- weight compounds, called odorants, which combine at different concentrations, to elicit this complex perception (…)". Thus, the olfactory perception results from the chemoreceptors in olfactory cells that can detect certain chemicals and transduce them into electrical impulses.

The olfactory system comprises both the main olfactory system and the vomeronasal olfactory system, which integrates several processing routes. In humans, the olfactory system distinct groups of sensory neurons which is are mainly localized within the olfactory epithelium of the nasal cavity [103]. Each neuron in these systems expresses a type of G-protein-coupled receptor (GPCR) superfamily, specializes in detecting a specific type of odor. Thus, the activity pattern of all sensory neurons in the olfactory system allows us to distinguish the different odors present in the environment [104]. In humans, natural odorants like pheromones and other odorants require seven-transmembrane G-protein-coupled receptors [105]. But how the transduction mechanism works? According to Villar et al. [106], the main olfactory epithelium or olfactory bulb comprises three main cell types, olfactory receptor cells, (Figure 3(a)), sustentacular cells, and basal cells. ORCs project a single dendrite to the epithelial surface, where it swells forming the dendritic knob (Figure 3(b)).

Therefore, the initial odor detection process begins in the posterior region of the nose, when volatile molecules enter the nasal cavity (Figure 3) binding, directly or through odorant-binding proteins, to receptors on the external surface of cilia and activate receptors on the olfactory epithelium. After this binding, a complex sequence of biochemical reactions occurs, similar to those found in rod photoreceptors in the human eye, i.e. olfactory receptor neurons contain a G-protein (Golf) protein, in which its Gαolf subunit dissociates from the G beta-gamma complex (Gβγ) complex and activates a specific olfactory adenylate cyclase (AC3) (Figure 3(c)), generating cyclic adenosine monophosphate (cAMP). Then is observed the neuron depolarization due to the increase of the cAMP that

promotes the opening of the channels allowing cations entry, sodium (Na^+), and mainly calcium (Ca^{2+}) ions. The ensuing increase in intracellular Ca^{2+} opens Ca^{2+} activated Cl^- channels causing an extra inner current due to a Cl^- efflux amplifying the olfactory receptor potential depolarization. This depolarization arises from the cilia until the axon hillock region of the olfactory receptor neuron, where action potentials are generated and transmitted to the olfactory bulb [107]. The axon hillock region of the olfactory receptor neuron, the last receptor of the depolarization that arises from the cilia, generates and transmits action potentials to the olfactory bulb [108].

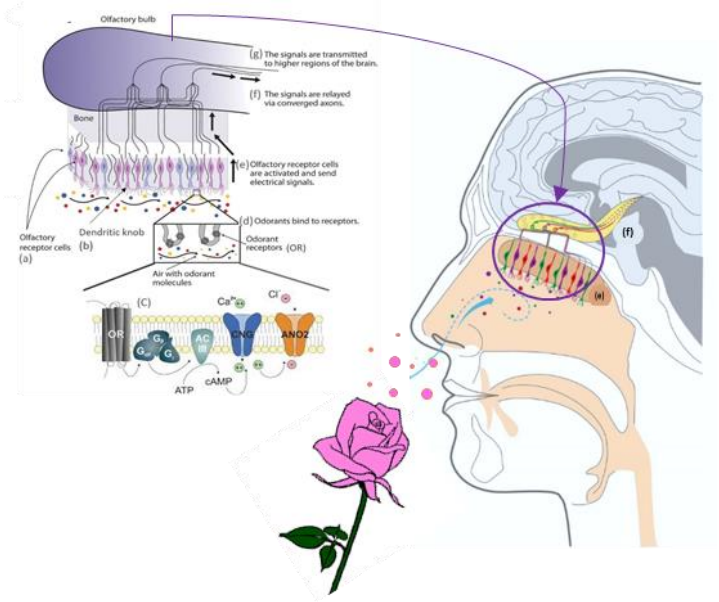


Figure 3: Schematic representation of olfactory transduction mechanism. OR – Odorant receptor protein, Golf - G-protein complex, made up of Gαolf (alpha (α)), Gβ (beta (β)), and Gγ (gamma (γ)) subunits, ACIII - Olfactory adenylate cyclase (AC3), CNG – Ca^{2+} Cyclic Nucleotide Gated channel, ANO^{2-} Anoctamin Ca^{2+} activated Cl^- channel, ATP - Adenosine triphosphate, cAMP - Cyclic adenosine monophosphate.

Consequently, olfactory transduction can be divided into ligand binding (Figure 3(d)), signal generation, and signal termination (Figure 3(e)), where the generating of action potentials conducted along the axon to the olfactory bulb. The signals are

relayed via converged neurons (Figure 3(f)) and then transmitted to higher brain regions (Figure 3(g)) [107].

And, what happens when it is present a mixture of 2 or more odorants? Here the answer is much more complex. Several authors have done studies in this area but still, many questions remain unexplained. According to Bushdid and co-workers [101], since neither the dimensions nor the physical limits of the olfactory stimulus are known, the strategies used for other sensory modalities, namely those used to regard the estimation of the visual and auditory systems' average resolution, are not possible to be enforced to the human olfactory system. In the presence of a mixture of two odorants, it is possible to determine the number of receptors activated by any concentration of the mixture, when in advance we know the affinity and efficiency of each of the components of the mixture alone because the OR stimulated with 2 different odorants will respond with sigmoid curves as concentration's function of the two odorants. Also, the number of ORs activated by the blend can be characterized by a logistic curve when two odorants compete for the same binding site [109,110].

Münch et al. [111] have done an important study where discusses how mixtures of odorants interact with olfactory receptors (ORs) supported by olfactory receptor neurons (ORNs) using *Drosophila melanogaster* ORNs. Their results agree with others made in the rat, confirming that the response of an ORN to a binary mixture can sometimes be predicted quantitatively by knowing the ORN responses to its components.

Other authors had studied this question and presented several hypotheses of the functioning of the olfactory system based on mathematical models [112]. Thus, if the mathematical model will be analyzed, concerning the number of activated ORs, based on elementary chemical kinetics, three interesting properties emerge. On the one hand, whenever the concentration of the odorant molecule increases, the activated ORs follow a hyperbolic curve. On the other hand, the affinity between the odorant and the OR does not depend on the total number of ORs but the rate constants of the 4 reversible reactions (binding x

release and activation vs. deactivation). Finally, these authors also conclude that the maximum number of receptors activated in a given time will depend on two things: the affinity of the OR and the rate constants of the activation-deactivation reaction (but not the release of the binding reaction).

Recent Sensory Analysis Techniques

Overview of Sensory Techniques: "Product Understanding" and "Consumer Understanding"

Sensory evaluation of food and beverages is concerned with the Human response to a food/beverage physical stimulus [113]. After the brain interprets the sensations into perceptions, the stimulus is recognized, and the brain expresses a response. The response can be objective "the drink is acid and sweet" or subjective, acceptance or rejection to the stimuli "I like this drink/I don't like this drink". The subject can also give an emotional response like "it gives me joy" or "it brings back happy memories of my summer vacations!" Sensory evaluation science focuses both on the objective measurement "product understanding" and on the subjective responses of individuals [114,115].

The sensory techniques that measure the product understanding, are well-thought-out as being objective measurements, discriminative, or descriptive. Discrimination tests answer the question "Are the products similar or different?" Examples of this kind of tests are the triangle tests, duo-trio-tests, or forced-choice tests [115]. Descriptive tests, qualitative and quantitative, are objective techniques once they require highly trained panelists and the degree of sensory restriction to which the sensory professional is subjected allows the reproducibility of the results that are "precise and consistent" [116].

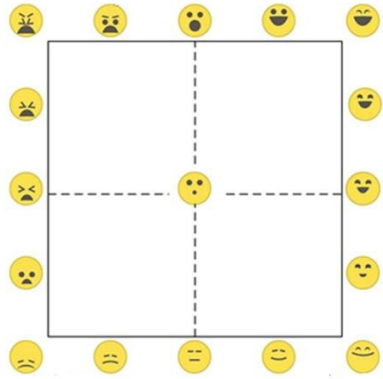
Many of the papers published in the field of descriptive sensory tests are concerned with the development of "sensory lexicons". A sensory lexicon plays an important role as an effective communication tool among diverse audiences such as sensory panels, sensory scientists, product developers, marketing professionals, and suppliers who may have different

understandings of the same sensory attribute due to differences in perception, background knowledge, and culture. Besides, carrying out descriptive sensory analysis using a lexicon with well-defined and referenced descriptors and standardized evaluation procedures provide accurate and repeatable information about sensory qualities of food products that could be used as a guidance tool for various activities in the research and development of food and beverage products, including new product development, quality control, product improvement and measuring changes during product shelf-life [117]. Sensory lexicons provide a source list to describe products, including beverages (wine, beer, spirits, coffee…). Over the years, descriptive lexicons have been developed for wine [118], beer [119], and spirits [116], among other alcoholic beverages like Pink Port Wines [120]. While the "lexicons" provide qualitative product discrimination based on attributes, the quantitative aspect is the intensity of each attribute. Different descriptive sensory methods differ in their scale usage. For example, in the QDA (Quantitative Descriptive Analysis) method a five-point scale can be used [120], while, in other methods, larger scales are utilized, such as the Spectrum™ method that uses a 15-point scale with ratio properties, where 0 is no detectable amount of attribute and 15 is a high amount [119].

The sensory techniques can also be used to measure the subjective personal reaction of consumers, acceptance, liking, or consumer´s preference [114]. These methods are called "hedonic". Also, the consumer´s perception of product benefits can be measured using semantic emotional words like "coziness", or "healthy" [121]. This "consumer lexicon" is important to brand identity and for accessing product quality. However, while testing with a trained panel of assessor requires a small group of people (12–20 persons), testing with consumers, due to the person-to-person variability in preferences, for achieving quantitative results, that can be statistically analyzed, requires a high number of participants (between 75 to 150) [114,115].

Hedonic sensory methods that measure preference and choices may be affected by food habits, attitudes, and beliefs [121],

culture, and tradition [122], food environment, and dietary [123], and, food beliefs affect the potential acceptability [123]. Nevertheless, many consumer studies have been conducted on the acceptability of commercial food products, including beverages, various consumer methods, perceptions, emotions, and cross-cultural studies [124-127]. Nowadays, and with the engagement of social media (Facebook, Instagram, Twitter, among others) food and emotions have been reported to share a bi-directional relationship: on the one hand, emotions can shape food and beverage choice, food intake, and liking, while, on the other hand, food and beverage consumption can influence consumers' mood and emotions [128]. So, the internet, and particularly social media, are an opportunity to obtain spontaneous consumer information obtained in real-life situations [129]. Pictographs, such as emoticons and emoji, have been considered a substitute for standard language as well as an easy and instinctive way of expressing emotions. They are widely used in electronic messages and Web pages to supplement or substitute written text [130]. These symbols are abstractions of facial expressions or human gestures, developed to help to communicate emotions or mood in computer-mediated communications [131]. Graphical characters are also used to convey emotional expressions, and these are called emoji, a Japanese word meaning ''picture word". So, in sensory evaluation of food and drinks, some authors have suggested replacing the subjective linguistic increments on rating scales with iconic facial expressions [132, 133]. These graphical tools, like the emoji grid (Figure 4), may also be useful for cross-cultural studies since they eliminate the need for translation and the problems associated therewith. Additionally, they may be more effective to measure and express mixed (complex) emotions that are hard to verbalize [134].



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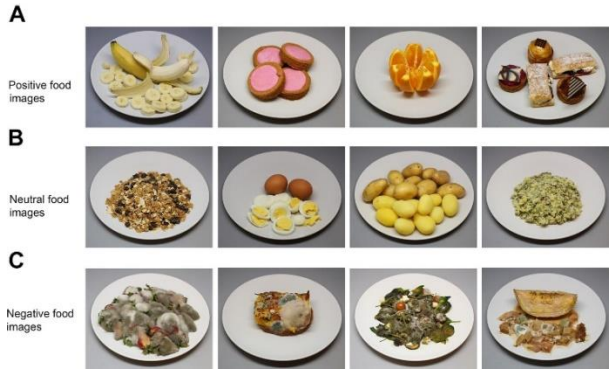

B

Figure 4: (A) The EmojiGrid: an emoji-labeled Affect Grid for the measurement of food-related affective associations, (B) Stimulus examples. (A) Positive food images (banana, cookies, orange, sweets), (B) neutral food images (cereals, boiled eggs, boiled potatoes, hotchpot), and (C) negative images of rotten food (strawberries, omelet on bread, Greek salad, melon) used in the work performed by Toet et al. [133].

Traditional and Novel Single Point Techniques

Reformulating a drink, like a fruit-juice, to reduce, e.g., its sugar content, will affect its consumer acceptance? Are we able to explain which sensory attributes elucidate consumer liking or

healthiness product perception? Is there an easy way to approach this information? Conventional sensory analysis methods, like QDA (Quantitative Descriptive Analysis), CATA (Check-All-That-Apply), Flash Profile, FCP (Free Choice Profiling), Polarized Sensory Positioning (PSP), and holistic sensory methods (Sorting, Napping), have long been used to provide this information. What these methods have in common is the use of a trained or untrained sensory panel, descriptive terminology, and single-point static rating measures.

The quantitative Descriptive Analysis (QDA) approach has been recognized and studied since the work of Stone and Sidel in 1974 [135], as an instrument for measurement and optimization of sensory attributes of diverse food and drink products. This technique involves training the sensory panelists to quantify the specific sensory attributes of the product aiming to produce quantitative product descriptors that can be analyzed statistically [136], and represented graphically (spider graph) for perceptual mapping.

FCP (Free Choice Profiling) belongs to the group of the descriptive analysis of sensory techniques [137]. Each evaluator can use its descriptors and there is no need for a common vocabulary. The individual data are summarized in a plot showing the products and the attributes of everyone. So, FCP does not require training making it a technique less expensive and time-consuming when compared to QDA that uses experts or trained assessors. However, since each panelist is using distinct words, the data obtained must be analyzed using a Generalized Procrustes Analysis (GPA) [137].

In the CATA methodology assessors are asked to mark sentences/statements, previously selected. They can mark as many options as are required to express their opinion [138,139]. CATA is a flexible, lengthy, and descriptive methodology that can be applied to consumers with no previous training.

PSP (Polarized Sensory Positioning) is a technique based on the evaluation of global differences between samples and a fixed group of references or poles (for instance, similar drinks). It is

one of the fasts sensory methodologies, and when compared with other methods, described above, it allows aggregation of data collected in different sensory sessions [140]. This issue is relevant when there is a need to analyze large group sets or samples with an intense sensory characteristic that can be difficult for assessors to evaluate in only one session.

As it was mentioned before, traditional sensory descriptive analysis is being substituted for faster sensory profiling techniques. Fleming and co-workers [141] compared the results of three fast sensory profiling techniques—CATA, Sorting, and PSP—using a scale of astringent stimuli. The data showed that similar plots, regardless of the method used, were obtained.

Sorting, also called Free Sorting Task (FST) or Free Multiple Sorting, was first used by Lawless, and Glatter in 1990 [142] to explore the perceptual structure of odors. For performing a Free Sorting Task only, a single session is needed. Products are randomly displayed and presented at the same time on a table with a different order per person. Tasters are asked first to sensory evaluate all the products and then to sort them into mutually exclusive groups grounded on product-perceived resemblances. After, assessors are asked to deliver a few sensory descriptors to characterize each group that they have previously formed [143].

In 1994, Risvik and co-workers [144] published a work named "Projective Mapping: a tool for sensory analysis and consumer research": the aim was requesting assessors to position products on a sheet of paper based on their sensory similarities. Also called Napping®, this fast-sensory technique uses a sheet of paper or table-top, where assessors can position the products according to their sensory similarities, producing a sensory map. Samples located closer are related and those located distant isolated are distinctive.

However, can we be sure of the coherence of the data obtained? Dehlholm and co-workers [145], compared three fast descriptive sensory evaluation methods: Free Multiple Sorting, Napping®, and Flash Profiling. Evaluations were carried out by diverse

expert assessors from two different investigation environments and within the same time. The authors concluded that semantic results from an assessor, with no training, are dependent on the assessors' semantic skills.

Time-Intensity Methods

Wine tasters debate how a wine "opens in the glass after swirling", spotting that the flavor, after the opening of the bottle, changed as a function of time. A sigh of high-quality wine is one with a pleasant and "long finish". So, the "time profile" of a beverage is important for its sensory appeal and flavor perception.

Flavor liberation from a food or a drink is not a unique occurrence, but an evolution of sensations and perceptions, that is not constant in time. Dijksterhuis and Piggott [146] proposed, in 2000, a two-step model intended to illustrate the different stages in the process providing a framework for their integration. Yet, according to the mentioned authors, time plays an important role, from the moment that the drinker contacts with the drink, to the moment, after swallowing, that the sensations disappear [146]. So, the best way of food sensory analysis is to have into account the duration of the perception stimulus. Several methods, that consider "time" are being applied and studied. One of them is time-intensity (T-I), a sensory method that measures the intensity of a sole sensory perception, over time, in response to a single contact to a food or a drink. So, the method implies a dynamic process [147]. The objective of T-I measurements is to establish the pattern of the progress of a specific sensory characteristic. This method is ideal to distinguish products that have diverse temporal characteristics and when measurements at a single time point are not enough. Examples may include short-term sweetness in a drink [148], or long-term astringency in wine (Figure 5).

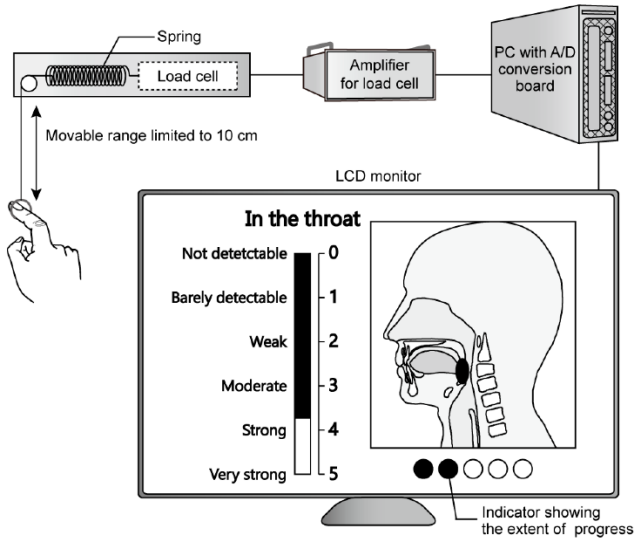

Figure 5: Outline of the TI evaluation system. PC: a personal computer, A/D: analog-to-digital, LCD: liquid crystal display [149].

Several methods for performing sensory attributes studies in time-intensity evaluations have been studied. Dual-Attribute Time-Intensity method (DATI) [150], Temporal Dominance of Sensations (TDS) method [138], and, more recently, the Multiple-Attribute Time-Intensity (MATI) method [151,152].

When attributes are presented in pairs, at a given time, the DATI method can be performed. Lekalake and co-workers [153] studied an expert panel for assessing bitterness and astringency of infusions of tannin and tannin-free sorghums. In the two infusions, bitterness developed and reached extreme intensity earlier than astringency (27.9 s). The time of the astringent sensation (69.9 s) took longer than bitterness (66.3 s). Inclusive, the temporal parameters for assessing bitterness distinguished tannin and tannin-free sorghums infusions somewhat more evidently than those for astringency. MATI method has a similar methodology, but, with multiple stimuli. The pioneering work of Kuesten and co-workers are good examples of studies where this method was applied: Kuesten et al. [151]—"Exploring taffy product consumption experiences using a multi-attribute time-intensity (MATI) method", Kuesten and Bi [152]—"Temporal

Drivers of Liking Based on Functional Data Analysis and Non-Additive Models for Multi-Attribute Time-Intensity Data of Fruit Chews".

Temporal dominance of sensations (TDS) aims at gathering the sequence of the dominant sensations perceived by the panelists throughout the tasting of a product/beverage. For example, while tasting a red-wine from intake to swallowing, the subject can successively perceive the attributes sweet and sour taste, body and viscosity, finishing with bitter taste and astringency as the dominant sensations. This method (TDS) was first proposed and studied by Pineau and co-workers, [150] in 2003. Since then, the authors have published several works, where the method is explained and compared with others [154,155].

Electronic Nose and Other Sensors

Electronic noses (e-noses) are devices created to recognize volatile odor compounds. They are created to mimic the Human nose, not in its shape or size, but its ability for entrapment of odors and sensory transduction mechanisms. E-noses usually possess cross-reactive sensing arrays that upon odor exposure generate patterned responses and analytical algorithms that catalog this patterned response [156-158].

While insects, and even sharks, depending on their movement through the habitat in which they live to get in contact with sensing elements, mammals can sniff, allowing contact of the odorants with the receptors, usually inside of their nasal cavities. For aroma detection by the e-nose, volatile molecules must come into physical contact with the detectors. This phenomenon occurs by contact with the detectors, or by moving the carrier air to the detector, or by moving the detector through the air allowing it to contact the volatiles [156].

In biological systems sensing surfaces are intricate structures that consist of augmented surfaces composed of cilia or microvilli. E-nose sensing surfaces are virtually flat and uniform [156]. Yet, e-noses devices can contain up to 40 sensors, each one standardized for a precise chemical compound. Compounds

and sensors combined to provide a measurement pattern. The electronic nose can only identify patterns of expected and known volatile compounds [159]. So, to be able to detect, analyze and process the information, an *e-nose* device must be built putting together three components, each with a specific function [160]: A sample delivery system consisting of a multisensory array, a detection system such as an Artificial Neural Network (ANN), and a computing system with appropriated software (digital pattern-recognition algorithms and reference-library databases) [161] (Figure 6).

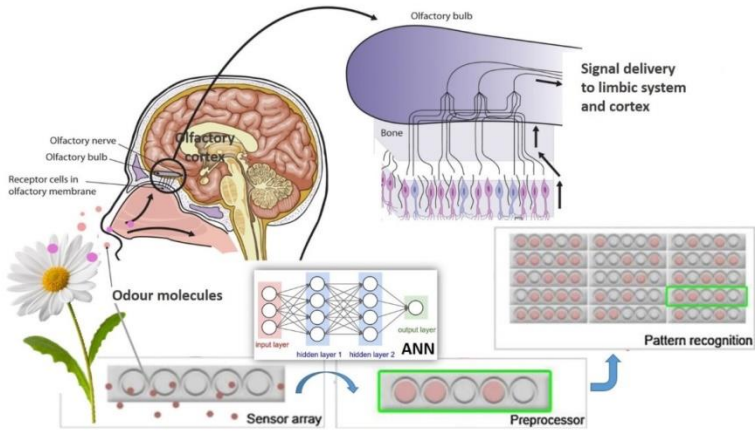

Figure 6: Schematic representation of an e-nose device, with the analogy to Human Nose. The electronic nose is an array of chemical sensors, connected to a pattern-recognition system that responds to odors passing over it. Different odors cause different responses that provide a signal pattern characteristic of a particular aroma. The computer evaluates the signal pattern and can compare the aromas of different samples, using pattern recognition. Artificial Neural Network (ANN).

E-nose devices can be classified according to the origin of their signal-transduction mechanisms. Several signal-transduction mechanisms have been reported: Metal oxide semiconductor (MOS) [157], conducting polymer films [162], acoustic wave devices [163], optical transducers [164], electrochemical systems [165], polymer film chemo-resistors [166], and quartz microbalance (QMB) sensors [167]. Regardless of the transduction mechanism, the higher the number of sensory

elements in a cross-reactive sensor array (CRSA), the better-off is the data collected, and the specificity of the analyte identification and classification. Recently, Fitzgerald and co-workers [168] developed cross-reactive sensor arrays to be used in e-nose devices. They developed a barcoded polymer sensor array based on porous polymer beads. Spectroscopic changes experienced by the porous spectroscopically encoded beads, after exposure to an analyte, could be used to identify and classify the marked analytes.

Drift correction is an important concern in e-nose techniques and devices, for maintaining a steady performance during nonstop work. The deviations normally caused by environmental and physicochemical influences disrupt the compatibility between the gas-sensor responses and artificial intelligence algorithms [169]. Drift component can be decomposed based on statistical characteristics employing multivariate statistical analysis such as Principal Component Analysis (PCA) and PCA-based Component Corrections [170] Independent Component Analysis [171], wavelet [157] and, more recently, by Active Learning on Dynamic Clustering [169]

Besides e-noses, science has arranged the manner of also mimic the Human tongue. The first e-tongue appeared in the 1990s. They were developed for application in ions and heavy metals analysis [172] as well as an evaluation of taste [173]. According to the International Union of Pure and Applied Chemistry (IUPAC) “An electronic tongue is a multisensory system, which consists of several low-selective sensors and cross-sensitivity to different species in solution, and an appropriate method of pattern recognition and/or multivariate calibration for data processing” [174,175]. An e-tongue is useful when human panels cannot/should not be used, due to beverage process circumstances, poisonous/extreme condition samples, and cost-effective reasons [176].

E-tongues can use arrangements of sensors constructed on a variety of transduction principles from electrochemical to optical or mass [177]. However, electrochemical sensors such as amperometric [178], voltammetric [179], potentiometric [180],

and especially, impedimetric sensors [181] are the most usually used in beverages like wine [182], or even semi-solid food such as honey [181].

The fingerprint of a given substance can be achieved by the fusion of data from different sensor types thus, allowing a better classification and identification of the analyte. This is possible due to multitransduction, i.e., by measuring different properties of the same sensor. One example is the quantification of electrochemical and optical changes observed for porphyrin electro-polymer films [183]. It is also possible to merge data from physically separated optical and electrochemical sensors as has been studied by Gutiérrez and co-workers [184] for quality control of wine. In recent years, the inclusion of biosensors with specificity to certain compounds in the array has been investigated. These couple devices are called bioelectronic tongues (bio-tongue) and can provide global information about the beverage or food products, whereas, simultaneously, provide data about a particular compound, due to the specificity of the biosensor [177].

Following the purpose of replacing human tasters, e-tongue devices can be combined with sensors for gaseous samples, e-noses [185], and even with computer vision for color and surface characteristics evaluation [186]. In 2011, Cole and co-workers [187] joint electronic tongue and nose for a flavor sensing system. The flavor is understood as being the joint experience of oral and orthonasal stimulus, a combination of human gustation and olfaction. So, the system proposed contained both an e-tongue made with Shear Horizontal Surface Acoustic Wave (SH-SAW) sensors, and an e-nose based on chemFET sensors (chemically-sensitive field-effect transistor sensors). They analyze the liquid phase and the gaseous phases, respectively [187]. But, can we call this sensor an e-flavor?

Recent Innovations in the Statistical Technique of Sensory Data Analysis

The amount of information needed for the creation of new products capable of arousing interest in the consumers leads to

the need to implement procedures capable of handling a large volume of data and, based on a representative sample of the population, obtain objectively and as accurately as possible the relevant information. Hence the importance of the role that Statistics play in Sensory analysis. During a long period, univariate statistical techniques such as univariate analysis of variance have traditionally been performed in sensory science. Over the last decades, the advances in computational technologies allow the development of new multivariate techniques more appropriate for handling multiple variables simultaneously and being able to understand the information they provide. The use of multivariate techniques require that statistical and conceptual assumptions are met, hence the need for knowledge of the type of data extracted and the purpose of the study. Therefore, we must be sure that the method used is the most suitable in the data, otherwise, the results obtained may not be reliable. The most common techniques used for identifying sensory characteristics in wine and food are Principal Component Analysis (PCA) [188, 189], Multivariate Analysis of Variance (MANOVA) [190], Cluster Analysis [189], Partial Least Squares (PLS regression) [191,192], Multiple Linear Regression (MLR) [192] and, more recently, Categorical Principal Component Analysis (CATPCA) [120,193]. Categorical principal components analysis (CATPCA) is a non-parametric statistical technique appropriate to reduce the dimensionality of variables of mixed measurement levels (nominal, ordinal, and numeric) to a lesser number of uncorrelated variables that characterize most of the information of the original variables. This technique generally referred by optimal scaling assigns numerical quantifications to the categories of each of the qualitative variables. The choice of an appropriate scale level for each variable is particularly important because it influences the structure of the correlation matrix. If all variables are scaled as numeric, CATPCA ends up with the same results as PCA.

In 2018 Vilela and co-workers [194] applied an innovative multivariate analysis technique, Structural Equation Modelling (SEM) for identifying wine sensory characteristics from monovarietal wine from Vinho Verde Portuguese wine

Demarcated Region. SEM is a statistical technique used to decrease the number of perceived variables (sensory descriptors) into a lesser number of latent (not observed) variables by examining the covariances between the observed variables [195,196]. This data analysis technique that can be viewed as a combination of factor analysis and multiple regression analysis had its origin at the beginning of the 20th century, from the important works of Charles Spearman [197], an English psychologist known to work in statistics, as a pioneer of factor analysis, and for Spearman's rank correlation coefficient. In the past decade, SEM received a great deal of attention from researchers in different areas of knowledge like ecology and forestry [198], social sciences [199,200], engineering [201] and recently in industry applications [202], it ranges from the psychometric validation of instruments to the analysis of invariance of models between groups. Structural Equation Modelling is a general and flexible framework for data analysis that includes traditional techniques such as regression analysis, factor analysis, confirmatory factor analysis, path analysis, discriminant analysis. In SEM the model is formulated as a system of equations that relates several random variables with assumptions about the variances and covariances of random variables and considers potential errors of measurements in all observed variables. The variables involved could be observed (manifest) or latent, i.e., variable for which there are no available observations but manifest themselves in other observed variables. They can also be defined as independent (exogenous) or dependent (endogenous) variables, whether they are observed or latent.

The main advantages of SEM are i) take measurement error into account by explicitly including measurement error variables in all observed variables, ii) incorporation unobserved variables with multiple indicators, iii) to model and test complex patterns of relationships, and iv) test local and global assessment and specific assumptions about parameters for their compatibility with the data.

Final Remarks

The increased consumer preference for natural and sustainable products makes the production of natural flavors an ever-challenging purpose for academic and industrial investigation. This consumer's choices and demands have triggered an evolution in the world of flavors. From simple extraction methodologies to engineered metabolic routes, scientists try to mimic nature and, in some cases, compete to obtain better, natural, ambient friendly, and flavorful products.

The advances are not only in terms of chemistry, biochemistry, microbiology, or sensory analysis, but also mathematics, computer and electronics help the flavor development technologies that allow faster, safer, economic, and precise aroma/flavor compounds synthesis, analysis, characterization, and quantification.

Major developments have been observed in the methods for obtaining aromatic compounds such as microbial and enzymatic biotransformation, *de novo* synthesis, and the use of genetic engineering tools such as *Saccharomyces cerevisiae* cells, also denominated as "microbial cell factories". These cells can be engineered using synthetic biological tools, to express synthetic pathways, applying computational tools and mathematical models, to guide synthetic biology design. So, the choice for natural and sustainable processes is growing, leading to the opportunity for bio-production alternatives.

Sensory techniques with the use of trained or untrained panelists have also evolved from traditional multiple points and structured scales techniques to novel single-point techniques and Time-intensity methods. Conventional sensory analysis methods have long been used to provide the beverages and food products sensory information. However, several methods, that consider "time" are being applied and studied. Time-intensity (T-I), methods, or Temporal Dominance of Sensation methods have been useful, once they are ideal to distinguish products that have very diverse temporal characteristics and when measurements at a single time point are not enough.

Sometimes, the use of a panel of tasters is not enough. Humans can be tired, and some subjectivity is implied in their evaluation, or the products are not yet ready to be tasted by Humans. To circumvent the limitations of the Human-being, science has arranged the manner of also mimic the Human nose and tongue by producing electronic noses (e-noses) and electronic tongues (e-tongues). Still, machines, as Humans, are also not one hundred percent reliable. Drift correction is an important concern in e-nose and e-tongue techniques and devices, for maintaining a steady performance during nonstop work. The deviations disrupt the compatibility between the sensor's responses and artificial intelligence algorithms. The drift component can be decomposed based on statistical characteristics employing multivariate statistical analysis and some of these statistical methods are also used to treat data obtained by traditional sensory techniques, using Human panelists.

Yet, strangely, in terms of electronics, it would be expected that a fully developed e-flavor system would be in the market, ready to be used for the many industries (food and wine) that work with flavor-perception and consumer preference, and aims in producing flavorful products. Perhaps there is a limit on what the man can achieve. Or perhaps it is not as easy as it seems to mimic the Human perception that we call "Flavor".

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